NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome

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6. **Consultee submissions from**:
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7. **Expert personal perspectives from**:
- Prof Fredrik Karpe – clinical expert, nominated by NHS England Specialised Endocrinology CRG
- Dr Charlotte Dawson – clinical expert, nominated by LPLD Alliance
- Dr Karishma Patel – patient expert, nominated by LPLD Alliance
- [redacted] – patient expert, nominated by LPLD Alliance
- Simon Williams - patient expert, nominated by HEART UK
- Dr Handrean Soran – clinical expert, nominated by Akcea Therapeutics

8. Evidence Review Group report prepared by School of Health and Related Research Sheffield (ScHARR)

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Any information supplied to NICE which has been marked as confidential has been

redacted. All personal information has also been redacted.

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Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

– the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
– the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

[redacted]

Key abbreviations

AE	Adverse event	MAA	Managed access agreement
AFT	Accelerated failure time	MCS	Multifactorial chylomicronaemia syndrome
ANCOVA	Analysis of covariance	mg	Milligram
AP	Acute pancreatitis	mg/dL	Milligram per decilitre
APOA5	Apolipoprotein A-V	mL	Millilitre
APOC2	Apolipoprotein C-II	mm	Millimetre
AUC	Area under curve	mmol/L	Millimoles per litre
CI	Confidence interval	NA	Not applicable
CP	Chronic pancreatitis	NHLBI	National Heart, Blood and Lung Institute
EAMS	Early Access to Medicines Scheme	OLE	Open-label extension
EMA	European Medicines Agency	PAS	Patient Access Scheme
EPAR	European Public Assessment Report	QALY	Quality-adjusted life year
EQ-5D	EuroQol 5 dimensions	RCT	Randomised controlled trial
EQ-5D-5L	EuroQol 5 dimensions 5 levels	SD	Standard deviation
FCS	Familial chylomicronemia syndrome	SF-36	Medical Outcomes Study 36-Item Short Form Survey Instrument
GLMM	Generalised linear mixed model	SmPC	Summary of product characteristics
HRQoL	Health-related quality of life	SoC	Standard of care
ICER	Incremental cost-effectiveness ratio	TEAE	Treatment-emergent adverse event
LPL	Lipoprotein lipase	TG	Triglyceride
LPLD	Type 1 hyperlipidaemia lipoprotein lipase deficiency		

History of the topic

- Following a submission in 2018 the company advised of changes to its anticipated marketing authorisation (MA) – **committee meeting delayed**
  - Updated submission provided in 2019 using final MA
- **Original anticipated indication:** an adjunct to a low-fat diet for the treatment of patients with FCS;
- **Final SmPC indication:** for adults with ***genetically confirmed*** FCS ***at high risk for pancreatitis***
- **SmPC dosing and discontinuation rules:**
  - **Treatment** should ***be discontinued at 3 months*** in patients ***with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L***
  - Posology consists of ***3 months of weekly dosing***, ***followed by down-titration to*** a maintenance dosing schedule of ***once every 2 week***s for those after 3 months; **possible re - up titration at 6 months** to weekly dosing, if response is not acceptable on 2-weekly dosing
- **Platelet monitoring rules:** were introduced in company's trial*; with clear indications for dose pausing or discontinuation

[redacted]

Key issues for consideration

Clinical effectiveness

Population: volanesorsen is indicated for adult patients with genetically confirmed FCS at high risk for pancreatitis. Not all patients in company's trials (APPROACH, APPROACH OLE, COMPASS) were genetically diagnosed (89.13%, 82/92):

- Are the study populations representative to people with FCS seen in the UK practice?
- How would "high risk for pancreatitis" be defined in clinical practice?

Clinical effectiveness and safety of volanesorsen at the licensed dose: the licensed dose was not used in trials. What is the committee's view on volanesorsen's effect, at the licensed dose, on:

- Change in TG levels and response to the treatment in long term?
- Clinical outcomes such as AP, CP, and type 2 diabetes, in which only very limited evidence of low quality from trials was reported *(no subgroup analysis by SmPC dosing conducted either)?*
- Safety outcomes (such as thrombocytopaenia)?
- Discontinuation?

TG levels as the surrogate outcome and the dose-response relationship between it and AP:

- What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Disease background

Familial chylomicronaemia syndrome (FCS): is a rare, genetic metabolic disorder of lipid metabolism caused by homozygous mutations in the lipoprotein lipase (LPL) gene

- The most common genetic mutations are: APOC2, APOA5, LMF1 or GPIHPB1 genes
- **Characterised by** high levels of triglycerides (TGs) in the plasma and a build-up of chylomicrons - the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body

- **Symptoms**: abdominal pain, fatigue, impaired cognition, numbness or tingling sensation
- **Morbidities/complications associated with FCS:** unpredictable and recurrent acute pancreatitis (AP), which occur in 60-80%* of patients with FCS; chronic pancreatitis (CP); pancreatic necrosis; fatty liver disease; diabetes
  - ➢ All thought to be a consequence of the build-up of chylomicrons particles which reduce blood follow through organs microcirculation (Valdivielso 2014)

Diagnosis

- Historically, FCS has been **diagnosed by clinical criteria**, including ***recurrent raised TG levels*** refractory to current lipid-lowering therapies and not due to other causes (e.g. type 2 diabetes, hypothyroidism), plus a ***history of recurrent AP*** and ***abdominal pain***
- Genetic diagnosis (*a condition of the license*) is becoming more usual
  - Not all patients with FCS have a known mutation, may not receive genetic confirmation if tested

Prevalence

- Estimated to be **1 to 2 per million people** which equates to approximately 55 to 110 people in England
- It is expected that between **80 and 100 people in England** are likely to be eligible for treatment with volanesorsen¤

¤ estimated by Akcea

Current treatment options

No standard clinical pathway or licensed treatment available

- Management consists of: severe restriction of dietary fat intake (10 to 20g/day), and no alcohol intake (to keep plasma triglyceride levels low)
  - Even severely restricted low-fat diet not sufficient to reduce the risk of a potentially fatal episode of AP for most patients
  - Fibrates and statins (lipid lowering agents) may be prescribed but have limited value
- Patients may be on a cocktail of drugs to control pain and other symptoms of FCS, including steroids, analgesics, anxiolytics, antidepressants, diabetes treatments and antithrombotics
- Essential fatty acids and fat soluble vitamin supplements are required for patients on a fat restricted diet

Related NICE guidance

- None

Patient experience of FCS - expert and support group comments (I)

Comments based on patient expert and patient support group comments

- Information provided by patient support group: based on written submissions and telephone interviews
  - Structure: NICE patient and professional group template
  - At the time of submission 20 patients and 8 caregivers responded
    - 18 patients live in England and Wales
    - 10 patients have taken volanesorsen

      + other evidence: discussions at patient meetings, Facebook support group and a webinar

Management of FCS

- FCS is ***poorly recognised,*** there is little dietetic support
- ***Lack of understanding, guidance and support*** amongst healthcare professionals

Delay in diagnosis, inappropriate treatment provided

- ***Misdiagnosis***: '*I had my gall bladder removed on recommendation of my consultant who thought it might reduce the number of episodes of pancreatitis*'
- ***Unprofessional treatment***: '…*One doctor told me it's in the mind and I thought well you live in my body for one day and you see what chronic pain is like. I even moved doctors because of it. That's how you get treated. The ignorance of someone who doesn't know anything about it.*'
- ***Range of different medications***:
  - Fibrate, statin: '*I've been on every fibrate going and any statin going and they haven't really done anything. Medication never worked*'
  - Fish oil: '*I was given fish oils but they made me bloated and repeated on me*'

Patient experience of FCS - expert and support group comments (II)

Pancreatitis, abdominal pain and hospitalisation

- Patients experience episodes of pain, severe pain and pancreatitis attacks, despite being on restricted diet
- ***Frequent and severe abdominal pains*** will necessitate the need for frequent self medication of pain relief
- ***Recurrent hospital admissions*** are frustrating and depressing for patients and worrisome for family; also have a severe impact on work/study
- Fear of a ***life threatening attack of acute pancreatitis*** is constant
- '*Abdominal pain and pancreatitis and the fear of the onset of both has been ever-present*'
  - '*I woke up one Saturday morning and collapsed and two weeks later I woke up in intensive care, they nearly lost me twice, it was that severe.*'
  - '*I was out of hospital every 10-15 days then three days in hospital. I feel tired and felt the effects for at least two days, get eventually better and then go to back to hospital again. Not a normal life*.'
- Fatigue impacts on ability to live lives fully

Burden of dietary restrictions

- Keep a strict diet is challenging → means not eating enough calories to maintain normal energy levels and nutrients for overall wellbeing
- There is a fear of eating food that has not been prepared by the individual
- '*It's always there – every time you eat, you're thinking about how much fat there is in it and what you've already had that day.*'
- Eating out is difficult and often impossible
- '*My life has been completely shaped by having FCS. It has hugely restricted the choices I have been able to make, made me fearful of attacks of pain and pancreatitis and made me really suspicious of food and what it contains*'

Patient experience of FCS - expert and support group comments (III)

Impact on work life

- Recurrent pain has an impact on the ability of patients to work, the choices they made about which jobs to do, and the number of manageable hours
  - People choose jobs that less responsible than might otherwise have attempted
  - Choice of job was limited to a role that did not involve much travel or attending social events
  - '*I always had a job, I shied away from jobs with any responsibility because I was concerned about having time off with pain, and not being able to think clearly because of the brain fog due to high triglyceride levels*'
  - Patients have varying experiences regarding the understanding of employers
    - '"*Your health isn't my problem. Your wellbeing isn't my problem. You're here to do a job". ….It was difficult going back knowing people didn't want you there*.'

Pregnancy

- Pregnancy can be difficult as triglycerides rise naturally in the third trimester; levels can be above 60mmol/L
  - Most women were unaware that there might be complications due to pregnancy
  - Some reported being sterilised after having particularly difficult pregnancies; for some the pregnancy was highly medicalised
- *'My trigs were about 70… I would have plasmapheresis every Monday and my trigs would drop to about 20. I would have a blood test on the Friday and they would be rising and then I'd be back in again on the Monday – this was from 16/17 weeks.'*

Patient experience of FCS - expert and support group comments (IV)

FCS associated diabetes

- A number of patients can develop diabetes as a result of FCS due to insulin insufficiency caused by decreased insulin production
- Patients food choice can be very limited, leaving very few choices to give energy and sustenance
- '*For years my triglycerides were very low - under five – until I developed diabetes. Since then they're creeping up and I don't seem to be able to do anything about it, despite being on two diabetes medications. … For the first time in years I'm scared I'll have pancreatitis.*'

Depression and emotional wellbeing

- FCS has an impact on emotional wellbeing
- Patient felt depressed and were taking anti-depressants; had suicidal thoughts
  - '*I've spent most of my life watching others get on with their lives while I felt completely restricted in the choices I can make and worrying about or being in pain. I have periods of depression where I feel I have nothing to offer anyone and can't see why people would want to have anything to do with me.*'
  - '*My attempts to be 'normal' would always lead to periods of pain, fatigue and self-hatred*'

Equity

- Women from some religions do not access health services and seek out treatment

Effect of FCS on carers and on patient's family and friends - Patient expert and support group comments

- **Effect on carers and partners' and their ability to work**: '*My mother gave up her work to look after me…So little was known about FCS that it would have been impossible to try and manage my condition safely without her being able to devote her full attention on how to manage the condition and how to accommodate and meet my dietary requirements*'
- '…*Couldn't get paid. For the second baby he had to take time off…. Held him back a little, things he didn't go to, when I was in hospital*.'
- **Effect on children**: children who see their parents in pain or in hospital, the experience can be deeply distressing and can prompt the child taking on the role of a carer: '…*I will often take her and pick up from school, she will stay at mine if Mum is in hospital because Dad will need to get up early – we have to try and keep things normal for everyone because life still goes on and school and work still has to happen'*
- **Family members have to apply restrictions in everyday life**: '*I feel bad because I'm imposing my lifestyle on them… it makes me feel bad that they can't eat, or they can't have stuff in the house because I will want to eat it. It puts restrictions on quite a few things*.'

Benefits of the technology – Patient expert and support group comments

Benefits of volanesorsen

- Volanesorsen has a very positive impact on every aspect of life
- Main areas of improvement:
  - ***Reduction of pain and fear of pain***
  - \+ ***incidence of pancreatitis reduced*** to almost zero
- Improvement allowed patients to ***engage more fully in their lives***, avoiding visits to A&E and hospital stays; retreating from daily routine to manage attacks of abdominal pain and pancreatitis
- ***Improved their ability to work, to study and to manage friendships → reduced the stress and anxiety***
- Benefits would ***allow carers and families*** the opportunity to live their lives in a manner that ***enables forward planning***
- '*I'll be able to have a full life. Everything I do - work, mentally physically, family, workwise, it's going to make my life a lot better, and if the lipids are down, make my life last a lot longer*.'
- '*the treatment has made me feel so very, very much better. My triglycerides have reduced by about 60% and with that reduction I have felt much more alert, do not feel fatigued, have not had any pain at all which. I am therefore no longer feeling paranoid about the onset of pancreatitis*'
- '*My diabetes is also looking better controlled and I feel in control, rather than out-of-control and anticipating the next 'off day' or period of abdominal pain*'
- '*I have not any abdominal pain since starting this treatment in December 2015 and zero days off work*'
- '*Now that I am not getting pancreatitis every 2 months or so I feel well in myself, and can consider starting my own family*'

Disadvantages of the technology – patient expert and support group comments

Disadvantages of taking volanesorsen are ***possible platelet reduction***, ***need for monitoring and difficulties with the injection site***

- ***Side effects were bloating, pain around the injection site*** and ***reduction in platelets*** flagged by blurred vision and headaches
- '*The main problem I suffered with when taking the drug was that I had blurred vision and headaches…. The following day my bloods were done, by the afternoon the hospital contacted me and said that my platelets were low and I shouldn't inject that week. I had to wait three weeks for my platelets level to come up and then I was told to inject every two weeks. My platelets level is checked every week and they have been normal….. I still feel nervous when I inject*'.
- 1 patient in the trial was asked to stop taking the therapy after experiencing symptoms attributable to the drug
- Patients ***who have not taken the therapy had different opinion on side effects and frequent monitoring*** (some might have opted for not taking the drug – with less severe form of the disease)
- '*I think I'd at least like to be able to have a full discussion with my consultant about whether, on balance it would be suitable for me. My triglycerides keep rising and I'm struggling to manage them. It's giving me a lot of stress thinking I might suddenly have an episode of pain and if I did have pain, I worry about the impact that might have on me both in the immediate and in the long term…. It's not an easy decision to make*.'
- People who have taken the drug felt that the ***platelet monitoring was a small price to pay for the benefits*** that the drug had brought them
- '*Notionally, the disadvantages are that there is regular monitoring and injection site reactions, however these are insignificant compared to the regular abdominal pains, pancreatitis and hospital admissions I was experiencing prior to my participation in the trial*.'

Comments from clinical experts

Condition and current treatment options

- FSC is a recessive disorder caused by rare gene variants
- There is a huge unmet need for people living with FCS
- Current treatment management varies considerably
- Low fat diet (difficult to follow and often unsuccessful); fibrates and statins (minimally effective); medication to treat complications of pancreatitis (analgesia, digestive enzymes, insulin)

New technology

- It has a potential for life-changing improvement for people living with FCS
- Easy to adhere to, but does require intense monitoring
- Innovative in reducing morbidity and mortality associated with pancreatiti***s***

Outcomes

- The ***most important outcome*** is ***reduction in frequency of pancreatitis events***
- Substantial reduction in plasma triglycerides in patients
- Reduction in hospital admissions for AP and in complications of acute and chronic pancreatitis (pain, requirement for analgesia, development of pancreatic insufficiency and diabetes)
- Improved quality of life, increased freedom with dietary choices, fewer days 'lost' to illness
- A ***clinically significant reduction of incidence of pancreatitis and its complications in the long term***

Service delivery

- There is a ***significant uncertainty about the diagnosis*** of the FCS
- The disease is best defined by genetics, although there is currently no testing centre available
- Reasonable to concentrate the treatment into a few specialist centres

[redacted]

NHS England comments

Pathway of care

- No specific treatment pathway, NHSE service specification or clinical commissioning exist
- Patients are managed via a strict fat restricting diet and restriction of alcohol alongside treatments for hypercholesteraemia

Commissioning

- Volanesorsen is likely to be a high cost drug
- Prescriptions expected to be initiated and monitored by a small number of expert lipid centres
  - Likely those centres already offering lipid apheresis and participated in the Early Access to medicines Scheme (EAMS)
- After initial dosing administration of the medicine is expected via home care
  - No difficulties expected in administration
- **Use of technology**
- Volanesorsen received a positive Scientific Opinion from the MHRA as part of the EAMS
- To date 29 patients* have accessed the treatment under this scheme
- Likely the 7 trusts accessed volanesorsen through the EAMS → will be commissioned if the treatment is approved

[redacted]

Volanesorsen
(Waylivra, Akcea)

Marketing authorisation	Indicated for an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate
Mechanism of action	Volanesorsen is an antisense oligonucleotide (ASO) inhibitor of apoC-III. ApoC-III inhibits the metabolism of TGs via the actions of LPL and LPL-independent pathway. It selectively binds to apoC-III mRNA, preventing production of the apoC-III protein and allowing metabolism of TGs
Administration & dose	285 mg in 1.5 ml injected subcutaneously once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks
List price	• List price: £11,394 per single-use syringe (285mg) • Simple discount PAS approved
Treatment course length and discontinuation rules	• Starting dose is 285 mg once-weekly for 3 months, followed by down-titration to a maintenance dosing schedule of once every 2 weeks for those after 3 months ○ If the patient has not achieved a >25% reduction in triglyceride levels, or if triglyceride levels remain above 22.6 mmol/L at 3 months, treatment should be discontinued ○ If response is inadequate (in terms of serum triglyceride reduction) after 6 months of treatment, an increase in dosing frequency to 285 mg once-weekly should be considered ○ Dosing may also change at 9 months and thereafter depending on response to treatment and platelet levels

Apoc-III: apolipoprotein C-III; ASO: antisense oligonucleotide, TG: triglyceride; LPL: Lipoprotein lipase; PAS: Patient access scheme; FCS: Familial chylomicronemia syndrome

Clinical effectiveness evidence

[redacted]

Decision problem I.

	Final scope issued by NICE	Company deviations	ERG comments
Population	Adults with FCS	***Narrower than scope***: The population is adult patients with ***genetically confirmed FCS and at high risk for pancreatitis*** in whom response to diet and triglyceride-lowering therapy has been inadequate	Population change ***matches final MA***; • ***License does not define "high risk" for pancreatitis***; • Any patient with a high TG level is clinically considered to be at high risk of pancreatitis; • Clinicians may have widely ***differing interpretations of the license*** → uncertainty about how patients will be selected for treatment • Some people with FCS may have unknown gene mutations and may ***not be diagnosed genetically*** →such patients ***may have entered the trial*** • ***Population in trials is likely to be generalisable to UK clinical practice***
Intervention	Volanesorsen in combination with established clinical management (incl. dietary fat restrictions)		The licensed dosing schedule was not used in clinical trials, including APPROACH, APPROACH open label extension (OLE), and COMPASS leading to ***uncertainty on the licensed dose's efficacy and safety*** outcomes, consequently on ***discontinuation rates***
Comparator	Established clinical management without volanesorsen (incl. dietary fat restrictions)		***Reflects established clinical practice in England*** Use of fibrates and statins not routinely recommended in patients

MA: Marketing authorisation, TG: triglyceride; FCS: Familial chylomicronemia syndrome

Decision problem II.

	Final scope issued by NICE	Company deviations	ERG comments
Outcomes	**The outcome measures to be considered include:** • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability) • incidence of acute pancreatitis (AP), chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions) • mortality (including all-cause and pancreatitis related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers)	***Data gaps and limitations***, and concerns regarding double counting mean that some outcomes are not explicitly considered in the model: e.g. pancreatic necrosis and fatty liver disease Cardiovascular disease (CVD) is not in the economic model as there is no clinical consensus regarding the impact of the disease on CVD outcomes	• ***Neurological and psychological impacts not recorded in clinical studies*** (depression, cognitive ability); • No results on hospitalisation reported in trials - *proportion of patients requiring hospitalisation was estimated for use within the health economic model* • ***Additional analyses relating to hard clinical outcomes submitted***, including rate of APs in APPROACH and APPROACH OLE patients for the 5 years before treatment versus on treatment • ***Fatigue, diabetes and mortality measured as adverse events only***

Clinical effectiveness evidence

[redacted]

Completed clinical trials

Trial	Intervention	Population	Treatment duration	Outcomes	Used in clinical effectiveness	Used in cost-effectiveness
APPROACH Phase III, double-blinded RCT**	Volanesorsen (285 mg) by SC injection, once weekly Placebo by SC injection	***N=66*** , adult patients with FCS with fasting triglycerides >=8.4 mmol/L (>=750 mg/dL)	52 weeks +13 weeks follow-up or *entry to APPROACH OLE open-label extension*	***Primary***: % change in TG level at Month 3 and over time ***Secondary***: • Abdominal pain; • AP; • Response rate ¥ , • Absolute change in TG level from baseline to month 3	YES	YES
COMPASS Phase III, double-blinded RCT	Volanesorsen (285 mg) by SC injection, once weekly Placebo by SC injection	Patients with hypertriglyceridemia including FCS ***(N=7)*** with fasting triglycerides +/- 500 mg/dL	26 weeks +13 weeks follow-up or *entry to APPROACH OLE open-label extension*	% change in TG level at Month 3*	YES	NO

AP: acute pancreatitis; *average of 12-13 week assessments; ⁺ baseline to 6, 12 months; ¥ (defined as 40% reduction in fasting TG between baseline and month 3; attaining levels <750 mg/dL in fasting TG between baseline and month 3), **RCT – randomised controlled trial; SC: subcutaneous; FCS: Familial chylomicronemia syndrome

[redacted]

Ongoing clinical trials

Trial	Intervention	Population	Treatment duration	Outcomes	Used in clinical effectiveness	Used in cost-effectiveness
APPROACH OLE Phase III	Volanesorsen (285 mg) by SC injection, once weekly	***N*=XX**, Adult patients with FCS, rolled over from: • APPROACH volanesorsen XXXX • COMPASS volanesoresen XXXX • Treatment naiive XXXX	Ongoing	• % change and absolute change from baseline in fasting TG level† ; • Frequency and severity of patient-reported abdominal pain during the treatment period; • % change from baseline in other fasting lipid measures at Months 3, 6 and 12	YES	YES – except results from the subgroup which used SmPC dosing during the trial (due to AE related dose adjustment)

AP – acute pancreatitis; † no formal designation of outcomes as 'primary' or 'secondary'; SC: subcutaneous; FCS: Familial chylomicronemia syndrome

ERG comment

- **APPROACH OLE**: characterised as a before-after study design → descriptive and of poor quality for the assessment of intervention efficacy
- Subject to risk of bias, including open label design; unclear if all eligible patients were enrolled; high level of withdrawals XXXX missing data were not factored in the main analysis (e.g., % change in TG levels), no *p* values reported for results on changes from baseline

Other sources used in clinical and cost-effectiveness evidence

Information	Interventions	Population	Treatment duration	Outcome	Used in clinical effectiveness	Used in cost-effectiveness
ReFOCUS, single-arm, retrospective web-based survey	Volanesorsen (285 mg) by SC injection, once weekly	***N=22***, patients from OLE who received at least 3 months of treatment with volanesorsen	NA	HRQoL/burden of the disease 3 months prior to enrolment vs. the latest 3 months on treatment	YES	NO
EAMS Early Access to Medicines Scheme	Volanesorsen (285 mg) by SC injection, bi-weekly dosing from inception	***N=20*** on treatment (25 eligible), including patients who have received treatment in APPROACH and OLE previously	Ongoing*	Not reported	NO	No data used, but basis for a scenario analysis
CALIBER Retrospective registry study	Data collected for ~1.8million patients with at least 1 TG record between 1997-2016 Contains linked electronic health records in England between the Clinical Practice Research Datalink, Hospital Episode Statistics and Office for National Statistics				NO	Yes

HRQoL: health-related quality of life; SC: subcutaneous; NA: not applicable, TG: triglycerides

[redacted]

*EAMS started in July 2018, mean follow-up time 7 months; no stopping rule in EAMS

Baseline characteristics

	APPROACH				[redacted]			COMPASS	
	Volanesorsen (n = 33)		Placebo (n = 33)		[redacted]			Volanesorsen (n = 5)	Placebo (n = 2)
Age, mean (range) years	47	(22 – 75)	46	(20 – 68)	[redacted]			47 (33 – 54)	51 (43 – 58)
Gender, % Male	48.5		42.4		[redacted]			40	0
Fasting TG, mean (range) mg/dL	2267 (347 – 5660)		2152 (631 – 5475)		[redacted]			2134 (1074 – 3998)	2644 (2422 – 2867)
History of acute pancreatitis, n (%)	24	(72.7)	26	(78.8)	[redacted]			NR	NR
Abdominal pain*	7	(21.2)	10	(30.3)	[redacted]			NR	NR
Platelet aggregation inhibitors	8	(24.2)	5	(15.2)	[redacted]			NR	NR

ERG comment

- Levels of abdominal pain in APPROACH high in comparison to the English population (although TG levels lower than average)
- In/exclusion criteria of APPROACH set a cap on patients with no history of pancreatitis at ***28%*** → ***24% of patients recruited had no prior history of AP***
- 11% in APPROACH received alipogene tiparvovec → may have lower baseline levels of pancreatitis than patients in England
- 25% of patients recruited to APPROACH with no known mutation (in keeping with levels in England)
- APPROACH OLE recruited [redacted] than APPROACH study – [redacted]
- [redacted]
- [redacted]

Impact of imbalances in baseline characteristics on the treatment effect is unclear

Clinical effectiveness results

[redacted]

Patient flow across trials - *APPROACH, COMPASS and APPROACH OLE*

[redacted]

Source: Figure 1 ERG report

CONFIDENTIAL

Discontinuation I.

Relatively high discontinuation rates observed across studies

APPROACH (N=66)

- **Volanesorsen arm** (n=33): ***42% (14/32) discontinued before Month 12***
  - 2 patients (6%) discontinued before week 13; 7 patients (21%) discontinued between weeks 13 and 26; and 5 (15%) discontinued after week 26;
    - Most common reason for discontinuation was adverse event
- **Placebo arm** (n=33): 1 patient voluntarily withdrew from the study, 1 lost to follow-up and 1 withdrew for other reason

APPROACH OLE ([redacted]) †

- **APPROACH volanesorsen group** [redacted]
- **Treatment naïve (at roll-over) group*** [redacted]
- **COMPASS volanesorsen group** [redacted]
- **SMPC dosing subgroup in APPROACH OLE** [redacted]

Discontinuation after the first 12 months of treatment in trials (APPROACH vs. APPROACH OLE) :

- At 12 months/52 weeks: 42% in APPROACH vs. [redacted] in APPROACH OLE
- At 104 weeks: 79% in APPROACH vs. [redacted] in APPROACH OLE
- *Note: (monitoring schedule was in place in APPROACH OLE due to protocol adjustment)*

† Exact duration of treatment for patients in APPROACH OLE is unclear as they have rolled over from APPROACH or COMPASS; ¥ 52 weeks of enrolment into APPROACH OLE

** Volanesorsen treatment naïve at roll-over from APPROACH or recruitment, all patients received treatment in APPROACH OLE*

Discontinuation II.

Relatively high discontinuation rates observed across studies

Mixed dose subgroup *(defined as people who changed to bi-weekly dosing any time after 3 months across trials, n=36);*

- 39% (14/36) discontinued *(exact discontinuation times unknown)*

ERG summary on discontinuation

- Discontinuation rate in clinical practice is currently unknown, unlikely to be zero
- Likely discontinuations in clinical practice between ***10% per annum and 20% in total***
- Main reasons are burden of monitoring and adverse events including injection site reactions and thrombocytopaenia

[redacted]

Clinical effectiveness: Treatment persistence

APPROACH and APPROACH OLE

Treatment persistence with volanesorsen up to Week 104: APPROACH OLE (FAS)

APPROACH

APPROACH OLE

Treatment persistence with volanesorsen up to Week 104: APPROACH OLE (**patients with history of acute pancreatitis)**

ERG comment:

- [redacted]
- Of the 33 patients enrolled in APPROACH, [redacted]
- [redacted]
  - [redacted]

[redacted]

Source: Clarification response, Table 12 and Table 13

Clinical effectiveness: % change in fasting TG (mg/dL) levels from baseline - *Substantial reduction in % TG levels observed*

	APPROACH		APPROACH OLE						
			Whole trial population			Subgroup of patients with licensed dose	Subgroup of patient with history of pancreatitis	
Timepoint	Volanesorsen (n=33)	Placebo (n=33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	-76.5	17.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	-52.5	25.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	<0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	-40.2	8.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0347 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	See Month 6 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	See Month 12 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source, Table 10, ERG report

* Treatment naïve at the enrolment of OLE; all patients received volanesorsen in OLE; SD: standard deviation

Clinical effectiveness: % change in fasting TG (mg/dL) levels from baseline to Month 3 and 6

COMPASS (number of FCS patients =7)

Month 3:

FCS patients: n=7, limited data reported from the trial:

- 73% reduction from baseline in volanesorsen arm (n=5) vs. an increase of 70% in placebo arm (n=2), (*p value not reported*)

Month 6:

- Patients receiving weekly doses of volanesorsen (n = 2): 78% reduction from baseline
- Patients (n=3) reduced to biweekly dosing after 13 weeks: 69% reduction (*p value not reported)*

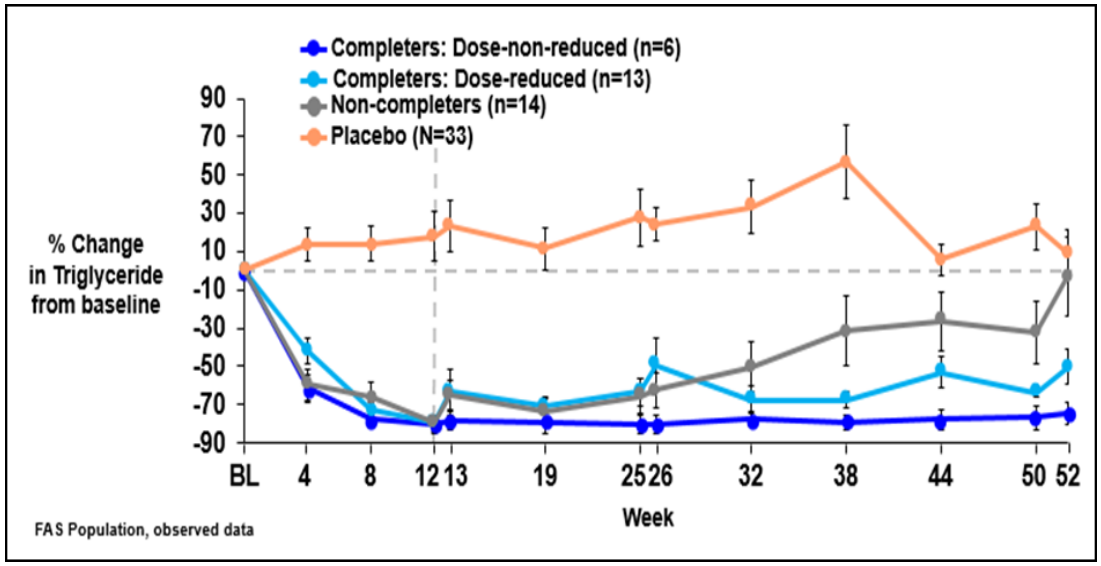
ERG

- Unclear when patients switched treatment
- Treatment effect of weekly dosing is unlikely to have fully washed out at month 6

[redacted]

Clinical effectiveness: % change in fasting TG (mg/dL) levels from baseline

APPROACH (n=66)



- Volanesorsen once-weekly treatment: consistent, sustained response
- Mean percent reduction clinically meaningful regardless of dose adjustments
- For patients with dose adjustments and non-completers: dose pauses lead to a lower reduction in TG level

[redacted]

*Source: Figure 12, ERG report; TG levels over time in **APPROACH,** including dose adjustments and non-completers*

Clinical effectiveness: % change in fasting TG (mg/dL) levels over time

*APPROACH and COMPASS through to APPROACH OLE**

Source: revised figure 20, company clarification, 2019; CS 6= APPROACH; CS16=COMPASS;

*

-
-
-

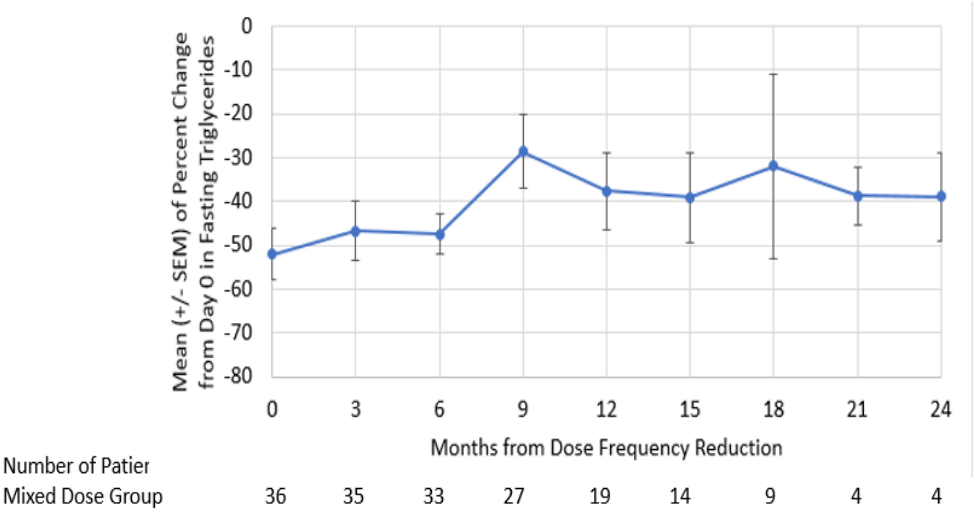
Clinical effectiveness: % change in TG levels (mg/dL) from baseline

Subgroup of people conforming to SmPC dosing (from APPROACH OLE, [redacted])

[redacted]

Source: Figure 5 ERG report

Mixed dose subgroup across APPROACH and APPROACH OLE, (n=36)



Source: Figure 11, Appendix, ERG report

ERG comment

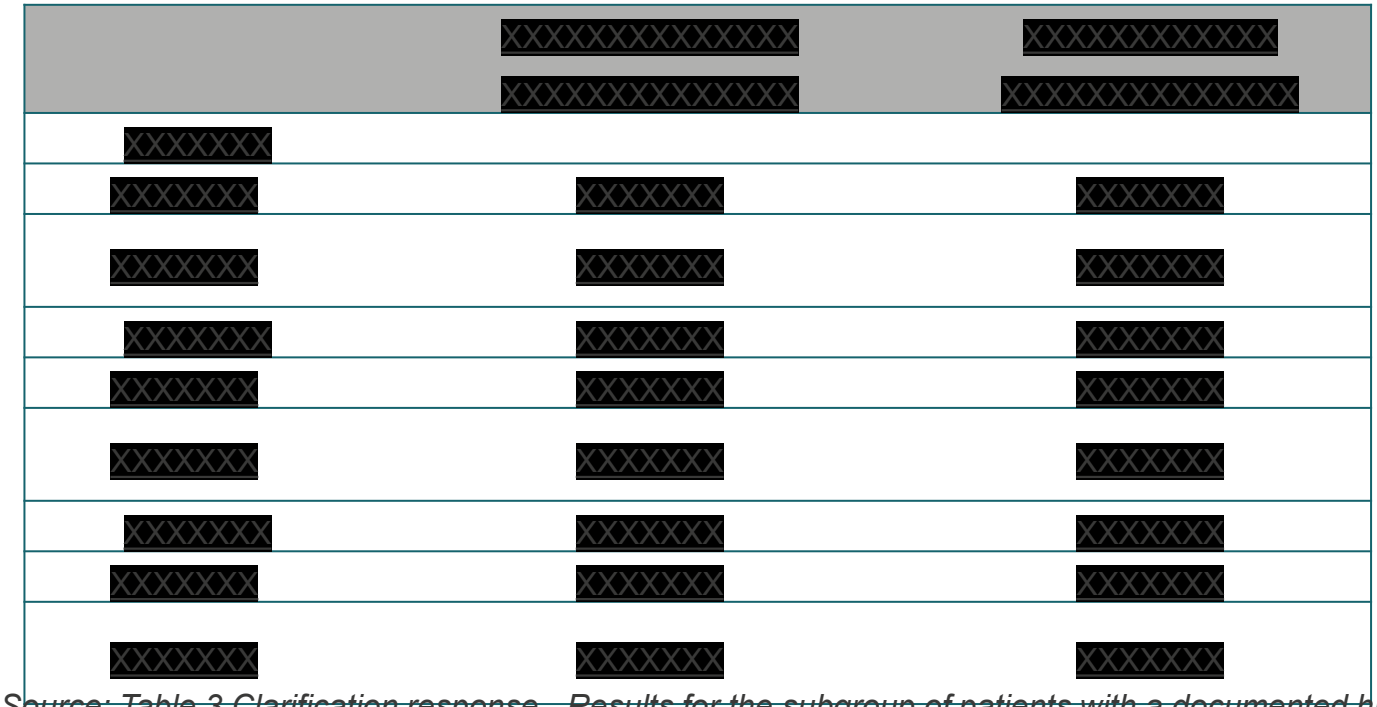
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

ERG comment

- Larger patient numbers than SmPC subgroup but patients could adjust dosing at any time after month 3, unclear when the switch occurred
- TG levels remained stable from Month 12 to 24, -40% change from baseline
- May be an overestimate of treatment effect as patients were on treatment for longer (exact length unknown), may still be washing out from full dose up to 6 months after treatment cessation

Clinical effectiveness: % change in TG levels (mg/dL) from baseline - *Subgroup of patients who had a history of pancreatitis (from APPROACH OLE, [redacted])*



ERG comment

- [redacted]
- [redacted]

Source: Table 3 Clarification response - Results for the subgroup of patients with a documented history of AP

SD: standard deviation

ERG comment

- [redacted]
- Clinical advisor: ***did not expect to see a greater effect in patients with a prior history of pancreatitis***, *or* ***by any other definition of "high risk"***

[redacted]

ERG summary on: % change in TG levels (mg/dL) from baseline - *responses seemed generally lower in later months*

- Responses across studies seemed generally lower in later months with a few exceptions
  - Possible waning effect of volanesorsen is probably small
    - Follow-up and clinical experience with the treatment do not appear to go beyond around 3 to 4 years, there is some uncertainty about long terms effects
- [redacted]
- [redacted]
- [redacted]
- [redacted]

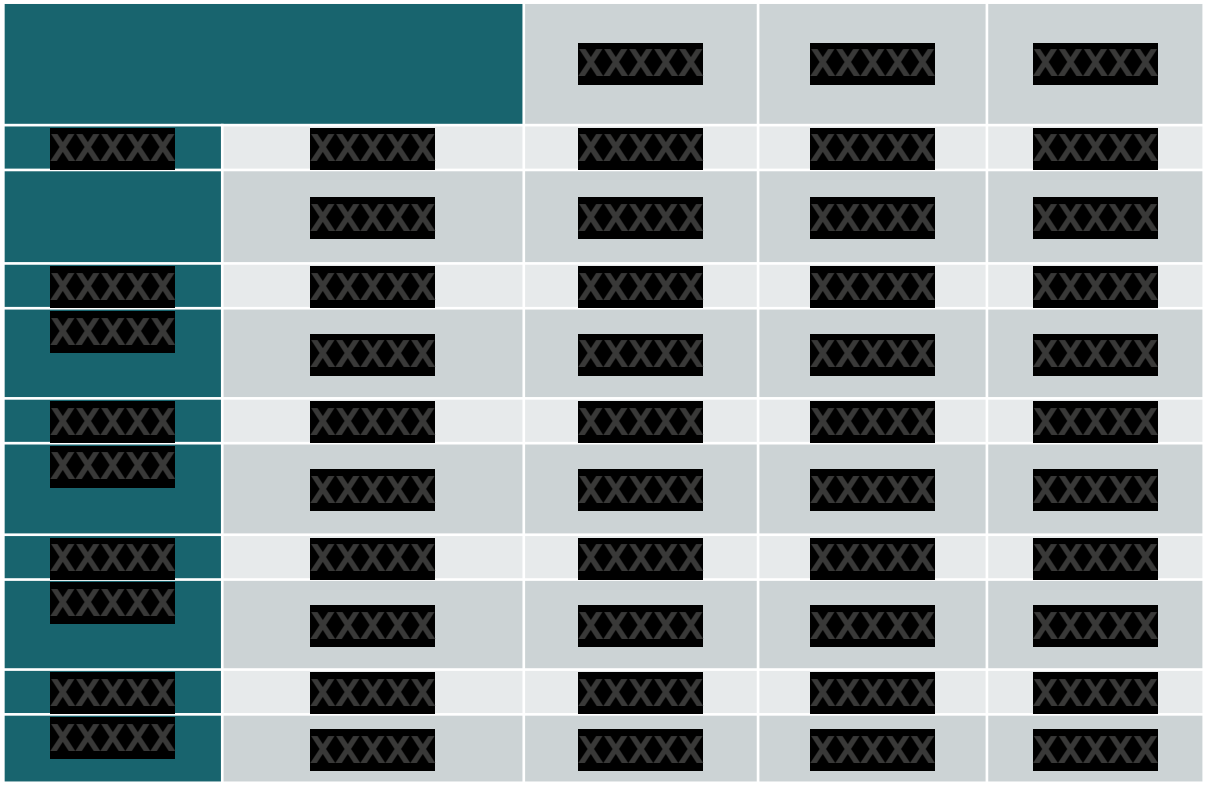
[redacted]

Clinical effectiveness: absolute change in fasting TG (mg/dL) levels from baseline to Months 3 and over time

APPROACH - Absolute change from baseline in fasting TG (mg/dL) at Month 3

	Volanesorsen	Placebo
Change from baseline, LS mean	*-1712* (19.4mmol/L)	*92* (1 mmol/L)
LS mean treatment difference	*-1804* (95% CI: -2306, -1302); -20.05 mmol/L (95%CI: 26.2, -14.8)	
p value	<0.0001 (ANCOVA)	

APPROACH OLE - Absolute change from baseline* in fasting TG (mg/dL) over time



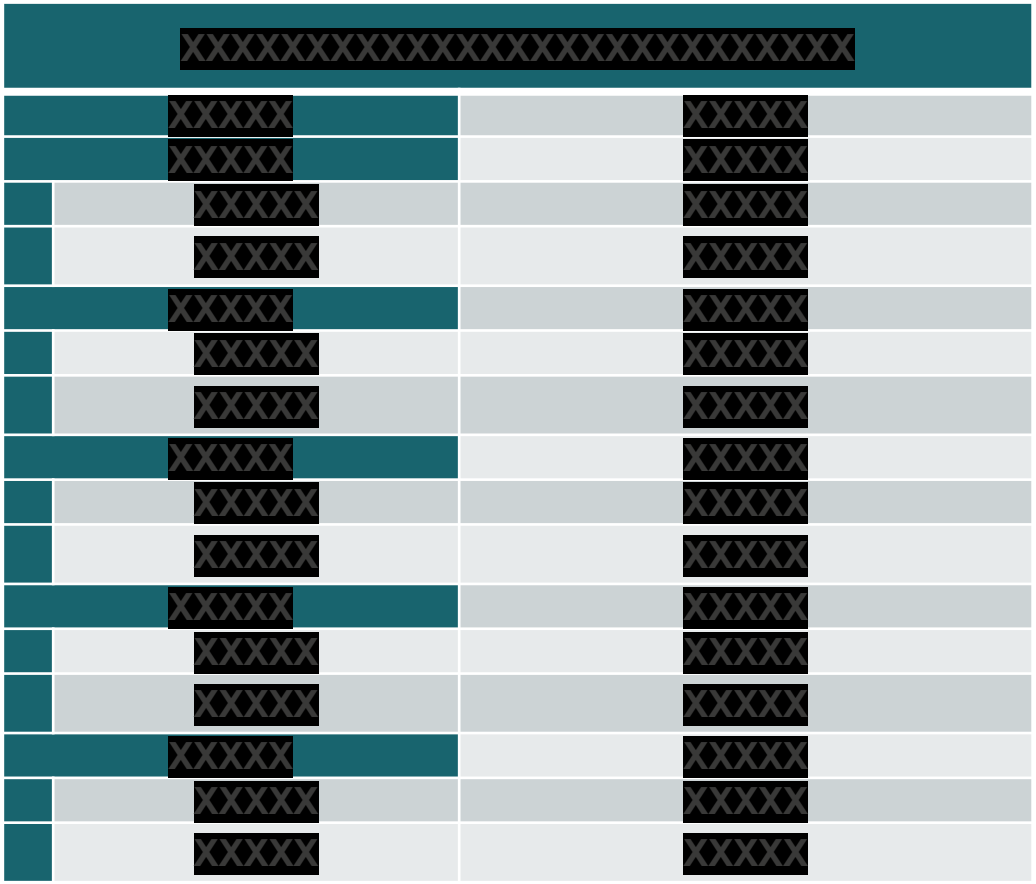
COMPASS (FSC patients in the trial, n=7)

- Mean absolute reduction in fasting TG levels at Month 3: 1,511 mg/dL in the volanesorsen group (n = 5)
  - 3 of the patients with FCS who received volanesorsen achieved fasting TG levels <500 mg/dL after 3 months of treatment

[redacted] *Source: Table C15 company submission*

Clinical effectiveness: absolute change in fasting TG (mg/dL) levels from baseline to Month 3 and over time

Subgroup analysis of patients conforming to SmPC dosing (from APPROACH OLE, n=14)



[redacted]

Source: Table 1 and Figure 1 of clarification response

Clinical effectiveness: absolute change in fasting TG (mg/dL) levels from baseline to Month 3 and over time - *Subgroup of patients who had a history of pancreatitis (from APPROACH OLE, n= 34)*

[redacted]			
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SD: standard deviation

[redacted]

Source: Table 3 of clarification response

* p values not reported in APPROACH OLE: could not conclude whether significant difference does exist before and after the treatment across groups;

ERG summary on: absolute change in fasting TG (mg/dL) levels from baseline to Months 3 and over time

- Substantial mean absolute change in TG levels on volanesorsen treatment
- Standard deviations indicate a great deal of variation → may reflect the very variable baseline TG values of patients, or may be due to dose pauses and reductions meaning treatment effect varies
- Clinical advisors indicated that nearly all patients, have a substantial TG response to treatment

[redacted]

Clinical effectiveness: Responder analysis at month 3

APPROACH (n=66)

Responder analysis (endpoint fasting TG <750 mg/dL at Month 3)		
	Volanesorsen	**Placebo**
n (%) of patients	23 (76.7)	3 (9.7)
Odds ratio	186.16 (95% CI: 12.86, N/A)	
p value	0.0001 (logistic regression model)	

Responder analysis (≥40% reduction in fasting TG at Month 3)		
	Volanesorsen	**Placebo**
n (%) of patients	29 (87.9)	3 (9.1)
Odds ratio	99.69 (95% CI: 15.75, 631.06)	
p value	<0.0001 (logistic regression model)	

ERG:

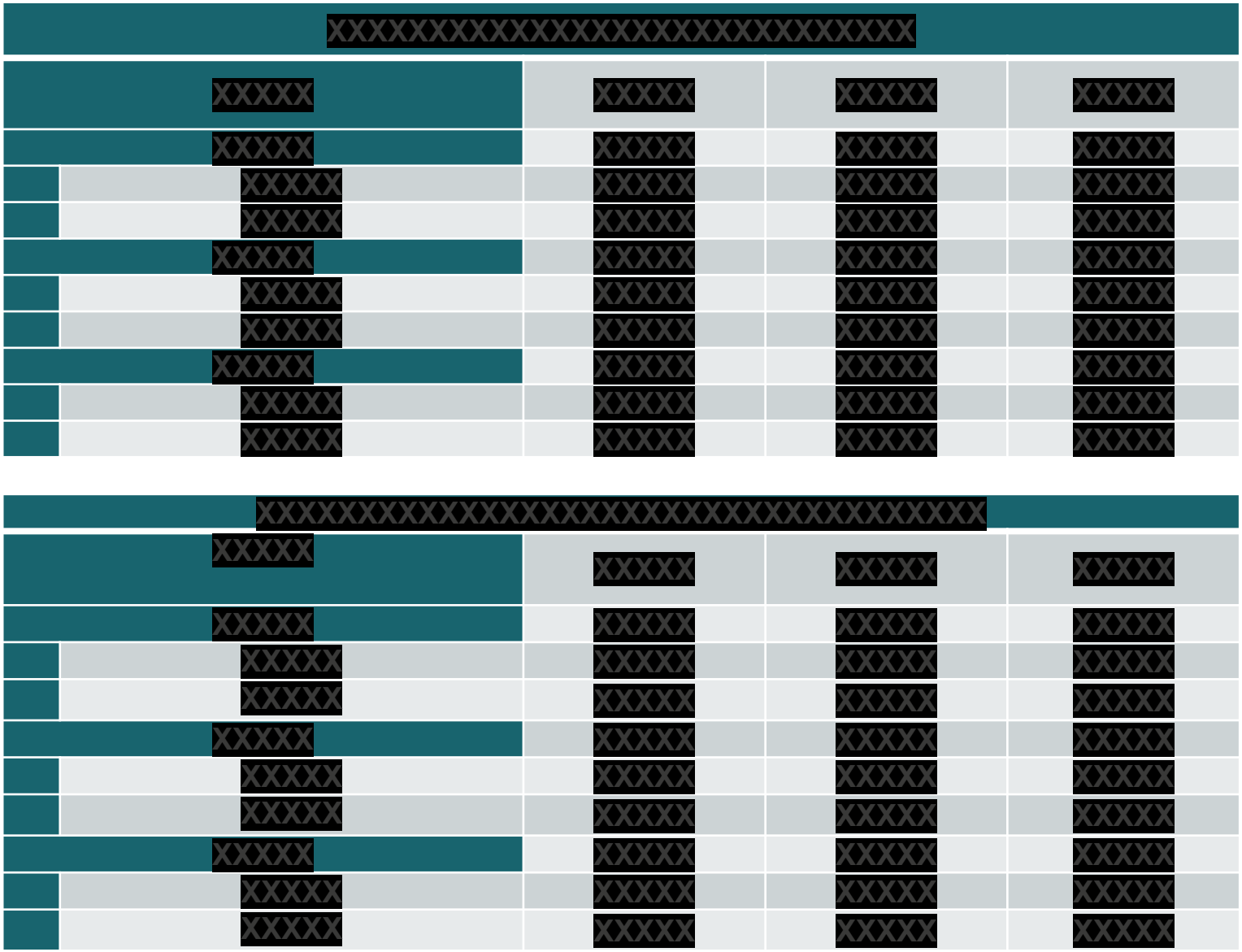
- The outcome was met, 76% of volanesorsen patients vs. 9.7% of placebo patients meeting the end point; the difference between the two groups was statistically different
- *12-month data from APPROACH were not reported;*

[redacted]

Source: Table C15, company submission

Clinical effectiveness: Responder analysis over time

APPROACH OLE (n=68)



Source: Table C19, company submission

ERG

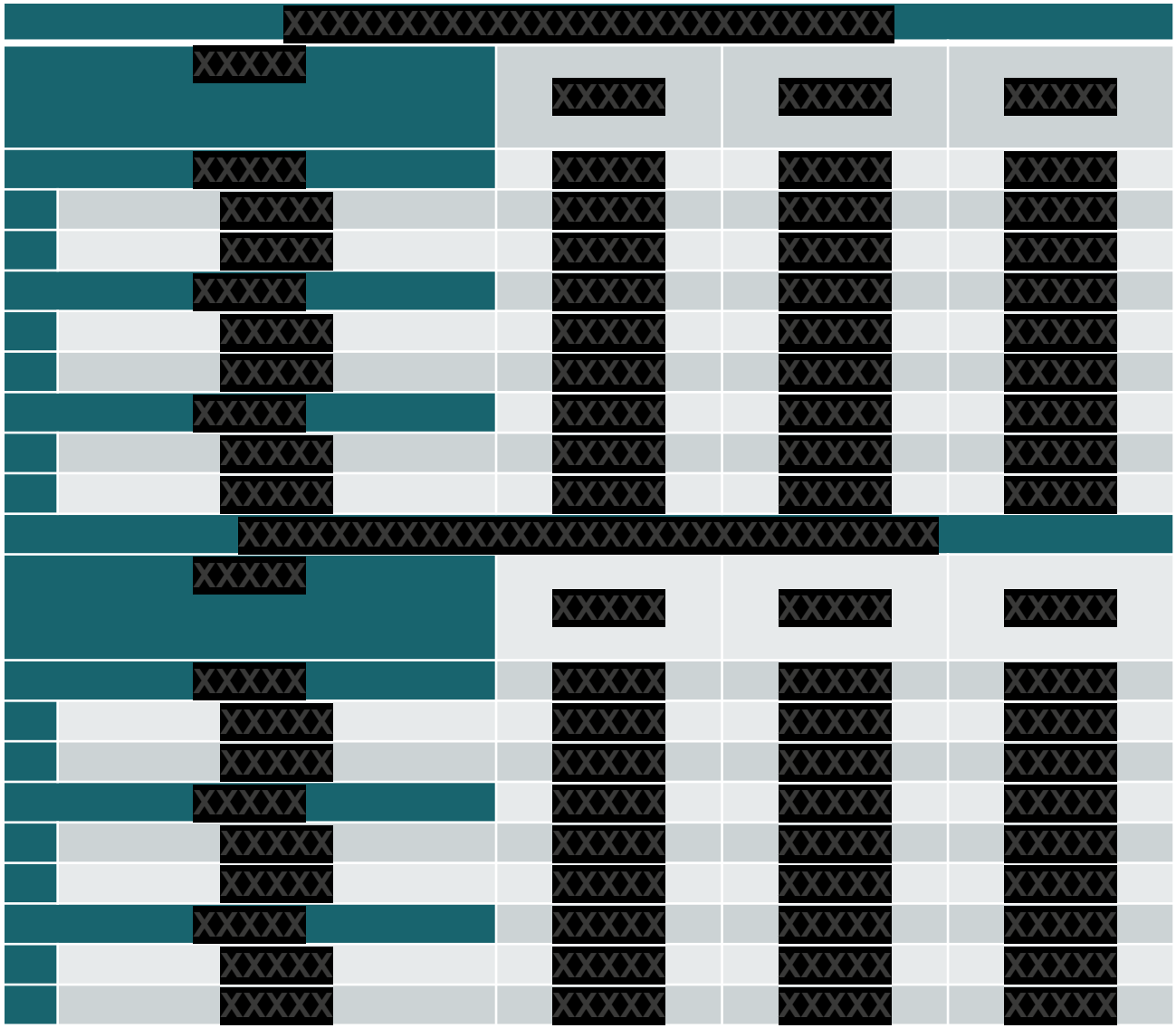
- [redacted]
- [redacted]
- [redacted]

[redacted]

** patients have received volansorsen in APPROACH and COMPASS before rolling over to APPROACH OLE, exact treatment time on volanesorsen is unclear*

Clinical effectiveness: Responder analysis over time

APPROACH OLE (n=68)



ERG

- [redacted]
- [redacted]

*Source: **Table C19**, company submission*

p values not reported in APPROACH OLE: could not conclude whether significant difference does exist between treatment arms or from baseline for each arm;

** patients have received volansorsen in APPROACH and COMPASS before rolling over to APPROACH OLE, exact treatment time on volanesorsen is unclear*

ERG summary on: responder analysis over time

- Most patients appear to achieve a reduction in TG levels at month 3 and/or a moderate-to-high relative reduction in TG levels
- Indicates that a good proportion of patients are likely to continue on the treatment after the assessment of stopping rule in the license
  - Stopping rule: TG levels <22.6mmol/L (around 2000mg/dL) or at least a 25% reduction in TG levels
- Response rates wanes over time → may reflect the very variable baseline TG values of patients, or may be due to dose pauses and reductions meaning treatment effect varies
- No data provided on licensed dose patients → 3 month data is the most relevant to the licence
- [redacted]

[redacted]

Clinical effectiveness: other lipid outcomes from baseline

APPROACH (n=66)

% change from baseline, mean (SD)			
	Volanesorsen (n = 33)	Placebo (n = 33)	P value
Fasting chylomicron TG (mg/dL)			
Month 3	-76.6 (22.1)	+37.7 (112.4)	<0.0001
Month 6	-65.3 (39.1)	+37.7 (75.3)	<0.0001
Month 12	-52.3 (44.9)	+21.9 (79.4)	<0.0001

Follows a similar pattern to TG levels over time, i.e., an initial response, somewhat decreasing over time

ERG

- Clinical advisers: chylomicron TG levels can be considered a better clinical indicator of risk of AP → directly responsible for causing AP
- The degree to which chylomicron TG levels will decrease at the licensed dose is unclear

[redacted]

Source: Table 16, company submission

Clinical effectiveness: abdominal pain - *average maximum intensity or abdominal pain during on-treatment period: APPROACH, OLE, subgroup of licensed dose + exploratory analysis of subgroup of people who had abdominal pain at baseline*

	APPROACH		APPROACH OLE			Subgroup of patients with licensed dose
Outcome	Volanesorsen (N=33)	Placebo (N=33)	[redacted]	[redacted]	[redacted]	[redacted]
Average maximum intensity of abdominal pain during on-treatment period**			[redacted]			
Mean (SD)	0.38 (0.83)	0.36 (0.79)	[redacted]	[redacted]	[redacted]	[redacted]
p value	0.8959 (two-sample t-test)		[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 11, ERG report

Pre-explained exploratory analysis: people with abdominal pain at baseline in APPROACH (n= 17; 7 on volanesorsen vs. 10 on placebo)

Statistically significant difference in reduction in the average maximum intensity of abdominal pain between volanesorsen treated group and placebo group (P**=** ***0.0227***)

ERG comments on the exploratory analysis

Baseline characteristics are unlikely to predict response to treatment

Result does not reflect a more responsive subgroup of patients but may be due to higher baseline events therefore an effect could be detected → ***effect of volanesorsen on abdominal pain is uncertain***

Clinical effectiveness: AP

Pancreatitis events (pre-planned safety analysis) - APPROACH

Outcome	Volanesorsen (n=33)	Placebo (n=33)
Patients (events)	1 (1)**	3 (4)
p-value	P = 0.6132	

Ad/post hoc analysis of AP rate: 5-year history of AP prior to study enrolment versus on-volanesoresen treatment

	APPROACH		APPROACH OLE
	Volanesorsen (n = 33)	Placebo (n = 33)	[redacted]
Patients in analysis	7	4	[redacted]
Events prior 5 years	24 events =0.69 per patient year	17 events =0.85 per patient year	[redacted]
Events on treatment	0 events	4 events	[redacted]
p-value	0.0242		[redacted]

NR: not reported

ERG comment

APPROACH

- Analysis restricted to patients with at least 2 APs in the 5 years prior to treatment (n=11); did not account for time on treatment → there may be some bias as discontinuation rates were high

APPROACH OLE

- [redacted]
- [redacted]

Source: Table 11, ERG report

Clinical effectiveness: outcomes relating to abdominal pain and AP - *Composite outcome: Incidence of AP and/or moderate/several abdominal pain*

	APPROACH		APPROACH OLE			Subgroup of patients with licensed dose
Outcome	Volanesorsen (N=33)	Placebo (N=33)	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of acute pancreatitis and/or moderate/severe abdominal pain†						
n (%) of patients	12 (36)	13 (39)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) number of events, per patient per year	2.73 (6.57)	2.04 (4.28)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	0.6131 (two-sample t-test)		[redacted]	[redacted]	[redacted]	[redacted]

NA: not available; NR: not reported; SD: standard deviation

ERG comment

- Results suggest patients continue to experience some abdominal pain whilst on treatment

[redacted]

Source: Table 11, ERG report

ERG summary on: AP

- Treatment may reduce AP events → however it remains uncertain, effect size is unclear, especially at the reduced dose indicated by the license;
- [redacted] and effects of being in a study with greater adherence to diet;
- In the model, AP rates are predicted by TG levels as well as using the rate ratio calculated from the APPROACH OLE analysis of AP rates 5 years before treatment and whilst on treatment

[redacted]

Clinical effectiveness: diabetes and mortality

APPROACH and APPROACH OLE

Diabetes rates were only reported for APPROACH (n=66)

- Volanesorsen arm: [redacted]
- Placebo: [redacted], p value not reported

No deaths in APPROACH or APPROACH OLE

[redacted]

Clinical effectiveness: health related quality of life measured by EQ-5D and SF-36

APPROACH (n=66)

Patients who have been on treatment for 3 months, HRQoL assessed along with other outcomes at month 3, 6, and 12

- Baseline values were high (utility >0.97 in both arms: [redacted] volanesorsen vs. [redacted] placebo)
- No significant change from baseline for the SF-36 or EQ-5D-5L at:
  - Month 3 (p = 0.6627 and p = 0.2920, respectively)
  - Month 6 (p = 0.9226 and p = 0.5923, respectively)
  - and Month 12 (P = 0.7912 and P = 0.4079, respectively)

APPROACH OLE (n=68)

- [redacted]
- [redacted]

ERG

- Baseline values seem high for the patient group
  - Although FCS has a considerable impact on patients' HRQoL
- Very little room for improvement → ceiling effect

[redacted]

Clinical effectiveness: health related quality of life

Retrospective web-based survey ReFOCUS conducted among APPROACH OLE patients (n=22)

- Entry to survey: patients on volanesorsen treatment for 3 months and were asked about the 3 months prior to enrolment and the latest 3 months on treatment
- % of patients who believe:
  - FCS was more effectively managed with volanesorsen (40% vs. 19% before treatment)
  - Symptoms controlled with adherence to diet (90% vs. 55% before treatment)
    - *No p values reported*

ERG comment

- ReFOCUS was a single-arm, retrospective design study asking patients to recall symptoms, subject to risk of recall bias → the period of recall would be over a year before
- Not clear how many patients were approached or were eligible
- The study is open-label → high risk of detection bias, may interact with recall bias
- No baseline characteristics presented; unclear how representative the enrolled patients were of the wider trial of patients in England → ***low quality and at high risk of bias to answer a question of efficacy***

[redacted]

Adverse events - Most frequent (≥1/10 patients) treatment-emergent AEs are injection site reaction, fatigue, headache and thrombocytopaenia

APPROACH

Most frequent (≥1/10) treatment-emergent AEs	Volanesorsen arm (n=33)	Placebo arm (n=33)
Type of AE: n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

APPROACH OLE

Most frequent (≥1/10) treatment-emergent AEs	[redacted]	[redacted]	[redacted]
Type of AE: n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Table C 22 and section 9.7 company submission; page 53 ERG report

[redacted]

Adverse events II.

APPROACH

Severe treatment emergent AEs

- Volanesorsen arm (n=33): 5 severe TEAEs - 4 related to study drug (severe thrombocytopaenia (n=2), fatigue (n=1) and musculoskeletal pain (n=1))
- Placebo arm (n=33): 3 patients had severe TEAEs, none considered potentially related to treatment

Serious AEs:

- Volanesorsen arm (n=33): 8 events experienced by 7 patients (21%, 7/33)
- Placebo arm (n=33): 6 events experienced by 5 patients (15%, 5/33)

SmPC dosing subgroup in APPROACH OLE [redacted]:

- Results showed that [redacted]

ERG comment

- Clinical advisors concerned about injections site reactions and platelet counts/thrombocytopaenia
- Revised dosing schedule and monitoring could reduce the events
  - Unclear to what extent the licensed dosing schedule and monitoring prevent the most serious and significant adverse events
- Impact of using the ***licensed dose on safety outcomes and discontinuation generally uncertain*** → long-term treatment and tolerance of treatment with volanesorsen is uncertain

[redacted]

ERG's comments on treatment effectiveness and dose-response relationship between TG levels and AP

Treatment effectiveness	• Treatment statistically significantly (p<0.05) reduced TGs levels • However, not all patients achieved TG levels below 8.4mmol/L (~750mg/dL) • Results relating to AP, abdominal pain and HRQoL were less certain • High rates of discontinuations in the clinical studies, mostly due to AEs **Long-term response and tolerance to the treatment is uncertain;** **Uncertainty relating to clinical effectiveness, treatment discontinuation and safety of the treatment at the licensed dose in clinical practice**
Dose response relationship between TG levels and AP; **Cut-offs for TG band levels**	Clinical studies measured a surrogate outcome (TG levels) **Dose response relationship:** • Evidence suggested that the general linear relationship between TG levels and the risk of AP is acceptable at population level; • However, uncertainties remain regarding whether this evidence is generalisable to people with FCS, as FCS patients may experience AP at lower TG levels than patients with raised TG levels by other causes. **TG level cut-offs at which AP risk appears increased in FCS patients:** • The cut-off of ≥10mmol/L and further increased at >22.6m mmol/L is appropriate according to the evidence available, however **Uncertainties remains in cut-offs of TG levels** at which **more severe consequences of AP arise in FCS patients**; so are the uncertainties **in magnitude of the differences** associated with those cut-offs

AP: acute pancreatitis, AE: adverse event; SmPc: Summary of product characteristics; TG: triglycerides; FCS: Familial chylomicronemia syndrome; HRQoL: health-related quality of life

ERG's comments on surrogate outcomes and clinical effectiveness

Surrogate outcomes and uncertainties	• **Uncertainties remain regarding whether the dose-response relationship between TG levels and the risk of AP is generalisable to FCS patients;** • Clinical evidence on volanesorsen's effect on hard clinical outcomes such as AP at the trial's dose, which is higher than the SmPC dosing, is of low quality and uncertain; • Clinicians: chylomicron TG levels is considered a better clinical indicator of risk of AP → directly responsible for causing AP
Summary on Outcomes	• **TG level bands and selected cut-offs:** used as surrogate for clinical outcomes such as AP, CP, type 2 diabetes, and death → uncertainties about its clinical significance and cut-offs in people with FCS ; • **AP:** volanesorsen's effect on AP was uncertain, no analyses was presented at the bi-weekly nor the licensed dosing • **Subgroup analyses for AP (by AP 5 years prior to study enrolment versus AP on treatment)** were subject to limitations such as underpowered, exploratory, singled-armed, and post-hoc in nature; • **Subgroup analysis by SmPC dosing is only available for:** TG levels, response, average maximum intensity of pain, and the composite of AP and pain; • Long-term response and tolerance to the treatment is uncertain; • Uncertainty relating to **clinical effectiveness**, **treatment discontinuation** and **safety of the treatment** at the licensed dose in clinical practice;

AP: acute pancreatitis, CP: chronic pancreatitis; SmPc: Summary of product characteristics; TG: triglycerides; FCS: Familial chylomicronemia syndrome

[redacted]

Info: Early Access to Medicines Scheme (EAMS)

- Volanesorsen has been available to eligible patients via the EAMS since March 2018
- From 25 eligible patients, 20 were on treatment as of 31 July 2019 (at the time of submission)
- EAMS uses a similar platelet monitoring and dose adjustment schedule as that in the SmPC
  - But no stopping rule at 3 months, and bi-weekly dosing administered from inception, lower than SmPC dosing
- No EAMS patient has had a platelet level < 50 x 10^9/L with the monitoring and dosing programme in place
- Patients initiate on every 2 weeks dosing, 1 patient has increased dosing frequency
- 1 person discontinuation in the programme (due to cancer recurrence)

[redacted]

Key issues for consideration

Clinical effectiveness

Population: volanesorsen is indicated for adult patients with genetically confirmed FCS at high risk for pancreatitis. Not all patients in company's trials (APPROACH, APPROACH OLE, COMPASS) were genetically diagnosed (89.13%, 82/92):

- Are the study populations representative to people with FCS seen in the UK practice?
- How would "high risk for pancreatitis" be defined in clinical practice?

Clinical effectiveness and safety of volanesorsen at the licensed dose: the licensed dose was not used in trials. What is the committee's view on volanesorsen's effect, at the licensed dose, on:

- Change in TG levels and response to the treatment in long term?
- Clinical outcomes such as AP, CP, and type 2 diabetes, in which only very limited evidence of low quality from trials was reported *(no subgroup analysis by SmPC dosing conducted either)?*
- Safety outcomes (such as thrombocytopaenia)?
- Discontinuation?

TG levels as the surrogate outcome and the dose-response relationship between it and AP:

- What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Equality:

- Volanesorsen is indicated for FCS patients who are genetically diagnosed, however some patients may have unknown mutations and could not be genetically diagnosed. What is the committee's considerations for that?

Cost-effectiveness evidence

Key issues for consideration

Cost-effectiveness

- Health states are defined by TG level bands in the model, clinical outcomes such as AP are included as events experienced by FCS patients conditional on TG-risk band. Does the model structure capture disease progression of people with FCS and aspects important for them?
- Clinical evidence on volansorsen's effect on AP, at the licensed dose, is lacking from the trials. What is the committee's considerations on TG levels as surrogate outcome for AP and the assumptions related to it in the model, including:
  - The risk of AP was conditional on TG-risk band in FCS patients; and
  - Volanesorsen has a direct protective effect on clinical outcomes, such as AP and mortality, independent of/not mediated through TG levels?
- What is the committee's view on the underlying utilities associated with TG level bands, which utility values does the committee prefer?
- Should the utility benefits to carers be included in the analysis?
- Is the company's assumption on patient discontinuation in the model, at the licensed dosing, appropriate?

[redacted]

Company model structure

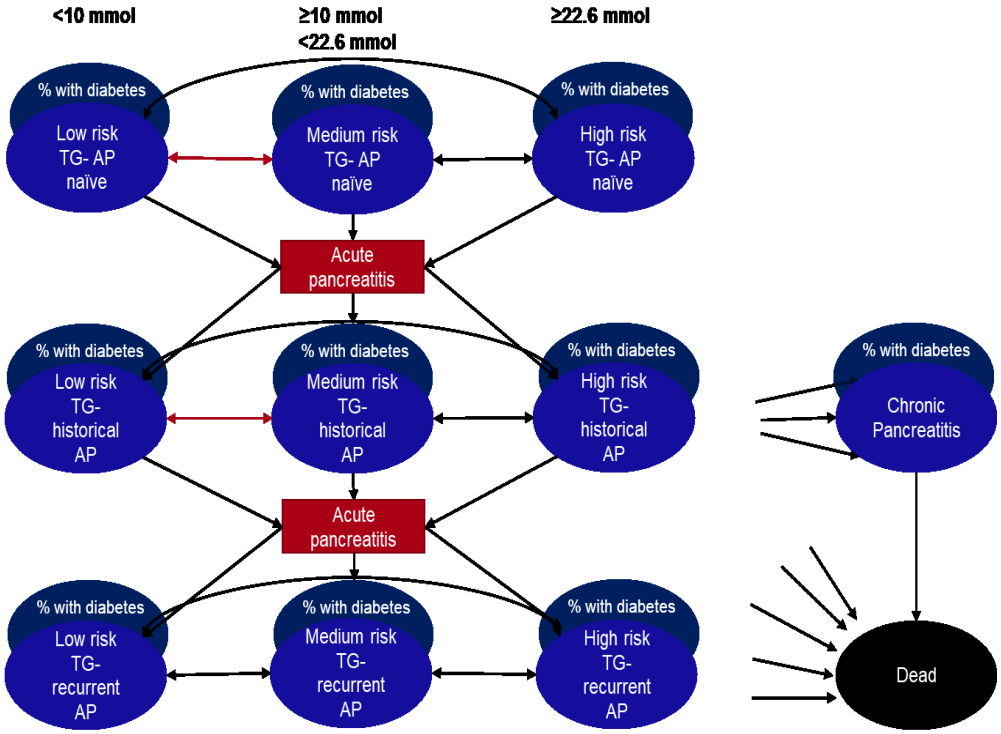
Three-month decision tree model

Continuation criteria applied in volanesorsen arm

[redacted]

QALYs half-cycle corrected

Longer-term Markov model



Cost and QALYs half-cycle corrected

Source: Figure 28 Company submission

Economic model

Model structure	2 components: 1) A decision tree model for the initial 3-month; and 2) Markov model for the long-term beyond 3 months;
Health states	Based on TG level bands and AP history of patients Cut-offs: (low risk: <10 mmol/L; medium risk: ≥10 and <22.6 mmol/L; and high risk: ≥22.6 mmol/L) AP; CP, diabetes or death as events experienced by patients
Population	Patients with genetically confirmed FCS who are at high-risk of pancreatitis Hypothetical cohort of patients assumed to be 41 years old and are comprised of 54.5% females Assumed to have the characteristics in terms of AP history and baseline TG bands as patients in APPROACH High-risk of pancreatitis defined as having had a previous AP event → population in the model have a history of AP (***different from APPROACH trial data***)
Dosing	Weekly for the initial 3 months and bi-weekly thereafter in the long-term Markov model until discontinuation or death
Benefits associated with treatment	Mainly come from it reducing patients' TG band level (to medium-risk) compared with SoC, with additional benefits on hard clinical outcomes assumed.
Discounting	3.5%
Perspective	NHS / PSS
Cycle length	3-month model cycle
Time horizon	59-year time horizon Assumed to represent the maximum remaining lifetime of a patient

TG: triglycerides; AP: acute pancreatitis; CP: chronic pancreatitis; SoC: standard of care; PSS: personal social services

Evidence sources and assumptions

	• Assumption and adjustments
Transition and volanesorsen's treatment effect on TG levels	• Evidence on actual reduction in TG levels from APPROACH at month 3 , and • GLMM techniques to predict TG levels beyond month 3 (using TG observations from both APPROACH and APPROACH OLE)
Treatment effect on safety/AEs	• AEs affecting 10% or more of patients that were moderate to severe and assessed as treatment-related from APPROACH OLE
Treatment duration	• Parametric survival functions fitted to time on treatment data for 32 patients who had bi-weekly dosing within the APPROACH OLE study
Benefits associated with volanesorsen	• Assumed to be through the favourable impact of volanesorsen on clinical outcomes associated with lower TG levels. Risk of AP was conditional on TG-risk band; • Volanesorsen was also associated with a protective effect with respect to AP events not mediated through/ independent of reducing TG levels; • Each AP event was associated with the risk of death; and developing CP; • AP history and TG-risk band was associated with the risk of developing type 2 diabetes;
Utility	• Patients [redacted] while patients [redacted]; utility values for health states estimated from a vignette study • Carers: (utility decrement) 0.1 from NICE HST submission for metreleptin for treating lipodystrophy
Resource use and cost	• No specific NHS reference costs or HRG codes applicable to management of FCS patients • Systematic literature review and clinical expert opinion sought

GLMM: Generalised linear mixed model; TG: triglycerides; AFT: accelerated failure time; AP: acute pancreatitis; CP: chronic pancreatitis

[redacted]

Population: population split at model entry

- Hypothetical cohort of patients assumed to be 41 years old and comprised of 54.5% females
- High-risk of pancreatitis defined as having had a previous AP event
- Patients assumed to have characteristics in terms of AP history and baseline TG bands as patients in APPROACH: (low risk: <10 mmol/L; medium risk: ≥10 and <22.6 mmol/L; and high risk: ≥22.6 mmol/L)
- The split of patients on model entry by risk of TG band:
  - low-risk: 4.0%; medium-risk: 42.0%; high-risk: 54.0%

ERG

- No patients have CP at the start of the model
- Contrast to APPROACH study where [redacted]
- The company implicitly assumed that the TG levels post-volanesorsen are not affected by CP status

[redacted]

Transition in the model

Health states

- Defined by TG band levels:
- Patients assumed to enter the model based on their TG band, and the number of APs experienced in the past 5 years (0 = historical, 1 or more = recurrent);
- In each 3-month model, patients moved between TG bands or remained in the same band, experienced an AP, had CP, or died

Transition in treatment arms between the decision tree and Markov models

The first 3 months:

- **Volanesoresen arm**: those who did not reduce their TG levels by 25% or who do not have a TG level < 22.6 mmol/L in the first 3 months did not continue on treatment, instead they discontinued and entered the SoC Markov;
- **Soc arm**: move to SoC Markov;

Beyond 3 months:

- **Volanesorsen arm**: after 3 months of treatment all patients continuing on treatment were in a medium-risk TG band unless they discontinued, experienced CP or died but they could move from historical AP to recurrent AP
- **SoC arm**: transition to high-risk TG band and remain there unless CP or death occurred but they could move from historical AP to recurrent AP

[redacted]

Transition in the model: *treatment effectiveness on TG levels*

Treatment effectiveness up to month 3

- Actual reduction in TG levels and absolute TG level at 3-month based on APPROACH trial used in deterministic base-case to determine whether a patient met the continuation criteria
  - APPROACH OLE subgroup of patients who conformed to the licensed dose not incorporated in model → small numbers "would likely have resulted in highly unstable ICER estimates

Beyond month 3

- TG levels for all patients were predicted using generalised linear mixed model (GLMM) techniques
- The analysis included 1,508 unique TG observations collected from 90 patients from both APPROACH and APPRAOCH OLE
- GLMM included 9 dosage regimens → the principle of maximum likelihood was used to guide the selection of duration for kick-in and washout period
  - Change in the length of kick-in or washout period had little impact on the estimates of the coefficients

ERG

Within the company's model the benefit associated with treatment was mainly due to moving patients to medium-risk TG band compared with SoC (high-risk band) with additional benefits assumed.

[redacted]

Model assumptions

Treatment safety

Adverse Event	Number per three-month cycle in the base case	Assumed associated cost per event	Assumed associated QALY decrement per event
Fatigue	Zero	Zero	0.004
Injection site reaction	0.130	Zero	0.00002
Thrombocytopaenia Grade 1	0.070	£70	Zero
Thrombocytopaenia Grade 2	0.017	£70	Zero
	Probability per three-month cycle in the base case (scenario analyses)	Assumed associated cost per event	Assumed associated QALY decrement per event
Thrombocytopaenia Grade 3	0.004	£70	0.004
Thrombocytopaenia Grade 4	0.004	£581	0.038

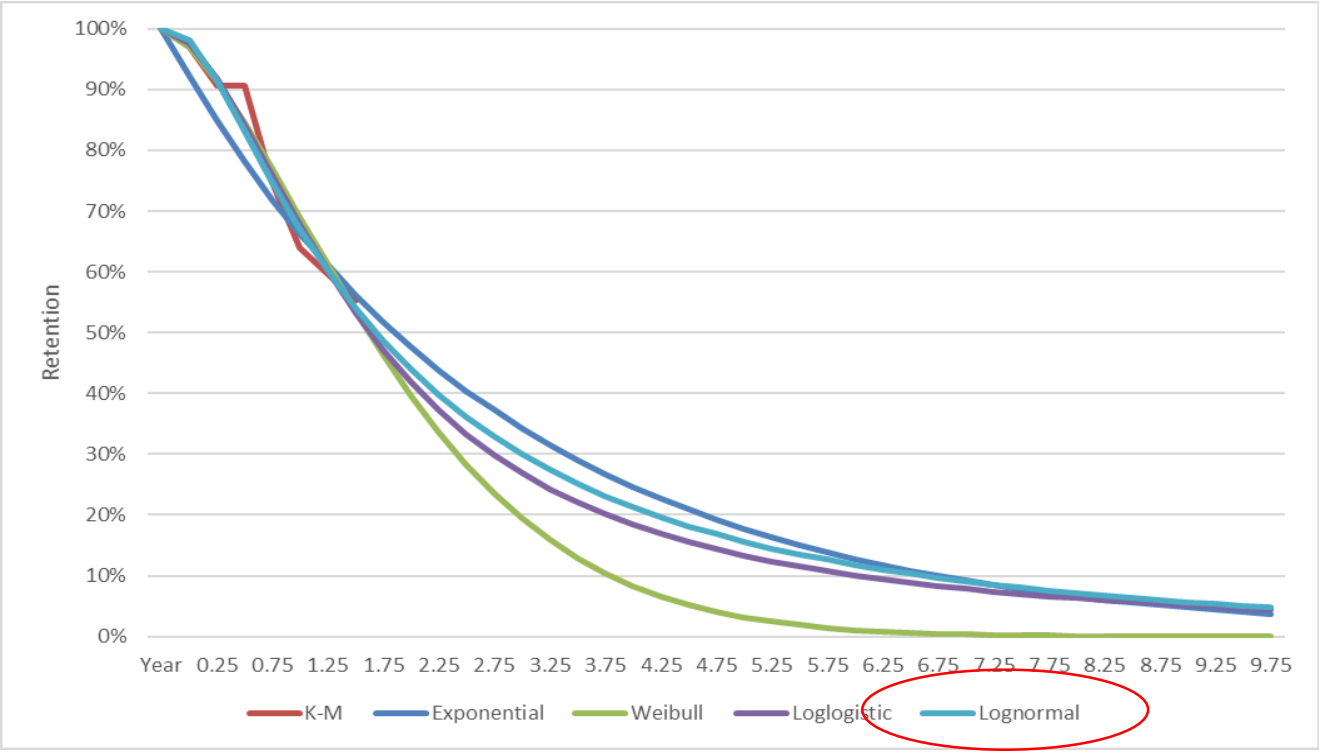
Source: Table 13 ERG report

- Estimating rate of AEs with volanesorsen compared with SoC difficult → no RCT with licensed posology of volanesorsen
- AEs used from APPROACH OLE
  - Entire study population, including AEs experienced by patients on long-term weekly dosing → may overestimate AE frequency
- Only AEs affecting 10% or more of patients included in model
  - No AEs assumed for the comparator arm

[redacted]

Model assumptions

Treatment duration



The parametric survival functions of time on treatment

- Discontinuation can be a consequence of 1 of 3 factors: not meeting the continuation criteria; the patient died, or the patient discontinued due to lack of adherence
- Parametric survival functions fitted to time on treatment data for 32 patients within the APPROACH OLE study (fortnightly treatment) → curve with a long tail that best represents a proportion of patients remaining on treatment over the long - term – **lognormal function-** as only 1 out of 20 patients in EAMS discontinued treatment due to recurrent cancer

[redacted] *Source: Figure 32 of company submission*

Model assumptions: benefits associated with treatment

- In company's model benefits associated with volansorsen were assumed to be through the favourable impact on clinical outcomes (such as AP, CP, and type 2 diabetes) associated with lower TL levels.

Relationship between TG levels and AP in patients with historical AP (defined as AP events occurred 5 years prior to study enrolment), received SoC

- An accelerated failure time (AFT) model was fitted to estimate the time to a first AP event, using observational data from CALIBER, which contains linked electronic health records in England
  - CALIBER included around 1.8 million patients (1997-2016) aged <40 years with at least 1 TG record and TG levels raised [redacted] → not just due to FCS
  - Covariates included in the analyses: age; sex; TG band; history of AP, and interaction terms between TG bands and history of AP
- Analysis results used to calculate the probability of an AP occurring in a cycle, assuming a constant hazard. Risk of AP did not change either when patients' ages increased
- **Company**: model under predicts AP rate on SoC, may slightly under predict AP costs, disutility and mortality and may under predict the benefit of volanesorsen → differences are likely to be small given the small absolute differences in AP rate between age 41 and 85
- **ERG**: survival models used to analyse the CALIBER data AFT models, the underlying distribution assumed for data was exponential

[redacted]
- Not clear if exponential model fits the data the best or whether including other covariates could improve the model fit

Model assumptions: benefits associated with treatment

Relationship between TG levels and AP in patients with historical AP (defined as AP events occurred 5 years prior to study enrolment) , received volanesorsen

- Treatment with volanesorsen would reduce the probability of experiencing APs, not only through the lower TG band, but also due to volanesorsen treatment itself
- Level of reduction associated with volanesorsen: **0.13,** estimated from a post hoc analysis comparing the rates of AP for patients in the 5 years prior to APPROACH OLE and the rates of AP when on treatment in APPROACH OLE

Assumed risk of AP per three-month cycle for patients in base case

TG band	Historical AP		Recurrent AP	
	SoC	Volanesorsen	SoC	Volanesorsen
Low	0.88%	0.12%	11.52%	1.51%
Medium	2.13%	0.28%	11.52%	1.51%
High	5.20%	0.70%	11.52%	1.51%

Source: Table 14 ERG report

[redacted]

ERG comment

- Factor has been calculated from a population who have already had a potential reduction in TG levels then this represents double-counting of the benefits
- ***ERG applied a multiplication factor related to the rate of APs within a specific TG-risk band of 0.50 through the use of volanesorsen***

Model assumptions: benefits associated with treatment

Relationship between TG band and AP events in patients with a recurrent AP (defined as had an AP within the previous 5 years), received SoC and volanesorsen

SoC

- AP event rate of patients in APPROACH who had an AP within the previous 5 years was used to estimate the probability of an AP in a 3-month period
- All TG bands were combined because the lower TG bands had a higher rate of AP than higher bands, not expected
  - ***Company's explanation***: observation may be spurious or due to the very low patient number in APPROACH, alternatively:
  - It's possible patients with a history of frequent AP may make greater effort to control their TGs, or
  - Patients who have had many events in the past are at higher risk of AP in the future regardless of TG levels

Volanesorsen

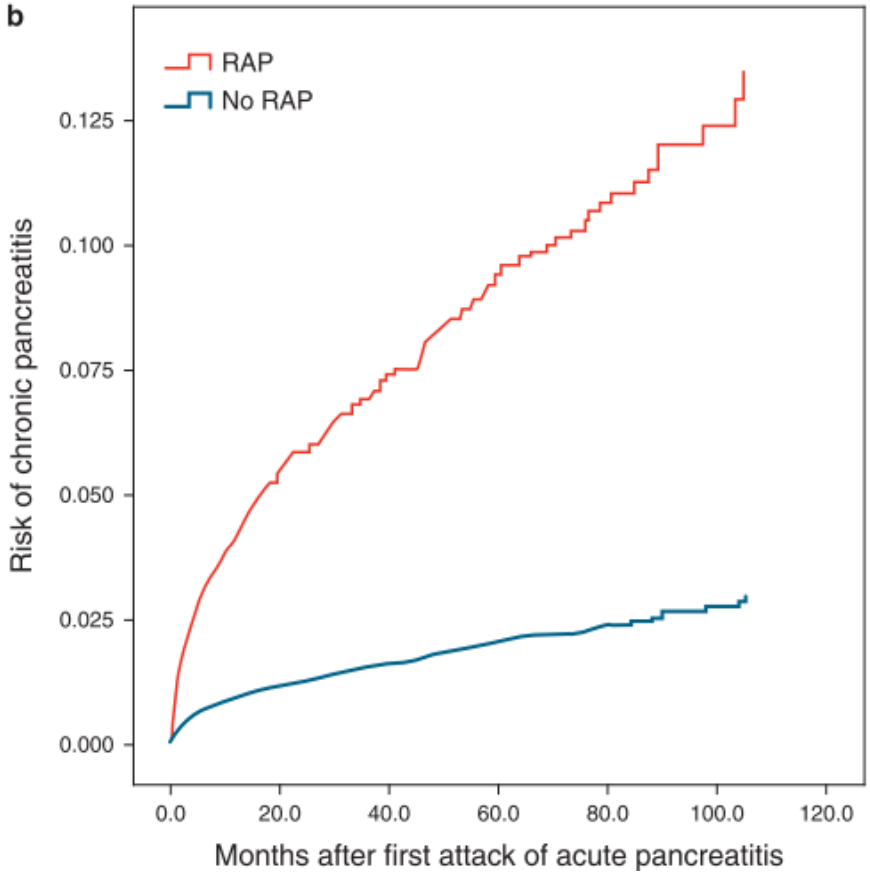
- Treatment with volanesorsen would reduce the probability of APs, with the same rate ratio of **0.13**

[redacted]

Model assumptions: *Relationship between AP events and developing CP*

- Frequency of CP is conditional on the incidence of AP
- Rates of CP development based on time since first AP based on literature (Yadav et al)
- Probabilities derived from 100-month timepoint assuming a constant risk
- At 100 months, CP had developed in approximately **12.5%** of people without recurrent AP, used for **historical AP** in the model, in approximately **12.5% of those with recurrent AP**
- Hazard rate of the curves in Yadav decreased over time, using the probabilities predicted only a 16% maximum prevalence of CP in the model
- Model calibrated so that the maximum prevalence was ~60%, representing the peak prevalence of CP in FCS estimated by the experts

Source: Figure 34 company submission



Time to development of CP – Yadav et al

[redacted] ***ERG: assumed in its base case that a multiplication factor of 28, which would be aligned with a lifetime CP prevalence of approximately 40%, may be more reasonable***

Model assumptions: *Relationship between TG bands, AP events, CP events and developing type 2 diabetes*

- AFT models fitted to the CALIBER data to estimate type 2 diabetes risk
- Covariates: age; sex; TG band; history of AP, and interaction terms between TG bands and history of AP
- Average time to type 2 diabetes, by TG band, assuming a constant hazard in patient with either historical or recurrent AP:
  - Predictions: low-risk TG band XXX years; medium-risk TG band XXX years; high-risk TG band XXX years, assumed to be applicable to patients with CP as well
- *The prevalence of diabetes in each health state was capped because the AFT model generated high levels of events in the model, based on the available literature*

	With historical AP	With recurrent AP
Low risk TG band	5.2%	5.2%
Medium risk TG band	14.6%	14.6%
High-risk TG band	23%	72%

- For those without CP, cap differentiated based on TG band and type of AP, historical or recurrent
- For patients with CP a cap of 80% was set

[redacted] - Caps applied to the cohort of patients across the entire modelling horizon

Source: Based on company submission, page 193

Model assumptions: *Relationship between TG bands, AP events, CP events and mortality*

Rate of death	Estimate (source)	Assumptions
Patients with an historic AP and no subsequent event	From England and Wales life tables (2014-2016)	--
Patients who have subsequent APs	**4.78%** in patients with FCS (Gaudet et al. 2016)	Risk of death was assumed independent of the number of previous APs
Impact of volanesorsen on the mortality rate following AP	**0.17** on volanesorsen compared with SoC (Wang et al. 2016)	• Risk of death would be reduced by volanesorsen treatment: use of volanesorsen would both reduce the number of APs, and the risk of the AP resulting in death. • All SoC patients would have high TG levels, people on volanesorsen have low TG levels
Relative risk of death following a CP	**5.83** (Nojgaard et al. 2011)	--
Relative risk of mortality for patients with type 2 diabetes	**1.28** (based on data from NHS Digital, 2017)	--

Health-related quality of life

Utility associated with health states

- EQ-5D data collected in APPROACH study → provided implausible values = values higher than the average UK index value
  - [redacted]
- Vignette study in order to collect [redacted]
- Study conducted with [redacted]

[redacted]	Utility value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	0.225
[redacted]	

Utility in CP state; QALY decrement of AP and type 2 diabetes assumed to be independent of treatment

- **ERG:** [redacted]
- [redacted]

Source: Table 15 ERG report

Health-related quality of life

QALY and utility decrements used in the model

*Decrements are assumed **additive***

Type of decrement	Method of calculation
QALY decrement of the AP [redacted]	Average decrement between the value for those in AP-naïve vignette health states and those in recurrent AP vignette health states; multiplied by duration of AP event in APPROACH; multiplied by two on the assumption that patients only went to hospital on 50% of AP episodes
QALY decrement of CP	Utility in the AP state minus the disutility of monthly AP flares
QALY decrement of type 2 diabetes = 0.225	Associated with uncomplicated diabetes (0.0621 - Sullivan et al) plus 50% of the additive decrements of complication of diabetes
Utility decrement for carers = 0.1	Values from 'Metreleptin for treating lipodystrophy' [ID861] Lipodystrophy is another metabolic disease sharing similar outcomes in scope with FCS and has similar challenges in daily dietary management
Utility decrement with AEs	Please see slide 9

Source: Based on company submission, section 10

ERG comment

- Unclear whether the CS met NICE reference case → participants of the vignette study [redacted]
- [redacted]
- [redacted]
- [redacted]

ERG used its own preferred utilities in its base-case

ERG prefers excluding utility gain for carers to represent no net change in carer utility between diseases –used in its base case

Resources and costs

- Health state costs - *no specific NHS reference costs or HRG codes applicable to management of FCS patients*
  - Lack of published data on healthcare resource use for UK FCS
  - Systematic literature review and clinical expert opinion sought

- Costs per three-month period

Variable used in model	Value
Quarterly cost of volanesorsen adjusted for dose pauses	XXXXX- includes a pricing scheme that has not been finalised
Costs of hospital admissions	Ranging from £717 for a person with a low-risk TG band to £1,070 for a person with a medium- or high-risk TG band
Specialist visits	ranging from £308 (low-risk TG band) to £316 (medium- and high-risk TG bands) and CP (£12,668)
Cost per annum of background treatment for FCS	£372 for all patients in all health states
Costs associated with each AE	Please see slide 68

Costs provided for all health-states (depending on risk, AP involvement and for CP)

- ICER is insensitive to the source of resource use

[redacted]

Cost-effectiveness results

[redacted]

Cost-effectiveness results (including PAS)

Company's deterministic results

Description	Incremental Discounted QALY	Cost per QALY gained
Dosing schedule - 285 mg weekly for three months followed by every 2 weeks maintenance dosing	XXX	£260,587

QALY, Quality-adjusted life year

Company base-case and majority of scenario analyses include an additional commercial arrangement which has not been formally agreed

Cost-effectiveness analysis results, including that associated with the additional arrangement, will be presented in Part2

[redacted]

Source: Table D26 clarification response letter

Limitations identified by the ERG in the company's modelling I.

Acquisition price of volanesorsen used in the model	• Base case presented with results incorporating additional reduction in price • ***ERG has produced results which do not include this additional price reduction as it has not been formally agreed***
Method for estimating the distribution of patients entering the model in terms of AP history and TG-risk	• ***ERG used absolute counts as it preserved the integrity of the data and ensured that the numbers were integers***
HRQoL – Data incorporated from vignette study	• Utility for a patient within a health state should not depend on whether a patient is on treatment as assumed in company's base case • Prefers utilities more aligned to the vignette results (not distinguishing patients on or not on treatment), assuming that values for patients with an historical AP lie halfway between those with no prior AP and those with an AP with lingering effects • ***Used ERG preferred utilities in base-case (see slide 86)***
Company's assumption on treatment discontinuation	• Assumption is of no discontinuation is not plausible, having noted that 6 of 14 (43%) of patients conforming to SmPc dosing in APPROACH OLE had discontinued at 2 years. • ***ERG deemed that 10% per year, would not be an unreasonable estimate of the discontinuation rate***
Half-cycle correction used in long-term Markov model	• It is not appropriate when doses are given at fixed intervals • ***ERG added the costs of half a dose in the discontinuation cycle for each patient who discontinues treatment in that cycle***

[redacted]

Limitations identified by the ERG in the company's modelling II.

Assumed reduction in APs associated with volanesorsen additional to that related to TG level reduction	• Factor has been calculated from a population who have already had a potential reduction in TG levels → double-counting of the benefits • Maybe an overestimate of the impact of patients enrolling in an open label study, by regression to the mean or through a higher dose of volanesorsen administered in the trial; • ***Regarding the multiplication factor related to the rate of APs within a specific TG-risk band through the use of vaolanesorsen, ERG believes that 0.50 would be more appropriate than the 0.13***
Assumed level of CP in the model	• ***ERG assumed that a multiplication factor of 28, which would be aligned with a lifetime CP prevalence of approximately 40%, may be more reasonable as a base case compared with 60% presented by the company***
Disutility with uncomplicated diabetes	• Company added 50% of the disutility associated with four major conditions and five concomitant conditions • ***ERG assumed that 50% of patients had congestive heart failure, which was the most impactful condition with a decrement of 0.1034. The ERG prefers a disutility value of 0.114 rather than the estimate of 0.225 used in the company base case***
Carer's disutility	• ***ERG prefers excluding utility gain for carers to represent no net change in carer utility between diseases***
Cost of CP	• £50,671 per year in company's model • ***ERG has arbitrarily used £30,000 per annum for CP patients***

[redacted]

Utility values preferred by the ERG

Patients receiving:	Utility value used by the company	Utility value preferred by the ERG
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Table 19 ERG report

Potential limitations in the original vignette study:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Exploratory analyses undertaken by the ERG

Scenario description	Incremental Discounted Costs	Incremental Discounted QALY	Cost per QALY gained
Using the currently agreed price of volanesorsen	[redacted]	[redacted]	£244,522
Amending the proportions in each TG-risk band	[redacted]	[redacted]	£216,260
Using the ERG's preferred utility values	[redacted]	[redacted]	£277,720
Assuming 10% discontinue treatment per year	[redacted]	[redacted]	£207,876
Amending half-cycle correction of volanesorsen drug costs	[redacted]	[redacted]	£218,400
Assuming a relative risk of 0.50 for AP instead of 0.13 due to volanesorsen treatment	[redacted]	[redacted]	£240,595
Calibrating the lifetime probability of CP to 40%	[redacted]	[redacted]	£226,926
Amending the disutility associated with type 2 diabetes	[redacted]	[redacted]	£231,030
Excluding the utility benefit to carers	[redacted]	[redacted]	£261,999
Changing the cost of CP care to £30,000 per year	[redacted]	[redacted]	£232,876
ERG-preferred deterministic ICER, incorporating all changes	[redacted]	[redacted]	£483,814
ERG-preferred probabilistic ICER, incorporating all changes	[redacted]	[redacted]	£492,364

Source: Table 20 ERG report

[redacted]

There was no single factor that caused the increase

ERG summary

A number of limitations within the company's base case analysis

- After correcting these the ICER increased to £490,000 per QALY
- There was no single factor that caused the increase. Assumptions having the greatest impact in one way sensitivity analyses from the company's deterministic base case were:
  - **Using the ERG-preferred utility** (£60,000)
  - **Excluding the utility benefit to carers** (£45,000)
  - Assuming that the **reduction in AP through volanesorsen independent of TG-level was not as large as assumed by the company** (0.13 vs. 0.50 assumed by ERG) (£25,000)
  - Assuming **volanesorsen's protective effect on mortality following an AP was removed**, with the relative risk changed from 0.17 to 1.00 → increased the deterministic ICER to £525,440 per QALY gained (an increase of £ 40,000);
- Substantial uncertainty remained in the utility associated with each TG-risk band
  - If a flat rate utility of 0.7 across all TG states is assumed, it further increases ICER by approximately £100,000
- Substantial uncertainty related to the robustness of the clinical evidence

[redacted]

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incremental QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr.)
Greater than or equal to 30	3

- Undiscounted incremental QALYs across all scenarios are <10

Impact of the technology beyond direct health benefits

Company comment

- Available research indicates that FCS is likely to have a substantial impact on work productivity
- The trial data demonstrate volanesorsen to be a step-change in the treatment of FCS
  - The relief that volanesorsen can offer patients and their family is profound
- Volanesorsen represents good value for money with a manageable budget impact due to the very low patient numbers

[redacted]

Equality

- Prevalence of FCS is higher in South Asian communities
- Consideration should also be given to women with FCS who may wish to become pregnant
  - In the IN-FOCUS study, 44% of respondents reported that having FCS impacted their decision on whether to have children, or how many children to have
  - No data available regarding the use of volanesorsen in pregnant women, it is not contra-indicated and the biochemistry suggests that it doesn't cross the blood placenta barrier
- FCS more likely to be found in people with distinct cultural/religious/ethnic background

Innovation

The company considers volanesorsen an innovative treatment because:

- It represent a 'step-change' in the management of FCS
- Demonstrates significant and sustainable TG lowering effect and reduction in pancreatitis events
  - Alleviating the broad and negative impact that FCS has physical, psychosocial, cognitive and economic aspects of patients' lives

[redacted]

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issues for consideration

Clinical effectiveness

Population: volanesorsen is indicated for adult patients with genetically confirmed FCS at high risk for pancreatitis. Not all patients in company's trials (APPROACH, APPROACH OLE, COMPASS) were genetically diagnosed (89.13%, 82/92):

- Are the study populations representative to people with FCS seen in the UK practice?
- How would "high risk for pancreatitis" be defined in clinical practice?

Clinical effectiveness and safety of volanesorsen at the licensed dose: the licensed dose was not used in trials. What is the committee's view on volanesorsen's effect, at the licensed dose, on:

- Change in TG levels and response to the treatment in long term?
- Clinical outcomes such as AP, CP, and type 2 diabetes, in which only very limited evidence of low quality from trials was reported *(no subgroup analysis by SmPC dosing conducted either)?*
- Safety outcomes (such as thrombocytopaenia)?
- Discontinuation?

TG levels as the surrogate outcome and the dose-response relationship between it and AP:

- What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Key issues for consideration

Cost-effectiveness

- Health states are defined by TG level bands in the model, clinical outcomes such as AP are included as events experienced by FCS patients conditional on TG-risk band. Does the model structure capture disease progression of people with FCS and aspects important for them?
- Clinical evidence on volansorsen's effect on AP, at the licensed dose, is lacking from the trials. What is the committee's consideration on TG levels as surrogate outcome for AP and the assumptions related to it in the model, including:
  - The risk of AP was conditional on TG-risk band in FCS patients; and
  - Volanesorsen has a direct protective effect on clinical outcomes, such as AP and mortality, independent of/not mediated through TG levels?
- What is the committee's view on the underlying utilities associated with TG level bands, which utility values does the committee prefer?
- Should the utility benefits to carers be included in the analysis?
- Is the company's assumption on patient discontinuation in the model, at the licensed dosing, appropriate?
- Equality: volanesorsen is indicated for FCS patients who are genetically diagnosed, however some patients may have unknown mutations and could not be genetically diagnosed. What is the committee's consideration for that?

[redacted]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Volanesorsen for the treatment of familial chylomicronaemia syndrome (FCS)

Company submission of evidence

20th June 2018

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested

in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with ‘see appendix X’. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

List of tables and figures

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Glossary of terms

Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
AP	Acute pancreatitis
apoC-III	Apolipoprotein C-III
ASO	Antisense oligonucleotide
CI	Confidence interval
CP	Chronic pancreatitis
CPRD	Clinical Practice Research Database
DM	Diabetes mellitus
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EQ-5D	EuroQol 5 dimensions questionnaire
FCS	Familial chylomicronaemia syndrome
HES	Hospital episode statistics
HRQL	Health-related quality of life
HTG	Patients with high triglycerides, including non-familial hypertriglyceridemia
ICER	Incremental cost-effectiveness ratio
ISM	Individual simulation model
ISR	Injection-site reaction
LPL	Lipoprotein lipase
LPLD	Lipoprotein lipase deficiency
LS	Least squares
NHS	National Health Service
OLE	Open-label extension
ONS	Office for National Statistics
PSS	Personal social services
QoL	Quality of life
RCT	Randomised controlled trial
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item short-form health survey
SoC	Standard of care
TG	Triglyceride

Executive Summary

The technology

Volanesorsen (Waylivra®) is an antisense oligonucleotide that inhibits the production of apolipoprotein C-III (apoC-III), a key regulator of plasma triglyceride (TG) levels. It is currently undergoing assessment by the European Medicines Agency (EMA) as an adjunct to diet in adult patients with familial chylomicronaemia syndrome (FCS).

Volanesorsen is supplied in pre-filled syringes containing 285 mg in 1.5 mL solution (each mL contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen). These are available as individual single-use syringes. The NHS list price is [redacted] per single dose pre-filled syringe. Dosing is by subcutaneous (SC) injection once every 2 weeks.

Nature of the condition

FCS is a rare, genetic disease characterised by extremely high levels of plasma TGs (between 10 and 100 times normal values) and a build-up of lipoprotein particles called chylomicrons (Ahmad and Wilson, 2014, Brunzell, 1999 Oct 12 [Updated 2011 Dec 15], Chokshi et al., 2014). Patients with FCS have inherited mutations that inhibit the activity of lipoprotein lipase (LPL), an enzyme that hydrolyses TGs and breaks down chylomicrons (Blom, 2010, NORD, 2016).

Patients with FCS often experience abdominal pain and are at risk of acute pancreatitis, which can be fatal. The risk of acute pancreatitis increases with increasing TG levels (Murphy et al., 2013, Pedersen et al., 2016, Rashid et al., 2016, Valdivielso et al., 2014). Recurrent episodes of acute pancreatitis may lead to long-term complications, including chronic pancreatitis and diabetes.

FCS imposes a considerable burden on patients, affecting their physical and emotional health, employment status, relationships and social life. Symptoms such as nausea and abdominal pain occur daily and can quickly worsen and become debilitating (Gelrud et al., 2017). Patients report that they feel

uncertainty about having pain or acute pancreatitis at any time, and that they can become depressed and isolated (Davidson et al., 2018).

There are currently no approved treatments for FCS. The standard of care is strict dietary control, where fat intake is restricted to 10 – 15 g/day (equivalent to one tablespoon of olive oil) (Valdivielso et al., 2014). However, for most patients even a severely restricted low-fat diet will not be sufficient to reduce the risk of a potentially fatal episode of acute pancreatitis (Bruno, 2010, Gaudet et al., 2010, Stroes et al., 2017). In addition, patients report that having to monitor what they eat restricts their social lives, as they find it hard to monitor their fat intake when not at home (Gelrud et al., 2017).

Some patients also receive lipid-lowering agents, such as fibrates, fish oils or niacin. However, these are generally ineffective as they act, at least in part, on the LPL-dependent metabolic pathway, which is absent in patients with FCS (Brahm and Hegele, 2015, Brisson et al., 2010, McCrindle et al., 2007). The risk of severe symptoms remains high in FCS patients despite receiving lipid-lowering drugs (Ahmad and Wilson, 2014).

Impact of the new technology

In the pivotal Phase 3 randomised, double-blind, placebo-controlled APPROACH study, patients treated with volanesorsen achieved statistically significant reductions in fasting TG levels that were sustained over the 52-week treatment period. These reductions translated into important clinical benefits for patients, such as a reduction in intensity and frequency of abdominal pain, and a reduction in pancreatitis attacks. These are events that severely impact patients' daily activities and quality of life and, in the case of pancreatitis, can be life-threatening.

Interim data from an open-label extension study suggest that the reduction in TG levels and associated clinical benefits seen with volanesorsen are sustained over the longer-term, with up to two years of follow-up.

The most frequent adverse events included mild-moderate injection site reactions and thrombocytopenia, including rare grade IV thrombocytopenia. Platelet reductions were generally managed with dose pauses, reductions, or discontinuation. Akcea recommends that patients undergo platelet monitoring at least every 2 weeks during treatment with volanesorsen, reflecting the Medicines and Healthcare products Regulatory Agency's recommended monitoring schedule set out in the Early Access to Medicines Scheme (EAMS) positive opinion.

Given the severity of FCS, the unmet need for patients who have no approved effective treatments, and the feasibility of routine platelet monitoring to support patient safety, the overall benefit/risk profile of volanesorsen is positive. Volanesorsen has the potential to fulfil a critical unmet need by providing important clinical benefits to patients with FCS.

The global clinical data presented in this submission are from the volanesorsen clinical development programme in patients with FCS. These include data obtained from double-blind placebo-controlled trials in an FCS population generalisable to the UK FCS population. Furthermore, data from the APPROACH OLE study support and characterise the longer-term efficacy and safety of volanesorsen and provide evidence supporting the extrapolation of cost-effectiveness past the initial 52-week trial period.

The trials clearly demonstrate the efficacy of volanesorsen and that it represents a step-change in the management of FCS. The potential impact of TG-lowering on important clinical outcomes of acute pancreatitis, chronic pancreatitis and diabetes has been demonstrated in the cost-effectiveness section using statistical models derived from a large UK patient database. This provides important information regarding the potential impact of volanesorsen in FCS patients consequent to its TG-lowering effects.

The burden of illness of FCS patients and the improvements experienced by those on volanesorsen have been assessed in the ReFOCUS study. These improvements in quality of life, which were unfortunately not captured in the APPROACH trial likely due to a non-FCS specific scale, have been shown to

be important and meaningful to members of the UK general public in a large health valuation study.

NICE guidance will raise awareness of the condition among both patients and clinicians, potentially permitting diagnosis and treatment before the onset of severe symptoms such as pancreatitis. Furthermore, positive guidance will potentially prevent existing patients from starting or continuing down the route of repeat acute pancreatitis and the associated progression to chronic pancreatitis and/or diabetes in some patients. Currently, eligible patients can receive volanesorsen under the Early Access to Medicines Scheme (EAMS); these patients would benefit from the opportunity to continue treatment under a nationally-commissioned service. Those patients not currently receiving treatment under EAMS would potentially benefit from being able to initiate treatment.

Treatment continuation rules

[redacted]

[redacted]

Value for money

A model was developed to estimate the expected cost-effectiveness of volanesorsen compared to current standard of care (dietary restriction alone) from an NHS perspective. The model structure was designed to capture the key aspects of FCS, including TG levels, acute pancreatitis events, chronic pancreatitis, comorbid diabetes and death. The model was informed by the APPROACH clinical trial, the literature and unpublished sources of real world evidence to support the relationship between TG levels and the risk of long-term events and outcomes. Healthcare resource utilisation was estimated from real world evidence sources and the literature. Utilities, to estimate quality-adjusted life years in the base case analysis, were derived from a vignette study. Utilities derived from EQ-5D-5L data collected in the APPROACH clinical trial are presented as a sensitivity analysis.

In the base case analysis, it is assumed that all patients remain on volanesorsen regardless of TG level with treatment discontinuation modelled according to the APPROACH study. A scenario is also presented alongside the base case in which a treatment continuation rule is implemented at [redacted] The threshold level is based on real world evidence from a large observational dataset and is endorsed by clinical experts.

[redacted] patients in the APPROACH study received treatment with volanesorsen on a weekly basis. [redacted]. Base case results are subject to a Patient Access Scheme.

Akcea has submitted a simple discount Patient Access Scheme. The PAS price per single use syringe of volanesorsen is [redacted]

In the base case, volanesorsen is associated with incremental costs of [redacted] (discounted) and [redacted] (discounted). The incremental cost-effectiveness ratio for the base case analysis is [redacted] per QALY gained (deterministic). However, Akcea proposes that a treatment continuation rule should be implemented at 3 months, and in this scenario, volanesorsen is associated with incremental costs of [redacted] (discounted) and [redacted] incremental QALYS (discounted). The incremental cost-effectiveness ratio for the treatment continuation rule scenario is [redacted] per QALY gained (deterministic).

FCS prevalence estimates for England are in the range of 55 to 110 people. Akcea is aware of [redacted] FCS patients in England within the current lipid clinic network. We estimate that a total of [redacted] patients would receive treatment with volanesorsen in Year 1, including those transitioning from the EAMS programme. By Year 5, a total of [redacted] patients cumulatively are expected to have started treatment with volanesorsen. The net budget associated with introducing volanesorsen is estimated at [redacted] in Year 1, and [redacted] in year 5 (undiscounted), with a cumulative budget impact over 5 years of [redacted] (undiscounted).

Impact of the technology beyond direct health benefits

Available research indicates that FCS is likely to have a substantial impact on work productivity. The In-FOCUS study supports this view (Davidson et al., 2017, Davidson et al., 2018). According to the results of this survey, almost all FCS patients who were unemployed or employed on a part-time basis (95%) reported that their employment status was a result of having FCS. There is also evidence in the literature that pancreatitis has a negative impact on work productivity. In a multicentre study, authors observed a profound impact on the ability to work and on interpersonal relationships for patients who experienced chronic pancreatitis (Gardner et al., 2010).

A published report from an advisory board (Gelrud et al., 2017) indicates that carer time may relate closely with the complications of FCS. It is plausible

that, since complications such as episodes of acute pancreatitis are thought to be under-reported by patients, carer burden may consequently be underestimated in FCS families. According to the advisory board authors, carers use their own holiday time to provide care for patients during FCS complications. It is likely that over the life-time of FCS patients, carer time burden will be very substantial, and particularly in patients developing comorbidities such as diabetes or chronic pancreatitis.

Akcea Therapeutics has discussed and obtained feedback from clinicians and patient groups on potential options for an appropriate service framework to support the delivery of volanesorsen to patients, in the anticipation that it is routinely commissioned within the NHS (post EAMS period).

At a recent advisory board, there was a consensus that a networked (hub and spoke) service, under the auspices of a service specification, would be necessary for the provision of adequate long-term dietetic support and coordination of care by a specialist nurse, without the need to significantly increase capacity and resource utilisation at specialist centres caring for FCS patients.

Akcea is committed to developing and commercialising further innovative medical technologies in disease areas of high unmet need. The availability of volanesorsen would positively impact the ability of Akcea to invest in further innovation and to forge collaborations with other UK-based innovators and to undertake further collaborative research into FCS (as with the Farr Institute for the CALIBER national history study) and other diseases and their treatment.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults with familial chylomicronaemia syndrome	None	
Intervention	Volanesorsen in combination with established clinical management (including dietary fat restrictions)	None	
Comparator(s)	Established clinical management without volanesorsen (including dietary fat restrictions)	None	
Outcomes	The outcome measures to be considered include: • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability) • incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions) • mortality (including all-cause and pancreatitis related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers).	None	

Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	None	
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)	None	
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used	None	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise	None	

Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements • The evaluation will include consideration of the costs and implications of genetic testing and measurement of enzyme level but will not make recommendations on specific diagnostic tests. • Consideration should be given to the precise definition and clinical diagnosis of familial chylomicronaemia syndrome. • If evidence allows, consideration will be given to the subgroup of patients with comorbid diabetes • If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues. • If appropriate, consideration may be given to whether factors contributing to, or exacerbating hypertriglyceridemia are associated with characteristics that are protected under equality legislation (for example, but not limited to, women using oral contraceptives).	None	

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Waylivra®

Approved name: volanesorsen

Therapeutic class: other lipid modifying agents (ATC code: C10AX)

2.2 What is the principal mechanism of action of the technology?

Metabolism of triglycerides (TGs) occurs primarily through the action of lipoprotein lipase (LPL) and via an LPL-independent pathway. Both metabolic pathways are regulated by the glycoprotein apolipoprotein C-III (apoC-III), which helps to maintain normal TG levels by inhibiting metabolism.

Patients with FCS do not have functional LPL, yet many current TG-lowering therapies act on the LPL pathway (making them largely ineffective in this patient group). Volanesorsen is an antisense oligonucleotide (ASO) inhibitor of apoC-III. It selectively binds to apoC-III mRNA, preventing production of the apoC-III protein and allowing metabolism of TGs via an LPL-independent pathway.

2.3 Please complete the table below.

Table A2 Dosing Information of technology being evaluated

Pharmaceutical formulation	Solution for subcutaneous (SC) injection. Supplied in pre-filled syringes containing 285 mg volanesorsen in 1.5 mL solution
Method of administration	SC injection
Doses	285 mg in 1.5 mL
Dosing frequency	[redacted]
Average length of a course of treatment	Life-long
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	Please see volanesorsen monitoring and treatment recommendations in Table A3 below. No dose adjustments are needed for elderly patients, or for patients with mild or moderate renal impairment. No data

	are available in patients with severe renal impairment. With respect to hepatic impairment, evidence is not available. However, volanesorsen is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment.

Source: Volanesorsen draft SmPC

In the draft SmPC, the dose of volanesorsen is given as 285 mg. However, in the CSRs for the studies included in this submission, this dose is given as 300 mg, which relates to its formulation as volanesorsen sodium. Please note that in this submission, the dose is referred to as 285 mg throughout to reflect the draft SmPC.

Table A3 Volanesorsen monitoring and treatment recommendations

[redacted]

Source: Volanesorsen draft SmPC

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The proposed indication for volanesorsen is as an adjunct to a low-fat diet for the treatment of patients with FCS. A marketing authorization application was submitted to the European Medicines Agency (EMA) in July 2017. [redacted]

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Assuming approval by the EMA in September 2018, volanesorsen will be commercially available in the UK from [redacted] However, volanesorsen has been available to eligible patients via the Early Access to Medicines Scheme (EAMS) since March 2018.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Volanesorsen does not currently have regulatory approval outside the UK. A new drug application was submitted to the US Food and Drug Administration (FDA) in September 2017, with approval expected on [redacted] In Canada, a submission was made in September 2017 with approval expected in [redacted]

3.4 If the technology has been launched in the UK provide information on the use in England.

Volanesorsen has not yet been launched in the UK. However, it is available via the EAMS.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table A4 shows completed and ongoing studies of volanesorsen in patients with FCS.

Table A4 List of completed and ongoing studies

Trial no. (Acronym) Phase	Interventions	Population	Treatment duration	Primary outcome	Status	Publications
NCT02211209 APPROACH Phase III	• Volanesorsen (285 mg) by SC injection, once weekly • Placebo by SC injection	Adult patients with FCS	52 weeks	Percent change in TG at Month 3, defined as average of Week 12 and Week 13 assessments	Completed	Baseline data accepted for publication (Blom et al., 2018) limited efficacy data published as abstracts (see Section 9.4.2)
NCT02300233 COMPASS Phase III	• Volanesorsen (285 mg) by SC injection, once weekly* • Placebo by SC injection	Adult patients with hypertriglyceridemia (including FCS)	26 weeks	Percent change in TG at Month 3, defined as average of Week 12 and Week 13 assessments	Completed	Manuscript in preparation
NCT02658175 APPROACH OLE Phase III	• Volanesorsen (285 mg) by SC injection, once weekly	Adult patients with FCS who: • rolled over from APPROACH • rolled over from COMPASS • did not take part in APPROACH or COMPASS	52 weeks	Percent change and absolute change from baseline in fasting TG†	Study is open for up to 2 years and will terminate upon receipt of MA. Interim data cuts are ongoing.	Unpublished

*All patients had dose frequency reduced to 285 mg every 2 weeks after 13 weeks of treatment with exemptions given to patients who had completed ≥5 months of dosing as of 27 May 2016. †No formal designation of outcomes as 'primary' or 'secondary' in APPROACH OLE; see Section 9.4.1 for a full list of study outcomes

OLE, open-label extension; SC, subcutaneous; TG, triglycerides

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file; COMPASS clinical study report, 2nd June 2017, Akcea data on file; APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

APPROACH and APPROACH OLE provide the pivotal evidence for this submission. In COMPASS, only 7 of the 113 patients enrolled had FCS; this study provides supportive evidence and is discussed briefly where information specific to these 7 patients is available.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Assuming EMA approval in [redacted] a submission to the Scottish Medicines Consortium is planned for [redacted] with their recommendation anticipated

[redacted]

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

We do not believe that this evaluation will result in any of these scenarios.

5.2 How will the submission address these issues and any equality issues raised in the scope?

N/A: no equality issues have been identified.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

FCS is a rare, genetic disease characterised by high levels of TGs in the plasma (a level of >8.8 mmol/L[1] was defined for the APPROACH trial) and a build-up of chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body) (Gaudet et al., 2014, NORD, 2016). Patients with FCS have inherited mutations in genes that encode key molecules involved in fat metabolism (Stroes et al., 2017). Over 80% of cases are caused by mutations that inhibit the production and/or activity of LPL, an enzyme that hydrolyses TGs and breaks down chylomicrons (Blom, 2010, NORD, 2016, Stroes et al., 2017); this specific form of FCS is known as lipoprotein lipase deficiency, or LPLD.

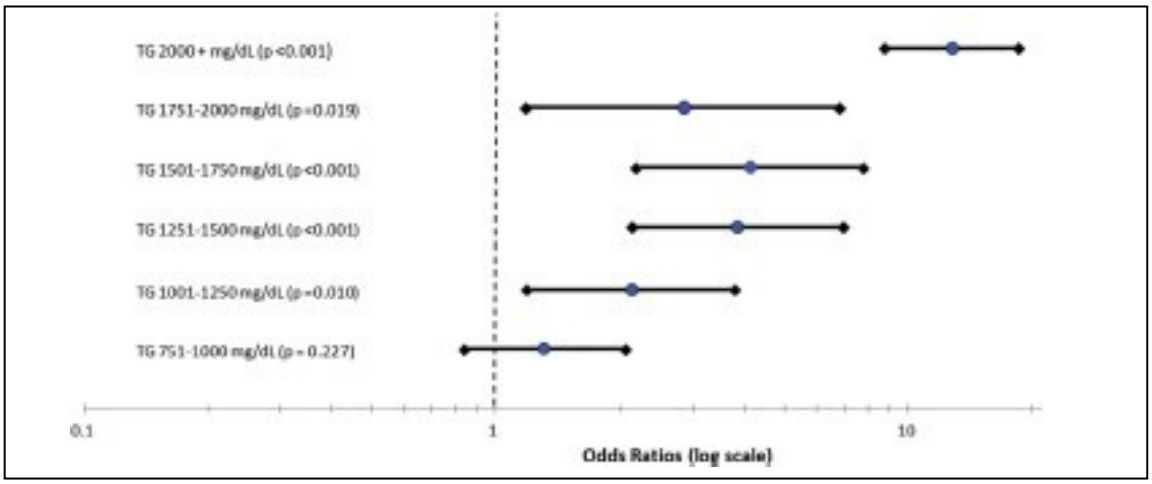
Patients with FCS often experience abdominal pain, ranging from mild to incapacitating (Chait et al., 1981), and are at risk of acute pancreatitis, which is unpredictable and often recurrent (Blom, 2010, Gan et al., 2006, Gaudet et al., 2016, Khokhar and Seidner, 2004, Valdivielso et al., 2014). These symptoms are caused by a build-up of chylomicron particles that reduce blood flow through the pancreatic microcirculation (Valdivielso et al., 2014).

It is estimated that approximately 65 – 80% of patients with FCS will experience acute pancreatitis (Blom et al., 2018, Gaudet et al., 2016). There appears to be a causal relationship between raised TG levels and acute pancreatitis; this is supported by evidence that fulfils several of the Bradford Hill criteria for causation, e.g. consistency, biological gradient (dose-

[1] Note on lipid conversion factors: there is no standard convention for reporting units for TG values – mmol/L and mg/dL are both commonly used. Both are used in this submission. The conversion factor between the units is approximately 88.

response), plausibility (Hill, 1965). A systematic review by Adiamah et al. (2017) that included 38 studies found that patients with hyperlipidaemia have a higher risk of acute pancreatitis, and that tight regulation of TG levels after presentation with acute pancreatitis reduced the risk of recurrence. The risk of acute pancreatitis increases with increasing TG levels (Valdivielso et al., 2014, Pedersen et al., 2016, Rashid et al., 2016, Murphy et al., 2013; Toth et al., 2014; Akcea data on file, 2018a). Toth et al. (2014) found a pronounced increase in risk for patients with TG levels >2000 mg/dL (22.7mmol/L, Figure 1).

Figure 1 Relationship between TG levels and acute pancreatitis



Source: Toth et al., 2014

The CALIBER study assessed linked electronic health records in England among patients aged <40 years with at least one TG record in Clinical Practice Research Datalink and categorised them into three cohorts (Akcea data on file, 2018a):

- [redacted]
- [redacted]

- [redacted]

[redacted] (Akcea data on file, 2018a).

Figure 2 Acute pancreatitis in patients with at least 1 TG recorded before age 40 years, stratified by peak TG (n = 271,571)

Source: Akcea data on file, 2018a

Patients with acute pancreatitis and TG levels >1000 mg/dL (11.4mmol/L) experience more severe pancreatitis with worse outcomes than those with normal TG levels (i.e. <150 mg/dL, 1.7mmol/L), including increased need for intensive care, higher rates of pancreatic necrosis, more frequent persistent organ failure, and higher mortality rates (Nawaz et al., 2015). In this study, all of the patients with TG levels >1000 mg/dL (11.4mmol/L) had pancreatitis caused by hypertriglyceridemia, whereas a biliary aetiology was more common among the patients with normal TGs.

Women with FCS have additional risks, as increases in oestrogen can further increase TG levels. TG-induced acute pancreatitis during pregnancy can lead to pre-term delivery, loss of the foetus, or even death for the mother (Amin et al., 2015, Tang et al., 2010).

Patients who suffer episodes of acute pancreatitis may develop long-term complications, including chronic pancreatitis, Type 3C diabetes, pancreatic insufficiency, and their attendant burdens (Makhija and Kingsnorth, 2002, Symersky et al., 2006). Pancreatitis can be fatal, as a result of necrosis, sepsis and multi-organ failure caused by local inflammation in the pancreas (Makhija and Kingsnorth, 2002). Mortality rates are higher in patients with pancreatitis caused by raised TG levels than in those with pancreatitis due to other causes (Bardia and Garg, 2015). Results of a survey of lipidologists found that patients with FCS have a high risk of developing recurrent acute pancreatitis and that death from pancreatitis-related complications is not uncommon despite modern medical care (Gaudet et al., 2016).

Other characteristics of FCS include (Brahm and Hegele, 2015, Brunzell, 1999 Oct 12 [Updated 2011 Dec 15], Tremblay et al., 2011, Yuan et al., 2007):

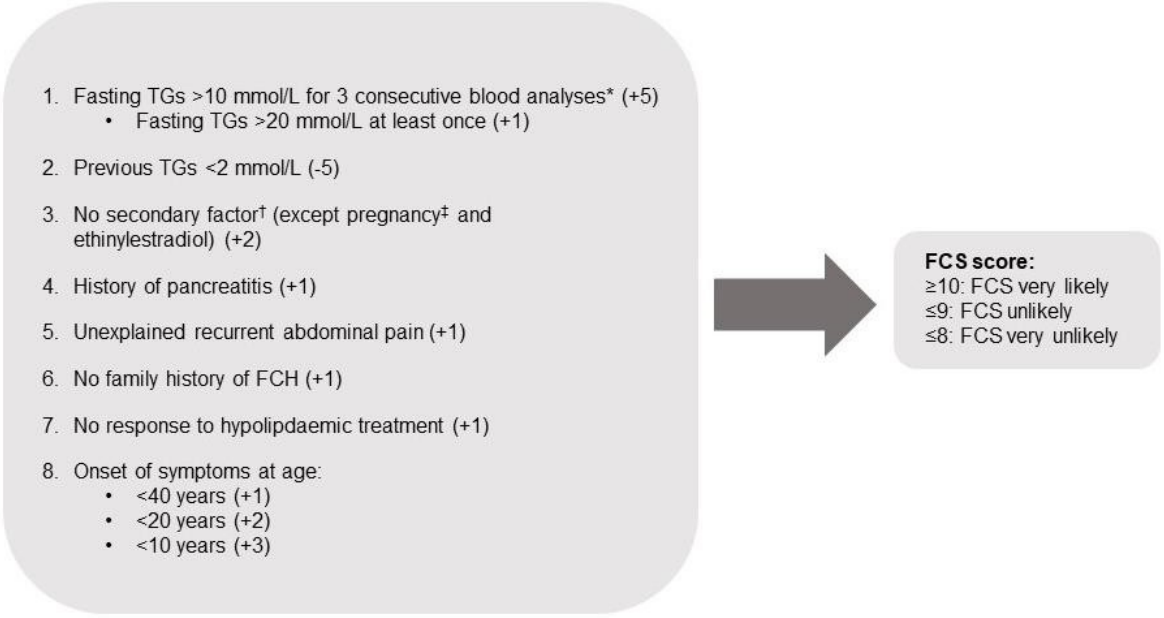
- eruptive cutaneous xanthomata (yellow papules that generally appear on the trunk, buttocks or extremities)
- lipemia retinalis (milky appearance of the retinal vessels and pink retina)
- lipemic blood (caused by the sustained presence of serum chylomicrons, even in the fasting state)
- hepatosplenomegaly (enlarged liver and spleen).

Patients with FCS may also experience episodes of fatigue, a lack of energy (asthenia), impaired cognition, and a numbness or tingling sensation (dysthesia) as well as a number of other burdens that span physical,

emotional and cognitive domains (Brown et al., 2016, Chait et al., 1981, Davidson et al., 2018).

Traditionally, patients have been diagnosed by assessment of several criteria, including recurrent raised TG levels that are refractory to current lipid-lowering therapies and are not due to other causes (e.g. type 2 diabetes, hypothyroidism), plus a history of acute pancreatitis and abdominal pain. However, recent expert consensus recommendations demonstrate that FCS can be diagnosed clinically using an FCS score, which can discriminate between FCS and multifactorial chylomicronaemia (Figure 3) (Moulin et al., in press). The eight items and their relative weightings were selected on a pragmatic basis following discussion by an expert panel.

Figure 3 FCS score



Numbers in parentheses = weighting given to each item. FCS score = sum of all items present. FCH, familial combined hyperlipidaemia. *Eruptive xanthoma may be used as a surrogate for high TG levels (rare). †Secondary factors include alcohol, uncontrolled diabetes, metabolic syndrome, hypothyroidism, corticotherapy. ‡If diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis post-partum.
Source: Moulin et al., in press

Some patients are diagnosed in infancy but those who are not are at risk of being caught in a cycle of misdiagnosis and diagnostic delay. Awareness of FCS is low among general practitioners and emergency physicians, and adult patients may find that healthcare professionals assume their attacks of acute pancreatitis are caused by an alcohol or drug problem. Consequently, it can

take several years before a patient is correctly diagnosed. This puts patients at greater risk of complications. Figure 4 shows how the patient journey differs depending on the time of first presentation.

Figure 4 The patient journey in FCS

A&E, accident and emergency; CT, computed tomography; GI, gastrointestinal; GP, general practitioner; ICU, intensive care unit; TG, triglycerides; US, ultrasound

Source: Akcea data on file, 2017

There is currently no indicated treatment for FCS, so patients rely on a highly restricted-low fat diet to control their plasma TG levels (see Section 8 for further details). However, in most patients this is not sufficient to reduce TGs to a low enough level to reduce the risk of acute pancreatitis (Stroes et al., 2017). Some patients may receive lipid-lowering agents; however, these are generally ineffective because they operate in part via LPL, which is functionally impaired in FCS. Plasmapheresis, a procedure that rapidly lowers TG levels, is rarely used in the UK as the reductions seen in TGs are transient, lasting only a few days (Diakoumakou et al., 2014, Ewald and Kloer, 2012). Plasmapheresis is also an acute rather than a longer-term solution.

Signs and symptoms of FCS are driven by extremely high plasma TGs. Volanesorsen offers patients a treatment option that significantly reduces TG levels which, in turn, may reduce the incidence of acute pancreatitis, and the frequency and intensity of abdominal pain.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

FCS is an ultra-rare condition that affects an estimated 3,000-5,000 patients globally. Prevalence estimates for England are between 55 and 110 people. To date (mid-June 2018), Akcea is aware of [redacted] patients in England within the current lipid clinic network.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

There is no reliable information on life expectancy for patients with FCS. As described in Section 6.1, acute pancreatitis, a complication of FCS, can be life-threatening. A proportion of patients will also develop comorbid diabetes or chronic pancreatitis, both having an impact on life expectancy.

7 Impact of the disease on quality of life

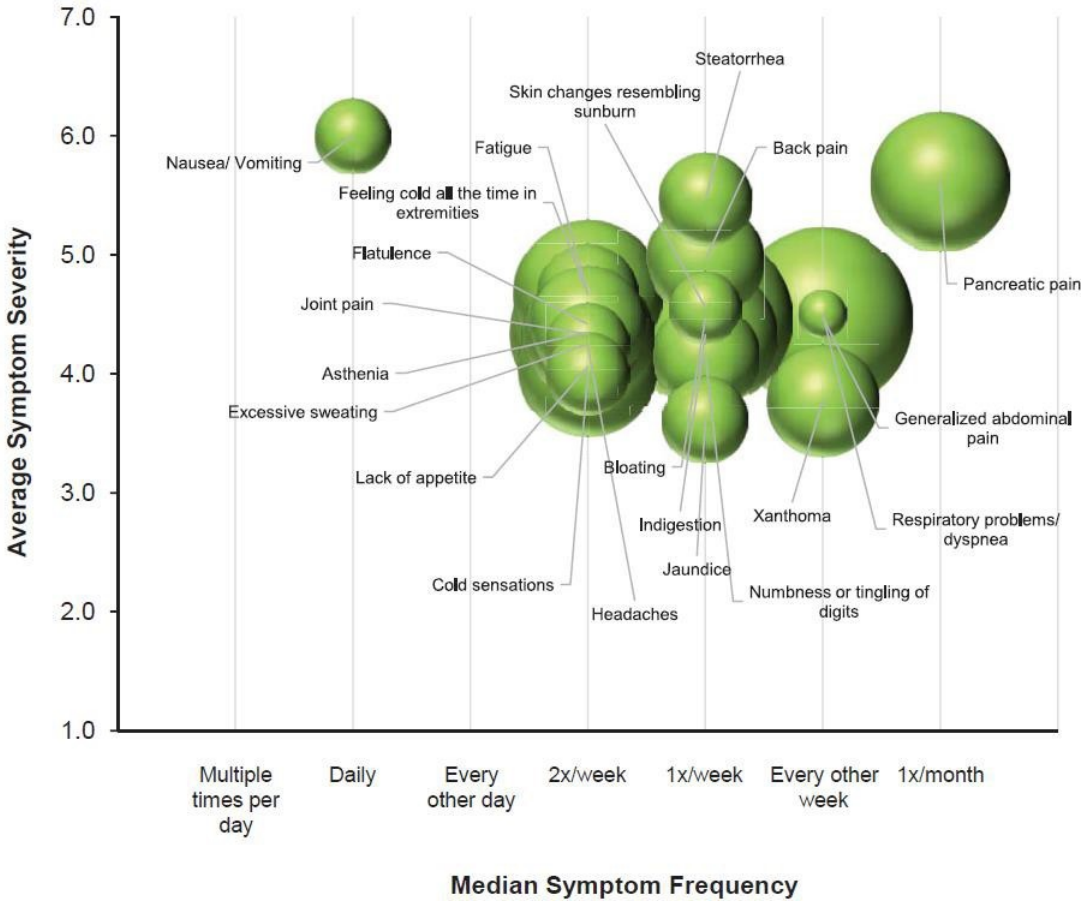
7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

FCS imposes a significant burden on patients and their carers, adversely affecting their physical and emotional health, employment status, relationships and social life.

Physical and emotional health

Patients with FCS experience a number of physical, emotional and cognitive symptoms. In a study by Davidson et al. (the IN-FOCUS study), 166 patients from 10 countries were shown a list of symptoms and were asked how frequently and at what severity they experience these symptoms. Figure 5 shows the incidence, frequency and severity of physical symptoms. The most common symptoms were generalised abdominal pain (41%), bloating (37%), asthenia (30%), indigestion (27%) and fatigue (23%); these symptoms were experienced between twice a week and once every 2 weeks (Davidson et al., 2018).

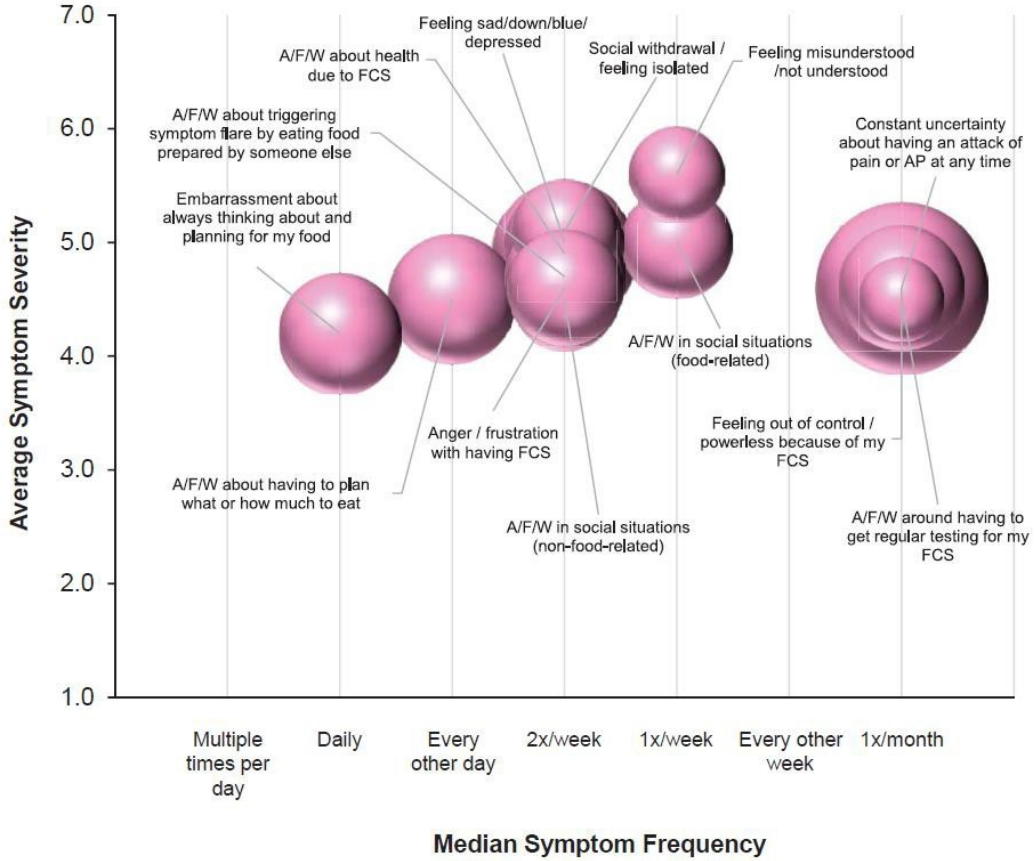
Figure 5 Physical symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
Source: Davidson et al., 2018

Figure 6 shows the results of this study for emotional symptoms. Patients reported feeling uncertainty about having pain or acute pancreatitis at any time, and that they were worried about their health and meal planning. They also said that they felt helpless or out of control.

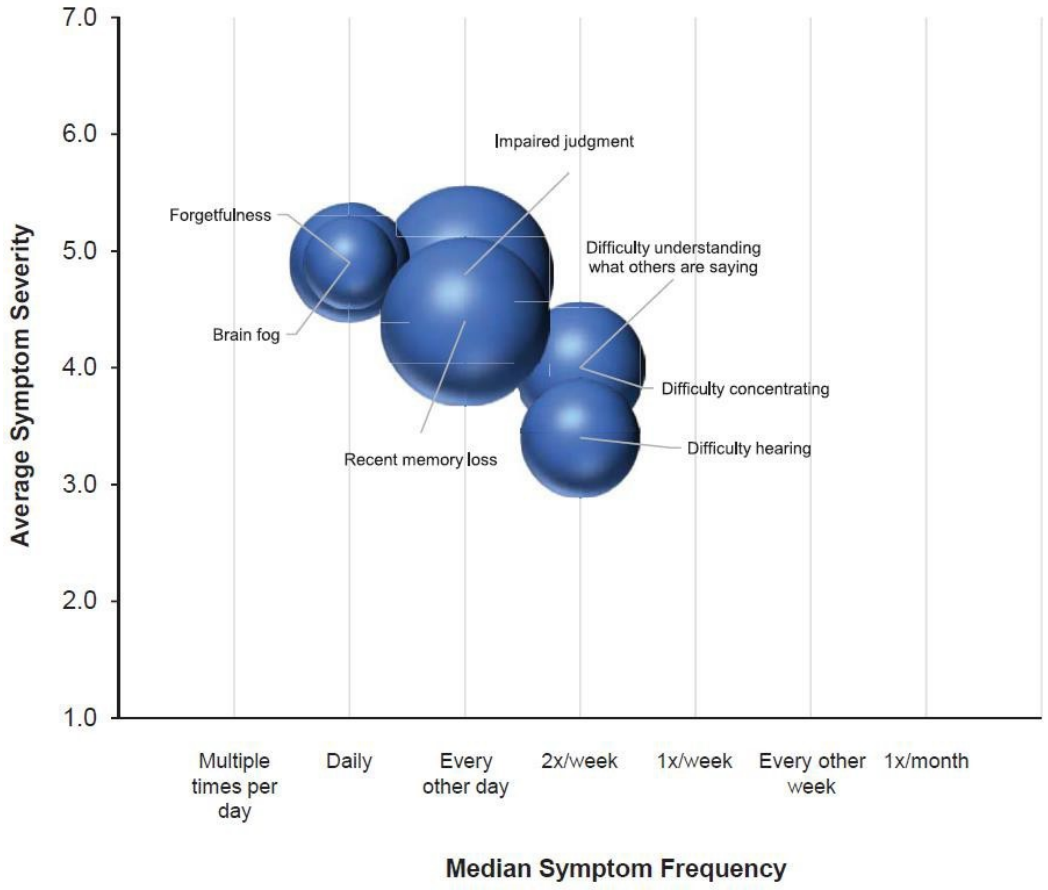
Figure 6 Emotional symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
A/F/W, anxiety, fear/worry; AP, acute pancreatitis
Source: Davidson et al., 2018

Figure 7 shows the study results for cognitive symptoms. The most common symptoms were difficulty concentrating (16%), impaired judgement (11%), ‘brain fog’ (8%) and forgetfulness (8%); patients experienced these symptoms daily or every other day.

Figure 7 Cognitive symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
Source: Davidson et al., 2018

Data from UK patients (n = 20) who took part in the survey support the overall findings. Patients reported a diverse range of symptoms, including generalised abdominal pain, fatigue, and anxiety/fear/worry about their health. Forty-five percent of UK respondents reported experiencing acute pancreatitis, averaging one episode in the last 12 months and 13 over the course of thier lives so far. All patients said they had been hospitalised during their episodes of acute pancreatitis (Soran et al., 2018).

In a study of patients with FCS by Gelrud et al., all 10 patients interviewed reported daily nausea and low-level abdominal pain that could quickly worsen and become debilitating. Patients also reported that their symptoms increased in frequency as they got older (Gelrud et al., 2017).

As yet, there is no specific tool to measure quality of life (QoL) in patients with FCS. Johnson et al. (2015) evaluated 11 patients with LPLD using the European Organisation for Research and Treatment of Cancer's quality of life questionnaires QLQ-C30 (all cancers) and QLQ-PAN26 (pancreatic cancer). They found that the most relevant QoL domains for patients with LPLD were pain, fatigue and sleeping problems, digestive and dietary factors, work, daily and social activity restrictions, impact on emotional functioning, and satisfaction with healthcare professionals, all consistent with the IN-FOCUS findings.

Employment status

In the IN-FOCUS study (Davidson et al., 2018), only 60% of patients with FCS were employed full- or part-time (37% part-time, 23% full-time). Most of those who were unemployed had been employed in the past and many attributed their unemployment to FCS. Forty percent of homemakers felt their lack of employment opportunities was due to FCS. Data from UK respondents were similar: 65% of patients were employed (15% full-time). Of the UK patients who worked part-time or were unemployed, 80% said that FCS had an impact on their employment status, and 90% said it impacted their choice of career (Soran et al., 2018).

The symptoms of FCS can limit patients' ability to train for or perform work in their preferred career, and patients find that they may miss out on promotion because of frequent absences from work (Gelrud et al., 2017). Patients report that fatigue and an inability to concentrate limit performance at work (Gelrud et al., 2017).

Relationships and social life

Patients' social lives can be limited by fatigue and dietary considerations (Davidson et al., 2018, Gelrud et al., 2017). This also has an impact on carers, with some finding it hard to adjust to a reduced social life (Gelrud et al., 2017). Friends and family may not always understand the seriousness of FCS, which can be difficult for the patient (Gelrud et al., 2017).

Impact of restricted diet

Following a strict low-fat diet places a burden on patients in terms of the time required to research and prepare fat-free meals, and the cost of buying fat-free food (Gelrud et al., 2017). There is also a considerable psychosocial burden as a result of following a strict low-fat diet. Patients report that they find it difficult to comply with their diet, particularly when not at home, that their satisfaction with the diet is low, and that it causes anxiety for both themselves and their carers. Having to comply with a strict diet also limits socialization and affects other members of the household who have no such dietary restrictions.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

The introduction of volanesorsen will have a considerable impact on patients, their families and carers. The current standard of care (strict restriction of dietary fat) is largely ineffective, leaving patients with dangerously-elevated TG levels (Blom et al., 2018, Stroes et al., 2017). The studies described in Section 9 showed that patients treated with volanesorsen experienced robust and sustained reductions in TG levels. In many patients, TG levels fell below thresholds that are known to be associated with an increased risk of pancreatitis.

Reductions in TGs translated into benefit in terms of reductions in the incidence of acute pancreatitis and the intensity and frequency of abdominal pain. Both of these comorbidities have a considerable impact on patients' QoL. Volanesorsen is therefore expected to not only improve patients' physical wellbeing by reducing the number of episodes of pancreatitis and abdominal pain, but also their emotional wellbeing (and that of their families

and carers) by reducing the anxiety and uncertainty caused by the prospect of experiencing these events.

In addition, reducing the frequency of acute pancreatitis and abdominal pain should reduce the number of associated hospitalisations and time lost from work, which will remove some of the restrictions that FCS patients feel in terms of employment prospects and in their reduced ability to contribute to the family income.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are currently no NICE, NHS England or other national guidelines for the treatment of FCS. As described in Section 6.1, a clinical diagnostic scoring system has recently been developed that is sensitive enough to discriminate between FCS and multifactorial chylomicronaemia (Moulin et al., in press).

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

There is currently no indicated treatment for FCS nor a definitive pathway of care. Most patients are currently managed in a small number of lipid clinics, mainly in tertiary referral centres in Birmingham, the Midlands, Manchester and London. Management requires specialist services (a consultant-led service plus dietician and nurse support). Patients may also need to access other NHS services to receive treatment for complications of FCS, such as abdominal pain and acute pancreatitis.

The current standard of care is strict restriction of dietary fat intake together with lifestyle changes, such as avoidance of alcohol. Potential secondary

causes of hypertriglyceridemia (such as obesity, diabetes and use of certain medications) also need to be avoided. Volanesorsen will be used alongside dietary control, not as an alternative to it.

Some patients may receive lipid-lowering drugs (including fibrates and statins). However, these are generally ineffective (Brahm and Hegele, 2015, Brisson et al., 2010, McCrindle et al., 2007). The risk of severe symptoms, such as pancreatitis, remains high, even in patients with FCS who receive lipid-lowering drugs (Ahmad and Wilson, 2014).

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Diet alone is not sufficient to reduce the risk of acute pancreatitis (Bruno, 2010, Gaudet et al., 2010, Stroes et al., 2017), and TG levels are difficult to control, even in those patients who manage to adhere to the low-fat regimen (Brisson et al 2010). The recommended fat intake for patients with FCS is approximately 10 to 15 g/day (Valdivielso et al., 2014), which is equivalent to around one tablespoon of olive oil. Patients find this regimen hard to adhere to and need close monitoring by a dietician or nutritionist, with regular assessment of their lipid profiles. However, access to expert dietary advice is limited outside the secondary/tertiary care setting, with only a few centres having access routinely to dieticians and nutritionists. Due to the rarity of FCS, only a limited number of clinicians in England (outside of the specialist centres) have had the opportunity to develop sufficient expertise to adequately manage patients with FCS, and to oversee the clinical aspects of introducing a novel class of therapy such as volanesorsen to the small patient cohort in England. In addition, FCS is associated with many comorbidities, and affected patients frequently require access to other NHS services. Optimal multi-disciplinary management of FCS patients is therefore likely to be only available in a few expert centres. This, in addition to the lack of a national clinical guideline for FCS, is likely to result in geographic variations of clinical practice. Support and training on injection technique, monitoring requirements and use of volanesorsen will be provided to specialist centres by the UK

Akcea medical team. [redacted]

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Volanesorsen is expected to be used in patients with a confirmed diagnosis of FCS, as an adjunct to low-fat diet and not as an alternative treatment. As described in Section 8.7, patients receiving volanesorsen will require regular platelet monitoring and training on how to self-administer the drug, and [redacted]

Due to the uncertainty about current best practice highlighted in Section 8.3, we would anticipate that volanesorsen is prescribed and patients are monitored by clinicians with an expertise in FCS, via a nationally commissioned service.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

With no licensed treatment currently available for FCS and strict dietary control having only a limited effect on reducing the significant burden that the condition constitutes for patients, including the lifelong risk of pancreatitis, the unmet need in the FCS patient population remains high. Volanesorsen is an innovative medical intervention that has demonstrated a significant and sustainable TG lowering effect, reduction of pancreatitis events, and decrease in both frequency and intensity of abdominal pain in FCS patients. It is therefore the first technology that has the potential to significantly alleviate the negative impact of FCS on physical, psychosocial, cognitive, and economic aspects of patients' lives. Akcea therefore considers volanesorsen to be a step-change in the treatment of FCS.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

At an advisory board held by Akcea, there was a consensus that a networked (hub and spoke) service would be the best way to provide adequate disease management and long-term patient support (including dietetic and specialist nurse services), without the need to significantly increase capacity and resource utilisation at specialist centres.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Monitoring

Volanesorsen is associated with reductions in platelet count in some patients with FCS, which may result in thrombocytopenia. Patients with FCS may also experience intermittent thrombocytopenia as part of the natural disease and in the absence of any therapy. Careful monitoring for thrombocytopenia is therefore important during treatment. Before starting treatment, patients should have a platelet count to establish a pre-treatment baseline (volanesorsen should not be initiated in patients with a platelet count <140,000/mm^3). Once treatment has started, platelet counts should be carried out every 2 weeks. Table B1 shows the recommended dosing and monitoring adjustments for patients who experience a reduction in platelet count.

Table B1 Recommended dosing and monitoring adjustments following reduction in platelet count

[redacted]			

Source: Volanesorsen draft SmPC

[redacted]

Administration

There will be a requirement to educate patients in best practice for self-administration- and rotation of injection sites. [redacted]

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

To ensure effective delivery of care, a formally-established consultant-led service, anchored around specialist centres with dietician and specialist nurse support, is needed. As described in Section 8.6, a networked (hub and spoke) service would be the best way to provide this without the need to significantly increase capacity and resource utilisation. As described in Section 8.7, there

is a need to educate patients in self-administration and a need for regular platelet monitoring. [redacted]

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

The introduction of volanesorsen has the potential to reduce the number of accident and emergency visits and hospital admissions due to abdominal pain and acute pancreatitis. There is also the potential that utilisation of other services (e.g. blood tests, surgery) related to treatment of other comorbidities and complications of FCS (such as pancreatic dysfunction leading to diabetes and malabsorption) will be reduced.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

Akcea conducted a systematic literature review of the published English language literature to identify and summarise outcomes related to the treatment of FCS. Searches were conducted in the following databases to identify literature published from database inception to February 2018: MEDLINE (via Ovid), Embase, the Cochrane National Health Service Economic Evaluation Database (NHS EED), the Cochrane Health Technology Assessment (HTA) Database, the Database of Abstracts of Reviews of Effects (DARE). The search strategy used is presented in Appendix 1.

The literature search was broad in scope to include all the interventions for FCS. Studies which did not involve the patient population specified in the scope were subsequently excluded after reading the abstract and title (level 1 screening) and reading the full text (level 2 screening).

In addition, reference lists of all accepted studies, and all relevant systematic reviews, meta-analyses were screened manually to identify any relevant

studies that were not identified using the above electronic search strategy. Moreover, grey literature (material that not published in peer-reviewed or indexed medical journals) was also searched for relevant conference abstracts and posters reporting interventional or observational studies in FCS.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Publication database searches were supplemented with unpublished data from completed and ongoing Akcea studies of volanesorsen. In addition to Ovid and EMBASE searches for published literature relevant to the decision problem and relevant to the NICE scope, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), the UK Clinical Trials Gateway, the EU Clinical Trials Register, and the World Health Organization International Clinical Trials Registry Platform were searched from inception to February 2018. Search terms used were: familial chylomicronaemia syndrome. Details of the search strategy used are presented in Appendix 1.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for published studies

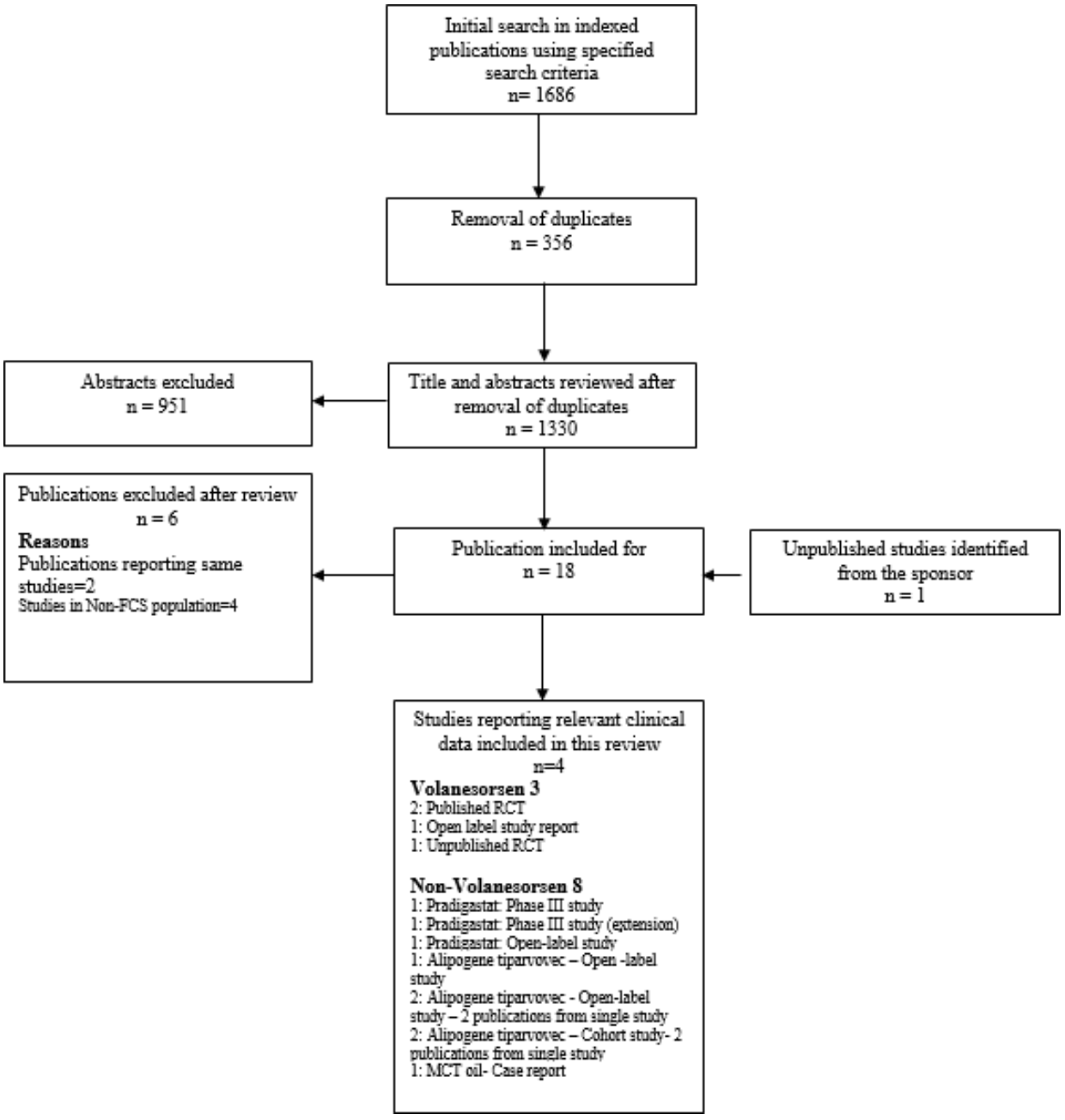
Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

As FCS is extremely rare, we included all sources of information (including case-reports and case-series) in our literature search.

The result of the search and subsequent screening is shown in Figure 8. No relevant clinical studies were identified other than the core studies comprising the volanesorsen clinical programme. Information on other clinical studies involving other potential treatment options for FCS are summarised from the available literature to provide context. Sections 9.3 to 9.7 include information from the volanesorsen clinical programme only.

Figure 8 PRISMA diagram of clinical studies



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

One unpublished study was identified from the sponsor – the APPROACH clinical trial, which has yet to be published in full. No unpublished studies were excluded from the SLR.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

The comparators in the scope are broadly defined as “Established clinical management without volanesorsen (including dietary fat restrictions)”. Aside from the APPROACH study and a smaller number of patients in the COMPASS study, there are no other clinical studies that we believe to be relevant to the decision problem. Given the paucity of clinical data, we provide an overview of all the potentially relevant clinical studies that were identified in searches. In particular we have listed all studies that have investigated technologies in FCS. These studies are included in Tables C3 and C4 but are not discussed further as they either do not compare with volanesorsen, and/or they investigate technologies that are not currently available as a treatment for FCS and so cannot be considered as appropriate comparators.

Table C3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
1. Gaudet, et al. Targeting APOC3 in the familial chylomicronemia syndrome. N Engl J Med. 2014 Dec 4;371(23):2200-6. doi: 10.1056/NEJMoa1400284		Patients with the familial chylomicronaemia syndrome and LPL deficiency (Open – label trial)	285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection	None
2. Gaudet et al. The APPROACH study: a randomized, double-blind, placebo-controlled, phase 3 study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome (FCS). J Clin Lipidol 2017;11 (3):814-5.	The APPROACH study NCT02211209	FCS patients with fasting triglycerides >=8.4 mmol/L (>=750 mg/dL)	Participants were randomised 1:1 to 52 weeks of weekly subcutaneous volanesorsen (285 mg) or placebo	Placebo
3. Gouni-Berthold et al. Apolipoprotein C-III inhibition with volanesorsen in patients with hypertriglyceridemia (COMPASS): A randomized, double-blind, placebo-controlled trial. J Clin Lipidol 2017;11 (3):794-5).	The COMPASS study NCT02300233	Patients with Hypertriglyceridemia including FCS with fasting triglycerides +/- 500 mg/dL	Patients were randomised 2:1 to receive 285 mg volanesorsen SC once a week or placebo, respectively for 26 weeks.	Placebo

Table C4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
The APPROACH open label study: a study of volanesorsen (formerly IONIS-APOCIIIRx) in patients with familial chylomicronaemia syndrome	The Approach Open Label Study (APPROACH OLE) NCT02658175	Patients with FCS	Volanesorsen (IONIS 304801) 285 mg administered subcutaneously to patients with familial chylomicronaemia Syndrome (FCS)	None (open label) (Phase 3 study)

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

See Section 9.3.1 for the reasons for excluding studies that have investigated technologies in FCS. Table C5 lists these excluded studies.

Table C5 List of excluded (published) studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Rouis M, Dugi KA, Previato L, et al. Therapeutic Response to Medium-Chain Triglycerides and ω-3 Fatty Acids in a Patient With the Familial Chylomicronemia Syndrome Arteriosclerosis, Thrombosis, and Vascular Biology. 1997;17:1400-1406		8-year-old black female patient (case report)	(15 to 30 g/d) of an MCT oil - containing diet or (15 to 30 g/d) of an MCT oil–containing diet	None	Triglyceride levels Abdominal pain
Stroes ES, Nierman MC, Meulenberg JJ, et al. Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients. Arterioscler Thromb Vasc Biol. 2008 Dec; 28(12):2303-4.	CT-AMT-010-01	8 LPL-deficient patients (open - label)	LPLS447X-adeno-associated virus subtype 1(AAV1) vector injected in the leg musculature at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight (40 and 60 injections of 500 microliters, respectively)	None	Reduction in individual median fasting plasma TG
Mingozzi F, Meulenberg JJ, Hui DJ, et al. AAV-1–mediated gene transfer to skeletal muscle in humans results in dose-dependent activation of capsid-specific T cells. Blood. 2009;114(10):2077-2086		8 LPL-deficient subjects with missense mutations in both LPL alleles (Cohort study)	Intramuscular administration of the AAV-1 vector encoding LPL (AAV-1-LPLS447X) at a dose of 10^{11} gc/kg (n=4) and 3×10^{11} gc/kg (n=4).	None	Immune response (B- and T-cell responses) to both vector capsid and transgene product

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Carpentier AC, Frisch F, Labbe SM, et al. Effect of Alipogene Tiparvovec (AAV1-LPLS447X) on Postprandial Chylomicron Metabolism in Lipoprotein Lipase-Deficient Patients, The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 5, 1 May 2012, Pages 1635–1644,	CT-AMT-011-02	5 LPLD subjects (Open-label trial)	1×10^{12} genome copies (gc)/kg	None	Triglyceride (TG) content of the chylomicron fraction Chylomicron-TG/total plasma TG ratio
Gaudet D, Méthot J, Déry S, et al. Efficacy and long term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open label trial. Gene Therapy. 2013;20(4):361-369. doi:10.1038/gt.2012.43.	CT-AMT-011-01 (ClinicalTrials.gov NCT01109498)	14 adult LPLD patients (Open-label trial)	Cohorts 1 (n=2) and 2 (n=4) received 3×10^{11} gc/kg, and cohort 3 (n=8) received 1×10^{12} gc/kg. Cohorts 2 and 3 also received immunosuppressants from the time of alipogene tiparvovec administration and continued for 12 weeks	None	Long-term safety of alipogene tiparvovec Reduction in fasting median plasma triglyceride
Ferreira V, Twisk J, Kwikkers K, et al. Immune Responses to Intramuscular Administration of Alipogene Tiparvovec (AAV1-LPLS447X) in a Phase II Clinical Trial of Lipoprotein Lipase Deficiency Gene Therapy. Human Gene Therapy. 2014;25(3):180-188	CT-AMT-011-02 (ClinicalTrial.gov #CT00891306)	Five subjects with LPL deficiency (Open-label trial)	1×10^{12} gc/kg alipogene tiparvovec administered intramuscularly	None	Impact of systemic and local immune responses against AAV1 on safety and the persistence of LPL transgene expression.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Meyers CD, Tremblay K, Amer A, et al. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome. Lipids Health Dis. 2015 Feb 18;14:8	NCT01146522	6 patients with FCS (open-label trial)	Pradigastat orally once daily for three weeks in each of the three periods in a non-randomised sequence at 20 (period 1), 40 (period 2), and 10 mg (period 3) in patients on the low-fat diet.	None	Changes in fasting and postprandial plasma triglycerides
Extension to a Randomized, Double-blind, Placebo Controlled Study of LCQ908 in Subjects With Familial Chylomicronemia Syndrome. Novartis Pharmaceuticals (ClinicalTrials.gov)	NCT01589237 CLCQ908B2305 2012-000802-32 (EudraCT Number)	Subjects with FCS	Patients initiated on LCQ908 at 10 mg/day. After at least 8 weeks of treatment with a dose, optional up-titration to the next possible dose will be allowed. One down titration allowed from the highest dose attained.	Placebo (Phase 3 study)	Adverse events, serious adverse events and death Changes from baseline in triglyceride, cholesterol HDL and non HDL cholesterol, free fatty acids, apolipoprotein A1, B-48 and B-100 levels up to 52 weeks
A Randomized, Double-blind, Placebo Controlled Study to Assess Efficacy, Safety and Tolerability of LCQ908 in Subjects With Familial Chylomicronemia Syndrome Novartis Pharmaceuticals (ClinicalTrials.gov)	NCT01514461 CLCQ908B2302 2011-005535-68 (EudraCT Number)	Subjects with FCS	Patients were randomised (1:1:1) to receive once daily oral pradigastat, 20 mg, 40 mg or placebo. An optional down titration was allowed for safety and tolerability reasons after week 12.	Placebo (Phase 3 study)	Percent change in fasting triglycerides from baseline to 12 weeks

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using the tables provided as appropriate. A separate table should be completed for each study.

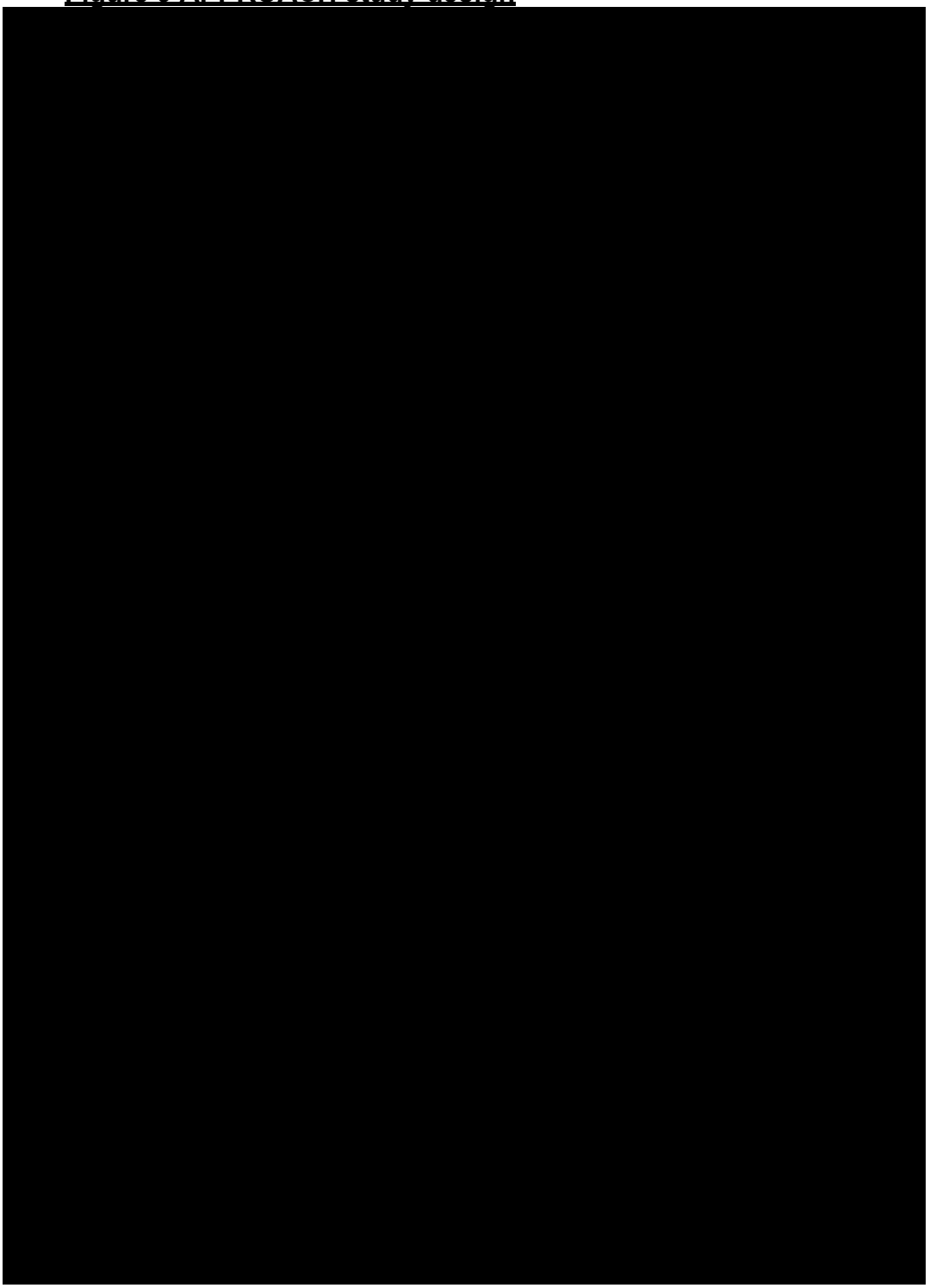
Sections 9.4 to 9.7 describe the methodology and results of the studies from the volanesorsen clinical development programme. The methodology of other studies identified in the literature search is described in Appendix 5.

APPROACH

APPROACH was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 52-week study in patients with FCS. The study design is shown in Figure 9. Briefly, the study consisted of three periods:

- Screening: up to 8 weeks, including a 6-week diet stabilization period. Baseline assessments were performed in the final 2 weeks of the screening period
- Treatment period: 52 weeks
- Follow-up: 13 weeks **or** entry into APPROACH OLE

Figure 9 APPROACH study design



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C6 summarises the study methodology.

Table C6 Summary of methodology for APPROACH

Study name	**The APPROACH Study: a randomised, double-blind, placebo-controlled, phase 3 study of ISIS 304801 administered subcutaneously to patients with familial chylomicronemia syndrome (FCS)**
Objectives	To evaluate the efficacy and safety of volanesorsen administered subcutaneously to patients with FCS
[redacted]	[redacted]
Design	Randomised, double-blind, placebo-controlled study
Duration of study	• Screening/diet stabilization: 8 weeks • Treatment: 52 weeks • Follow-up: 13 weeks
Sample size	66 patients
Key inclusion criteria	• ≥18 years of age • Diagnosis of FCS by documentation of at least one of: (a) Confirmed homozygote, compound heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1) or (b) Post heparin plasma LPL activity of ≤20% of normal • Fasting TG ≥750 mg/dL (8.4 mmol/L) at screening • Documented history of chylomicronaemia • Agreed to follow a diet comprising ≤20 g fat per day • History of pancreatitis (defined as a documented diagnosis of acute pancreatitis or hospitalisation for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made). Patients without a documented history of pancreatitis were also eligible but their enrolment was capped at 28% (i.e. ≤20 of the 70 patients)

Key exclusion criteria	• Diabetes mellitus if newly diagnosed or if HbA1c ≥9.0% • Other types of severe hypertriglyceridemia • Active pancreatitis within 4 weeks of screening • Acute or unstable cardiac ischaemia within 6 months of screening • Major surgery within 3 months of screening • Treatment with Glybera® therapy within 2 years of screening • Previous treatment with volanesorsen • Any other conditions that, in the opinion of the investigator, could interfere with the patient participating in or completing the study
Method of randomisation	1:1, stratified by prior history of pancreatitis and concurrent treatment with fibrates and/or prescription omega-3 fatty acid. Patients were allocated to treatment using an Interactive Voice/Web-Response System.
Method of blinding	Double-blind. Patients and study personnel were blinded until all patients had completed treatment and the database was locked. To maintain the blind, study personnel were not allowed access to any lipid panel results, including apoC-III.
Intervention(s) (n =) and comparator(s) (n =)	Volanesorsen 285 mg, given as a single 1.5 mL subcutaneous injection, once a week (n = 33) Placebo, given as a single 1.5 mL subcutaneous injection, once a week (n = 33)
Baseline differences	None (see Section 9.4.3)
Duration of follow-up, lost to follow-up information	13 weeks. Not all patients entered the 13-week follow-up period, as at the end of the treatment period they could choose to enter the APPROACH OLE instead.

[redacted]	[redacted]
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the percentage change in fasting TG levels between baseline and the end of Month 3. The value at the end of Month 3 was defined as the average of the Week 12 (Day 78) and Week 13 (Day 85) fasting assessments.
[redacted]	[redacted]

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

APPROACH OLE

APPROACH OLE is an ongoing, Phase 3 open-label study in patients with FCS. It includes patients who have previously received volanesorsen in the double-blind APPROACH and COMPASS studies (N.B. only FCS patients), and patients who are treatment naïve (i.e. received placebo in either APPROACH or COMPASS, or did not take part in either of these studies). Figure 10 shows the study design.

Figure 10 APPROACH OLE study design

Table C7 summarises the methodology for APPROACH OLE.

Table C7 Summary of methodology for APPROACH OLE

Study name	**APPROACH OLE: an open-label study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome (FCS)**
Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen administered subcutaneously to patients with FCS
[redacted]	[redacted]
Design	Open-label. Three patient groups are being enrolled: • Group 1: FCS patients rolling over from APPROACH • Group 2: FCS patients rolling over from COMPASS • Group 3: Patients who did not take part in either APPROACH or COMPASS
[redacted]	[redacted]
Key inclusion criteria	• ≥18 years of age • Able and willing to take part in a 65-week study Groups 1 & 2: • Satisfactory completion of APPROACH or COMPASS Groups 2 & 3: • Documented history of chylomicronaemia • Diagnosis of FCS by documentation of the following: confirmed homozygote, compound

	heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1) • Group 2: fasting TG ≥750 mg/dL (8.4 mmol/L) at screening for double-blind APPROACH study • Group 3: fasting TG ≥750 mg/dL at screening for APPROACH OLE
Key exclusion criteria	• Unwilling to comply with lifestyle requirements for the duration of the study Groups 1 & 2: • Any new condition or worsening of existing condition that made the patient unsuitable for participation in the study Group 3: • Diabetes mellitus if newly diagnosed or if HbA1c ≥9.0% • Other types of severe hypertriglyceridemia • Active pancreatitis within 4 weeks of screening • Acute or unstable cardiac ischaemia within 6 months of screening • Major surgery within 3 months of screening • Treatment with Glybera® therapy within 2 years of screening • Previous treatment with volanesorsen • Any other conditions that, in the opinion of the investigator, could interfere with the patient participating in or completing the study
Method of randomisation	N/A: volanesorsen was the only intervention in this study
Method of blinding	N/A: this is an open-label study
Intervention(s) (n =) and comparator(s) (n =)	Volanesorsen 285 mg, given as a single 1.5 mL subcutaneous injection, once a week (n = 29)
[redacted]	[redacted]
Duration of follow-up, lost to follow-up information	13 weeks

Efficacy outcomes (including scoring methods and timings of assessments)	• Percent and absolute change from baseline in fasting TG levels at Months 3, 6 and 12 • Treatment response rates at Months 3, 6 and 12

Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

Data presented in this submission are from two interim analyses of the data. The first, with a cut-off date of 6th January 2017, was carried out for the marketing authorisation application (MAA). Baseline and efficacy outcomes data presented in this submission are derived from this analysis. The second, with a cut-off date of 31st

December 2017 was carried out to address questions form the regulatory authorities. Safety data presented in this submission are derived from this analysis.

COMPASS

COMPASS was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 26-week study in patients with hypertriglyceridemia, including FCS. It comprised 3 study periods:

- Screening: 8 weeks, including a 6-week diet stabilisation period
- Treatment: 26 weeks
- Follow-up: 13 weeks **or** entry into APPROACH OLE

Following screening, patients were randomised 2:1 to SC volanesorsen 285 mg once-weekly or placebo. However, a protocol amendment saw the dose of volanesorsen adjusted to 285 mg every 2 weeks at or after 13 weeks of treatment (patients, who had already received at least 5 months of dosing when this amendment came into effect, were exempt).

As for APPROACH, the primary efficacy outcome was the percent change from baseline in fasting TG levels at Month 3, defined as the average of the Week 12 and Week 13 assessments.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Baseline data from patients enrolled in APPROACH have been published in The Journal of Clinical Lipidology (Blom et al., 2018). Efficacy data were presented at the National Lipid Association 2017 Scientific Sessions and the 85th Annual Congress of the European Atherosclerosis Society 2017 (Gaudet et al., 2017a, Gaudet et al., 2017b). However, unless otherwise stated, all data included in this submission are taken from the clinical study report.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

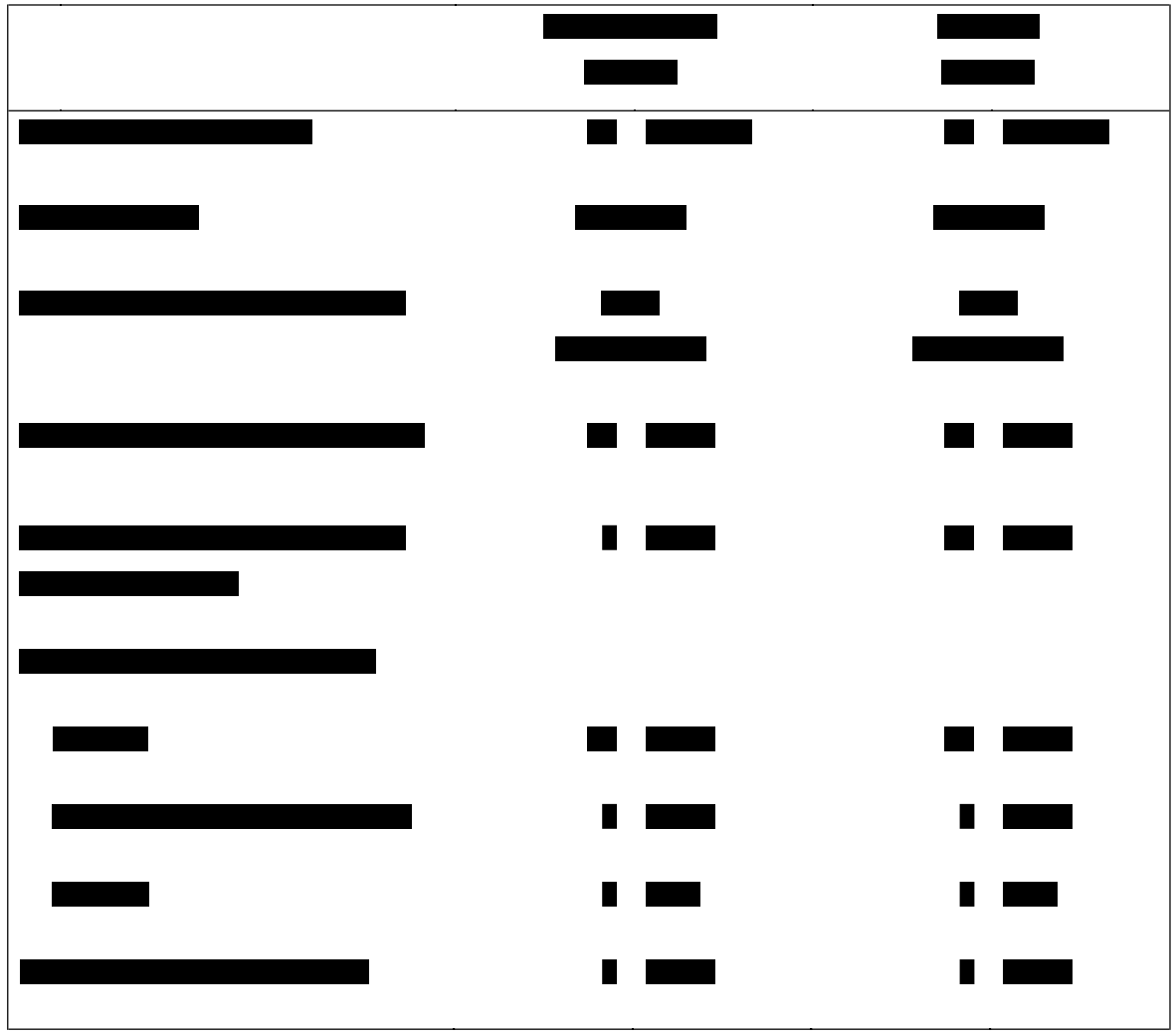
APPROACH was a randomised, double-blind trial that compared volanesorsen with placebo, whereas APPROACH-OLE was an open-label trial in which all patients received volanesorsen. COMPASS was also a randomised double-blind trial that compared volanesorsen with placebo; however the population included patients with various types of hypertriglyceridemia (not just FCS), patient were randomised 2:1 (volanesorsen:placebo) and treatment lasted 26 weeks, not 52. As described in Section 4.1, COMPASS is therefore not considered pivotal to this submission, but provides some supportive evidence in an included subset of patients with FCS (n=7).

Given that all but one of the patients included in APPROACH OLE interim analysis had previously taken part in APPROACH, there were no differences between the patient populations in these two studies. Baseline characteristics and demographics are described below for each study.

APPROACH

There were no differences in baseline characteristics and demographics between the treatment groups in APPROACH (see Table C8).

Table C8 Patient demographics and baseline characteristics in APPROACH

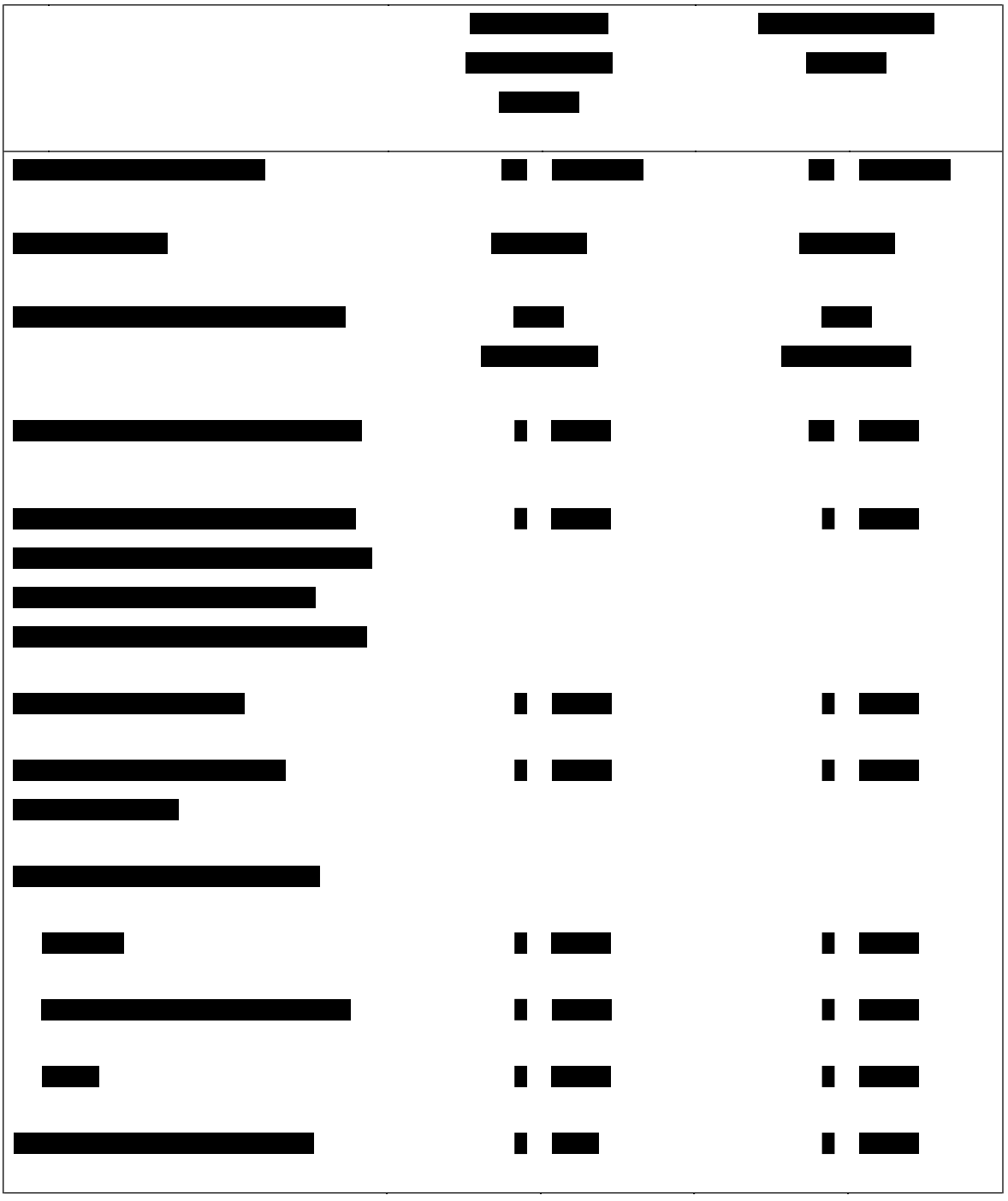


Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

APPROACH OLE (data cut off: 6th January 2017)

Baseline characteristics and demographics were broadly similar between treatment groups (Table C9). As would be expected, patients in the treatment-naïve group had higher TG levels at study entry than those who had previously taken volanesorsen during APPROACH.

Table C9 Patient demographics and baseline characteristics in APPROACH OLE

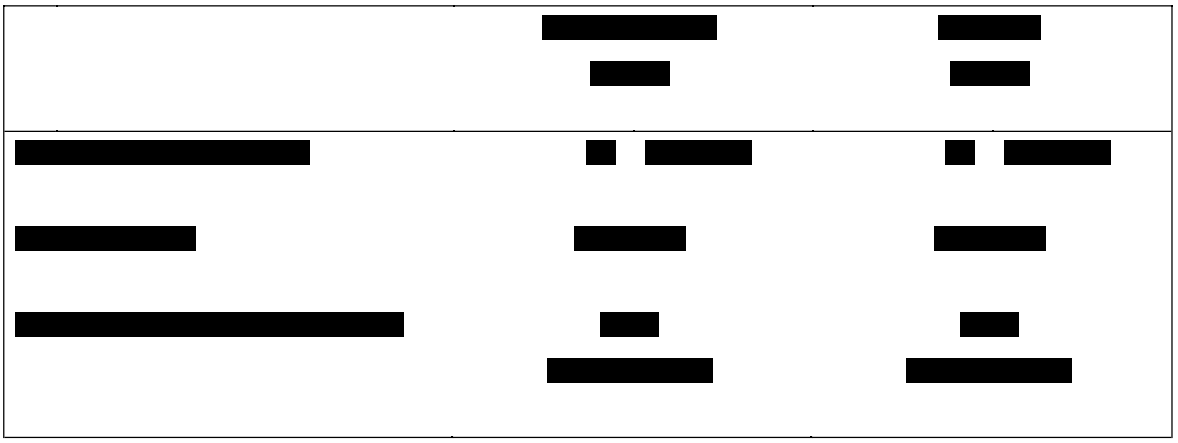


Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

COMPASS

In the subset of patients with FCS, baseline characteristics and demographics were balanced between treatment groups, although there were no male patients in the placebo group (Table C10).

Table C10 Patient demographics and baseline characteristics in COMPASS



TG, triglyceride

Source: COMPASS clinical study report, 2nd June 2017, Akcea data on file

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In APPROACH, the percent change from baseline in TG levels was evaluated by gender, race, age, ethnicity and region. These analyses were pre-planned and were designed to investigate any potential effect of these factors on response to treatment with volanesorsen.

TG data were also analysed for the following subgroups:

- Patients who completed treatment and had a dose adjustment or a pause in dosing
- Patients who completed treatment without dose adjustment or a pause in dosing
- Patients who withdrew early

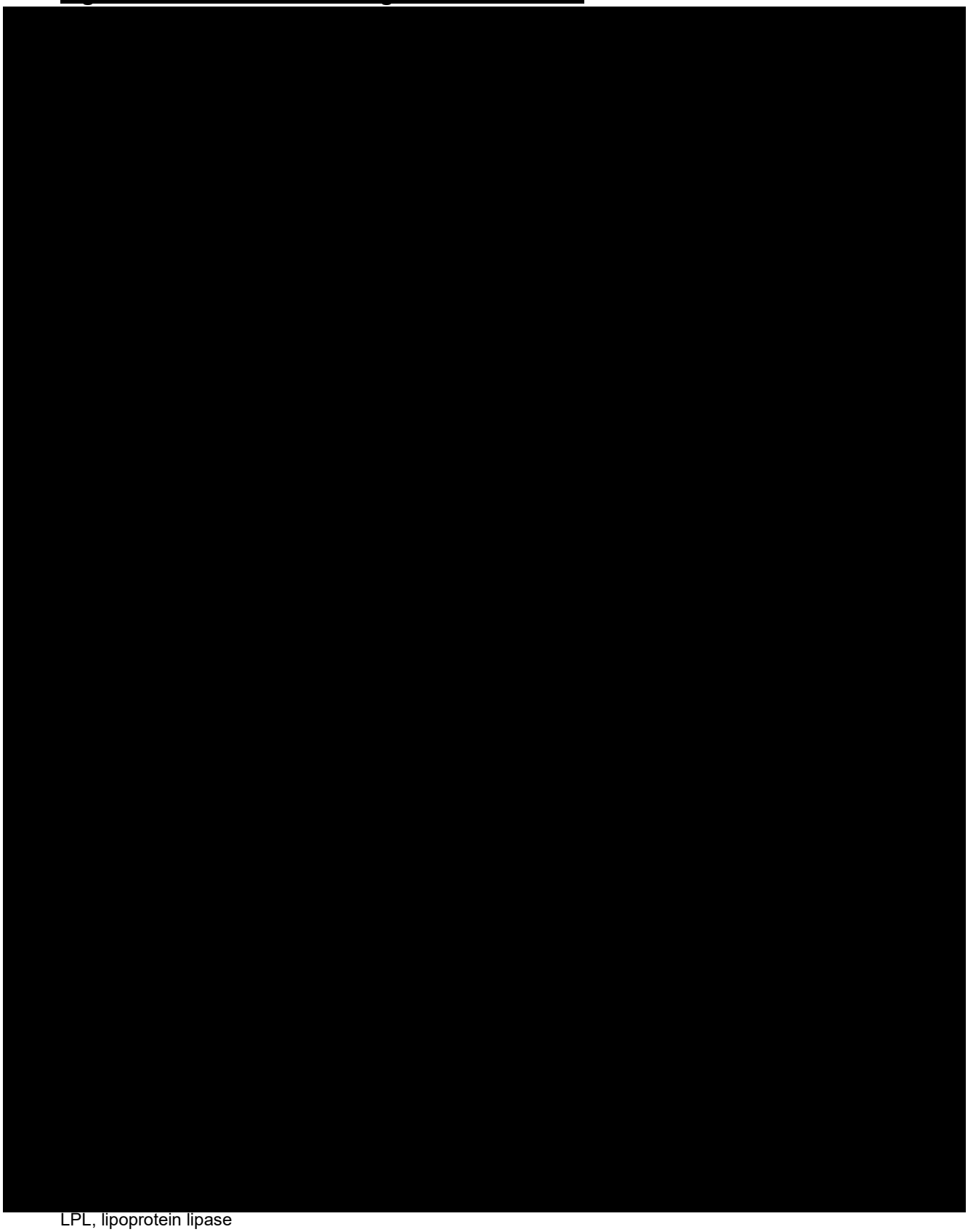
This was a *post-hoc* analysis designed to evaluate the effect of dosing on the primary endpoint.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

APPROACH

Figure 11 shows patient flow in the APPROACH study

Figure 11 CONSORT flow diagram: APPROACH

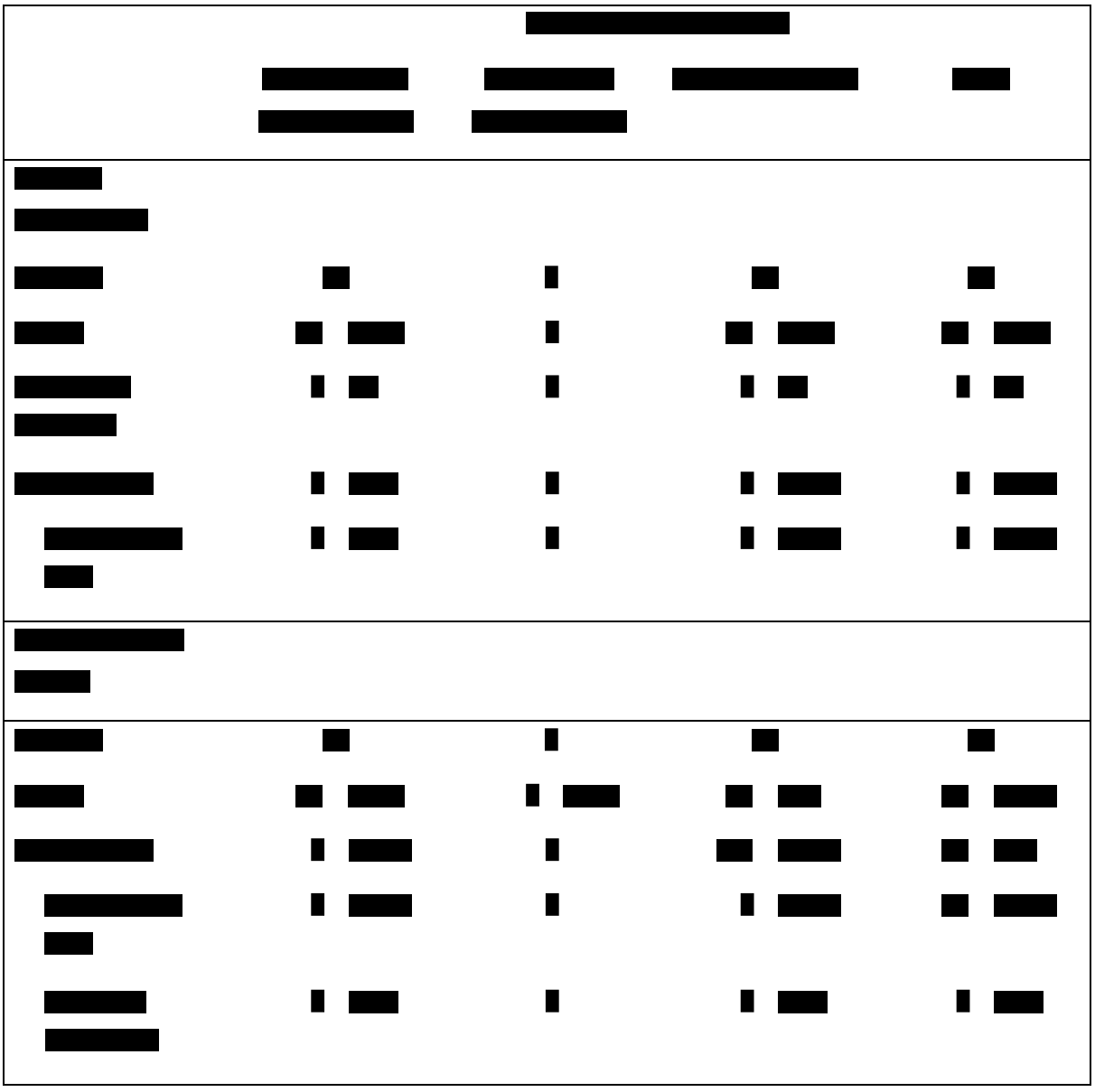


LPL, lipoprotein lipase
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

APPROACH OLE

Table C11 shows the disposition of patients enrolled at the time of the MAA submission (data cut-off 6th January 2017), and at the data cut-off of 31st December 2017.

Table C11 Patient disposition: APPROACH OLE



Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file; Volanesorsen (ISIS 304801) Akcea Therapeutics response to Day 180 questions, Akcea data on file

COMPASS

In total, 7 patients with FCS were enrolled in COMPASS: 5 in the volanesorsen group and 2 in the placebo group. All 7 patients completed study treatment.

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

APPROACH

[redacted]

APPROACH OLE

Details of patients who withdrew from the study are given in Section 9.4.5.

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown below.

APPROACH is the only randomised controlled trial (RCT) relevant to this submission. Table C12 shows a critical appraisal of this study.

Table C12 Critical appraisal of APPROACH

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

The key outcomes for the decision problem (TG levels and acute pancreatitis) were captured within the clinical trials.

APPROACH

The primary hypothesis of APPROACH was that volanesorsen would show superior efficacy over placebo in the treatment of adult patients with FCS. Please refer to Table C6 for a description of the statistical analyses.

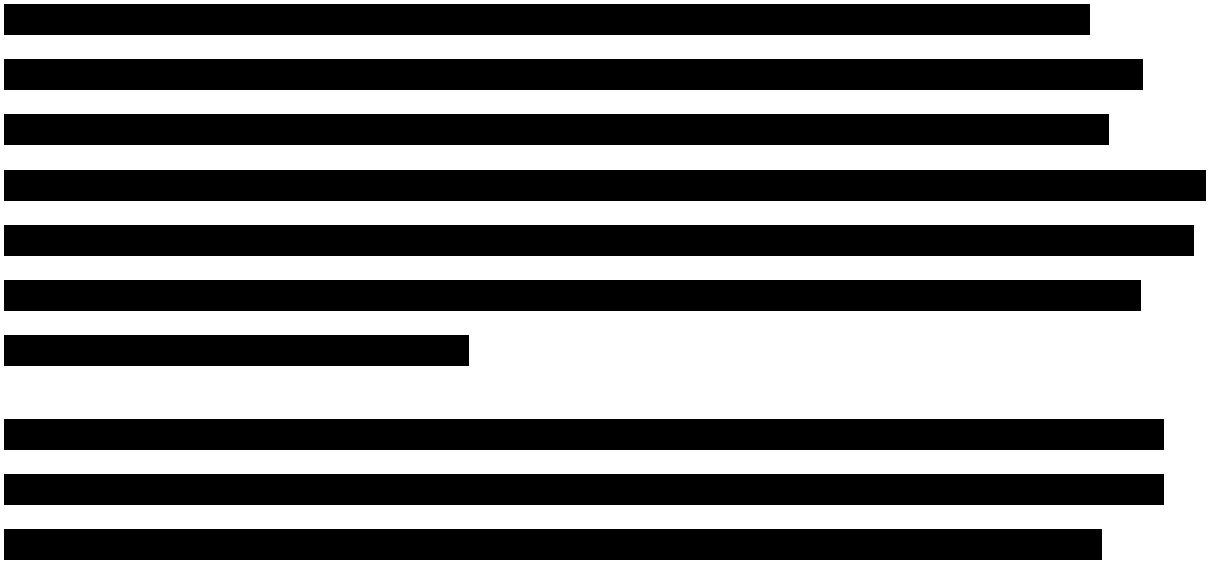
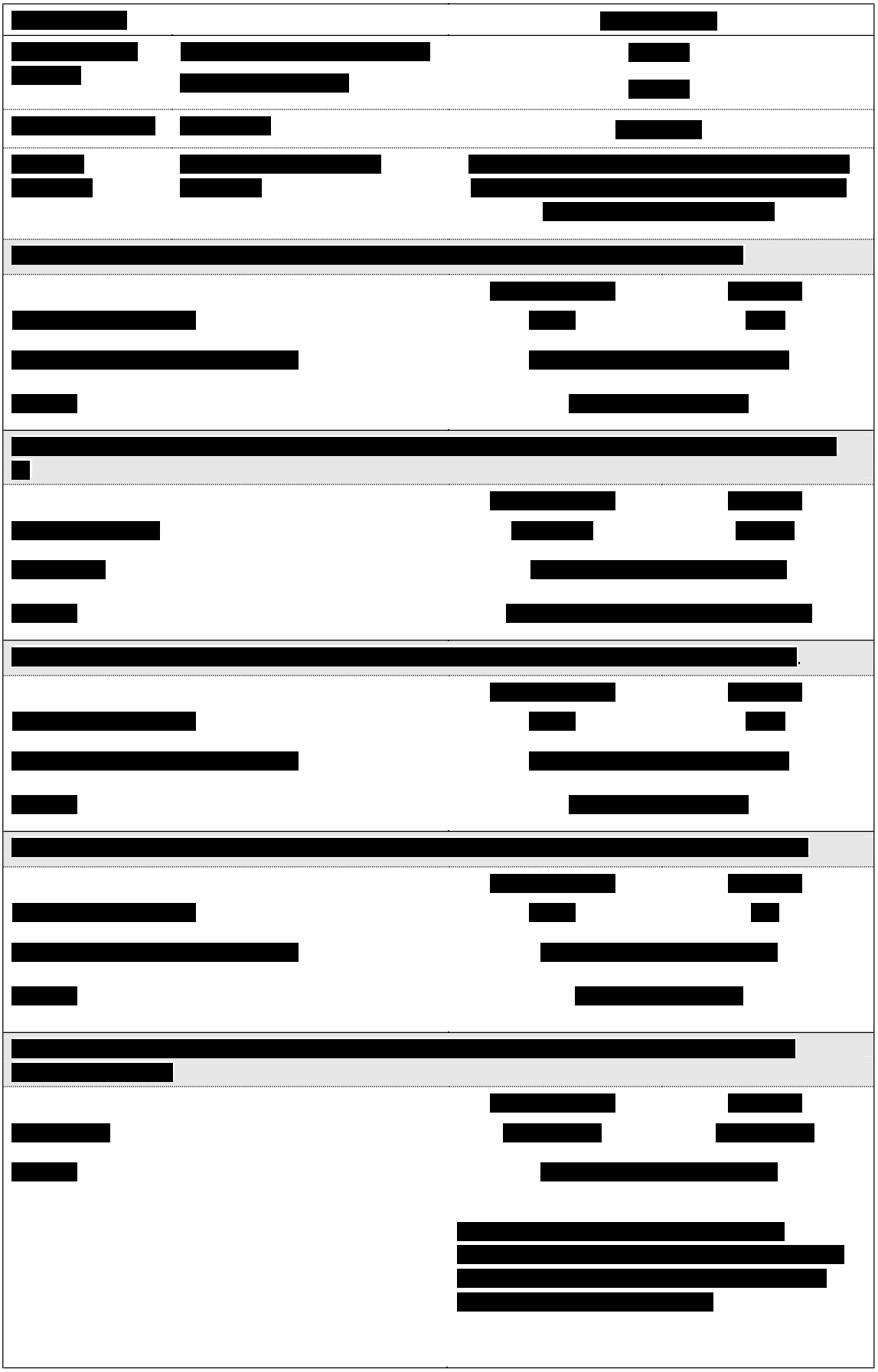
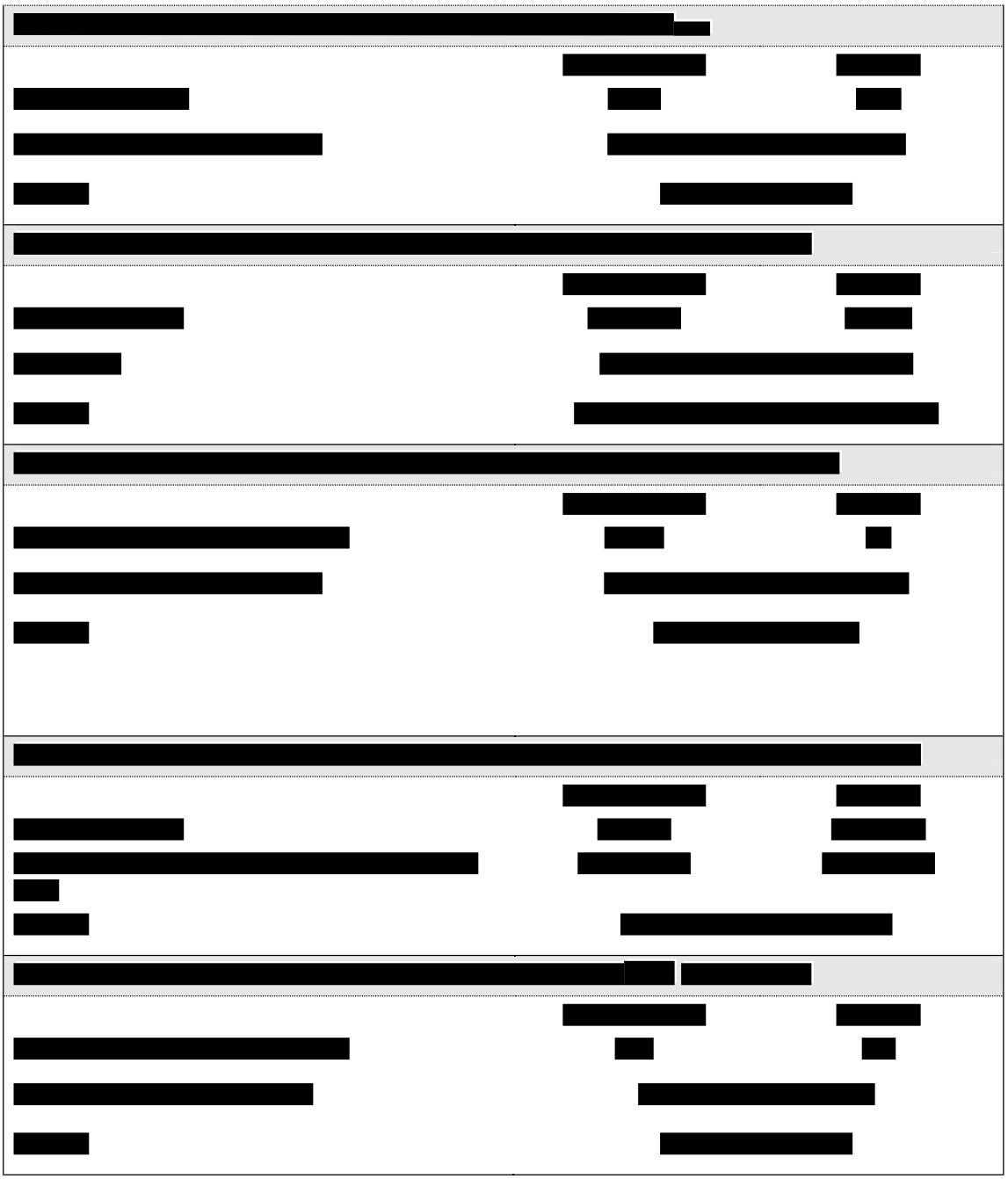


Table C13 Outcomes from APPROACH





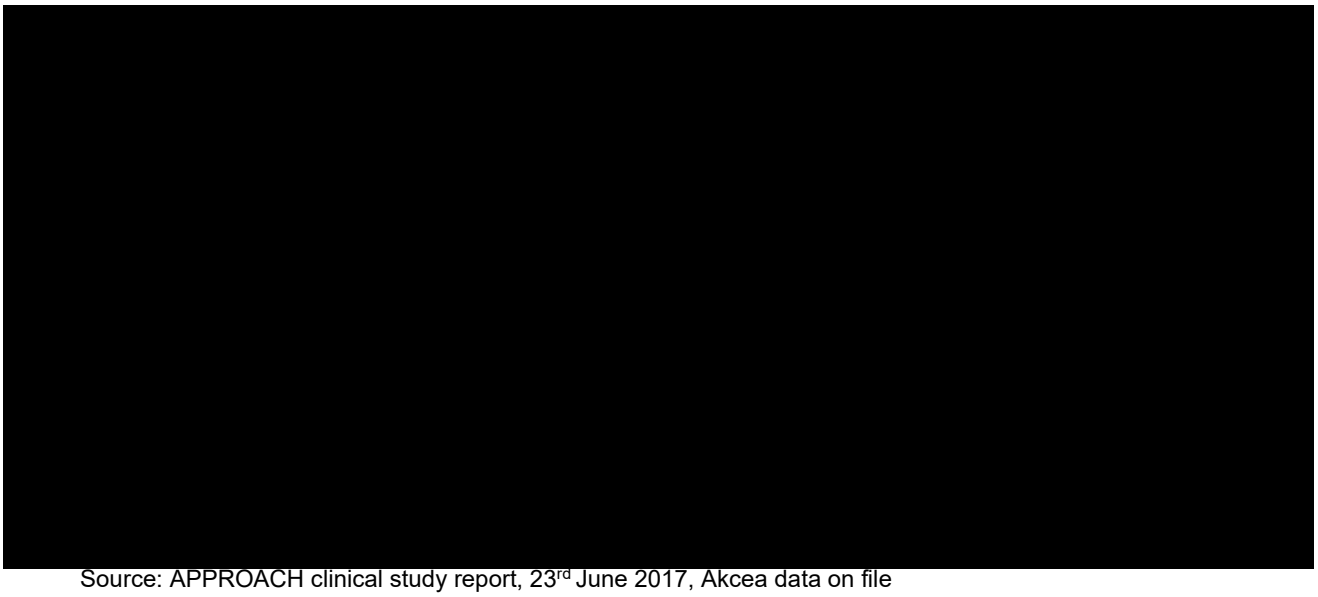
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Effect on TG levels

Volanesorsen-treated patients achieved robust reductions in TG levels. In the volanesorsen group, there was a mean reduction in fasting TG levels of 77% at Month 3, compared with an 18% increase in the placebo group (P<0.0001) (Table

C13).

Figure 12 Waterfall plot of % change in fasting TG levels from baseline to Month 3



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Figure 13 LS mean % change in fasting TG levels to Month 12

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

Impact on quality of life

Health-related quality of life (HRQL) was assessed as an exploratory endpoint in the APPROACH study using the EQ-5D-5L and SF-36 questionnaires. These tools have limited sensitivity to pick up QoL differences in slow-progressing chronic diseases and are therefore not ideal for FCS; however, there is currently no specific, validated QoL tool for FCS. [redacted]

[redacted]

APPROACH OLE (data cut off: 6th January 2017)

[redacted]

Table C14 Outcomes from APPROACH OLE (interim analysis)

[redacted]

[redacted]

Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

[redacted]

[redacted]

Figure 14 Percent change in fasting TG levels over time

[redacted]

[redacted]

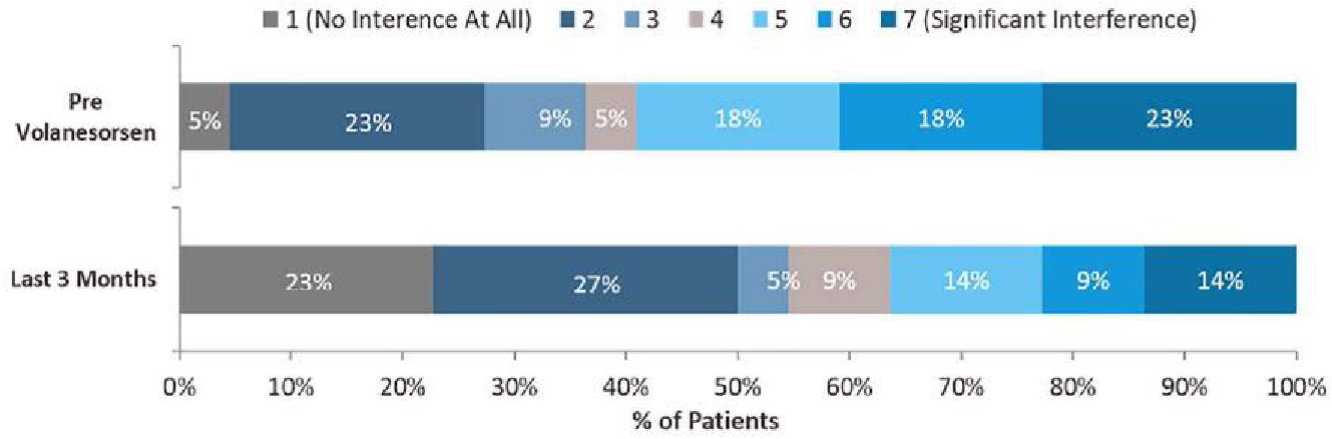
Patients who received volanesorsen for at least 3 months in APPROACH OLE took part in a retrospective web-based survey to assess the burden of disease (Arca et al., 2018). They were asked about their experiences during the 3 months before starting treatment and the most recent 3-month period while on treatment. Twenty-two patients completed the survey.

Overall, patients reported that they believed their FCS was more effectively managed with volanesorsen than with their previous regimen. After volanesorsen treatment, more patients said that strategies for managing their symptoms were effective (40% *vs*. 19% before treatment) and that their symptoms were controlled with adherence to diet (90% *vs.* 55% before treatment).

The mean number of symptoms experienced decreased from 9 before starting volanesorsen to 5 after at least 3 months of treatment. This represents a 44% reduction ($P<0.05$). There were significant decreases from baseline for steatorrhea, pancreatic pain, and constant worry about an attack of pain or acute pancreatitis.

When considering the overall impact of FCS on their lives, the proportion of respondents who reported “no interference” increased from 5% prior to volanesorsen to 23% while on therapy, whereas those reporting a high level of interference (levels 5 to 7 on a 7-point scale) decreased from 59% prior to treatment to 37% while on volanesorsen (Figure 15). Symptoms of FCS had a significantly lower impact on respondents’ lives during volanesorsen treatment, with a 22% reduction in mean score from baseline ($P<0.05$). The proportion of respondents who reported no interference of FCS with work or school increased from 36% before starting volanesorsen to 64% during treatment. In addition, treatment with volanesorsen improved patients’ ability to socialise and engage with others. Patients reported reduced stress over managing diet and less difficulty planning meals while on volanesorsen treatment.

Figure 15 Overall impact of FCS on patients' lives before and during volanesorsen treatment (n = 22)



Source: Arca et al., 2018

Several aspects of emotional and mental well-being, including stress and anxiety, feelings of self-worth, and sleep quality also improved significantly after treatment with volanesorsen.

COMPASS

[redacted]

9.6.2 Justify the inclusion of outcomes in the tables above from any analyses other than intention-to-treat.

N/A. All outcomes in Tables C13 and 14 are presented for the FAS population, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

N/A. There are no studies that were designed to primarily assess safety outcomes.

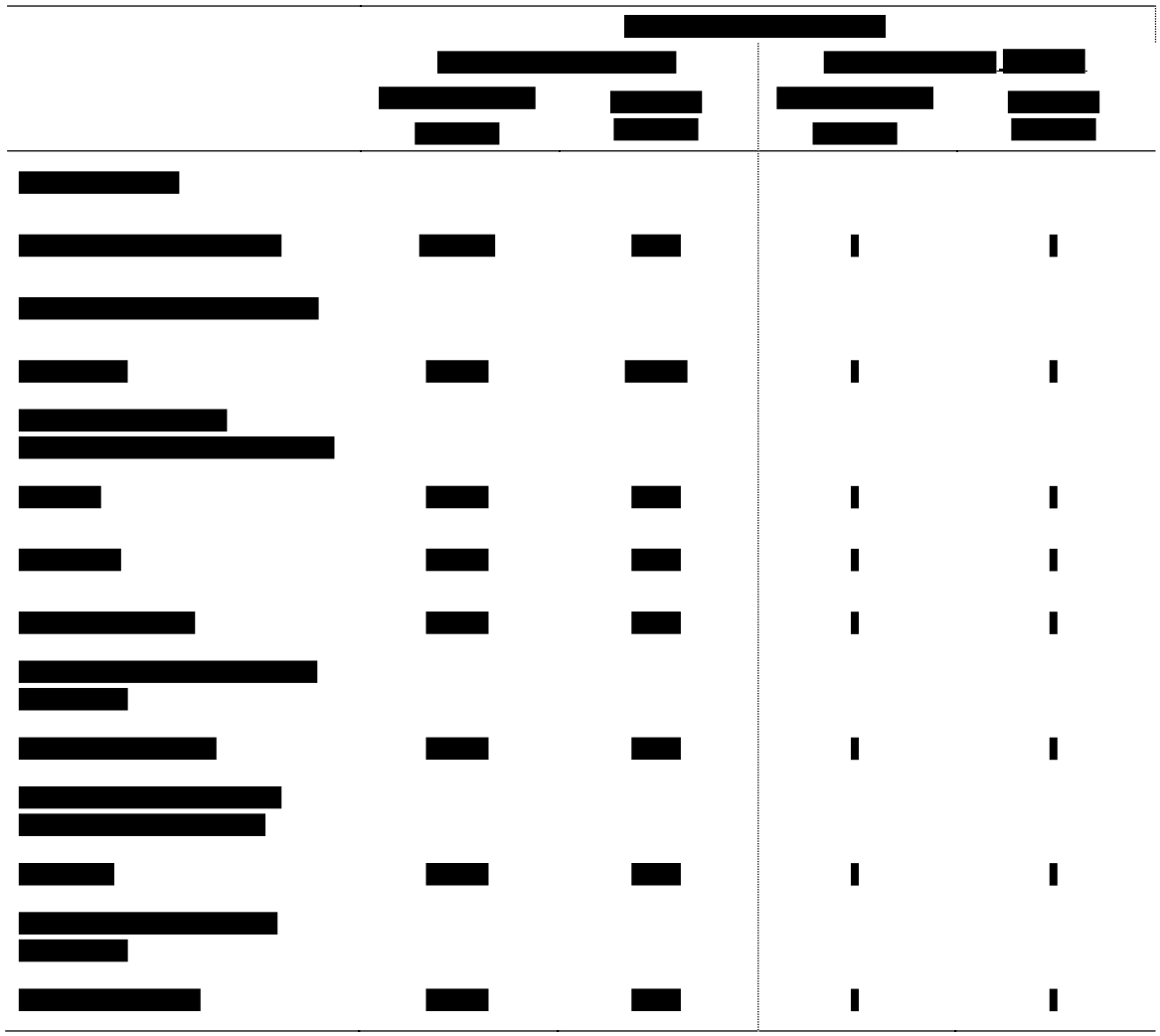
9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown below.

APPROACH

The safety population (i.e. those patients who were randomised and received at least one dose of study drug) included 66 patients (33 in each treatment group). Table C15 shows the treatment-emergent AEs (TEAEs) occurring in >10% of patients in the volanesorsen group. [redacted]

Table C15 Treatment-emergent adverse events across patient groups: APPROACH

[redacted]



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Adapted from European Public Assessment Reports published by the European Medicines Agency

The most common events with volanesorsen were related to local tolerability, i.e. TEAEs at the injection site (see Table C15) or local cutaneous injection site reactions (any cutaneous reaction at the injection site that lasted more than two days). Most were mild and most resolved. One patient discontinued treatment because of a local cutaneous injection site reaction. There were no local cutaneous injection site reactions in the placebo group.

[redacted]

[redacted] The reductions in platelet counts were generally well managed with dose adjustments. Two patients in the volanesorsen group experienced Grade 4 thrombocytopenia (platelet count <25,000/mm^3) and were withdrawn from the study. There were no major or severe bleeding events.

Most TEAEs were mild in severity. [redacted]

[redacted] The most frequent events leading to withdrawal from the study were thrombocytopenia, decreased platelet count and fatigue.

There were no hepatic, renal or cardiac safety signals, and no increase in liver fat. There were no deaths during the study.

[redacted]

APPROACH OLE (data cut: 31 December 2017)

[redacted]

[redacted]

Table C16 Treatment-emergent adverse events across patient groups (excluding reactions at the injection site): APPROACH OLE

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Volanesorsen (ISIS 304801) Akcea Therapeutics response to Day 180 questions, Akcea data on file

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

COMPASS

In COMPASS, only local cutaneous injection site reactions and flu-like reactions were analysed separately for the subset of FCS patients.

[redacted]

[redacted]

[redacted]

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Volanesorsen was generally well tolerated during APPROACH and APPROACH OLE. [redacted]

The most common TEAEs were related to local tolerability at the injection site (as would be expected given the SC administration) and reductions in platelet counts. With appropriate monitoring (i.e. every two weeks), any reduction in platelet counts should be detected in a timely manner and can be managed with dose adjustment.

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

N/A: an indirect treatment comparison is not appropriate.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The studies identified in the SLR comprised:

- Studies of volanesorsen, which have been discussed already within this submission
- Studies of tiparvovec, which has been withdrawn from the UK and is therefore not a relevant comparator as it is not available for use in FCS patients
- Studies of pradigastat, an unlicensed experimental treatment developed by Novartis, which is not a relevant comparator as it is not available for use in FCS patients
- One case report of the use of medium chain triglycerides in an FCS patient

The identified studies do not therefore provide sufficient evidence to justify either quantitative or qualitative evidence syntheses, as the treatments are either unavailable in the UK or were in a single patient.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

Volanesorsen-treated patients in APPROACH achieved a statistically significant reduction in fasting TG levels from baseline that was maintained over the 52-week treatment period. [redacted] These high baseline TG levels clearly show the inefficiency of the current standard of care (as all patients underwent a diet stabilisation period before their baseline measurement during which their fat intake was controlled at <20 g/day) and a lack of response to

conventional lipid lowering therapies (as 49% of patients were receiving fibrates, 20% were receiving statins, and 29% were on other lipid modifying treatments).

The robust percent reduction in TG levels achieved with volanesorsen meant that patients' absolute TG levels fell below important thresholds (Table C17). For example, a TG level ≥750 mg/dL (8.5mmol/L) is associated with TGs being predominantly in chylomicrons; [redacted]

Table C17 Percentage of patients achieving TG levels below clinically important thresholds

[redacted]

[redacted]

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

The significant reductions in TGs translated into important clinical benefits for patients, such as reductions in pancreatitis attacks and the intensity and frequency of abdominal pain. These are events that severely impact patients' daily activities and QoL, and in the case of pancreatitis, can be life-threatening.

Interim data from APPROACH OLE suggest that the reduction in TG levels and associated clinical benefits seen with volanesorsen are sustained over the longer-term.

Considering the safety profile, the rarity and severity of FCS, the unmet need for patients who have no approved effective treatments, and the feasibility of routine platelet monitoring to ensure patient safety, the overall benefit/risk profile of volanesorsen is positive. Volanesorsen has the potential to fulfil a critical unmet need by providing important clinical benefits to patients with FCS.

Discussion on reduced dosing frequency

[redacted]

[redacted]

Platelet counts

Table C18 shows a summary of platelet counts by dose for patients in COMPASS (note that these data are for the overall population, not the subpopulation with FCS). There were no cases of severe thrombocytopenia in this study but there was an approximately 30% reduction in mean platelet count for all patients on volanesorsen 285 mg once-weekly dosing for 13 weeks. As per a protocol amendment, some patients were switched to volanesorsen 285 mg once every 2 weeks. In a comparison of the regimens after 13 weeks of treatment, the mean platelet count continued to decrease past Week 13 in those on weekly treatment compared to a stabilisation, or slight trend toward recovery, for those patients receiving volanesorsen every 2 weeks.

Table C18 Summary of platelet counts by dose in COMPASS

[redacted]

[redacted]

[redacted]

Table C19 Exposure-adjusted discontinuations with or without dose adjustment (APPROACH OLE)

	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Figure 16 Percentage of treatment-naive patients remaining on treatment in APPROACH and APPROACH OLE

Table C20 shows a summary of dose interruptions and reductions for all patients in APPROACH, APPROACH OLE and COMPASS.

[redacted]

Table C20 Dose interruptions/reductions in APPROACH, APPROACH OLE and COMPASS (APPROACH OLE)

	[redacted]		[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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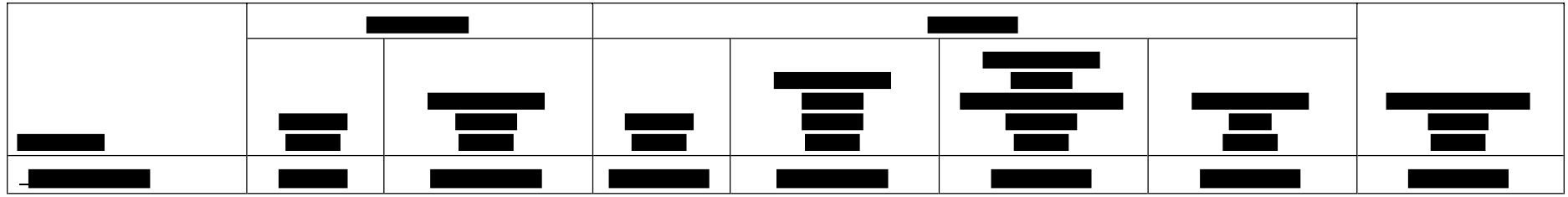

[redacted]

A population PK/PD model-based simulation was used to predict percent change in TG with the proposed dosing regimen [redacted]

Table C21 Predicted TG and percent change in TG from baseline with once every 2 weeks dosing regimen by body weight

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

Although 285 mg once-weekly is predicted to provide the highest TG reduction, 285 mg every 2 weeks can serve as an adequate therapeutic dose: the predicted level of TG reduction is expected to result in a reduction in pancreatitis, given the relationship between TG levels and risk of pancreatitis.

[redacted]

To address the effect of dose pauses or dose adjustment on safety data, treatment emergent AEs for study completers were summarised. Table C22 shows the number and type of AEs with and without dose adjustment or pause.

[redacted] Overall, it appears that common AEs experienced with volanesorsen treatment may occur in fewer patients with dose pause or adjustment.

Table C22 TEAEs occurring in ≥10% of patients by dose pause/adjustment in APPROACH

[redacted]	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]						

[redacted]

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

APPROACH was a randomised, controlled trial in the patient population under consideration. It included more than 60 patients from across the world, which is remarkable considering that FCS is an ultra-rare disease. The trial results (in terms of the benefits offered by volanesorsen) are impressive and unprecedented in this patient population. The significant decrease in TGs observed in response to volanesorsen translated to a decreased risk of acute pancreatitis and abdominal pain. In turn, it is anticipated that this would result in improved QoL for both patients and their families.

The study included clinically relevant endpoints. Reductions in acute pancreatitis and abdominal pain are particularly important to patients as they are extremely debilitating manifestations of the disease.

Limitations

In the studies in the clinical development program, the initial dose of volanesorsen was 285 mg once-weekly. [redacted]

APPROACH was not powered to detect differences in patients' HRQL; this was only included as an exploratory endpoint. There is currently no specific, validated QoL tool for FCS. Tools such as the EQ-5D and SF-36 have limited sensitivity to pick up QoL differences in slow-progressing chronic diseases and are therefore not ideal for FCS. The vignette study, provided as an appendix and described in more detail in Section 10.1.9, provides supporting evidence with regard to the expected impact of FCS and acute pancreatitis episodes on HRQL (Akcea data on file, 2018b).

When enrolling patients with a rare disease in clinical studies there are inherent restrictions on potential sample size, study design and respondent recruitment options. For example, to be eligible for ReFOCUS, patients had to have received at least one dose of volanesorsen during APPROACH-OLE. This limited the sample size to 22 respondents (representing 6 of the 12 countries that participated in APPROACH); the low sample size necessitated a retrospective pre-/post-treatment study design. The potential influence of recall bias in patient reported outcomes, particularly the risk of overstating the efficacy in the context of a new treatment option being offered for an underserved population and/or misremembering their symptoms, must also be considered. To mitigate this effect in ReFOCUS, survey responses were gathered several months following volanesorsen initiation (median time on therapy of 222 days) and from respondents from both arms of APPROACH who entered APPROACH OLE. However, given that FCS is a chronic disease that patients in APPROACH had lived with for many years, respondents were likely to accurately recall their symptoms and life experiences from the period before initiating volanesorsen.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical evidence base described in this submission is derived principally from the APPROACH clinical trial. Data from APPROACH are centrally relevant to the scope for this appraisal, capturing evidence on TG reduction,

acute pancreatitis episodes, and rates of important AEs such as thrombocytopenia, all of which feature in the final scope.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

In APPROACH, 76% of patients reported ≥1 lifetime episode of acute pancreatitis. By way of comparison, it is estimated that approximately 65 – 80% of patients with FCS will experience acute pancreatitis (Blom et al., 2018, Gaudet et al., 2016), indicating that the population enrolled in APPROACH are relatively experienced compared with an overall population of FCS patients.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

No criteria beyond the clinical diagnosis of FCS are required to select patients who are likely to benefit from treatment with volanesorsen.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

The impact of FCS on patients' quality of life is described in Section 7.1.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

There is a lack of evidence in the literature with regard to HRQL for FCS patients and no validated, disease specific instruments are currently available. The IN-FOCUS study (Davidson et al., 2018) provides considerable insight into the impact of physical, cognitive and emotional symptoms in patients with FCS. It also explores the impact of comorbidities such as acute pancreatitis (AP), diabetes and chronic pancreatitis (CP).

It seems reasonable to postulate that HRQL in FCS patients might correlate with pancreatitis history, with HRQL declining over time as patients experience repeated episodes of AP. The literature on HRQL in AP is limited. However, a review on QoL after AP (Pendharkar et al., 2014) found that QoL tends to decline following AP. Concerns were noted by the authors regarding the lack of a specific QoL instrument for AP and the use of generic instruments, such as the SF-36, that were intended designed to assess QoL for chronic conditions over a longer-term follow up.

Repeated episodes of AP, in patients with recurrent AP, are associated with a risk of CP (Symersky et al., 2006). Again, evidence on HRQL in patients with CP is very limited in the literature, however our hypothesis, supported by clinical expert opinion is that HRQL for patients with CP is likely to be similar to that for patients with a history of recurrent AP (see Appendix 7).

Overall therefore, there is expected to be a trend towards declining HRQL over time.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

In both APPROACH and APPROACH OLE, QoL was measured using the EQ-5D-5L and SF-36 questionnaires. However, it should be noted that as these are not disease-specific tools, it is unlikely that they were sensitive enough to detect changes in a population of patients with FCS, escpecially given the small sample size. QoL was not assessed in COMPASS.

APPROACH

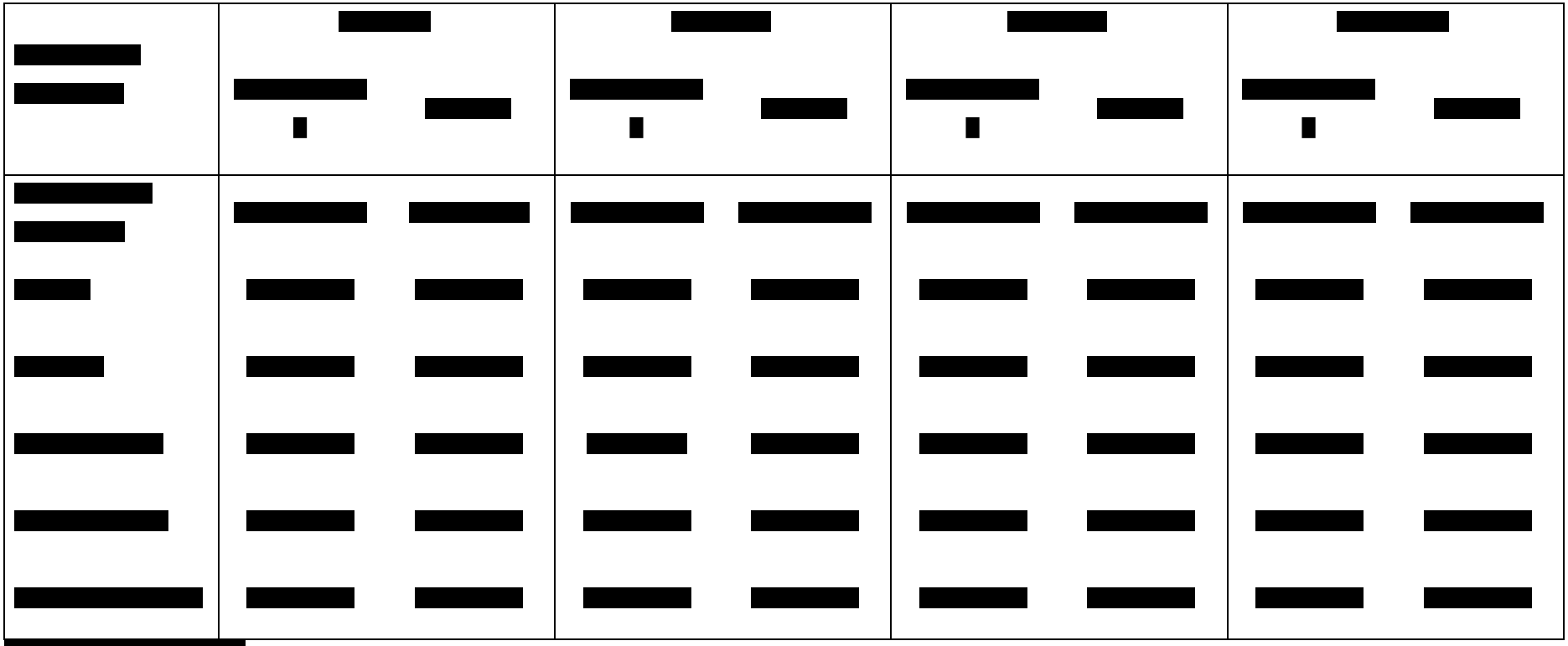
QoL was an exploratory outcome in APPROACH. Patients completed the EQ-5D and SF-36 questionnaires at baseline, Week 13 (Month 3), Week 26 (Month 6) and Week 52 (Month 12). The results are shown in Tables C23 (ED-5D-5L) and C25 (SF-36). [redacted]

[redacted]

[redacted]

[redacted]

Table C23 EQ-5D-5L scores (FAS, n = 66)



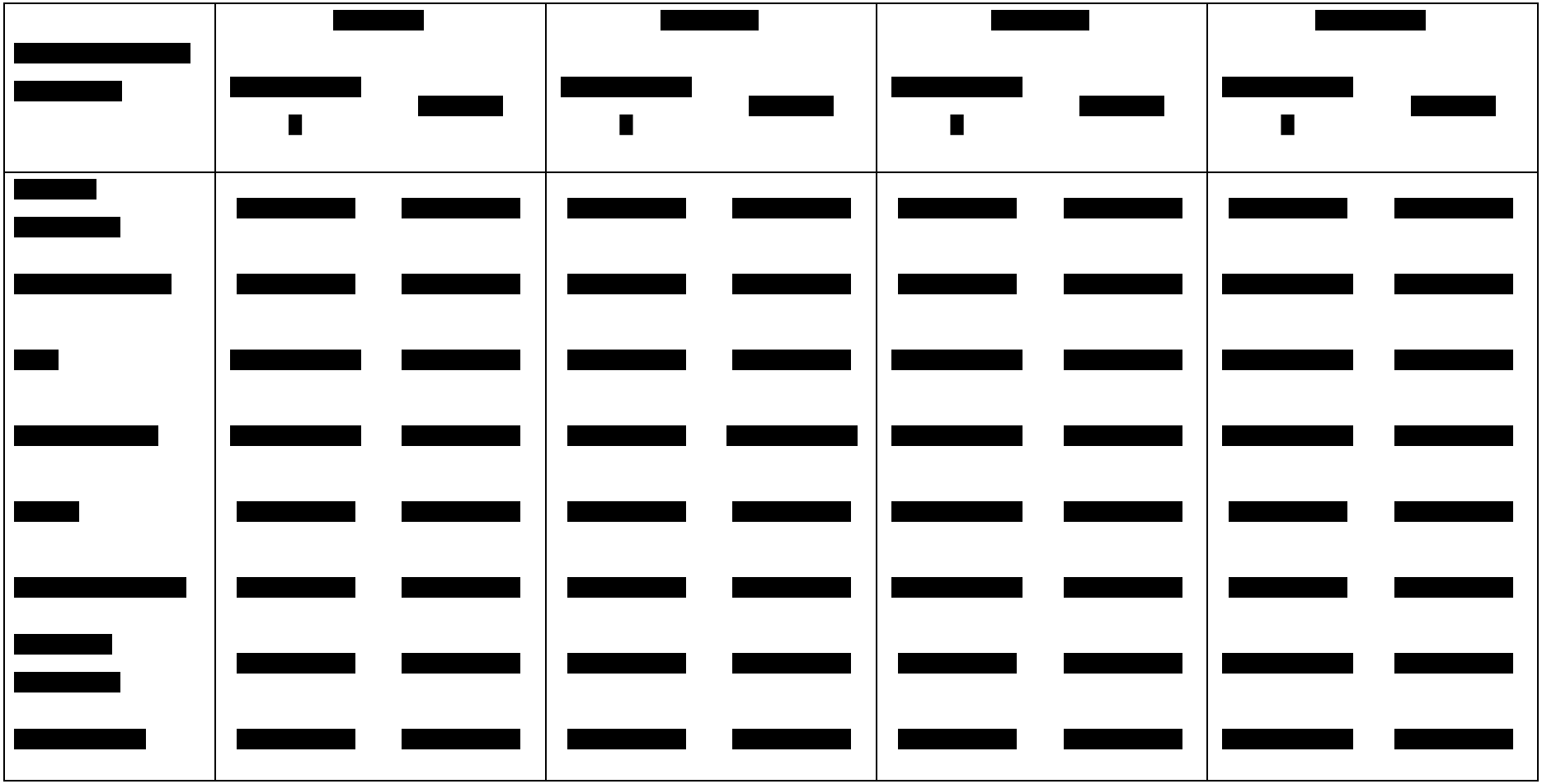
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C24 EQ-5D-5L index scores (95% CI) by treatment arm and study period

[redacted]

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C25 SF-36 weighted sum scores (FAS, n = 66)



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

APPROACH OLE (data cut off: 6th January 2017)

In this ongoing study, patients will complete ED-5D-5L and SF-36 questionnaires at Weeks 1, 13, 26, 52 and 65.

At the time of the interim analysis, 13 patients had data available at Week 13. The results are shown in Tables C26 (ED-5D-5L) and C27 (SF-36).

Table C26 EQ-5D-5L scores (FAS)

VAS, visual analogue scale
Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

Table C27 SF-36 weighted sum scores (FAS)

Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

HRQL data derived from clinical trials: summary

[redacted]

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

A mapping study was not undertaken.

HRQL studies

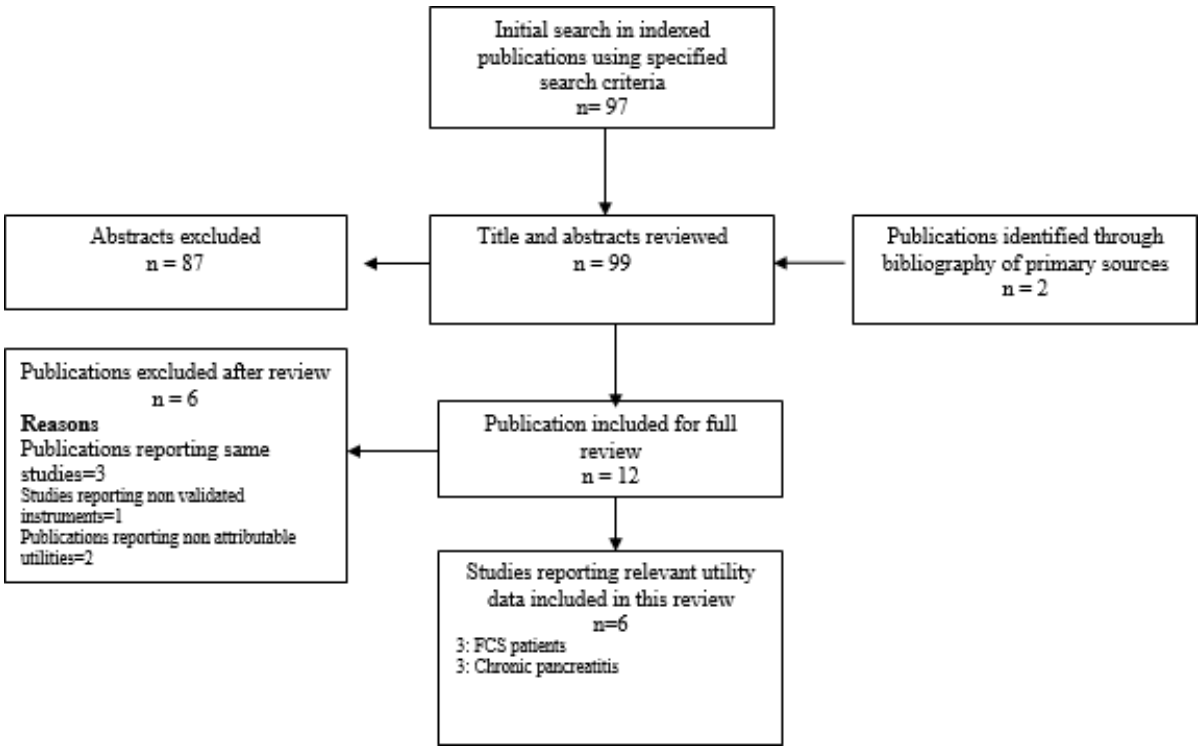
10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic search of published literature was conducted using the bibliographic databases, EMBASE via Ovid®; MEDLINE via Ovid® (1973 to May 2018); Cochrane Database of Systematic Reviews via the Cochrane Library; Database of Abstracts of Reviews of Effects via the Cochrane Community; Health Technology Assessment Database via the Cochrane Library; NHS Economic Evaluation Database via the Cochrane Community. In addition, Pubmed and Google was searched separately using key words related to main search strategy.

A systematic search for HRQL was performed simultaneously with a systematic search for economic studies and resource use in familial chylomicronaemia syndome and hypertriglyceridemia (Section 11.1.1). Since familial micronemia predisposes to acute pancreatitis, the search strategy was

broadened to include MESH terms as well as key words to represent pancreatitis. No date restriction was applied, however, the search was limited to publications in English language. Details of the search strategy are provided in Appendix 4. The search yielded 6 results.

Figure 17 PRISMA diagram for HRQL sytematic review



10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

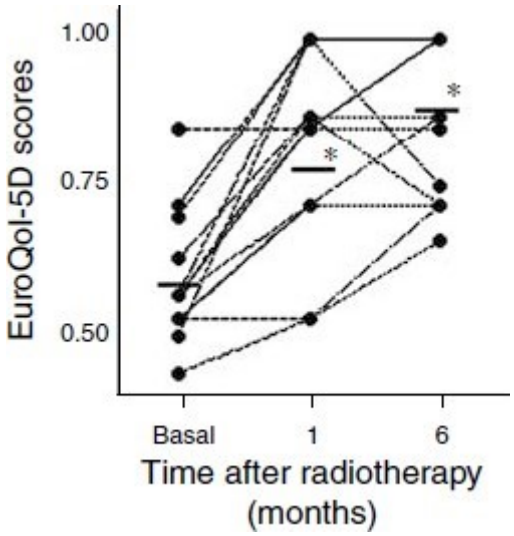
- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.

- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

A total of 6 studies were included and are summarised.

Table C28 HRQL studies found in the systematic review potentially relevant to the decision problem

Guarner et al. 2009	
Population in which health effects were measured	Patients with chronic pancreatitis who had two or more flare-ups of pancreatitis in the preceding 6 months and / or persistent pain for more than 3 months duration included in the study
Information on recruitment	The treated group comprised 4 women and 11 men with a mean age of 42 years (range: 32 – 80). The median duration of illness from diagnosis to enrolment in this study was 6 years, with a range from 6 months to 16 years. The number of flare-ups of pancreatitis after diagnosis of chronic pancreatitis ranged from 2 flare-ups to more than 15, with a median of 7.
Interventions and comparators	All 15 patients were administered a single radiation dose of 8 Gy to the pancreas.
Sample size	15 patients
Response rates	Not reported
Description of health states	Patients who had good response to radiotherapy also had significant improvement in their QoL. The mean of this group before treatment was 0.585 ± 0.103 with a highly significant difference compared with the mean at 1 month 0.809 ± 0.158 ($P < 0.001$) and at 6 months 0.866 ± 0.136 ($P < 0.001$). Difference between one and 6 months was not statistically significant.
Adverse events	No patients suffered perceptible side effects from radiotherapy apart from transient mild episodes of nausea and / or vomiting that, when present (11 out of 15 patients), appeared during the initial 12 h after treatment.

Appropriateness of health states given condition and treatment pathway.	This study is included to highlight changes in HRQL in patients with chronic pancreatitis during the treatment and follow-up of after a single dose of radiation. Data in this study are potentially relevant for longer-term health states (CP), but the patient population studies is very different to that enrolled in APPROACH
Method of elicitation	HRQL was evaluated after the administration of the EQ-5D questionnaire. The questionnaire was administered right before radiotherapy (at least 1 month after the last acute attack of pancreatitis) and at 1 and 6 months after radiotherapy.
Method of valuation	EQ-5D questionnaire has been adapted and validated to be used in Spanish. The preference value scores assigned to health states used in this study were obtained from a sample of the Spanish population.
Mapping	Not conducted
Uncertainly around values	Data are expressed as mean ± SEM.
Consistence with reference case	The data has been collected using the EQ-5D, the NICE preferred measure of HRQL and is consistent with the reference case.
Results with confidence intervals	The self-administered generic questionnaire EQ-5D was used to generate a number of discrete health states that can be assigned "preference values" ranging from 0, which represents the worst health state, to 1.  Fig. Individual preference values of the EQ-5D questionnaire beforeand after treatment (1 and 6 months) (* P < 0.001).

Laramée et al. 2014	
Population in which health effects were measured	Post-hoc analysis; long-term patient follow-up (mean of 79 months).
Information on recruitment	Trial-based cost-utility analysis, where symptomatic patients with chronic pancreatitis and a distal obstruction of the pancreatic duct but without an inflammatory mass were eligible for the study.
Interventions and comparators	Thirty-nine patients underwent randomisation toto endoscopic drainage of the pancreatic duct (19) and to surgery (20).
Sample size	39 patients enrolled
Response rates	Prospective data were collected for 31 patients (of whom 16 were endoscopically treated and 15 had undergone surgery).
Description of health states	Patient-level EQ-5D data from the trial were used to generated utility scores for both arms at baseline, 6 weeks, 3, 6, 12, 18, 24 and 79 months using the UK time trade-off tariff. The baseline utilities scores for endoscopy and surgery 0.275 (SEM=0.073, n=18) vs 0.335 (SEM=0.069, n=19); at 12 months, 0.639 (SEM=0.052, n=15) vs 0.823 (SEM=0.038, n=19) and at 24 months: 0.686 (SEM=0.062, n=13) vs 0.793 (SEM=0.052, n=17).
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway.	Study in non-FCS population, but given paucity of relevant HRQL data in CP, this study indicates the potential HRQL impact of CP.
Method of elicitation	EQ-5D questionnaire was completed by patients (EQ-5D-3L) which was used to generate utility scores.
Method of valuation	The health state preference values (utilities) for EQ-5D profiles were based on time-trade-off valuations by members of the UK general public (Dolan et al 1997).
Mapping	Not conducted
Uncertainly around values	SEM
Consistence with reference case	Given the data has been collected using the EQ-5D and valued using the UK general population preferences, it is consistent with the reference case.

Results with confidence intervals	As long-term EQ-5D data (post 24 months) were collected only at 79 months, and no difference between groups was demonstrated at 79 months (endoscopy 0.79±0.21; surgery 0.82±0.26; difference −0.03, 95% CI (−0.20 to 0.14), p=0.75)3, after 24 months, it was assumed no difference in utility score between the cohorts and applied a constant utility score of 0.79 (from the endoscopy group) to both groups.

Winter Gasparoto et al. 2015	
Population in which health effects were measured	Patients who had one single episode of acute necrotizing pancreatitis (ANP) and aged between 18 and 70 years were included in the study.
Information on recruitment	Patients admitted to hospital with acute necrotizing pancreatitis in a ten-year interval were identified. 16 patients out of the 38 survivors who were contacted to enrol in the study were included.
Interventions and comparators	No treatment intervention
Sample size	16
Response rates	Not reported
Description of health states	The average health status of all three patients across four of the five domains (mobility, self-care, usual activities and pain/ discomfort) of the EQ-5D-3L descriptive system was level 3 during acute attacks and level 1 at the time of the interview.
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	This study assessed patients' long-term QoL, after a single episode of ANP with the mean interval between the diagnosis and the study being 2.9 years (range 12 to 90 months). Although carried out in non-familial chylomicronaemia patients, the study, nevertheless, measures long term QoL outcome in patients whose symptomology closely relates to that observed in FCS.
Method of elicitation	QoL was measured by the Medical Outcomes Study - 36-item short-form health survey (SF-36).
Method of valuation	SF-36 has been validated and culturally adapted for Portuguese speaking population in Brazil (Ciconelli et al. 1999). Results obtained were compared to Brazilian sex- and age-matched normative data (Cruz et al. 2013).
Mapping	Not conducted

Uncertainly around values	Data were reported as mean ± standard deviation, frequencies and interquartile range. QoL results were compared with normative data through interquartile range.
Consistence with reference case	Data were not recorded using EQ-5D, the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Data were reported as mean ± standard deviation, frequencies and interquartile range. Note: scoring reported here is based on the 0 to 100 total score (higher scores better). Caution when comparing with the data reported from APPROACH where a mean of 50 method was reported.

Domain	Mean	Standard deviation	95% confidence interval	Percentiles			Normative data (Median)	Status by percentiles
				25th	50th (Median)	75th		
Physical functioning	79.33	15.80	71.34-87.32	75.0	80.0	90.0	87.5	Inside
Role physical	65.00	39.87	44.83-85.17	25.0	75.0	100.0	100.0	Inside
Bodily pain	62.00	20.06	51.85-72.15	41.0	61.0	84.0	72.0	Inside
General health	65.67	21.20	54.94-76.40	57.0	65.0	85.0	72.0	Inside
Vitality	60.33	20.57	49.92-70.74	45.0	55.0	75.0	75.0	Inside
Social functioning	80.00	20.49	69.63-90.37	62.5	87.5	100.0	87.5	Inside
Role emotional	66.65	37.80	47.52-85.78	33.3	66.6	100.0	100.0	Inside
Mental health	61.60	22.92	50.00-73.20	52.0	60.0	76.0	84.0	**Out**

Neelamekam et al. 2017	
Population in which health effects were measured	Patients with a clinical diagnosis of LPLD confirmed by genetic testing were eligible for study inclusion. Patients also had to have fasting triglyceride levels above 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis
Information on recruitment	Potential participants were contacted by their regular LPLD clinician and were invited to join the study to enable 3 patient case examples to be investigated. Of four patients identified and screened, three were recruited (two from Manchester and one from London, UK) to participate in the study (patients 1, 2 and 3).
Interventions and comparators	No treatment intervention
Sample size	3
Response rates	Two of the three recruited patients completed the pre-interview diary, and all three completed the face-to-face interview, post-interview diary and follow-up telephone interview. However, patient 2, did not complete the pre-interview diary.

Description of health states	The average health status of all three patients across four of the five domains (mobility, self-care, usual activities and pain/ discomfort) of the EQ-5D-3L descriptive system was level 3 during acute attacks and level 1 at the time of the interview.
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	The study was carried out in patients with a clinical diagnosis of LPLD confirmed by genetic testing. Furthermore, patients also met fasting triglyceride levels or more than 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis, thus excluding patients with secondary causes of hypertriglyceridaemia.
Method of elicitation	EQ-5D was completed by patients (EQ-5D-3L).
Method of valuation	
Mapping	Not conducted
Uncertainly around values	The mean of individual ratings for each patient was calculated for each time point (during the most severe attack compared with at the time of the interview) to obtain overall mean scores in the EQ-5D-3L and the VAS for all three patients.
Consistence with reference case	Data was collected using the EQ-5D and is consistent with the reference case
Results with confidence intervals	Results are not presented with confidence interval

Davidson et al. 2017	
Population in which health effects were measured	Patients diagnosed with FCS
Information on recruitment	Patients were recruited via recruitment flyers, word of mouth via clinicians informing patients, through patient support/advocacy groups, and social media outlets. Respondents were further screened through a series of screening questions in order to confirm their eligibility. The data from the web-based survey were collected from US respondents between 24 June 2016 and 18 November 2016
Interventions and comparators	No treatment intervention

Sample size	67 completed the screening questions and qualified for the study
Response rates	Of the 67 patients who qualified for the study, 60 completed the survey within this time frame
Description of health states	
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	The study was carried out in FCS patients in USA. Furthermore, patients also met fasting triglyceride levels or more than 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis, thus excluding patients with secondary causes of hypertriglyceridaemia.
Method of elicitation	Patient-reported outcome responses were recorded using a questionnaire designed by consulting existing QOL instruments, including Short-Form 36 (SF-36) and the Pancreatitis Quality of Life Instrument (PANQOLI) as well as based on inputs from physicians treating patients with FCS, dietitians, and patients with FCS.
Method of valuation	Not conducted
Mapping	Not conducted
Uncertainly around values	
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Results are not presented with confidence interval

Gelrud et al. 2017	
Population in which health effects were measured	Patients diagnosed with FCS
Information on recruitment	Patients diagnosed with FCS were referred by lipid specialists or were self-identified and self-referred. Diagnosis of FCS was determined based on genetic analysis in five of the ten patients. The remaining five patients reported receiving a clinical diagnosis by lipid specialists.
Interventions and comparators	No treatment intervention

Sample size	10 patients
Response rates	All the 10 FCS patients participated in the advisory board discussion
Description of health states	
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	The study was carried out as a face-to-face panel discussion in USA cohort. The results provide the impact on QoL in terms of clinical and psychosocial burden of having FCS. As the study was unstructured and the methodology was qualitative, it does not provide absolute utility values for the health states.
Method of elicitation	Patients were asked questions related to the clinical burden and psychosocial consequences of living with FCS. The questions were not developed from a validated instrument but based on advisory board proceedings with lipidologists who care for FCS patients. The outcome was reported as common complaints.
Method of valuation	Not conducted
Mapping	Not conducted
Uncertainly around values	The analysis was based on more descriptive assessment of the HRQL
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Results are not presented with confidence interval

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Values derived from the literature searches are not comparable to HRQL data collected in the APPROACH clinical trial in an FCS population. The literature searches emphasise the lack of evidence available on HRQL in FCS. Some data are available in patients with chronic pancreatitis, though these are likely non-FCS populations with a different aetiology.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

[redacted]

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

As described earlier in Section 10.1.3, data collected in the APPROACH study is not suitable as a source of utility data for the base case cost-effectiveness modelling. These data are, however, used in a sensitivity analysis. Following extensive literature searches which revealed that suitable alternative utility data were not available in published form, a vignette study was commissioned by Akcea, in order to derive appropriate utility values to inform cost-effectiveness modelling. A summary of the vignette study is presented in Appendix 6. A full study report describing the methods and results of the vignette study is available on request.

Table C29 Summary of quality-of-life values for cost-effectiveness analysis

State	[redacted]	[redacted]	Justification
Low risk triglyceride level- AP naïve	[redacted]	[redacted]	*See section 10.1.3*
Med risk triglyceride level- AP naïve	[redacted]	[redacted]	*See section 10.1.3*
High risk triglyceride level- AP naïve	[redacted]	[redacted]	*See section 10.1.3*
Low risk triglyceride level- 1AP	[redacted]	[redacted]	*See section 10.1.3*
Med risk triglyceride level- 1AP	[redacted]	[redacted]	*See section 10.1.3*
High risk triglyceride level- 1AP	[redacted]	[redacted]	*See section 10.1.3*
Low risk triglyceride level- 2+AP	[redacted]	[redacted]	*See section 10.1.3*
Med risk triglyceride level- 2+AP	[redacted]	[redacted]	*See section 10.1.3*
High risk triglyceride level- 2+AP	[redacted]	[redacted]	*See section 10.1.3*
Chronic Pancreatitis	[redacted]	[redacted]	*Assumption: same as state High TG and AP experienced. HRQL for patients with CP likely to be similar to those with high TGs and prior acute pancreatitis*

Events	[redacted]	[redacted]	Justification
Acute Pancreatitis	[redacted]	[redacted]	*See section 10.1.3*
Diabetes	[redacted]	[redacted]	*Diabetes is a well-described comorbidity associated with FCS. The chronic nature of diabetes and associated impact on HRQL supports the inclusion of an appropriate utility decrement in the model, based on targeted literature review.*
Thrombocytopenia, Grade 3 (25,000-50,000/µL)	[redacted]	[redacted]	*See section 10.1.8*

Events	[redacted]	[redacted]	Justification
Thrombocytopenia, Grade 4 (< 25,000/μL)	[redacted]	[redacted]	*See section 10.1.8*
Asthenia	[redacted]	[redacted]	*See section 10.1.8*
Epistaxis	[redacted]	[redacted]	*See section 10.1.8*
Erythema	[redacted]	[redacted]	*See section 10.1.8*
Fatigue	[redacted]	[redacted]	*See section 10.1.8*
Headache	[redacted]	[redacted]	*See section 10.1.8*
Injection site reaction	[redacted]	[redacted]	*See section 10.1.8*
Myalgia	[redacted]	[redacted]	*See section 10.1.8*
Nausea	[redacted]	[redacted]	*See section 10.1.8*
Pruritus	[redacted]	[redacted]	*See section 10.1.8*
Urticaria	[redacted]	[redacted]	*See section 10.1.8*

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were asked to address the issue of HRQL for patients with CP. Very limited evidence was identified in the SLR with respect to CP, which is an important long-term, chronic complication, expected to affect a substantial proportion of patients with FCS. Specifically, for the economic evaluation of volanesorsen, we required an estimate of the utility associated with CP. Advice was sought from a small number of experts who were engaged either in a face to face interview, or on the telephone.

A total of 8 clinical experts were approached and 7 participated. The one respondent who did not participate did not feel they had sufficient, relevant expertise to address the specific questions in the survey. Akcea invited clinical experts to participate on the basis of clinical expertise in the field of FCS. The number of clinical experts in the UK fitting this description is limited and Akcea relied upon the existing clinical expert network. The focus of the survey related to the impact of chronic pancreatitis on patients with FCS and this influenced the selection of experts to approach.

Included in the sample of clinical experts who participated in the survey were Consultants in Diabetology, Endocrinology, Chemical Pathologist and Metabolic Medicine. Two broad areas of questioning were included – firstly with regard to the symptoms associated with CP for patients with FCS and the NHS resources associated with management of CP. Secondly, the impact of CP in terms of HRQL and the likely incidence of CP in patients with FCS. A copy of the survey questions and a summary of the participant responses is included in Appendix 7.

Specifically regarding HRQL for patients with CP, we explored the rationale for assuming the same utility for CP as for those patients with a history of acute pancreatitis (AP) and high TG levels. The latter had been derived from the vignette study. All clinical experts who participated in the survey agreed with the rationale – i.e. that it was reasonable to assume HRQL for patients

with CP would be ‘at best equivalent’ to that for “High triglycerides, history of acute pancreatitis”.

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The characteristics of the model health states in terms of HRQL experience were described in the vignette study (Akcea data on file, 2018b). High TG and low TG health states were supported by a vignette, developed with clinical and patient experts. Vignettes were also developed to explore the HRQL impact of acute pancreatitis. Further details are provided in Appendix 6. The HRQL of patients with FCS is expected to vary significantly according to TG level and history of pancreatitis. This is supported by the findings in the vignette study. Within the model, we therefore capture the way in which HRQL is expected to vary for patients over time, according to their TG levels and associated risks of AP. In addition, patients with FCS may experience comorbidities. In the model, we capture the impact of comorbid diabetes as an annual utility decrement. Finally, the HRQL of patients is impacted by the adverse effects of treatment, and in the model we capture this as utility decrements associated with the more severe (grade III and above) adverse events observed in the APPROACH study.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

[redacted]

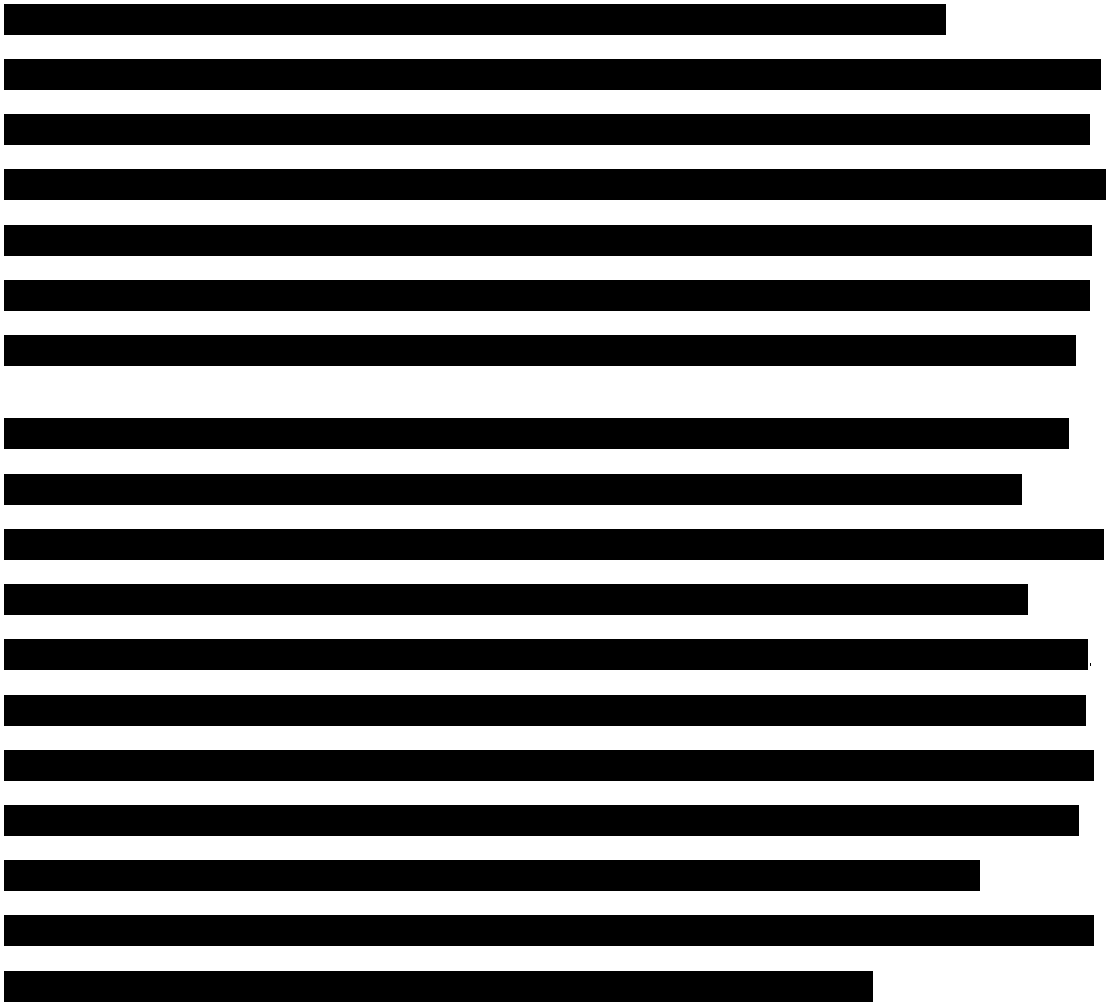
[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]



Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

Akcea conducted a systematic literature review of the published English language literature to identify and summarise outcomes related to the treatment of FCS. Searches were conducted in the following databases to identify literature published from database inception to February 2018: MEDLINE (via Ovid), Embase, the Cochrane National Health Service Economic Evaluation Database (NHS EED), the Cochrane Health Technology Assessment (HTA) Database, the Database of Abstracts of Reviews of Effects (DARE). The search strategy used is presented in Appendix 1.

The literature search was broad in scope to include all the interventions for FCS. Studies which did not involve the patient population specified in the scope were subsequently excluded after reading the abstract and title (level 1 screening) and reading the full text (level 2 screening).

In addition, reference lists of all accepted studies, and all relevant systematic reviews, meta-analyses were screened manually to identify any relevant studies that were not identified using the above electronic search strategy. Moreover, grey literature (material that not published in peer-reviewed or indexed medical journals) was also searched for relevant conference abstracts and posters reporting interventional or observational studies in FCS

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

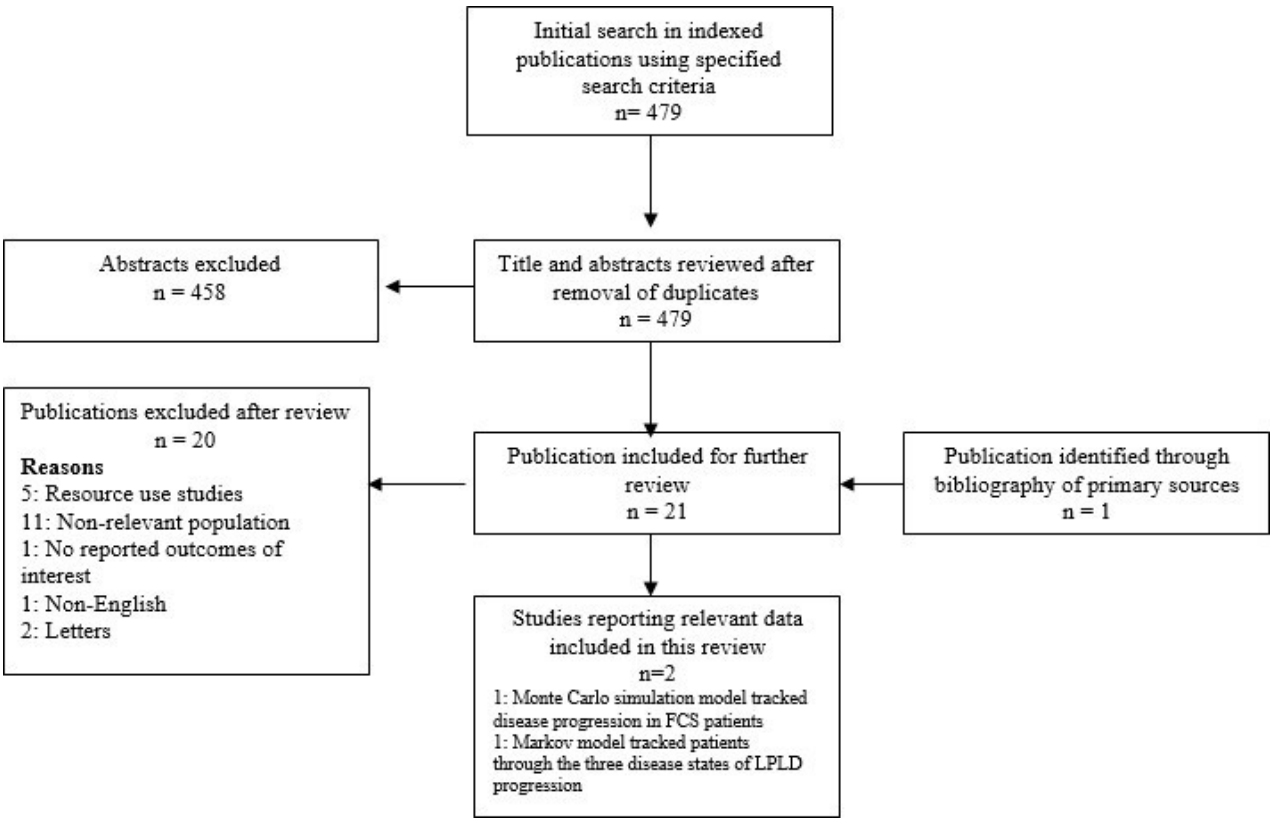
Table D1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with familial chylomicronaemia, lipoprotein lipase deficiency and hypertriglyceridemia
Interventions	Volanesorsen or usual care
Outcomes	• Direct and indirect costs • Cost-effectiveness • Resource utilisation
Study design	In the review, studies of the following study designs are eligible: • Systematic reviews • Randomised controlled trials (RCTs) • Prospective comparative studies - such as cohort studies • Retrospective comparative studies - such as case-control studies • Prospective case series/registry studies • Non-randomised non-control studies • Non-randomised non-concurrent control trials • Natural history epidemiological studies • Studies must include more than 2 participants for inclusion Studies with any duration of follow up are eligible for inclusion. Eligible systematic reviews must meet the same inclusion criteria as the RCTs. Abstracts or conference presentations for clinical studies are eligible for inclusion, providing sufficient detail is available to allow appraisal and assessment of results to be undertaken and thereby inform the review. Systematic reviews are used as a source of references only
Language restrictions	Only publications in English will be included
Search dates	No date limits applied to the searches.
Exclusion criteria	
Population	Other than those described above
Interventions	Other than those described above
Outcomes	No restrictions
Study design	No restrictions
Language restrictions	Restricted to publications in English language only
Search dates	No date limits applied to the searches

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Two studies were identified for economic studies in FCS, potentially relevant to the decision problem. Specifics of the search are provided in Appendix 3. Subsequently, the literature search was broadened to include resource use in the UK in conditions of pancreatitis and diabetes with the aim of extrapolating the resource use to FCS.

Figure 18 PRISMA diagram for economic systematic review



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

Table D2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Lin F et al. 2014	USA	An individual Monte Carlo simulation model was built to track disease progression of a cohort of FCS patients. The model projected the number of acute pancreatitis events, mortality and medical costs. Benefits of a hypothetical triglyceride reduction intervention were assessed.	A cohort of FCS patients with a mean age of 37.8 years, 60% male, and a mean triglyceride level of 2,741 mg/dL.	The discounted lifetime cost of acute pancreatitis was projected to be $154,126 per patient.	With standard diet control, the average life expectancy of the studied cohort was estimated to be 16.45 years. These patients were expected to experience 10.16 episodes of acute pancreatitis during their lifetime, resulting in 80.7 inpatient days.	The discounted lifetime cost of acute pancreatitis was projected to be $154,126 per patient. The cumulative mortality due to acute pancreatitis was estimated to be 54.3%. Should an intervention reduce triglyceride levels by 50% in FCS patients, the life expectancy would be increased by 3.16 years and 7.72 fewer episodes of acute pancreatitis would occur, preventing 61.21 inpatient days and saving $118,594 in medical cost.
Han et al. 2015	USA	Markov model tracked patients through the three disease states of	Markov model was used to track patients through disease states. No other information	The cost data for each disease state was derived from the	Not available	The incremental cost-effective ratio (ICER) of Glybera was € 51,789/QALY

		LPLD progression, defined by the symptoms of pancreatitis. The effectiveness of the novel gene therapy based on published clinical trial data was evaluated. QoL, utility scores and cost data for each disease state was derived from the published literature. We estimated the discounted costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) was estimated. Univariate sensitivity analyses were conducted to assess the impact of parameter uncertainty on the results.	on patient characteristics is presented	published literature; and the discounted costs were estimated. However, the actual data is not presented for these parameters.		gained when compared with no intervention. The net monetary benefit (NMB) is €667,478, given the willingness-to-pay (WTP) is €114,875.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

Table D3 Quality assessment of health economic studies

Lin et al. 2014		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The stated objectives of the analysis were to estimate long term disease progression, costs and consequences of FCS.
2. Was the economic importance of the research question stated?	Yes	There is limited literature regarding long-term progression, the burden of illness or consequences of acute pancreatitis for FCS.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Perspective of analysis likely USA, but not clearly stated
4. Was a rationale reported for the choice of the alternative interventions compared?	No	Standard dietary restriction was compared to hypothetical triglyceride reduction intervention.
5. Were the alternatives being compared clearly described?	Yes	Compared to benefits of a hypothetical triglyceride reduction
6. Was the form of economic evaluation stated?	Yes	Cost-consequence analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	The limited information available states that the simulation model was built to track disease progression in a cohort of FCS patients with a mean age of 37.8 years, 60% male, and a mean triglyceride level of 2,741 mg/dL. The model projected the number of acute pancreatitis events, mortality and medical costs. Benefits of a hypothetical triglyceride reduction intervention were assessed.

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	The source for the demographic data used in the model is not stated.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life expectancy would be increased by 3.16 years and 7.72 fewer episodes of acute pancreatitis would occur, preventing 61.21 inpatient days and saving $118,594 in medical cost, if the triglyceride levels were reduced by 50% in FCS patients by the hypothetical intervention.
12. Were the methods used to value health states and other benefits stated?	N/A	QALYs were not estimated.
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	Neither unit costs nor the quantities of the resources reported.
17. Were the methods for the estimation of quantities and unit costs described?	No	Merely states that a simulation was undertaken.
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	Only that a Monte Carlo simulation model was built to track disease progression.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	The risk of FCS patients experiencing episodes of acute pancreatitis during their lifetime and the resultant inpatient days were modelled.

22. Was the time horizon of cost and benefits stated?	No	Implies lifetime but not explicitly stated.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	The conclusion was an effective triglyceride lowering intervention could mitigate the consequences of FCS significantly. This was based on the estimate that should an intervention reduce triglyceride levels by 50% in FCS patients, the life expectancy would be increased by 3.16 years and 7.72 fewer episodes of acute pancreatitis would occur, preventing 61.21 inpatient days and saving $118,594 in medical cost.
35. Were conclusions accompanied by the appropriate caveats?	No	

36. Were generalisability issues addressed?	No	
Han et al. 2015		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The stated objectives of the analysis were to assess the relative costs and effectiveness of Glybera compared to no treatment for LPLD.
2. Was the economic importance of the research question stated?	Yes	Although Glybera can improve the health condition of patients with LPLD, the price tag of 1.1 million euros is controversial.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	The study assesses the relative costs and effectiveness of Glybera from a societal perspective.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	Glybera was compared to no treatment for LPLD. Glybera approved my European Commission in 2012 is the only effective treatment available for LPLD.
5. Were the alternatives being compared clearly described?	Yes	Glybera was compared to no treatment for LPLD.
6. Was the form of economic evaluation stated?		The stated analysis was cost-effectiveness.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	The effectiveness of the novel gene therapy was evaluated based on published clinical trial data. QoL, utility scores and cost data for each disease state were derived from the published literature.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Markov model tracked a cohort of patients through the three disease states of LPLD progression, defined by the symptoms of pancreatitis. Effectiveness of the novel gene therapy was evaluated based on published clinical trial data. QoL utility scores and costs data for

		each disease state were derived from the published literature.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No meta-analysis was conducted.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	The incremental cost-effective ratio (ICER) of Glybera was € 51,789/QALY gained when compared with no intervention. The net monetary benefit (NMB) is €667,478, given the willingness-to-pay (WTP) is €114,875.
12. Were the methods used to value health states and other benefits stated?		QoL, utility scores and cost data for each of the three disease states of LPLD progression were derived from the published literature.
13. Were the details of the subjects from whom valuations were obtained given?	No	The HRQL of patients was derived from the published literature.
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	N/A	Costs data for each disease state derived from the published literature.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs data for each disease state derived from the published literature.
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Markov model was developed that tracked a cohort of patients through the three disease states of LPLD progression, defined by the symptoms of pancreatitis.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Although the justification not stated explicitly, the Markov model tracks patients through the three possible disease states of

		LPLD progression, defined by the symptoms of pancreatitis.
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	Available information states that the discounted costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were estimated.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		Univariate sensitivity analyses were conducted to assess the impact of parameter uncertainty on the results.
27. Was the approach to sensitivity analysis described?	Yes	Univariate sensitivity analyses were conducted to assess the impact of parameter uncertainty on the results.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	The incremental cost-effective ratio (ICER) of Glybera compared with no intervention was presented.
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	Yes	The incremental cost-effective ratio (ICER) of Glybera was € 51,789/QALY gained when compared with no intervention. The net monetary benefit (NMB) is €667,478, given the willingness to-pay (WTP) is €114,875.
34. Did conclusions follow from the data reported?	Yes	The conclusion was that although the price is high, Glybera is a cost-effective treatment for lipoprotein

		lipase deficiency compared with no treatment based on available clinical data.
35. Were conclusions accompanied by the appropriate caveats?	No	The conclusion drawn is robust as per the sensitivity analyses which illustrated that the model was robust to the majority transition probabilities and utility of each health state.
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The patients included in the cost-effectiveness analysis are adults with FCS.

Technology and comparator

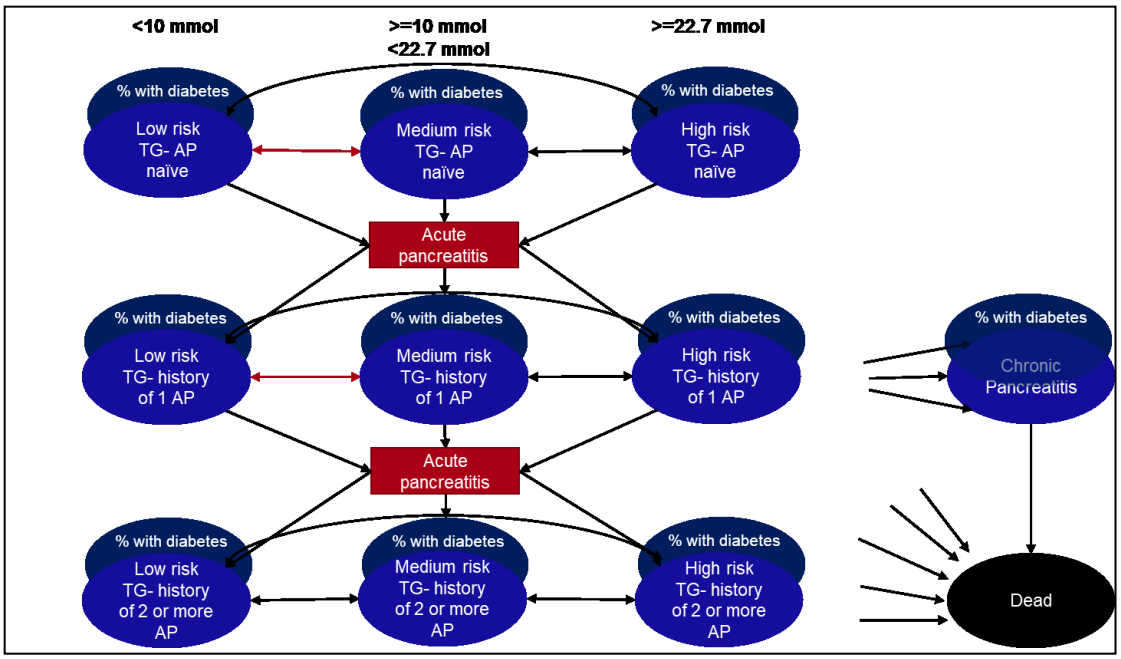
12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The proposed indication for volanesorsen is “as an adjunct to diet for the treatment of patients with FCS”, therefore the comparator includes established clinical management without volanesorsen (including dietary fat restrictions), referred to as ‘standard of care’ (SoC) in the economic analysis. Use of TG-lowering medications (e.g. statins, fibrates) is off-label and there is no evidence to support consistent use. Furthermore, there is no evidence that these medications would be discontinued by patients receiving volanesorsen. As these medications would be used in both the intervention and comparator arms of the cost effectiveness model they would cancel out, so are excluded in the base case.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

Figure 19 Model structure



Key: TG, triglyceride; AP, acute pancreatitis; Low risk TG is <10 mmol, Medium risk TG is ≥10 mmol and <22.7 mmol and High risk TG is ≥ 22.7 mmol.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model is a Markov structure with a 3-month cycle time and a lifetime horizon. The analysis is from an NHS and personal social services (PSS) perspective with costs and QALYs discounted at 3.5%.

The model consists of 11 core health states. The 11 health states can be broken down as follows:

- Three core TG risk levels of low (TG<10 mmol), medium (10 mmol ≥TG<22.7 mmol) and high (TG ≥22.7 mmol) representing different day-to-day symptomatology and risks of developing TG-induced acute pancreatitis and its sequelae.

- These three core TG levels are further stratified according to the patient's history of acute pancreatitis (AP); whether they are AP naïve, have had 1 prior AP event (in the last 5 years or prior to this) or have had 2+ prior AP events in the past 5 years (i.e. have recurrent AP). The

latter permits comparison with the APPROACH trial, which provided baseline information on whether a patient had ever had an AP attack, and number of adjudicated AP attacks in the past 5 years.

- Considering both TG levels and AP history of patients as risk factors results in nine health states representing 3 TG levels x 3 AP history levels. Patients can move between TG states during any cycle of the model but cannot move 'backwards' in terms of their AP history.

- Patients have a risk of developing chronic pancreatitis (CP) in any state in the model, but the risk increases with history of AP (Sankaran et al., 2015).

- Patients who do not already have diabetes at baseline have a risk of developing diabetes in any state of the model.

- Patients in the CP state have a risk of dying from natural causes or chronic pancreatitis. Patients in other states have a risk of dying from AP, diabetes or natural causes.

- Patients have a risk of developing AP in all health states apart from CP, where pancreatic symptoms are chronic. AP is modelled as an event due to its short disease course relative to the 3-month model cycle, similar to the approach used by Faria et al. (2014) to model the disutility, cost and mortality risk of asthma exacerbations *vs*. everyday asthma symptoms.

To adjust for dose adjustment of volanesorsen, as observed in the clinical study, a dose adjustment structure was developed in parallel with the TG category structure. The dose adjustment structure considered patients on a once weekly dose, a once every 2 week dose and those who discontinued. [redacted] Dose pauses are accounted for by applying a dose intensity reduction to weekly and every 2 week drug costs. Dose pauses and discontinuations are modelled according to the APPROACH OLE analysis, as

the enhanced monitoring and dose adjustment requirements implemented during APPROACH OLE are more generalisable to the proposed SmPC.

- In the base case, patients who discontinue follow the TG transition matrix of patients who discontinued in the volanesorsen arm of APPROACH. There is also an option in the model to assume that patients follow the transitions of patients in the placebo arm of APPROACH.

[redacted]

There is currently no definitive pathway of care for FCS. The current standard of care is strict restriction of dietary fat intake together with lifestyle changes, such as avoidance of alcohol; secondary causes of hypertriglyceridemia also need to be controlled. If a patient develops AP, they may undergo plasmapheresis, but this is not a consistent approach and its frequency of use in FCS patients in England is unknown. Chronic pancreatitis also has no consistent pathway of care, as highlighted in recently published draft NICE clinical guidelines (NICE, 2018). The model therefore does not reflect a specific care pathway, but rather captures as far as possible the management of the major clinical consequences of FCS such as AP, CP and diabetes.

[3] In our ITT analysis, we assume that one additonal patient discontinues vs. the ITT analysis. This patient had minimal response (3% reduction in TGs) and it is assumed that in clinical practice this patient would be taken off treatment after 3 months.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D4 List of model assumptions

Assumption	Rationale
Patients come off volanesorsen if they develop chronic pancreatitis (CP)	There is no evidence for clinical benefit in CP, where patients have sustained irreversible pancreatic damage. [redacted]
The baseline distribution of patients and the transitions between states is based on the APPROACH clinical data.	The trial baseline characteristics are generalisable to FCS populations in practice
Patients who discontinue in a cycle follow the volanesorsen transition matrix for discontinued patients the next cycle onwards.	Following discontinuation, there may be some residual treatment effect which would not be captured by using transitions from the SoC arm. An option has been included in the model for patients to follow SoC transitions when they discontinue volanesorsen.
State changes and death are assumed to occur at the end of the cycle.	The short cycle length does not justify a half-cycle correction.
Only TEAEs experienced by 3 or more patients in the treatment arm were retained in the model.	These were judged to be common (~10%) by Akcea's clinical advisors; lower incidences are likely to be due to random variation.

TEAEs judged as mild in the APPROACH trial were excluded in the analysis.	Mild events would be unlikely to impact HRQL or incur a treatment cost.
Model takes a lifetime horizon up to age 100 years	The majority of the UK population is dead by age 100.
All-cause mortality is subtracted uniformly from all states in the transition matrices, with the Relative Risk (RR) of death related to health states applied to the all-cause mortality for that state.	All-cause mortality is the same across all health states. Where there is a greater risk of death this is captured via the applied Standardised Mortality Ratio (SMRs) or RRs applied.
Excess risk of mortality due to AP events is assumed to be additional to any health state risks.	AP is an infrequent event with a small mortality risk, therefore any SMR or RR applied to health states will likely be reflective of other causes of mortality.
Aggregate values for the TG transitions across the 3 to 9-month period are converted to 3-month cycles to inform health state transitions.	[redacted]
The probabilities of AP stratified by peak TG and AP history from CALIBER is assumed to be generalisable to FCS patients in the 1AP and AP naïve health states. The 2+ AP health states are considered as a separate group with high rates of AP which were obtained from APPROACH. Here, the risk of an AP is assumed to be halved by moving from the high-risk TG state to the medium-risk TG state. This is consistent with the relative risk of AP associated with the different TG levels, but assumes higher	5-year adjudicated AP history was available for patients in APPROACH. Where patients had had 1 event in the past 5 years, it was not known whether this was the only event or whether the patient had experienced multiple prior events. These patients were therefore considered as being equivalent to the 'AP experienced' subgroup from CALIBER. While this CALIBER group will include some patients with frequent recurrent pancreatitis, they are likely to be rare relative to a pure FCS population and their contribution to CALIBER event rates is likely to be small.

absolute risks of AP for this patient group.	APPROACH did not provide any information on risk of AP in patients without a history of AP, therefore only a large dataset such as CALIBER could capture the effect of TG-lowering on risk of clinical events with a degree of statistical confidence.
Patients on once every 2 weeks dosing are assumed to remain on this dose over their lifetime.	[redacted]
Dose pauses or discontinuations post-12 months (for the once every 2 weeks scenario) were assumed to follow the pattern of APPROACH OLE	[redacted]
For dose adjustments, the frequency of doses is reduced (i.e.Q1W to Q2W) rather than the doses themselves	Only one dose form is currently available for volanesorsen.
Cases of diabetes included in this model are only those resulting from an AP event. Diabetes occurring uniquely as a direct consequence of FCS is not considered	Literature only supports diabetes as a consequence of pancreatitis, not high TGs.

Treatment emergent adverse events (TEAE) are assumed to have their cost and QoL impact within the same cycle	[redacted]
Platelet monitoring will not incur any costs.	[redacted] Occasional use of NHS resources for monitoring would have minimal impact on the ICER.
Resource use (excluding that for managing acute pancreatitis, chronic pancreatitis and diabetes) is assumed to be the same in the High-risk and Medium-risk TG health states	No evidence is available to suggest that resource use is different between the medium-risk and high-risk TG levels other than that associated with managing pancreatitis and diabetes.
HRU other than that associated with platelet monitoring and AEs is determined by TG levels and not by treatment type.	All of volanesorsen's clinical effect is assumed to be achieved via TG - lowering.
Utility decreases with increasing fasting TG levels	The ReFOCUS study demonstrated that FCS patients had fewer day-to-day symptoms while on volanesorsen vs. before treatment. These symptoms were independent of whether the patient was experiencing an attack of acute pancreatitis.
The utility value of patients in the medium-risk TG state is the mean of those in the low and high-risk states.	Utility values stratified by TG levels other than 'high' or 'low' were not available from the vignette study. Therefore, the worst utility values were assumed to apply to the high-risk TG states, with utility increasing as patients' TG levels approach levels <10 mmol.

The utility of chronic pancreatitis is equal to the utility of the high-risk TG state for AP-experienced patients	No suitable values for CP were identified in the literature. Given that patients with chronic pancreatitis are assumed not to receive volanesorsen and their TGs will be high, utility in the chronic pancreatitis state was assumed to be the same as that in the high TG state with a history of AP from the vignette study.

12.1.6 Define what the model's health states are intended to capture.

As described in Section 6.1, elevated TG levels are associated with an increased risk of AP. Risk has been shown to increase in a dose-response relationship both in the published literature (Pedersen et al., 2016, Toth et al., 2014) and in the CALIBER study (Akcea data on file, 2018a). TG levels below 10 mmol are associated with a very low risk of AP. Risk increases above 10 mmol and becomes particularly high at levels ≥2000 mg/dL (22.7 mmol) (Toth et al., 2014). These published AP risk categories underpinned the choice of TG health states of low risk (<10 mmol), medium (10<22.7 mmol) and high risk (≥22.7 mmol).

Patients who have had prior AP are at increased risk of further AP, with recurrent events increasing the risk of developing CP. The risk of CP has been shown to be greatest in patients with recurrent AP (defined as 2 or more episodes) than those with 1 prior AP, which is greater than that in the general population (Sankaran et al., 2015). Hence the TG states are further stratified by AP history, as the presence of prior AP would be expected to further increase the risk of AP in a patient who already has high TGs.

Higher TG states with a history of prior pancreatitis are predicted to have a high risk of developing CP due to the much higher frequency of AP. By inference, there is great potential benefit in not only lowering TG levels in patients who are at high risk of AP, but also in lowering TG levels sufficiently

to prevent patients from developing AP in the first place. The model is designed to capture these beneficial aspects of volanesorsen.

The pancreas plays a major role in glucose homeostasis and damage to the pancreas following AP is thought to contribute to development of diabetes. Patients with AP often develop prediabetes and/or diabetes mellitus (DM) after discharge from hospital and have a greater than twofold increased risk of DM over 5 years (Das et al., 2014). The model therefore captures the increased incidence of DM in the health states subsequent to development of AP.

Setting aside the risks of pancreatitis and its sequelae, the TG health states also represent different day-to-day HRQL and resource use associated with higher TGs. Reduced disease burden was demonstrated in the ReFOCUS study, where respondents reported that volanesorsen improved overall management of symptoms and reduced interference of FCS with work/school responsibilities. Reductions in the negative impact of FCS on personal, social, and professional life were also reported. In a chart review of FCS patients and patients with high triglycerides (HTG) (Akcea data on file, 2018c), HTG patients with higher peak TG levels had higher resource use, including resource unrelated to pancreatitis (FCS patients could not be stratified by peak TG level in this study as all patients had at some point had TGs above 22.7 mmol).

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below.

Table D5 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime	FCS is incurable and patients are at risk of having high TGs and its sequelae for their lifetime.	
Discount of 3.5% for costs	3.5%	As per NICE reference case	
Perspective (NHS/PSS)	NHS/PSS	As per NICE reference case	
Cycle length	3 months	a) the primary endpoint of the APPROACH study is evaluated at 3 months and the largest drop in TG levels occurs between 0-3 months; b) a 3-month cycle length offers the necessary granularity within the first year on therapy to account for the varying discontinuation and dose adjustment rates (concentrated between 3-6 months and tapering off afterwards), as well as health benefits and health care resource use	APPROACH study
NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

The APPROACH trial captured the effect of volanesorsen on fasting TG levels. Short-term transition probabilities between the TG risk states and transition probabilities between the different doses were derived directly from the patient data in the APPROACH trial, as well as incidence of drug-related thrombocytopenia and other AEs (see Sections 9.4, 9.6 and 9.7. Incidence of AP, CP and diabetes are extrapolated from the TG levels using methods described in Section 12.2.3. [redacted]

[redacted]

Derivation of dose transition matrices

In the model patients could move both between dose categories and between TG categories conditional on the dose received in the quarter of the TG reading (TGs were measured near the end of the quarter in APPROACH). To capture dose changes, patients in APPROACH were categorised into one of three mutually exclusive dose categories in each quarter, as described in Table D6 below. Dose pauses were not categorised into a separate dosing category and were instead applied as a dose intensity reduction to drug costs in full and reduced dose health states. 3x3 patient transition matrices were then extracted to capture movement between doses over each quarter, with movements in quarters 2-4 being grouped to create transition probabilities that could be used in a post year-1 extrapolation of the ITT data.

Table D6 Derivation of dose categories for economic model

Dose category	Coding algorithm
Full dose	Assumed on full dose if patient was classed as being on weekly dosing and had at least 7 doses in that cycle.
Reduced dose	Assumed on reduced dose if patient was classed as being on once every weeks dosing or had 6 or more pauses in that cycle. (The majority of patients who reduced dose did so in the first half of the cycle).
Discontinued	Assumed to have discontinued if discontinued in the first half of that cycle. If drug was discontinued in the second half of the cycle, the discontinuation was counted as taking place in the next cycle, as the effect of discontinuation on TGs was unlikely to manifest until then.
Dose pause (full dose)	Applied as a dose intensity % to drug costs in cycles where patient was on full dose, calculated using the mean number and duration of pauses for patients in APPROACH OLE.
Dose pause (reduced dose)	Applied as a dose intensity % to drug costs in cycles where patient was on reduced dose, calculated using the mean number of missed doses out of 26 planned per patient year for patients in APPROACH OLE while under once every 2 weeks exposure of 3 months or more.

Derivation of TG transition matrices

The trial baseline, Month 3, Month 6 and Month 12 endpoints informed the respective TG levels used in the model. Where there was missing data [redacted] these clinical endpoints were imputed via bootstrap imputation (base case) and multiple imputation assuming Missing at Random. In the multiple imputation analysis fasting TG values were imputed using a model that contained the following variables: baseline fasting TG and fasting TG values at post-baseline visits, the two randomisation stratification factors, with analysis stratified by treatment. Following a request by the FDA, a bootstrap analysis was carried out which considered the effect of discontinuation, as described below:

- For volanesorsen patients who terminated before Month 6, missing Month 6 TG results were imputed from volanesorsen patients who terminated before Month 6 but with Month 6 TG measured.

- For volanesorsen patients who terminated early with Month 12 TG result missing, missing data were imputed from volanesorsen patients who terminated early but with Month 12 TG measured.

- Missing data for placebo patients at Month 6 or Month 12 was imputed using bootstrap method from placebo patients with TG results at Month 6 or Month 12.

- The bootstrap imputation was repeated 5000 times. The estimates from 5000 fitted models for each of the 5000 imputed datasets were combined to provide an overall estimate with corresponding confidence intervals and p-value.

This analysis is used as the more conservative base case, as the FDA felt that the multiple imputation analysis might overestimate treatment effect due to not adequately capturing the impact of discontinuation of volanesorsen. The multiple imputation results have nevertheless been retained as a scenario.

As there was no formal Month 9 endpoint in APPROACH, TG levels collected between the end of Month 6 and start of Month 10 were used where available and missing values for Month 9 imputed using the average of the Month 6 and Month 12 endpoints for that patient (including imputed endpoints).

A summary of the clinical data used to derive the transition probabilities between TG states is provided in Table D7 below:

Table D7 Derivation of fasting TG levels in economic model

Fasting TG measurement in model	**Clinical data informing TG measurement**
Baseline fasting TGs	Baseline TG levels were obtained in the final two weeks of the 8-week screening period.
Month 3 fasting TGs	Average of the Week 12 and Week 13 assessments.
Month 6 fasting TGsx	Average of Week 25 and Week 26 fasting assessments.
Month 9 fasting TGs	No formal endpoint value was available for this time point. Therefore, TGs were estimated as follows: • Use Week 38 TG value. If this is missing: • Use Week 32 value. If this is missing: • Use the average of the Week 6 and Week 9 endpoints.
Month 12 fasting TGs	Average of the Week 50, Week 51 and Week 52 fasting assessments.

After extraction of the TG values per quarter, TGs values for each patient were categorised into one of the three TG risk categories, with TGs<10 mmol placed in the 'low risk', 10≤TG<22.7 mmol 'medium risk' and ≥22.7 mmol 'high risk' categories respectively. 3x3 transition matrices were then created to capture the movements of patients between each TG category, conditional on volanesorsen dose by quarter using the following algorithms:

- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if on full dose in quarter (T+1)
- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if on reduced dose in quarter (T+1)
- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if discontinued in quarter (T+1)
- Dosing category$_{(\text{Quarter T})}$->Dosing category$_{(\text{Quarter T+!})}$

The patient transitions for Months 4 to 12 (Quarters 2 to 4) were summed to derive a constant transition matrix for Months 4 to 12. This allowed the extrapolation of transitions beyond 1 year in the ITT analysis to be based on the average over the last 9 months rather than simply the last observation carried forward.

[redacted]

[redacted]would be as presented in Table D8 below (see Section 9.9.1 for clinical effectiveness evidence leading to these values).

Table D8 Comparison of % TG lowering effect of once every 2 weeks vs. weekly dosing

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Whenever a patient was on full (weekly) dose in a 3-month cycle (including cycles with <6 pauses), the TG reading was adjusted using the following procedure:

- The % TG reduction vs. baseline was calculated
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

[redacted]

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

TG transitions

In the [redacted] patients are assumed to follow the average of the grouped 4 to 12-month TG category transitions, conditional on dose category (as described in Section 12.2.1) for the remainder of the model time horizon. This is assumed because there is no evidence of treatment effect waning in either the APPROACH or APPROACH OLE trials.

Dose transitions

[redacted]

In the ITT analysis, patient dose transitions from 4-12 months were grouped. Because extrapolating this would have overestimated annual discontinuation rate (due to APPROACH discontinuations being concentrated in the 4-12 month period), the patient transitions were adjusted as follows:

- [redacted] To maintain total patient numbers in the transition matrix, the excess patients who discontinued in the trial [redacted]

- [redacted]

As a scenario, patients are assumed to remain in their dose categories and in their TG categories post-year 1 for the remainder of the model time horizon for both the [redacted]

Given the numerous timepoints and dosing matrices, the transition matrices are too numerous to be provided within the submission. These can be found within the model sheets “Trial data-updated” and “Trial dose data”.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Increasing blood levels of TGs lead to increasing risk of AP via a likely causal dose-response mechanism (Pedersen et al., 2016, Toth et al., 2014). CP and diabetes are known to be more common following AP (Das et al., 2014, Sankaran et al., 2015) therefore their incidence can be indirectly linked to high TG, but there is no published evidence of a direct relationship.

In order to fill this evidence gap, Akcea commissioned an observation study using the CALIBER database held by the Farr Institute in London (Akcea data on file, 2018a). CALIBER contains linked electronic health records in England between the Clinical Practice Research Datalink (CPRD - primary care data, including records for patient demographics, diagnoses, clinical biomarkers, prescribed drugs, procedures), Hospital Episode Statistics (HES - hospital admissions including records for diagnoses and procedures) and Office for National Statistics (ONS - cause specific cause of death, and patient level

deprivation quintiles). The CALIBER 1997-2016 data used for the analysis included ~1.8million patients with at least 1 triglyceride (TG) record in CPRD.

In the CALIBER analysis cohorts were stratified by highest TG level and plots of cumulative (first) incidence of AP, CP and diabetes over time obtained. Kaplan-Meier plots of these analyses are shown in Figures 20, 21 and 22 respectively.

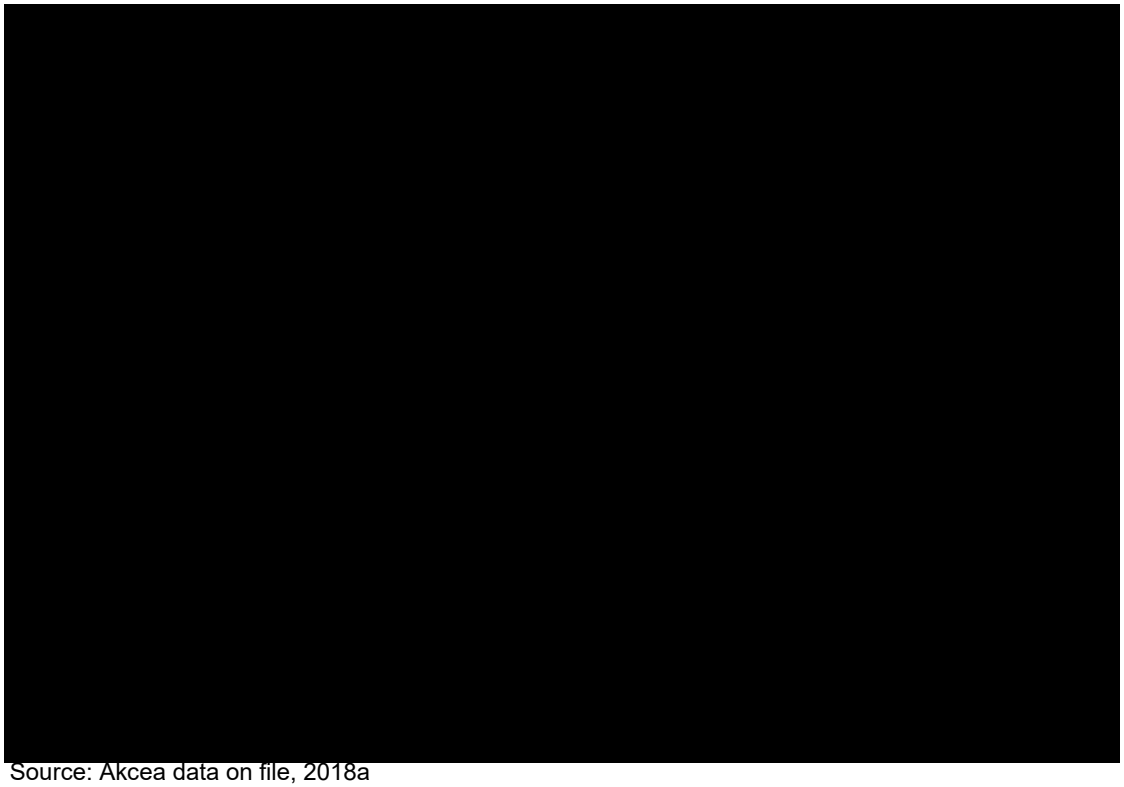
Figure 20 Kaplan-Meier plot for acute pancreatitis in the whole population with at least one TG recorded before age 40 years (n = 271,571) stratified by peak TG

Source: Akcea data on file, 2018a

Figure 21 Kaplan-Meier plot for chronic pancreatitis in the whole population with at lease one TG recorded before age 40 years (n = 271,571) stratified by peak TG

Source: Akcea data on file, 2018a

Figure 22 Kaplan-Meier plot for type 2 diabetes in the whole population with at least one TG recorded before age 40 years, excluding those with diabetes at baseline (n = 270,287) stratified by peak TG



Source: Akcea data on file, 2018a

To inform the incidences of AP, CP and diabetes by model health state, exponential models were fitted to the CALIBER data including covariates for history of AP (binary variable), highest TG level (categorical, using the TG categories in the health states) and interaction terms for TG level * history of AP.

The coefficients from the AFT models were then used to predict the incidence of AP, CP and diabetes in the AP naïve and experienced health states (the exception being incidence of AP in the AP2+ states, see below). Constant AFT models were selected as patients could move between multiple TG states during every cycle in the economic model and, due to the Markov 'memoryless' property, time spent in any TG state could not be captured. Therefore time-varying hazards from alternative time-to-event models could not be applied. The AFT model outputs are shown in Appendix 8.

The predicted incidences from the AFT models were used as follows:

- Predicted incidence of CP in a particular heath state informed the transition probability of moving to the CP health state.
- In the AP-naïve and 1AP health states, predicted incidence of AP not only triggered the cost, disutility and mortality risk associated with an AP event, but also informed the transition probability of movement to the more experienced AP health states (i.e. from AP-naïve to 1AP, or 1AP to 2+AP). In the 2+AP states the predicted incidence of AP triggered the cost, disutility and mortality of an event only.
- Predicted incidence of diabetes in a particular health state was used to inform the prevalence of diabetes in that health state (incremental to patients who already had diabetes at baseline).

For incidence of AP in the 2+AP health states the assumption was made that the absolute incidences would be much higher than predicted for the AP-experienced groups of CALIBER, as this represents a more severe patient

group with recurrent AP. [redacted]

The risk of developing CP and diabetes in the 2+AP health states were assumed to be the same as in the 1+AP health states.

The source of data linking to final outcomes for the risk of clinical events is summarised in Table D9 below.

[4] Allthough this patient group from APPROACH included patients with lower TGs at baseline, their 5-year historical TG values were unknown. It was therefore conservatively assumed that these patients had experienced frequent spiking above 22.7 mmol in the past.

Table D9 Linking of TG levels to risk of clinical events

Health state	Outcome	Source of link
AP-naïve, low-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG <10 mmol without a history of AP
AP-naïve, medium-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG 10-22.7 mmol without a history of AP
AP-naïve, high-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG ≥22.7 mmol without a history of AP
1AP, low-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG <10 mmol with a history of AP
1AP, medium-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG 10-22.7 mmol with a history of AP
1AP, high-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG ≥22.7 mmol with a history of AP
2+AP, low-risk TG	Risk of AP, risk of CP, risk of diabetes	CALIBER regressions, highest TG <10 mmol with a history of AP
2+AP, medium-risk TG	Risk of AP Risk of CP, risk of diabetes	Half the event rate of the 2+ AP, high-risk TG state CALIBER regressions, highest TG 10-22.7 mmol with a history of AP
2+AP, high-risk TG	Risk of AP	The event rate of patients in APPROACH with a

	Risk of CP, risk of diabetes	history of 2 or more events in 5 years CALIBER regressions, highest TG ≥22.7 mmol with a history of AP

Incidence of CP in the model was calibrated to ensure that prevalence did not exceed 23-27%. The peak prevalence of CP following one AP event was 10% and following recurrent AP was 36% in a systematic review of the prevalence of CP following acute pancreatitis (Sankaran et al., 2015). Clinical experts were highly discordant on the prevalence within FCS patients (see section 17.7.2) and there is uncertainty associated with this parameter. We assumed a roughly 1:2 split of patients with a history of 1 vs. multiple AP events in the CP health state. This was achieved by applying a user-modifiable adjustment factor to the failure time coefficients in the CALIBER regressions to achieve a peak prevalence of 23.7-27%.

Prevalence of diabetes in the model was calibrated by applying a cap to the prevalence over time in the Markov health states based on the published literature. The cap was set at 70% for CP (Ewald and Hardt, 2013), 20% in the 1 AP states (prevalence following AP after short follow-up; Das et al., 2014) and 40% in the 2+ AP states (prevalence after longer-term follow-up, Das et al., 2014).

Health states were survival adjusted for the mortality from AP, CP and diabetes. These were obtained from the literature, with parameters and sources described in Table D10.

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The model includes only moderate to severe AEs affecting >10% of patients and assessed as being related to treatment only. Mild events are assumed not

to incur any cost or disutility. There are therefore no AEs included in the comparator arm.

Excluding thrombocytopenia, the only moderate to severe adverse events were injection-site reactions [redacted] and fatigue [redacted] neither of which were assumed to incur any resource use costs. [redacted] There is no specific healthcare intervention for fatigue. Active medical treatment for ISRs, if required, would likely involve the use of steroid cream which is inexpensive and can be used for multiple ISRs.

The event rate for the patients experiencing fatigue and injection-site reactions was calculated by dividing the number of events experienced by each patient by their exposure time. The event rates were summarised, and the means applied to % of patients experiencing the event in the model, adjusted to the 3-month cycle time. The duration of AEs was determined from individual patient reports contained within the appendix of the CSR.

For thrombocytopenia, the event rate for all patients was calculated by dividing the number of relevant grade events experienced by each patient by their exposure time. The event rates were summarised and converted to cycle probabilities. The duration of thrombocytopenia was calculated as the number of days between the last normal platelet count and the next normal platelet count. A normal platelet count was defined as 100 x 10^9/L or above.

[redacted] For ISRs, this is because injections are half as frequent. Discontinuations, which were largely due to thrombocytopenia, were more than halved for patients who dose adjusted. We therefore assume that the rate of thrombocytopenia would at least be halved.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

None of the parameters used in the model were obtained via expert elicitation. All were obtained either from the APPROACH trial, the published literature, or the CALIBER study. Agreement on the general model structure and applicability of parameters regarding impact of TGs on incidence of AP, CP and diabetes was sought via an advisory board. Here the model structure was presented along with evidence from the literature used to inform the model (see Section 12.7 for further details).

The clinical expert survey described earlier in Section 10.1.10 and summarised in Appendix 7 was used to explore a number of model assumptions and parameters. Specifically, clinical experts were asked to comment on the HRQL impact and utility estimate for patients with chronic pancreatitis, the symptomatology and resource use profile of patients with CP and the risk of CP for patients with FCS. Model assumptions or parameters were not derived directly from the survey. Rather the survey was used to check assumptions where these had been derived from the literature or real-world evidence.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided below.

Where no confidence interval has been provided, no uncertainty values were available. Where that variable has been included in the probabilistic sensitivity analysis (which included the vast majority of parameters) a standard error of 10% of the mean has been assumed.

Table D10 Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source

Age	46 years	20 - 75	APPROACH study
% male	45.50%	N/A	APPROACH study
Cost of volanesorsen	[redacted]	N/A	Akcea
% dose intensity on weekly dosing (due to pauses)	[redacted]	Not available	APPROACH OLE study
% dose intensity on once every 2 weeks dosing (due to pauses)	[redacted]	[redacted]	APPROACH OLE study
Relative risk of mortality with chronic pancreatitis	5.83	(4.21, 8.09)	Nojgaard et al., 2011
Probability of mortality with acute pancreatitis	4.10%	(2.86%, 5.34%)	Adiamah et al., 2017
Relative risk of mortality with diabetes	1.28	(1.27, 1.29)	NHS Digital, 2017
Relative risk of mortality with a history of acute pancreatitis	1.63	(1.62, 1.64)	Nojgaard et al., 2011
Cycle probability of acute pancreatitis (and probability of transitioning to 1AP if AP-naïve, or 2+AP if 1AP)			
Low risk naïve AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
Medium risk naïve AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
High risk naïve AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
Low risk history of 1AP, AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
Medium risk history of 1AP, AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data

High risk history of 1AP, AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
Low risk history of 2+AP, AP event	[redacted]	N/A	Exponential model for time to first pancreatitis fitted to CALIBER data
Medium risk history of 2+AP, AP event	[redacted]	[redacted]	Assumed to be half of high-risk rate
High risk history of 2+AP, AP event	[redacted]	[redacted]	[redacted]
Cycle probability of transitioning to chronic pancreatitis			
Low risk naïve to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
Medium risk naïve to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
High risk naïve to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
Low risk history of 1AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
Medium risk history of 1AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
High risk history of 1AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
Low risk history of 2+AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
Medium risk history of 2+AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data
High risk history of 2+AP to chronic pancreatitis	[redacted]	N/A	Exponential model for time to first diagnosis of chronic pancreatitis fitted to CALIBER data

Annual Incidence of diabetes (lambda from AFT model			
Lambda for diabetes in Low risk AP-naïve	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in Medium risk AP-naïve	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in High risk AP-naïve	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in Low risk 1AP	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in Medium risk 1AP	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in High risk 1AP	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in Low risk 2+AP	[redacted]	N/A	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in Medium risk 2+AP	[redacted]	[redacted]	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in High risk 2+AP	[redacted]	[redacted]	Exponential model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
HRU per year (regardless of whether on volanesorsen or not)			
All low risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in 'Normal TG' cohort from CALIBER (see section 12.3.2).

Specialist visit	[redacted]	[redacted]	Rates of resource use in 'Normal TG' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Rates of resource use in 'Normal TG' cohort from CALIBER (see section 12.3.2).
All medium risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Specialist visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
All high-risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Specialist visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption

General hospital admission	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
All low risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	[redacted]	-	[redacted]
Specialist visit	[redacted]	[redacted]	[redacted]
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Assumes the rate of low TG patients in CALIBER
A&E visits	[redacted]		[redacted]
All medium risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	[redacted]	[redacted]	Manchester study
Specialist visit	[redacted]	[redacted]	Sum of urgent and routine visits, Manchester study
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Manchester study

A&E visits	[redacted]	[redacted]	Manchester study
All high-risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	[redacted]	[redacted]	Manchester study
Specialist visit	[redacted]	[redacted]	Sum of urgent and routine visits, Manchester study
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Manchester study
A&E visits	[redacted]	[redacted]	Manchester study
HRU per cycle for regular platelet monitoring			
Once every 2 week			
Nurse (GP practice)	[redacted]		[redacted]
Thrombocyte test	[redacted]		
Weekly			
Nurse (GP practice)	[redacted]		[redacted]
Thrombocyte test	[redacted]		

Platelet count drop 100-140k/mm^3 management			
Specialist phone call	[redacted]		[redacted]
Supplemental thrombocyte test	[redacted]		[redacted]
Platelet count drop 75-100k/mm^3 management (Grade 1)			
Specialist phone call	[redacted]		[redacted]
Supplemental thrombocyte test	[redacted]		[redacted]
Platelet count drop 50-75k/mm^3 management (Grade 2)			
Specialist phone call	[redacted]		[redacted]
Supplemental thrombocyte test	[redacted]		[redacted]
Platelet count drop 25-50k/mm^3 management (Grade 3)			
Specialist phone call	[redacted]		[redacted]
Supplemental thrombocyte test	[redacted]		[redacted]
Platelet count drop <25/mm^3 management (Grade 4)			
Specialist phone call	0.00		Assumption
Supplemental thrombocyte test	[redacted]		[redacted]
Admission (thrombocytopenia)	[redacted]		[redacted]

			[redacted]
Haematologist visit	0		Included in admission HRG
Steroids	[redacted]		[redacted]
Monitoring and management costs			
Nurse (GP practice)	£7.17		Unit costs for 10 mins nurse time at GP practice (£43 per hour). Curtis, 2017
GP visit	£37.00		Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit). Curtis, 2017
Lipidologist visit	£122.00	(£92.00, £144.00)	WF01A - cardiology non-admitted face to face appointment. NHS Reference Costs 2016
Triglyceride blood test	£1.00	(£1, £1)	Unit cost for NHS pathology services - Clinical biochemistry DAPS04. NHS Reference Costs 2016
Thrombocyte test	£0.00	£0.00	[redacted]
Dose administration training	£0.00		[redacted]
Chronic pancreatitis management	£83,000.00		Annual cost of managing CP inflated from £79,000 (using 1.02238 PSSRU inflation rate). Hall et al., 2014
General hospital admission	£2,953.00	(£2,149, £3,466)	Unit costs for Non-elective inpatient stays (long stays). Curtis, 2017
A&E Attendance	£189.26	(£74, £367)	Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z. NHS Reference Costs 2016

Specialist phone call (for non-grade 4 platelet events)	£104.00	(£43, £108)	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up. NHS Reference Costs 2016
Admission (thrombocytopenia)	£594.18	(£368.89, £818.25)	Non-elective short stay, Thrombocytopenia with CC Score 8+. NHS Reference Costs 2016
Steroids	£14.56		Includes pack wastage. Calculated
Acute pancreatitis admission	£4,390.00	(£3,245, £5,778)	Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days). NHS Reference Costs 2016
Steroid cost/dose	£0.04		QD dosing - 1.25mg/kg (midpoint of recommended range 0.5-2 mg/kg/d) for a 75kg person. BNF Drug tariff price of 28-pack of 5mg gastro-resistant tablets is £1.15. Average duration from APPROACH.
Health state utilities			
Vignette study data			
Low risk triglyceride level, AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, AP-naive
Medium risk triglyceride level, AP-naïve	[redacted]	[redacted]	Assumption
High risk triglyceride level, AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, AP-naïve
Low risk triglyceride level, 1AP	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, history of AP

Med risk triglyceride level, 1AP	[redacted]	[redacted]	Assumption
High risk triglyceride level, 1AP	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, history of AP
Low risk triglyceride level, 2+AP	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, history of AP
Med risk triglyceride level, 2+AP	[redacted]	[redacted]	Assumption
High risk triglyceride level, 2+AP	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, history of AP
APPROACH study data			
Low risk triglyceride level, AP-naïve	[redacted]	[redacted]	Mean EQ-5D where fasting TG was <10mmol on volanesorsen, APPROACH patient data
Medium risk triglyceride level, AP-naïve	[redacted]	[redacted]	Mean EQ-5D where fasting TG was 10mmol<22.7mmol on volanesorsen, APPROACH patient data
High risk triglyceride level, AP-naïve	[redacted]	[redacted]	Mean EQ-5D where fasting TG was >=22.7mmol on volanesorsen, APPROACH patient data
Low risk triglyceride level, 1AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was <10mmol on volanesorsen, APPROACH patient data
Med risk triglyceride level, 1AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was 10mmol<22.7mmol on volanesorsen, APPROACH patient data
High risk triglyceride level, 1AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was >=22.7mmol on volanesorsen, APPROACH patient data
Low risk triglyceride level, 2+AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was <10mmol on volanesorsen, APPROACH patient data

Med risk triglyceride level, 2+AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was 10mmol<22.7mmol on volanesorsen, APPROACH patient data
High risk triglyceride level, 2+AP	[redacted]	[redacted]	Mean EQ-5D where fasting TG was >=22.7mmol on volanesorsen, APPROACH patient data
Chronic pancreatitis	[redacted]	[redacted]	Assumed to be same as high TG state with history of AP from vignette
Disutilities (annual decrement)			
Acute pancreatitis (value used with APPROACH EQ-5D dataset)	[redacted]	N/A - calculated value	Calculated as difference between the mean EQ-5D score from APPROACH (all TG levels) and the HRQL of acute pancreatitis (Morris et al., 2014).
Acute pancreatitis (used with vignette utility dataset)	[redacted]	N/A - calculated value	Average of the difference between utility in the low TG AP-naïve state with vs. without active AP, and the difference between utility in the high TG AP-naïve state with vs. without active AP. Values from vignette study. Duration calculated from APPROACH data
Duration of acute pancreatitis	[redacted]	[redacted]	Duration calculated from APPROACH data
Grade 1 thrombocytopenia (75,000-100,000/µL)	0		Gauer R.L., 2012
Grade 2 thrombocytopenia (50,000-75,000/µL)	0		Gauer R.L., 2012
Grade 3 thrombocytopenia (25,000-50,000/µL)	0.184		Attard et al., 2014
Grade 4 thrombocytopenia (< 25,000/µL)	0.184		Attard et al., 2014

Fatigue	0.115		Attard et al., 2014
Injection site reaction	0.08		Shabaruddin et al., 2013
Diabetes	0.0621		Sullivan et al., 2011
Frequency of moderate to severe AEs (volanesorsen arm)			
% patients experiencing fatigue	[redacted]	[redacted]	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
% patients experiencing injection-site reaction	[redacted]	[redacted]	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Rate/cycle of fatigue for affected patients	[redacted]	[redacted]	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Rate/cycle of injection site reaction for affected patients	[redacted]	[redacted]	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Probability of grade 1 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH patient data
Probability of grade 2 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH patient data
Probability of grade 3 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH patient data
Probability of grade 4 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH patient data
Duration of fatigue (days)	[redacted]	[redacted]	Analysis of APPROACH patient data
Duration of injection site reaction (days)	[redacted]	[redacted]	Analysis of APPROACH patient data
Duration of grade 1 thrombocytopenia/cycle (days)	[redacted]	[redacted]	Analysis of APPROACH patient data

Duration of grade 2 thrombocytopenia/cycle (days)	[redacted]	[redacted]	Analysis of APPROACH patient data
Duration of grade 3 thrombocytopenia/cycle (days)	[redacted]	[redacted]	Analysis of APPROACH patient data
Duration of grade 4 thrombocytopenia/cycle (days)	[redacted]	[redacted]	Analysis of APPROACH patient data

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There are currently no specific NHS reference costs or healthcare resource group (HRG) codes applicable to management of FCS patients. Patients will have regular appointments with a clinical endocrinologist/lipidologist (the latter usually in cardiology) to monitor their triglyceride status and manage TG-lowering medications. Regular medical appointments with diabetologists will be required by patients with diabetes. Pancreatitis is managed based on need via a multidisciplinary team of surgeons, gastroenterologists, radiologists, critical care specialists and therapists. There are no pancreatitis-specific HRG codes available in NICE reference costs (NICE, 2018). Assigning costs to the management of FCS and its sequelae is therefore challenging.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Given the lack of published data on the healthcare resource use for UK FCS patients, the search criteria for the systematic literature review were revised to include resource use in pancreatitis and diabetes. The search strategy for the resource use is summarised in Appendix 4.

Table D11 List of relevant published studies

Primary study reference	Study title
Diabetes	
Gerard et al. 1989	The cost of diabetes
Laing and Williams. 1989	Diabetes
Fenton-Lee et al. 1993	Pancreatic necrosis: Assessment of outcome related to QoL and cost of management
Neoptolemos et al. 1998	Acute pancreatitis: the substantial human and financial costs.
Govan et al. 2011	Inpatient costs for people with type 1 and type 2 diabetes in Scotland: a study from the Scottish Diabetes Research Network epidemiology group
Hex et al. 2012	Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs.
Prescribing and Medicines Team, NHS Digital (2017)	Prescribing for Diabetes - England 2006/07 to 2016/17
Pancreatitis	
Fenton-Lee et al. 1993	Pancreatic necrosis: Assessment of outcome related to QoL and cost of management
Garcea et al. 2013	Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis
Laramée et al. 2013	Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis.
Morris et al. 2014	Cost-effectiveness of early laparoscopic cholecystectomy for mild acute gallstone pancreatitis.
Hall et al. 2014	The socio-economic impact of chronic pancreatitis: a systematic review
Dennison et al. 2015	Economic Burden of Chronic Pancreatitis and Implications of Total Pancreatectomy and Autologous Islet Cell Transplantation

Table D12 Summary of cost and resource use studies

Study	Country	Population	Study type	Resource use and costs	
				Direct cost	Indirect cost
Diabetes					
Gerard et al. 1989	England and Wales	Diabetes	Estimation of the cost of diabetes using 'cost of illness' framework in England and Wales in 1984	£259.5-£602.5 million	£86 million
Laing and Williams. 1989	England and Wales.	Diabetes	Report-estimation for the year 1986/7	£484 million	
Govan et al. 2011	Scotland	Diabetes	Cost estimation using 2007/08 Scottish National Tariff and national register of people with diagnosed diabetes in Scotland—The Scottish Care Information – Diabetes Collaboration (SCI-DC)	Type 1 diabetes: £26million Type 2 diabetes: £275million	Not included

Hex et al. 2012	UK	Diabetes	A top-down approach to estimate costs (direct and indirect) for 2010/2011 from aggregated data sets and literature.	£9.8bn (Type 1 diabetes: £1bn; Type 2 diabetes: £8.8bn)	£13.9bn (Type 1 diabetes: £0.9bn Type 2 diabetes: £13bn)
Prescribing and Medicines Team, NHS Digital (2017)	England	Diabetes	Prescribing trends on medicines prescribed in primary care in England for the treatment and monitoring of diabetes during the period April 2006 to March 2017	Cost of prescribing drugs in diabetes in 2016/17: £983.7 million	
Pancreatitis					
Fenton-Lee et al. 1993	UK	Patients with necrotizing pancreatitis	Study of the cost of management of patients with necrotizing pancreatitis admitted consecutively between August 1990 and August 1991	£9296 to £33,796	
Garcea et al. 2013	UK	Chronic Pancreatitis patients	Costs estimation on the prospective database of patients undergoing total	TP + IAT (admission and analgesia costs) over the 16-year period: £110,445	

			pancreatectomy (TP) + islet cell autotransplantation (IAT)	No TP + IAT (admission and analgesia costs) over the 16-year period: £101,608
Laramée et al. 2013	UK	Obstructive chronic pancreatitis patients	Trial-based (ISRCTN04572410) cost-utility analysis combining the frequency of each diagnostic and therapeutic procedure performed during the trial with UK unit costs from the 2010 to 2011 National Schedule of Reference Costs.	Total cost (mean) of endoscopic drainage: £22443 Total cost (mean) of surgical drainage: £15410
Morris et al. 2014	UK	Mild acute gallstone pancreatitis patients	A model-based cost–utility analysis. Costs are based on 2011–2012 prices	Cost of laparoscopic cholecystectomy performed within 3 days of admission: £2748 Laparoscopic cholecystectomy performed beyond 3 days but in the same admission: £3543 Laparoscopic cholecystectomy performed electively in a subsequent admission: £3752
Hall et al. 2014	UK	Chronic pancreatitis	Literature review	£285.3 million per year
Dennison et al. 2015	UK	Chronic pancreatitis	Estimates of direct and indirect costs as a result of	£454 million per year

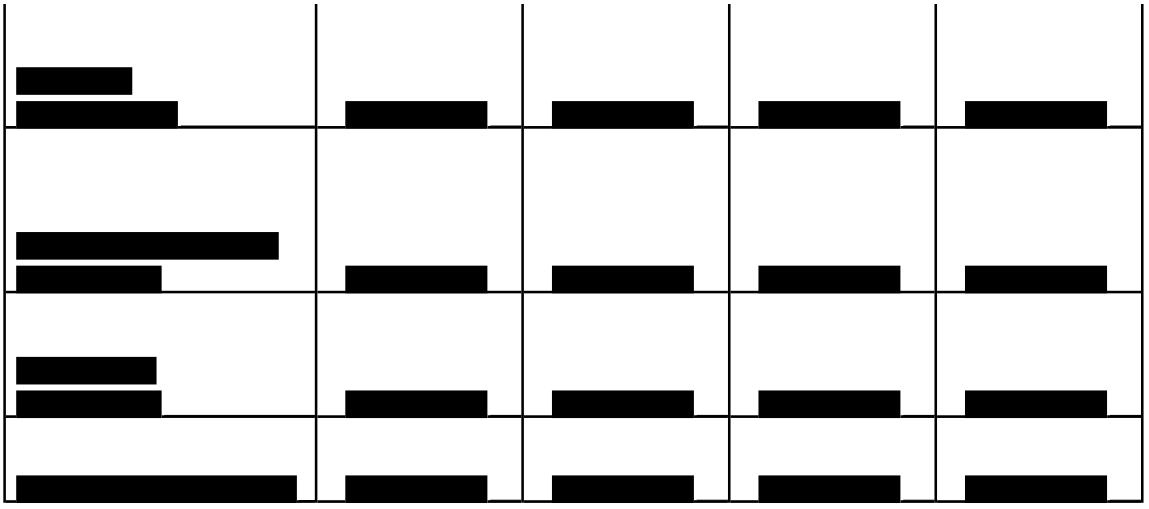
			CP are calculated from the available data from the USA and extrapolated to UK setting	

The search strategy for the cost-effectiveness evidence carried out in Section 11.1.1 included search terms for resource use and costs of managing FCS. Limited information relevant to the UK or England was identified during this search, which was part of the rationale for initiating two studies with the objective of gaining more data on the resource use of FCS patients: a chart review ("Manchester study") and the CALIBER study already discussed. Given that the Manchester study provided data from "true" FCS patients, the Manchester data, where available, has been chosen as the base case.

Manchester study

In the Manchester study, a chart review of patients with FCS [redacted] and non-familial hypertriglyceridaemia (HTG; [redacted] was carried out which included, where available, highest and lowest TG readings as well as resource use. In this dataset all FCS patients had had peak TG readings above 22.7 mmol, therefore it was not possible to stratify patients by peak TG. Patients with HTG could be stratified by peak TG, with resource use shown in Table D13.

Table D13 Resource use of patients with FCS and HTG by highest TG level in Manchester study



In the CALIBER study, a cohort of ‘FCS-like’ patients was created, defined as follows:

Information on resource use was collected including GP appointments, outpatient appointments and hospitalisations for AP. ICD-10 codes and OPCS procedure codes were also extracted where available. The ‘FCS-like’ cohort was compared with a ‘high triglyceride’ (HTG) cohort, with the TG cut-off as per the FCS-like cohort but without exclusion of co-morbidities. A third cohort of ‘normal TG’ patients, with no record of TG>1.7mmol/l by the age of 40, was also used as a control. Resource use for these populations is shown in Table D14, which were used as inputs for the model. Resource use was assumed to be driven by the patient’s TG levels and not whether they were on volanesorsen or not.

Table D14 Resource use for populations in CALIBER

[redacted]

Separate rapid searches using were carried out to identify costs and resource use involved in the management of FCS-related co-morbidities, including AP, CP and diabetes. No UK-specific information was found for the costs of managing AP or CP, as confirmed in the recent pancreatitis draft guidelines (NICE, 2018). One publication was identified which provided the cost of diagnosis and management of type 2 diabetes in the UK.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[5].

General resource use assumptions were explored with clinical experts during an advisory board meeting convened in November 2017 as described elsewhere (Section 12.7.1). Advisers were not however engaged to elicit resource use estimates. Resource use is an area of significant uncertainty in FCS, particularly with respect to the resources associated with longer term outcomes such as Chronic Pancreatitis. Clinical expert input was sought to gain a clearer understanding of the type of resource use associated with managing CP in FCS patients.

The clinical expert survey described earlier in Section 10.1.10 and summarised in Appendix 7 was used to explore the likely resource use associated with chronic pancreatitis. In summary, the clinical experts agreed that CP was a very varied syndrome and it was difficult to give precise information on management and resource use. However, they listed a variety of potential resource items that would be expected to be associated with CP including attendance at HPB clinics, CT/MRI scans of the pancreas, investigations for cause of chronic abdominal pain, hospitalisation for pain control, hospital admission for diabetes and referral to HPB surgeon. The volanesorsen model presented in this submission relies on an estimate for the annual cost of CP that is uncertain. This assumption was tested in sensitivity analyses. We were not able to construct a detailed resource profile and cost estimate for patients experiencing CP on the basis of the survey and it was not designed for this purpose. However, the information gathered from the survey supports our understanding that CP management is complex and varied and that CP is likely to be associated with significant resource utilisation including hospitalisation and surgical intervention for some patients. For the economic evaluation of volanesorsen, the resource use and costs

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

associated with CP remain an important area of uncertainty and the evidence in the literature is very limited.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price will be £[redacted] per single-use syringe.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A simple discount PAS has been submitted with a discounted price of £[redacted] per single-use syringe. All analyses have used this discounted price.

[redacted]

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables

below. Table D16 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The only incremental resource use anticipated to be required for treatment with volanesorsen are platelet monitoring tests and a single session with a nurse to teach self-injection. No costs to the NHS are expected to be incurred as [redacted] respectively. Otherwise, no incremental healthcare provider appointments will be required in addition to current standard of care.

Table D15 Costs per treatment/patient associated with the technology in the cost- effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	[redacted]	Akcea
Administration cost	None	Self-administered
Training cost	[redacted]	Akcea
Other costs (monitoring, tests etc)	[redacted]	Akcea
Total cost per treatment/patient	[redacted]	

Table D16 Costs per treatment/patient associated with the comparator technology in the cost- effectiveness model

Not applicable, as any resource use for the comparator of dietary management will also apply to patients receiving volanesorsen, as it is licensed as an adjunct to current SoC.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Health state costs were calculated by applying the resource use estimates provided in Section 12.3.2 to NHS or PSSRU unit costs in the references in Table D17. Note that the ICER was insensitive to the source of resource use, therefore health state costs for the CALIBER resource use scenario are not povided. Diabetes is not included in table D14 as costs vary according to prevalence over time.

Table D17 List of health states and associated costs in the cost-effectiveness model (per 3-month cycle)

Additional volanesorsen costs apply to all health states bar the chronic pancreatitis state but vary according to the % of patients on and off treatment.

Health states	Items	Value	Reference
Low-risk TG, 0 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017

Health states	Items	Value	Reference
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£73.45	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£174.97	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£0.47	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Medium-risk TG, 0 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.61	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017

Health states	Items	Value	Reference
	Specialist visit	£75.27	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£261.05	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£23.27	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£4.37	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
High-risk TG, 0 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.61	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£75.27	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016

Health states	Items	Value	Reference
	General hospital admission	£261.05	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£23.27	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£9.11	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Low-risk TG, 1 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£73.45	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£174.97	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016

Health states	Items	Value	Reference
	acute pancreatitis hospitalisations	£40.86	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Medium-risk TG, 1 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	CALIBER study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.61	CALIBER study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£75.27	CALIBER study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	CALIBER study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£261.05	CALIBER study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£23.27	CALIBER study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£99.23	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)

Health states	Items	Value	Reference
	TOTAL	[redacted]	
High-risk TG, 1 AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.61	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£75.27	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£261.05	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£23.27	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£242.17	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Low-risk TG, 2+ AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017

Health states	Items	Value	Reference
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Specialist visit	£73.45	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£174.97	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£40.86	CALIBRE probability *, Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Medium-risk TG, 2+ AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for 10 mins nurse time at GP practice (£43 per hour), Curtis, 2017
	Urgent GP visit	£0.61	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017

Health states	Items	Value	Reference
	Specialist visit	£75.27	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	General hospital admission	£261.05	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	A & E admission	£23.27	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£390.61	Assumption; half of the high-risk 2+ AP rate
	TOTAL	[redacted]	
High-risk TG, 2+ AP	**Volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£7.17	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2017
	Urgent GP visit	£0.61	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2016
	Specialist visit	£75.27	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2016
	Triglyceride blood test	£1.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2017
	General hospital admission	£261.05	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2016

Health states	Items	Value	Reference
	A & E admission	£23.27	Manchester study, Mobile phlebotomy service includes thrombocyte testing, NHS Reference Costs 2016
	acute pancreatitis hospitalisations	£746.47	The AP rate of patients with 2 or more events in 5 years * Average of HRG costs G17E and G17H Non-Malignant, Hepatobiliary or Pancreatic Disorders, with Single Intervention, with CC Score 4-8 and No Intervention, with CC Score 5-7 (equal to 7.4 inlier bed days)
	TOTAL	[redacted]	
Chronic pancreatitis	**Total cost of health state/cycle**	£20,750.00	0.25* the annual cost of managing CP inflated from £79,000 (using 1.02238 PSSRU inflation rate), Hall et al., 2014

Adverse-event costs

12.3.8 Complete table below with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The model includes moderate to severe AEs affecting >10% of of patients and assessed as being related to treatment only. There are therefore no AEs included in the comparator arm.

Excluding thrombocytopenia, the only moderate to severe adverse events were injection-site reactions ([redacted] of patients) [redacted] of patients). Given the nature of these AEs, and the fact that patients on volanesorsen are likely to receive advice concerning treatment of common AEs during specialist appointments, it is difficult to predict how often patients would seek medical help. Injection site reactions (ISRs) might for example require a single visit for a prescription of steroid cream which thereafter could

be used for multiple ISRs. Therefore, neither fatigue nor ISRs were assumed to incur any resource use costs.

Thrombocytopenia was assumed to require a phone call to the specialist service and would incur additional healthcare provider costs as detailed in Table D18. [redacted]

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Table D18 List of adverse events and summary of costs included in the cost- effectiveness model

Adverse events	Items	Value	Reference
Fatigue	No costs are assumed [redacted] and there is no specific treatment for fatigue.		
Injection-site reaction	No costs are assumed [redacted] ISRs requiring medical treatment will be rare, and topical steroid treatment inexpensive.		
Grade 1 thrombocytopenia	Specialist phone call	£104.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up, NHS Reference Costs 2016
Grade 2 thrombocytopenia	Specialist phone call	£104.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up, NHS Reference Costs 2016

Grade 3 thrombocytopenia	Specialist phone call	£104.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up, NHS Reference Costs 2016
Grade 4 thrombocytopenia	Hospital admission	£594.18	Non-elective short stay, Thrombocytopenia with CC Score 8+, NHS Reference Costs 2016
	Steroids	£14.56	QD dosing - 1.25mg/kg (midpoint of recommended range 0.5-2 mg/kg/d) for a 75kg person. BNF Drug tariff price of 28-pack of 5mg gastro-resistant tablets is £1.15. Average duration from APPROACH.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None foreseen.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None foreseen.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Uncertainty around structural assumptions has been explored as summarised in Table D19:

Table D19 Uncertainty around structural assumptions

Structural assumption	Base case	Other scenarios considered
Dosing schedule	[redacted]	[redacted]
Continuation rule	[redacted]	[redacted]
		[redacted]
Transitions for patients on volanesorsen who discontinue	Patients follow the actual TG transitions observed in APPROACH	Patients follow the transitions of placebo arm patients
Extrapolation beyond year 1	Assume that patients discontinue at the same rate in later years as in APPROACH OLE (conditional on dose) and that patients follow the grouped month 4-12 TG transitions conditional on dose.	Assume that patients remain in the same dose category and also the same TG category (based on the grouped 4-12 months transitions) after year 1

Structural assumption	Base case	Other scenarios considered
Choice of HRU inputs	HRU from Manchester study (using CALIBER inputs where data unavailable)	HRU from CALIBER study
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level
Missing data imputations	Imputed via bootstrap imputation	Imputed via multiple imputation

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Both one-way deterministic and probabilistic sensitivity analyses (PSA) were carried out. For the deterministic analysis, parameters were varied between their confidence intervals where available, or by +/- 25% of the mean (Table D20). In the PSA, parameters were varied around their standard errors (SEs) where available or assuming a SE of 10% of the mean where measures of uncertainty were unavailable (Table D22).

12.4.3 Complete tables below as appropriate to summarise the variables used in the sensitivity analysis.

Table D20 Variables used in one-way scenario-based deterministic sensitivity analysis

Parameter	Base case	Lower	Higher	Source of range
Relative risk of mortality with chronic pancreatitis	[redacted]	[redacted]	[redacted]	Within confidence interval
Relative risk of mortality with diabetes	[redacted]	[redacted]	[redacted]	Within confidence interval

Parameter	Base case	Lower	Higher	Source of range
Relative risk of mortality with history of AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Probability 1st acute pancreatitis is fatal	[redacted]	[redacted]	[redacted]	Within confidence interval
Manchester Low risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
Manchester Medium risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
Manchester High risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
CALIBER Low risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
CALIBER Medium risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
CALIBER High risk triglyceride level costs	[redacted]	[redacted]	[redacted]	+/-25%
Chronic pancreatitis costs	£20,750	£15,563	£25,938	+/-25%
Acute pancreatitis costs	£4,390	£3,245	£5,778	Within NHS upper and lower quartiles
Utility of Chronic pancreatitis	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette				
Vignette Low risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette Med risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette High risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette Low risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette Med risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]	Within confidence interval

Parameter	Base case	Lower	Higher	Source of range
Vignette High risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette Low risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette Med risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Vignette High risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]	Within confidence interval
Disutility of Acute pancreatitis (vignette study)	[redacted]	[redacted]	[redacted]	+/-25%
APPROACH utilities				
APPROACH Low risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Low risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Low risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval

Parameter	Base case	Lower	Higher	Source of range
APPROACH Low risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Low risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Low risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH Med risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
APPROACH High risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]	Within confidence interval
Utility Acute pancreatitis (literature), used to calculate disutility with EQ-5D values	[redacted]	[redacted]	[redacted]	Within confidence interval
Disutility of Acute pancreatitis (calculated), used with EQ-5D values	[redacted]	[redacted]	[redacted]	+/-25%

Table D21 Variables used in multi-way scenario-based sensitivity analysis

Not applicable.

Table D22 Variable values used in probabilistic sensitivity analysis

Variable	Base Case value	Distribution
Age	46 years	Not varied - determine baseline characteristics
% male	45.50%	Not varied - determine baseline characteristics
Cost of volanesorsen	[redacted] per syringe	Not varied - set price
Transition matrices for dose transitions	Multiple – see *"Trial Dose data"* sheet	Dirichlet
Transition matrices for TG transitions	Multiple – see *"Trial data - updated"* sheet	Dirichlet
% dose intensity on weekly dosing (due to pauses)	[redacted]	Not varied - data not available and N/A to base case
% dose intensity on once every 2 weeks dosing (due to pauses)	[redacted]	Beta
Relative risk of mortality with chronic pancreatitis	[redacted]	Log normal
Probability of mortality with acute pancreatitis	[redacted]	Beta
Relative risk of mortality with diabetes	[redacted]	Log normal
Relative risk of mortality with a history of acute pancreatitis	[redacted]	Log normal
Cycle probability of acute pancreatitis (and probability of transitioning to 1AP if AP naïve, or 2+ AP if 1 AP)		
Low risk naïve AP event	[redacted]	Multivariate normal
Medium risk naïve AP event	[redacted]	Multivariate normal
High risk naïve AP event	[redacted]	Multivariate normal

Variable	Base Case value	Distribution
Low risk history of 1 AP AP event	[redacted]	Multivariate normal
Medium risk history of 1 AP AP event	[redacted]	Multivariate normal
High risk history of 1 AP AP event	[redacted]	Multivariate normal
Low risk history of 2+ AP AP event	[redacted]	Multivariate normal
Medium risk history of 2+ AP AP event	[redacted]	Beta
High risk history of 2+ AP AP event	[redacted]	Beta
Cycle probability of transitioning to chronic pancreatitis		
Low risk naïve to chronic pancreatitis	[redacted]	Multivariate normal
Medium risk naïve to chronic pancreatitis	[redacted]	Multivariate normal
High risk naïve to chronic pancreatitis	[redacted]	Multivariate normal
Low risk history of 1 AP to chronic pancreatitis	[redacted]	Multivariate normal
Medium risk history of 1 AP to chronic pancreatitis	[redacted]	Multivariate normal
High risk history of 1 AP to chronic pancreatitis	[redacted]	Multivariate normal
Low risk history of 2+ AP to chronic pancreatitis	[redacted]	Multivariate normal
Medium risk history of 2+ AP to chronic pancreatitis	[redacted]	Multivariate normal
High risk history of 2+ AP to chronic pancreatitis	[redacted]	Multivariate normal
Annual Incidence of diabetes (lambda from AFT model)		
Lambda for diabetes in Low risk AP naïve	[redacted]	Multivariate normal
Lambda for diabetes in Medium risk AP naïve	[redacted]	Multivariate normal
Lambda for diabetes in High risk AP naïve	[redacted]	Multivariate normal
Lambda for diabetes in Low risk 1 AP	[redacted]	Multivariate normal

Variable	Base Case value	Distribution
Lambda for diabetes in Medium risk 1 AP	[redacted]	Multivariate normal
Lambda for diabetes in High risk 1 AP	[redacted]	Multivariate normal
Lambda for diabetes in Low risk 2+ AP	[redacted]	Multivariate normal
Lambda for diabetes in Medium risk 2+ AP	[redacted]	Multivariate normal
Lambda for diabetes in High risk 2+ AP	[redacted]	Multivariate normal
HRU per year (regardless of whether on volanesorsen or not)		
All low risk TG states - CALIBER data		
Nurse visit (TG blood test)	[redacted]	Gamma
GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma
General hospital admission	[redacted]	Gamma
All medium risk TG states - CALIBER data		
Nurse visit (TG blood test)	[redacted]	Gamma
GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma
General hospital admission	[redacted]	Gamma
All high risk TG states - CALIBER data		
Nurse visit (TG blood test)	[redacted]	Gamma
GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma
General hospital admission	[redacted]	Gamma
All low risk TG states - Manchester data		
Nurse visit (TG blood test)	[redacted]	Gamma
Urgent GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma

Variable	Base Case value	Distribution
General hospital admission	[redacted]	Gamma
A&E visits	[redacted]	Not varied - 0 assumed
All medium risk TG states - Manchester data		
Nurse visit (TG blood test)	[redacted]	Gamma
Urgent GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma
General hospital admission	[redacted]	Gamma
A&E visits	[redacted]	Gamma
All high risk TG states - Manchester data		
Nurse visit (TG blood test)	[redacted]	Gamma
Urgent GP visit	[redacted]	Gamma
Specialist visit	[redacted]	Gamma
Triglyceride blood test	[redacted]	Gamma
General hospital admission	[redacted]	Gamma
A&E visits	[redacted]	Gamma
HRU per cycle for regular platelet monitoring		
Once every 2 weeks		
Nurse (GP practice)	[redacted]	Not varied - 0 assumed
Thrombocyte test	[redacted]	
Weekly		
Nurse (GP practice)	[redacted]	Not varied - 0 assumed
Thrombocyte test	[redacted]	
Platelet count drop 100-140k/mm3 management		
Specialist phone call	[redacted]	Not varied - 1 per event assumed
Supplemental thrombocyte test	[redacted]	Not varied - 0 assumed
Platelet count drop 75-100k/mm3 management (Grade 1)		
Specialist phone call	[redacted]	Not varied - 1 per event assumed
Supplemental thrombocyte test	[redacted]	Not varied - 0 assumed
Platelet count drop 50-75k/mm3 management (Grade 2)		

Variable	Base Case value	Distribution
Specialist phone call	[redacted]	Not varied - 1 per event assumed
Supplemental thrombocyte test	[redacted]	Not varied - 0 assumed
Platelet count drop 25-50k/mm3 management (Grade 3)		
Specialist phone call	[redacted]	Not varied - 1 per event assumed
Supplemental thrombocyte test	[redacted]	Not varied - 0 assumed
Platelet count drop <25/mm3 management (Grade 4)		
Specialist phone call	[redacted]	Assumption
Supplemental thrombocyte test	[redacted]	Not varied - 0 assumed
Admission (thrombocytopenia)	[redacted]	Not varied - 1 per event assumed
Haematologist visit	[redacted]	Not varied - 0 assumed
Steroids	[redacted]	Not varied - 1 per event assumed
Monitoring and management costs		
Nurse (GP practice)	£7.17	Gamma
GP visit	£37.00	Gamma
Lipidologist visit	£122.00	Gamma
Triglyceride blood test	£1.00	Gamma
Thrombocyte test	£0.00	Not varied - 0 assumed
Dose administration training	£0.00	Not varied - 0 assumed
Chronic pancreatitis management	£83,000.00	Gamma
General hospital admission	£2,953.00	Gamma
A&E Attendance	£189.26	Gamma
Specialist phone call (for non-grade 4 platelet events)	£104.00	Gamma
Admission (thrombocytopenia)	£594.18	Gamma
Steroids	£14.56	Not varied (only number

Variable	Base Case value	Distribution
		of doses unknown)
Acute pancreatitis admission	£4,390.00	Gamma
Steroid cost/dose	£0.04	Not varied - fixed price
Health state utilities		
Vignette study data		
Low risk triglyceride level- AP naïve	[redacted]	Beta
Medium risk triglyceride level- AP naïve	[redacted]	Beta
High risk triglyceride level- AP naïve	[redacted]	Beta
Low risk triglyceride level- 1AP	[redacted]	Beta
Med risk triglyceride level- 1AP	[redacted]	Beta
High risk triglyceride level- 1AP	[redacted]	Beta
Low risk triglyceride level- 2+AP	[redacted]	Beta
Med risk triglyceride level- 2+AP	[redacted]	Beta
High risk triglyceride level- 2+AP	[redacted]	Beta
APPROACH study data		
Low risk triglyceride level- AP naïve	[redacted]	Beta
Medium risk triglyceride level- AP naïve	[redacted]	Beta
High risk triglyceride level- AP naïve	[redacted]	Beta
Low risk triglyceride level- 1AP	[redacted]	Beta
Med risk triglyceride level- 1AP	[redacted]	Beta
High risk triglyceride level- 1AP	[redacted]	Beta
Low risk triglyceride level- 2+AP	[redacted]	Beta
Med risk triglyceride level- 2+AP	[redacted]	Beta

Variable	Base Case value	Distribution
High risk triglyceride level- 2+AP	[redacted]	Beta
Chronic pancreatitis	[redacted]	Beta
Disutilities (annual decrement)		
Acute pancreatitis (value used with APPROACH EQ-5D dataset)	[redacted]	Beta
Acute pancreatitis (used with vignette utility dataset)	[redacted]	Beta
Duration of acute pancreatitis	[redacted]	Gamma
Grade 1 thrombocytopenia (75,000-100,000/μL)	[redacted]	Not varied - 0 assumed
Grade 2 thrombocytopenia (50,000-75,000/μL)	[redacted]	Not varied - 0 assumed
Grade 3 thrombocytopenia (25,000-50,000/μL)	[redacted]	Beta
Grade 4 thrombocytopenia (< 25,000/μL)	[redacted]	Beta
Fatigue	[redacted]	Beta
Injection site reaction	[redacted]	Beta
Diabetes	[redacted]	Beta
Frequency of moderate to severe AEs (volanesorsen arm)		
% patients experiencing fatigue	[redacted]	Beta
% patients experiencing injection-site reaction	[redacted]	Beta
Rate/cycle of fatigue for affected patients	[redacted]	Gamma
Rate/cycle of injection site reaction for affected patients	[redacted]	Gamma
Probability of grade 1 thrombocytopenia/cycle	[redacted]	Beta
Probability of grade 2 thrombocytopenia/cycle	[redacted]	Beta
Probability of grade 3 thrombocytopenia/cycle	[redacted]	Beta

Variable	Base Case value	Distribution
Probability of grade 4 thrombocytopenia/cycle	[redacted]	Beta
Duration of fatigue (days)	[redacted]	Gamma
Duration of injection site reaction (days)	[redacted]	Gamma
Duration of grade 1 thrombocytopenia/cycle (days)	[redacted]	Gamma
Duration of grade 2 thrombocytopenia/cycle (days)	[redacted]	Gamma
Duration of grade 3 thrombocytopenia/cycle (days)	[redacted]	Gamma
Duration of grade 4 thrombocytopenia/cycle (days)	[redacted]	Gamma

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

A brief rationale for parameters omitted from the PSA is provided under the “Distribution” column of Table D22. These largely comprise values assumed to be zero – i.e. where Akcea is funding the healthcare service, or where the scenario relates to weekly dosing e.g. the dose pause frequency on weekly dosing, where insufficient data were available for appropriate uncertainty estimates at the time.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available below.

Table D23 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The APPROACH trial only captured the clinically relevant outomes of acute pancreatitis and thrombocytopenia.

[redacted]

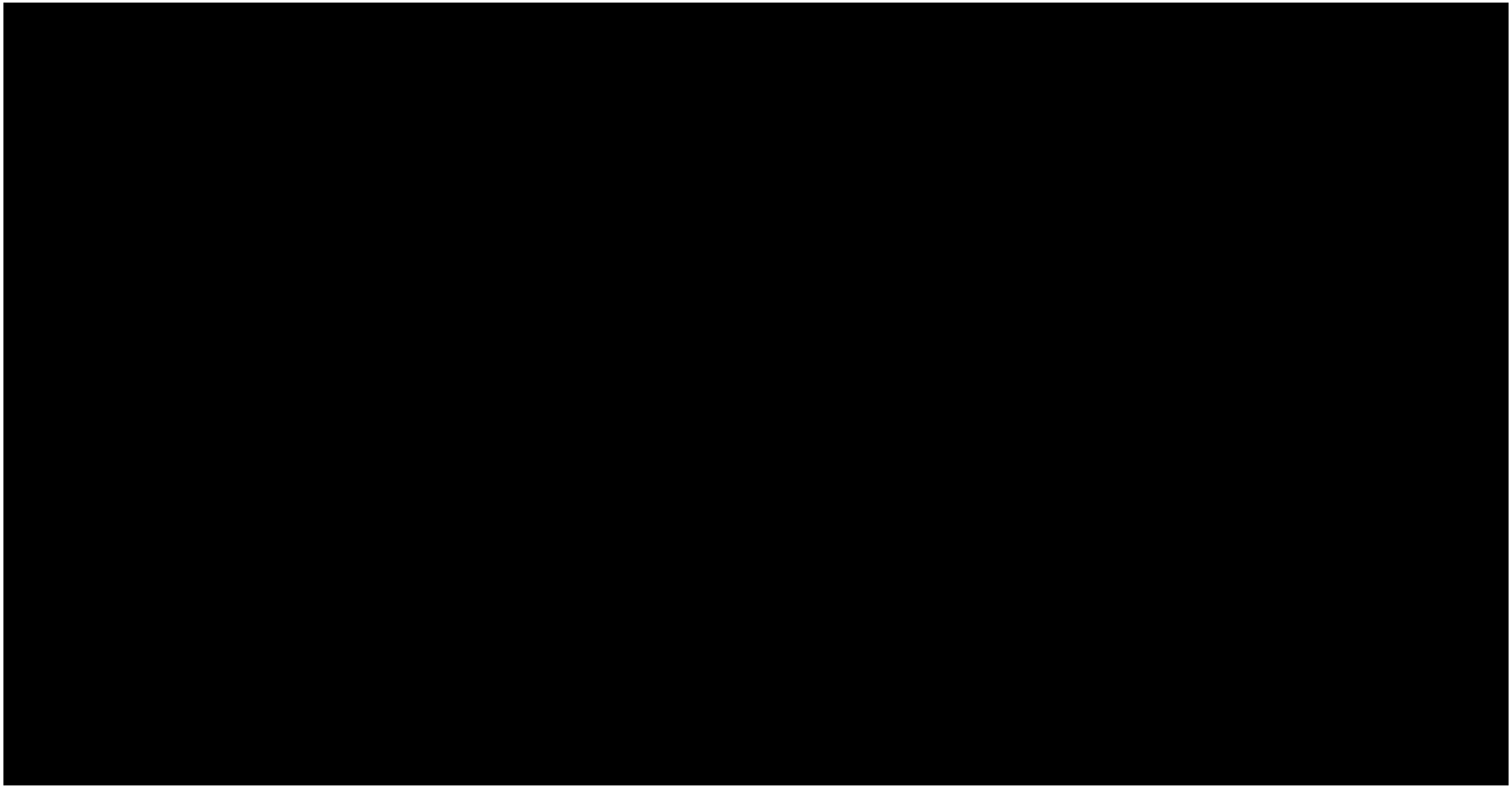
[redacted]

[redacted]

Table D24 Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Acute pancreatitis	[redacted]	[redacted]
Thrombocytopenia grade 1 (75-100,000/mm^3)	[redacted]	[redacted]
Thrombocytopenia grade 2 (50-75,000/mm^3)	[redacted]	[redacted]
Thrombocytopenia grade 3 (25-50,000/mm^3)	[redacted]	[redacted]
Thrombocytopenia grade 4 (<25,000/mm^3)	[redacted]	[redacted]

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.



12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The accrual of QALYs is based on time spent in lower-risk TG states, where health state HRQL is higher and there is a lower risk of experiencing acute pancreatitis and diabetes and their associated disutilities and mortality risk. Staying in lower-risk TG health states also reduces transition to the chronic pancreatitis health state with its associated low HRQL and raised mortality risk.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table D25 Model outputs by clinical outcomes

This is not relevant to our model: QALYs and costs by health state are presented in Sections 12.5.6, 12.5.8 and 12.5.9.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table D26 Summary of QALY gain by health state

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Low risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Med risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis-disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events-disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care.

	Total QALYs
Standard of care	[redacted]
Volanesorsen	[redacted]
Incremental	[redacted]

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented below.

Table D27 Summary of costs by category of cost per patient

Item	Cost standard of care	Cost volanesorsen	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other health care resource costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic pancreatitis costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented below.

Table D28 Summary of costs by health state per patient

Health state	Cost *intervention (X)*	Cost *comparator (Y)*	Increment	Absolute increment	% absolute increment
Low risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Cost *intervention (X)*	Cost *comparator (Y)*	Increment	Absolute increment	% absolute increment
Med risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- History of 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- History of 2 or more AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis-cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events-cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided below.

Table D29 Summary of costs by adverse events per patient

Adverse event	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D20.

Table 30 Results of deterministic one-way sensitivity analysis

Parameter	ICER with lower value	ICER with upper value	Difference
Vignette High risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]
Vignette High risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]
Vignette Low risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]
Probability 1st acute pancreatitis is fatal	[redacted]	[redacted]	[redacted]

Parameter	ICER with lower value	ICER with upper value	Difference
Vignette High risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]
Vignette Low risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]
Vignette Low risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]
Utility of Chronic pancreatitis	[redacted]	[redacted]	[redacted]
Vignette Med risk triglyceride level- 1AP	[redacted]	[redacted]	[redacted]
Chronic pancreatitis costs	[redacted]	[redacted]	[redacted]
Vignette Med risk triglyceride level- 2+AP	[redacted]	[redacted]	[redacted]
Relative risk of mortality with chronic pancreatitis	[redacted]	[redacted]	[redacted]
Vignette Med risk triglyceride level- AP naïve	[redacted]	[redacted]	[redacted]
Acute pancreatitis costs	[redacted]	[redacted]	[redacted]
Manchester High risk triglyceride level costs	[redacted]	[redacted]	[redacted]
Manchester Low risk triglyceride level costs	[redacted]	[redacted]	[redacted]
Manchester Medium risk triglyceride level costs	[redacted]	[redacted]	[redacted]
Relative risk of mortality with history of AP	[redacted]	[redacted]	[redacted]
Acute pancreatitis disutility (calculated from vignette study)	[redacted]	[redacted]	[redacted]
Relative risk of mortality with diabetes	[redacted]	[redacted]	[redacted]
APPROACH EQ-5D scenario utilities			
APPROACH Low risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]

Parameter	ICER with lower value	ICER with upper value	Difference
APPROACH Low risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH Low risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH Low risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH Low risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH Low risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH Med risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- 1AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH Med risk triglyceride level- 2+AP (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH Med risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]
APPROACH High risk triglyceride level- AP naïve (on treatment)	[redacted]	[redacted]	[redacted]

Parameter	ICER with lower value	ICER with upper value	Difference
APPROACH Med risk triglyceride level- 1AP (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH Med risk triglyceride level- AP naïve (off treatment)	[redacted]	[redacted]	[redacted]
APPROACH Med risk triglyceride level- 2+AP (off treatment)	[redacted]	[redacted]	[redacted]
Utility Acute pancreatitis (literature), used with EQ-5D values	[redacted]	[redacted]	[redacted]
Acute pancreatitis disutility (calculated from EQ-5D and literature)	[redacted]	[redacted]	[redacted]
CALIBER scenario costs			
CALIBER High risk triglyceride level costs	[redacted]	[redacted]	[redacted]
CALIBER Low risk triglyceride level costs	[redacted]	[redacted]	[redacted]
CALIBER Medium risk triglyceride level costs	[redacted]	[redacted]	[redacted]

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D21.

Not applicable.

12.5.13 Present results of the probabilistic sensitivity analysis described in table D22.

Table D31 Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table D32 shows the results of the structural sensitivity analyses (see Section 12.5.14).

Table D32 Results of structural sensitivity analyses

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
	[redacted]		[redacted]	[redacted]	[redacted]
Dosing schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		[redacted]			
Continuation rule	No continuation rule	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
Transitions for patients on	Patients follow the actual TG transitions observed in APPROACH	Patients follow the transitions of placebo arm patients	[redacted]	[redacted]	[redacted]

[redacted]

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
volanesorsen who discontinue					
Extrapolation beyond year 1	Assume that patients discontinue at the same rate in later years as in APPROACH OLE (conditional on dose) and that patients follow the grouped month 4-12 TG transitions conditional on dose.	Assume that patients remain in the same dose category and also the same TG category (based on the grouped 4-12 months transitions) after year 1	[redacted]	[redacted]	[redacted]
Choice of HRU inputs	HRU from Manchester study (using CALIBER inputs where data unavailable)	HRU from CALIBER study	[redacted]	[redacted]	[redacted]
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level	[redacted]	[redacted]	[redacted]

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Missing data imputations	Imputed via bootstrap imputation	Imputed via multiple imputation	[redacted]	[redacted]	[redacted]

12.5.14 What were the main findings of each of the sensitivity analyses?

In the base case, the model was most sensitive to the health utility values, with the utility of the high risk 2+ AP group being the most sensitive value, followed by the high-risk AP naïve group then the low risk 2+ AP group. These results are unsurprising, given the chronicity of the disease and the fact that large QALY gains can be achieved through day-to-day lowering of TGs from higher levels, where patients are highly symptomatic, to lower levels where patients experience less symptoms such as abdominal pain and fatigue. The model was not very sensitive to health state costs, which are relatively low due to the infrequency of hospitalisation, and the disutility of AP, which is an infrequent event. Both utility and costs of chronic pancreatitis were important drivers of value, reflecting the chronicity of the condition and that much of the value of volanesorsen is derived through avoidance of chronic pancreatitis.

[redacted] This likely relates to the multiple health states and non-linearity in the model, as well as skew due to the Dirichlet distributions in the patient TG and dose transition matrices.

Structural sensitivity analyses are presented in Table D32. [redacted]

The model was very sensitive to assumptions regarding trajectory of patients who discontinue, the ICER increasing significantly when assuming SoC transitions. We would argue that the actual trial transitions are more realistic

because (1) patients may retain some residual treatment effect following discontinuation (2) discontinuation of volanesorsen was not at random; implementing the transitions of the entire SoC group may not apply to the transitions of the group of patients who discontinued in the volanesorsen arm, who tended to be lighter and have lower starting TGs.

The model was highly sensitive to assumptions regarding long-term adherence and treatment effect. Clearly, assuming that patients remain on treatment in the longer-term greatly increases drug costs vs. assuming a longer-term discontinuation rate.

12.5.15 What are the key drivers of the cost results?

The major driver of cost are the drug costs. Other than these, the major cost driver is the cost of chronic pancreatitis.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

The analysis included an analysis of probability of cost-effectiveness via a CEAC. Volanesorsen had a [redacted] probability of being cost-effective at a willingness to pay threshold of £50,000 and a [redacted] probability of being cost-effective at a willingness to pay threshold of £100,000 (Figure 23).

Figure 23 Cost-effectiveness acceptability curve for volanesorsen

Prob CE; probability that arm is cost-effective

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup has been specified as per the scope.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

A number of separate steps have been taken to validate the modelling presented in this submission.

Presentation to expert clinical advisory board

An advisory board meeting was convened on November 14th, 2017 in Birmingham, UK. The purpose of the meeting was to review the proposed health economic model structure and key assumptions and to request clinical and economic expert input. The meeting was attended by 3 clinical experts (one Consultant Physician & Endocrinologist, two Consultants in Metabolic Medicine) and a Professor of Health Economics.

A short presentation was given on the clinical data, including results from the APPROACH study. Following this, an outline of the proposed economic model structure was shared with the experts. During the presentation on the economic model structure, the experts were consulted on a range of questions including:

- Whether economic model structure accurately reflects important clinical aspects of the disease pathway.
- Whether history of acute pancreatitis is associated with increased risk of future episodes and whether experts were aware of sources of evidence to characterise this relationship.
- Whether experts expected any waning of treatment effect in the longer term that did not relate to dose pauses or discontinuations.
- What the appropriate methods would be to capture impact of dose pauses and discontinuations in the model.
- Appropriate way to incorporate diabetes within the model.
- Potential options for incorporating a treatment continutation rule to be introduced in the model.

Independent model review

A review of the economic model was undertaken by an independent health economics consultant in February 2018. The scope of the review was to assess the model structure, input parameters and assumptions. The model review was carried out with reference to the NICE methods guide by an

experienced health economist. Following the review, a workshop was convened to address queries regarding the model structure and assumptions and to identify model amendments and improvements.

Model QA checking

In May 2018 a final model QA was undertaken by an independent health economist. The independent consultant conducted a full technical validation of the model, this process involved: i) checking for technical programming or calculation errors, and ii) looking for logical errors or common-sense issues related to structure, assumptions, inputs and results.

External validation

FCS is a very rare condition and consequently evidence to support validation of the economic model is limited. There are several key outcomes in the model that influence the costs and outcomes – acute pancreatitis, chronic pancreatitis and mortality. Diabetes is also captured as a comorbidity. Outcomes which were not captured in APPROACH, such as incidence of chronic pancreatitis and diabetes, were calibrated using the literature, including several systematic reviews.

Model outputs for acute pancreatitis rates have been compared with APPROACH and the Manchester study in **Error! Reference source not found.**.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is very limited evidence in the literature on the cost-effectiveness of treatment interventions for FCS. The only cost-effectiveness analysis that provides a possible source for comparison with the modelling reported here is a simulation model exploring a hypothetical treatment for FCS (Lin, 2014). The model has only been published in abstract form. Consequently, the

reporting is not sufficiently detailed to allow a proper comparison of the modelling approach and outputs.

The Lin model estimates average life expectancy of 16.45 years for patients on standard care (dietary control alone). Patients were expected to experience 10.16 episodes of acute pancreatitis during their lifetime. This appears to over-estimate AP as an event compared to our model (approximately 5 AP events on average in the standard care arm). However, without further model detail it is difficult to provide further insight.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes, as all patients relevant to the draft SmPC indication were included.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Key strengths

- The analysis has captured all the outcomes specified in the scope.
- TG outcomes on volanesorsen and standard of care have been obtained from a double-blind placebo-controlled trial in a population that is generalisable to the UK FCS population.
- Some data on longer-term efficacy and safety are available from the APPROACH OLE, which informed the model extrapolation beyond the length of clinical trial.
- The model is structured to capture the clinical benefits of volanesorsen at all baseline levels of TG, taking into account patient history of pancreatitis.
- Outcomes of acute pancreatitis, chronic pancreatitis and diabetes have been extrapolated from TG levels using statistical models derived from a large UK patient database, CALIBER.

- Both CALIBER and the Manchester study provided significant resource use information in UK patients with raised triglycerides and, in the case of the Manchester study, an English FCS patient population.

Key weaknesses

- [redacted]

- The memoryless feature of the model means that cumulative incidence of diabetes could not be captured. The model may therefore underpredict the benefits of volanesorsen on incidence of diabetes and the ICER overestimated

- The memoryless feature of the model means that only exponential models could be used to derive probabilities of developing AP, CP and diabetes. These models may not have been the best fit to the CALIBER data and may either over or under-predict event rates.

- There is a paucity of information on both the day-to-day HRQL and costs of managing chronic pancreatitis. As both of these are strong divers of model results, there is considerable uncertainty associated with the values used.

- Due to the lack of a disease-specific instrument, coupled with the potential issue of adaptation, the utility values collected during the trial likely overestimate HRQL of FCS patients.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

- An individual simulation model (ISM) may have been more appropriate to the analyses, in order to capture the impact of incremental disease-related morbidities and patient heterogeneity. However, it is unclear to what extent this would change the results, given the lack of availability of functions linking TG levels to cost and utility.

- Further studies on the resource use and cost of patients with chronic pancreatitis would provide more robust estimates of the cost of managing these patients.

- Further studies on the HRQL of patients with chronic pancreatitis would provide more robust estimates of the utility associated with HTG-induced chronic pancreatitis.

Design and validation of an appropriate disease-specific Patient-Reported Outcome Measure (PROM) would more appropriately capture FCS patients' day-to-day HRQL, and the impact on it of blood TG levels.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

To date, [redacted] with FCS have been identified in England.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

The upper end of the epidemiologic estimates for FCS in England is 110. The total number of patients with FCS over a five-year timeframe is not expected to change.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Costs associated with the management of FCS include those relating to routine appointments in primary care and with specialists, costs associated with the management of acute pancreatitis episodes, costs associated with the management of comorbid diabetes, and costs associated with the management of chronic pancreatitis.

13.4 Describe any estimates of resource savings associated with the use of the technology.

In Year 1, volanesorsen is estimated to save approximately in NHS resources, compared to standard of care management. By Year 5, cumulative NHS resource savings associated with volanesorsen are estimated at [redacted]

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

As described elsewhere in the submission (Section 7.1), FCS has a significant impact on work productivity. In the IN-FOCUS study (Davidson et al., 2018), only 60% of patients with FCS were employed full- or part-time. Most of those who were unemployed had been employed in the past and many attributed

their unemployment to FCS. Forty percent of homemakers felt their lack of employment opportunities was due to FCS.

The symptoms of FCS can limit patients' ability to train for or perform work in their preferred career, and patients find that they may miss out on promotion because of frequent absences from work (Gelrud et al., 2017). Patients report that fatigue and an inability to concentrate limit performance at work (Gelrud et al., 2017).

Evidence to quantify the impact of treatment with volanesorsen on work productivity is limited. The ReFOCUS study reported that the proportion of respondents who reported no interference of FCS with work or school increased from 36% before starting volanesorsen to 64% during treatment (Arca et al 2018). However, for those patients responding to treatment and where there are associated improvements in HRQL and reductions in episodes of pancreatitis, this is likely to be reflected in higher levels of work productivity.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Estimated net budget impact (undiscounted) for the NHS and PSS over a 5-year period, is set out in the table below. The net cumulative budget impact over the 5-year period is estimated at £[redacted]

Table D33 Estimated 5-year budget impact

Year	1	2	3	4	5
Net budget impact (in year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The main limitations relate to uncertainties around NHS resource utilisation (as per the economic evaluation) and to uncertainties with regard to patient numbers and expected uptake.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

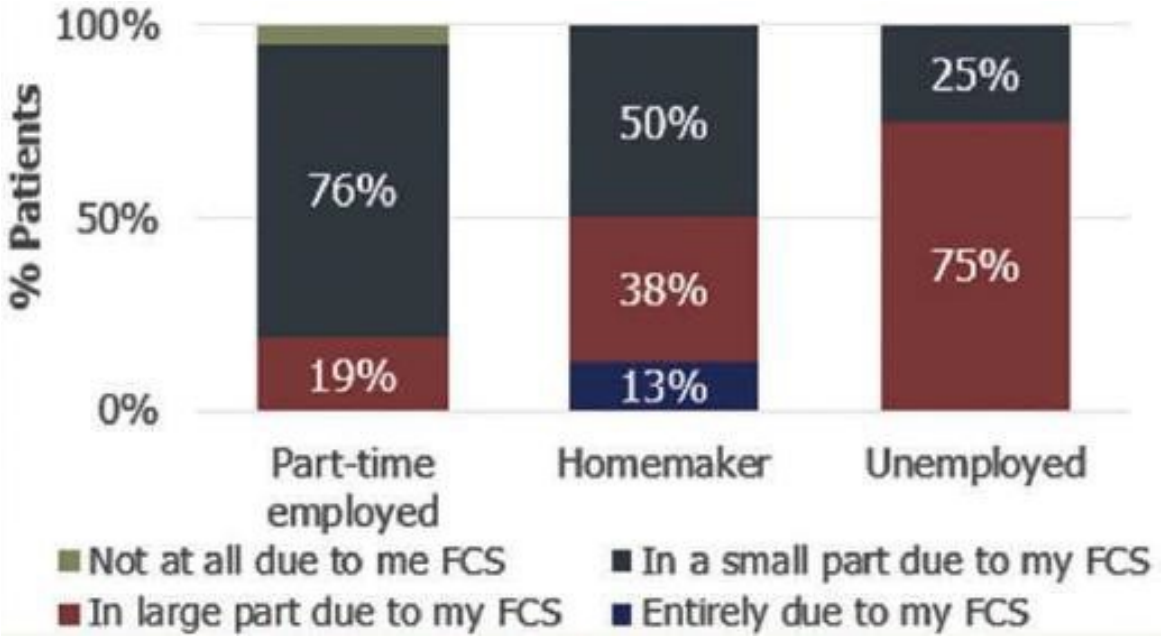
14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

Data on the wider impact of FCS, beyond the NHS and personal social services, are limited. However, available research indicates that FCS is likely to have a substantial impact on work productivity. The In-FOCUS study support this view (Davidson et al., 2017, Davidson et al., 2018). According to the results of this survey, among FCS patients who were unemployed or employed on a part-time basis, almost all of them (95%) reported that their employment status was a result of having FCS. Of those who reported being unemployed, 65% attributed this to FCS (Davidson et al., 2017).

FCS also has an impact on productivity in relation to time taken off from work, for those in part-time or full-time positions. Of those in the survey, 68%

patients reported taking time off. The mean number of days of work missed in the past 12 months was 30 (median = 24, range: 0–210) (Davidson et al., 2017).

Figure 24 Impact of FCS on employment status and unemployed patients



Note percentages may not add up to 100 due to rounding

Source: Davidson et al., 2017

In the literature on pancreatitis there is also evidence of an impact on work productivity. In a multi-centre study, authors observed a profound impact on the ability to work and interpersonal relationships for patients who experienced chronic pancreatitis (Gardner et al., 2010). Data from their survey of 111 patients found that 74% of patients had their work life altered by chronic pancreatitis, 60% reported that it affected their social lives, and 46% reported that it had an effect on relationships with family and friends.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Not applicable.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Patients are likely to incur costs associated with travel relating to the management of their condition. Additional costs for items relating to the management of their diet may also be incurred. Data relating to these elements are not currently available.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

There is very limited evidence available with regard to the time spent by family providing care to patients with FCS. A published report from an advisory board (Gelrud et al., 2017), indicates that carer time may relate closely with the complications of FCS. It is plausible that since complications such as episodes of acute pancreatitis are thought to be under-reported by patients, carer burden may consequently be underestimated in FCS families.

According to the advisory board authors, carers use their own holiday time to provide care for patients, during FCS complications.

Data on the impact of longer term complications arising from FCS is very limited, but a proportion of patients with FCS are expected to develop chronic pancreatitis in the longer term, as a result of repeated episodes of acute pancreatitis. Since carers of patients with FCS report that caring is focused around the complications of FCS, it is likely that over the life-time of FCS patients, carer time burden will be very substantial, and particularly in patients developing comorbidities such as diabetes or those developing chronic pancreatitis.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or

disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Epidemiological, observational, interventional clinical research conducted in relation to the technology has significantly contributed to a much-improved understanding of the natural history of FCS, the burden of FCS on patients and their families and carers and the clinical and wider benefits the technology offers to address the high unmet need in FCS. A number of further studies are ongoing, due to commence or in planning. [redacted] to a general population cohort, and several studies aimed at developing a FCS-specific outcome measure. Akcea is also currently undertaking a single-centre, open-label phase 2 study to evaluate the efficacy of novel compound for reduction of TG levels in patients with FCS (https://www.clinicaltrials.gov/ct2/show/study/NCT03360747?cond=FCS+Syndrome&rank=4). All these research initiatives will result in an improved understanding of the condition and possible new approaches for treatments.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Adoption of volanesorsen in the NHS would strengthen Akcea's footprint in the UK and result in consolidation and expansion of the company's European headquarter in Surrey. Akcea is committed to developing and commercialising further innovative medical technologies in disease areas of high unmet need. The availability of volanesorsen would positively impact the ability of Akcea to invest in further innovation and to forge collaborations with other UK-based innovators and to undertake further collaborative research into FCS (as with the Farr Institute for the CALIBER national history study) and other diseases and their treatment.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Assessments of the effectiveness of volanesorsen in routine clinical practice will be facilitated by triglyceride measurements. Triglycerides are typically measured approximately every three to six months in patients with FCS.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The first injection administered by the patient or carer should be performed under the guidance of an appropriately qualified health care professional. Patients and/or cares should be trained in the administration of this medicinal product in accordance with the patient information leaflet.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Akcea Therapeutics has discussed and obtained feedback from clinicians and patient groups on potential options for an appropriate service framework to support the delivery of volanesorsen to patients, in the anticipation that it is routinely commissioned within the NHS (post EAMS period).

At a recent advisory board, there was a consensus that a networked (hub and spoke) service, under the auspices of a service specification, would be necessary for the provision of adequate long-term dietetic support and coordination of care by a specialist nurse, without the need to significantly increase capacity and resource utilisation at specialist centres caring for FCS patients.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Not applicable.

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*
- *What evidence will be collected to reduce uncertainty*
- *How this evidence will be collected and analysed*
- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*
- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*
- *Funding arrangement, including any commercial proposals or financial risk management plans*
- *The roles and responsibilities of clinical and patient groups during the MAA*
- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

Not applicable.

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Not applicable.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched to identify the relevant clinical information:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)

17.1.2 The date on which the search was conducted.

The published literature searches were conducted on 19 March 2018. The searches of clinical trials registers were conducted on 29 March 2018.

17.1.3 The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Medline

1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.
12. LMF1.tw.
13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.
14. GPIHBP1.tw.
15. dyslipid?emia.tw.
16. Hypertriglyceridemia/
17. or/1-16
18. Fibric Acids/
19. (medium adj chain adj triglycerides).tw.
20. Fatty Acids, Omega-3.tw.
21. (Nicotinic acid or Niacin).tw.
22. Statins.tw.
23. Volanesorsen.tw.
24. IONIS-APOCIIIRx.tw.
25. ISIS304801.tw.
26. Plasmapheresis.tw.
27. Alipogene tiparvovec.tw.
28. Lomitapide.tw.
29. Mipomersen.tw.
30. Pradigastat.tw.
31. IONIS-ANGPTL3Rx.tw.
32. Evinacumab.tw.
33. or/18-32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized controlled trials/
37. random allocation/
38. double blind method/
39. single blind method/
40. or/34-39
41. clinical trial.pt.
42. exp Clinical Trials as topic/
43. (clin$ adj trial$).tw.
44. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

45. placebos/
46. placebo$.tw.
47. research design/
48. or/40-47
49. exp evaluation studies/
50. prospective studies/
51. or/49-50
52. 40 or 48 or 51
53. Observational studies/
54. 52 or 53
55. case report.tw.
56. Letter.pt.
57. historical article/
58. or/55-57
59. 54 not 58
60. "animal"/
61. "human"/
62. 60 not 61
63. 17 and 33 and 59
64. 63 not 62

Embase

1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.
12. LMF1.tw.
13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.
14. GPIHBP1.tw.
15. dyslipid?emia.tw.
16. Hypertriglyceridemia/
17. or/1-16
18. Fibric Acids/
19. (medium adj chain adj triglycerides).tw.
20. Fatty Acids, Omega-3.tw.
21. (Nicotinic acid or Niacin).tw.
22. Statins.tw.
23. Volanesorsen.tw.
24. IONIS-APOCIIIRx.tw.
25. ISIS304801.tw.
26. Plasmapheresis.tw.
27. Alipogene tiparvovec.tw.

28. Lomitapide.tw.
29. Mipomersen.tw.
30. Pradigastat.tw.
31. IONIS-ANGPTL3Rx.tw.
32. Evinacumab.tw.
33. or/18-32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized controlled trials/
37. random allocation/
38. Single Blind Procedure/
39. Double Blind Procedure/
40. Crossover Procedure/
41. Placebo/
42. randomi?ed controlled trial$.tw.
43. rct.tw.
44. (random$ adj2 allocat$).tw.
45. single blind$.tw.
46. double blind$.tw.
47. ((treble or triple) adj blind$).tw.
48. placebo$.tw.
49. Prospective Study/
50. or/34-49
51. case report.tw.
52. abstract report/ or letter/
53. Editorial.pt.
54. Letter.pt.
55. Note.pt.
56. historical article/
57. or/51-57
58. 50 not 57
59. animal/
60. human/
61. 59 not 60
62. 17 and 33 and 58
63. 62 not 61
64. limit 63 to (abstracts and human and english language and (abstract report or article or article in press or conference abstract or conference paper or "conference review"))

Pubmed
Search (((chylomicronemia[MeSH Terms]) OR pancreatitis[MeSH Terms]) OR hypertriglyceridemia[MeSH Terms]) AND cost effectiveness[MeSH Terms]

Cochrane Central Register of Controlled Trials
1. "Familial chylomicronemia syndrome"
2. MeSH descriptor: [Hyperlipoproteinemia Type I] this term only
3. Lipoprotein adj Lipase adj deficien*
4. MeSH descriptor: [Hypertriglyceridemia] this term only
5. "Volanesorsen"

6. "IONIS-APOCIIIRx"
7. "ISIS 304801"
8. #1 or #2 or #3 or #4
9. #5 or #6 or #7
10.#8 and #9

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website

17.1.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

17.1.7 The data abstraction strategy.

Data were extracted from all appropriate search results and supplemented with data obtained secondary publications as a result of manual search of bibliography primary publications. Full tect of each study was reviewed by one investigator and validated independently by a second investigator. Any discrepancies with regard to the data elements presented and extracted in an article were resolved by reaching a consensus. The study reports provided by the sponsor have also been included as primary data sources and the data was extracted for analysis from these sources. The abstratcs related to volanesorsen trials that were identified by systematic literature review were listed as related publications.

Specific outcomes from relevant studies are reported in section 9.6

17.2 Appendix 2: Search strategy for adverse events

The clinical SLR revealed no published or unpublished studies relevant to the PICO other than those within the volanesorsen programme (see Section 9.3). For this reason, a separate search for studies specifically addressing adverse events in the relevant population was not carried out.

17.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable.

17.2.2 The date on which the search was conducted.

Not applicable.

17.2.3 The date span of the search.

Not applicable.

17.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

17.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

17.2.6 The inclusion and exclusion criteria.

Not applicable.

17.2.7 The data abstraction strategy.

Not applicable.

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following databases were searched to identify the relevant clinical information:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)
- PubMed

17.3.2 The date on which the search was conducted.

The searches of clinical trials registers were conducted on 29 March 2018. The published literature searches in Ovid (Medline) was conducted on 27 April and in Ovid 9Embase) was conducted on 3 May 2018. The search on Cochrane was conducted on 2 May 2018. The search on PubMed was carried out on 4 May 2018.

17.3.3 The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline via Ovid

1. (Lipoprotein adj Lipase adj deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.

9. Apolipoprotein AV.tw.

10. APOA5.tw.

11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. (acute adj2 pancrea*).tw.

24. (chronic adj2 pancrea*).tw.

25. (pancrea* adj3 inflam*).ti,ab.

26. or/18,21-25

27. diabetes mellitus.mp.

28. exp diabetes mellitus/

29. exp Diabetes Mellitus, Type 2/

30. diabet*.ti,ab.

31. Diabetic Ketoacidosis.mp.

32. IDDM.tw.

33. NIDDM.tw.

34. (insulin? depend$ or insulin?depend$).tw.

35. ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.

36. ((typ$ 1 or typ$ I) adj diabet$).tw.

37. ((typ$ 2 or typ$ II) adj diabet$).tw.

38. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.

39. or/27-38

40. 17 or 26 or 39

41. Economics/

42. Socioeconomics/

43. Cost$.tw.
44. "costs and cost analysis"/
45. Cost allocation/
46. Cost-benefit analysis/
47. exp Cost effectiveness analysis/
48. ((Cost effectiveness or Cost-effectiveness) adj3 analysis).tw.
49. ((Cost utility* or Cost-utility*) adj3 analysis*).tw.
50. Cost control/
51. Economic aspect/
52. Financial management/
53. Cost savings/
54. exp Cost of illness/
55. Cost sharing/
56. "deductibles and coinsurance"/
57. Medical savings accounts/
58. exp Health care costs$/
59. Direct service costs/
60. exp Drug costs/
61. Employer health costs/
62. Hospital cost$/
63. Health care financing/
64. Health economics/
65. exp Health expenditures/
66. Capital expenditures/
67. Value of life/
68. exp economics, hospital/
69. exp economics, medical/
70. Economics, nursing/
71. Economics, pharmaceutical/
72. exp "fees and charges"/
73. exp budgets/
74. (low adj cost).mp.
75. (high adj cost).mp.
76. (health?care adj cost$).mp.
77. (fiscal or funding or financial or finance).tw.

78. exp Cost minimization analysis/

79. (cost adj estimate$).mp.

80. (cost adj variable).mp.

81. (unit adj cost$).mp.

82. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

83. or/41-82

84. letter/

85. Review/

86. Comment/

87. or/84-86

88. animal/

89. human/

90. 88 not (88 and 89)

91. (United Kingdom or UK or England or Scotland or Wales or Northern Ireland).tw.

92. NHS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

93. 40 and 83 and 87 and 91

94. 93 not 90

Embase via Ovid

1. (Lipoprotein adj Lipase deficien*).tw.

2. LPL.tw.

3. Hyperlipoprotein?emia Type I.tw.

4. (Familial adj chylomicronemia adj syndrome).mp.

5. chylomicron?emia.tw.

6. Apolipoprotein C-II.tw.

7. APOC2.tw.

8. Apolipoproteins C.tw.

9. Apolipoprotein AV.tw.

10. APOA5.tw.

11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. (acute adj2 pancrea*).tw.

24. (chronic adj2 pancrea*).tw.

25. (pancrea* adj3 inflam*).ti,ab.

26. pancreatectomy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

27. or/18,21-26

28. 17 and 27

29. diabetes mellitus.mp.

30. exp diabetes mellitus/

31. exp Diabetes Mellitus, Type 2/

32. diabet*.ti,ab.

33. Diabetic Ketoacidosis.mp.

34. IDDM.tw.

35. NIDDM.tw.

36. (insulin? depend$ or insulin?depend$).tw.

37. ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.

38. ((typ$ 1 or typ$ I) adj diabet$).tw.

39. ((typ$ 2 or typ$ II) adj diabet$).tw.

40. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.

41. or/29-40

42. 17 or 27 or 41

43. Economics/

44. Socioeconomics/

45. Costs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

46. "costs and cost analysis"/

47. Cost allocation/

48. Cost-benefit analysis/

49. exp Cost effectiveness analysis/

50. (Cost effectiveness or Cost-effectiveness).tw.

51. ((Cost utility* or Cost-utility*) adj3 analysis*).tw.

52. Cost control/

53. Economic aspect/

54. Financial management/

55. Cost savings/

56. exp Cost of illness/

57. Economic burden.tw.

58. Cost sharing/

59. "deductibles and coinsurance"/

60. Medical savings accounts/

61. exp Health care cost$/

62. Direct service costs/

63. Drug costs/

64. Employer health costs/

65. Hospital cost$/

66. Health care financing/

67. Health economics/

68. Health expenditures/

69. Capital expenditures/

70. Value of life/

71. exp economics, hospital/

72. exp economics, medical/

73. Economics, nursing/

74. Economics, pharmaceutical/

75. exp "fees and charges"/

76. exp budgets/

77. (low adj cost).mp.

78. (high adj cost).mp.

79. (health?care adj cost$).mp.
80. (fiscal or funding or financial or finance).tw.
81. exp Cost minimization analysis/
82. (cost adj estimate$).mp.
83. (cost adj variable).mp.
84. (unit adj cost$).mp.
85. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
86. or/43-85
87. letter/
88. Review/
89. Comment/
90. or/87-89
91. animal/
92. human/
93. 91 not (91 and 92)
94. 90 and 93
95. (UK or United Kingdom or England or Wales or Scotland or Ireland).tw.

96. 42 and 86
97. 28 and 86
98. 96 not 94
99. 97 not 94

Pubmed

Search (((chylomicronemia[MeSH Terms]) OR pancreatitis[MeSH Terms]) OR hypertriglyceridemia[MeSH Terms]) AND cost effectiveness[MeSH Terms]

Cochrane Central Register of Controlled Trials

1. "Familial chylomicronemia syndrome"
2. MeSH descriptor: [Hyperlipoproteinemia Type I] this term only
3. Lipoprotein adj Lipase adj deficien*
4. MeSH descriptor: [Hypertriglyceridemia] this term only
5. "Volanesorsen"
6. "IONIS-APOCIIIRx"

7. "ISIS 304801"
8. #1 or #2 or #3 or #4
9. #5 or #6 or #7
10.#8 and #9

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Manual checking of the references lists of relevant systematic literature reviews as well as in publications identified as primary source was also carried out.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The following databases were searched to identify the relevant data on health outcomes and resource use:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)

- PubMed

17.4.2 The date on which the search was conducted.

The searches of clinical trials registers were conducted on 29 March 2018.The published literature searches for utilities in Medline and Embase using Ovid were conducted on 1st May 2018. The search on Cochrane was conducted on 2 May 2018. The search on PubMed was carried out on 4 May 2018.

17.4.3 The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategy used in the electronic searches for utilities associated with chylomicronaemia and pancreatitis is presented below.

Embase and Medline

1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. pancreatitis.af.

24. (acute adj2 pancrea*).tw.

25. (chronic adj2 pancrea*).tw.

26. (pancrea* adj3 inflam*).ti,ab.

27. or/18,21-26

28. 17 and 27

29. "Quality of Life"/ or Quality Adjusted Life Year/

30. quality adjusted life years/

31. (qaly or qaly$).af.

32. qaly$.tw.

33. ((quality-adjusted or quality adjusted) adj life).tw.

34. (qaly$ or qald$ or qale$ or qtime$).tw.

35. disability adjusted life.tw.

36. daly$.tw.

37. health status indicators/

38. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

39. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

40. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

41. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

42. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

43. (euroqol or euro qol or euro-quol* or euro-qol* or eq5d or eq 5d or eq-5d).tw.

44. (euroqol or euro qol or euro-quol* or euro-qol* or eq5d or eq 5d or eq-5d).af.

45. (hql or hqol or h qol or hrqol or hr qol).tw.

46. (hye or hyes).tw.

47. health$ year$ equivalent$.tw.

48. health utilit$.tw.

49. (hui or hui1 or hui2 or hui3).tw.

50. disutili$.tw.

51. rosser.tw.

52. quality of wellbeing.tw.

53. qwb.tw.

54. willingness to pay.tw.

55. standard gamble$.tw.

56. time trade off.tw.

57. time tradeoff.tw.

58. tto.tw.

59. exp models, economic/

60. *models, theoretical/

61. *models, organizational/

62. economic model$.tw.

63. markov chains/

64. markov$.tw.

65. monte carlo method/

66. monte carlo.tw.

67. exp decision theory/

68. (decision$ adj2 (tree$ or analy$ or model$)).tw.

69. or/29-68

70. letter.pt.

71. editorial.pt.

72. comment.pt.

73. or/70-72

74. animal/

75. human/
76. 74 not (74 and 75)
77. 73 and 76
78. 28 and 69
79. 78 not 77

The complete search strategy used in the electronic searches for resource use:

Please see Section 17.4.7

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Supplementary searches were performed to complement the literature database searches and provide data from recent or ongoing trials. Sources for these searches included:

Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website.

17.4.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome or pancreatitis
Interventions	Volanesorsen or usual care
Outcomes	Health-related quality of life (for patients and carers) outcomes • Symptoms such as pain and fatigue • SF-36 • EQ-5D Economic outcomes • Direct and indirect costs • Cost-effectiveness (QALYs, ICERs) • Productivity • Resource utilisation
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

17.4.7 The data abstraction strategy.

The results obtained from search strategies for economic evidence in section 17.3 (Appendix 3) and for utilities in section 17.4 (Appendix 4) were screened to identify relevant studies for resource utilisation. Data were extracted from all appropriate search results and supplemented with data obtained secondary publications as a result of manual search of bibliography of primary publications. Full text of each study was reviewed by one investigator and validated independently by a second investigator. Any discrepancies with

regard to the data elements presented and extracted in an article were resolved by reaching a consensus.

Specific outcomes were captured to reflect the final NICE scope as below.

Quality of life outcomes:

- SF-36
- EQ-5D
- Pain

Economic outcomes:

- Direct and indirect costs
- Cost-effectiveness (QALYs, ICERs)
- Productivity
- Resource utilisation

17.5 Appendix 5: Methodology of non-RCT studies in FCS

Sections 9.1 and 9.2 provide full details of the methodology of the systematic literature review which was carried out but could not identify any studies that compared Volanesorsen with one or more other comparator in a head-to-head RCT. All the studies that were identified for which patient characteristics and treatments have been summarised in Table C3 in Section 9.2.5. However, an indirect comparison is not feasible due to the nature of the design of studies or in the case of pradigastat where the technology is not licenced in UK. For the purpose of illustrating this difficulty, all the study methodologies have been summarised in the following tables.

Study name	Gaudet D, Brisson D, Tremblay K, et al. Targeting APOC3 in the familial chylomicronemia
Objective	
Location	Chicoutimi Hospital
Design	Open-label, single arm
Duration of study	13 weeks
Patient population	3 patients
Sample size	3 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 3) and comparator(s) (n = 0)	Patients abstained from alcohol consumption for 48 hours before each study visit. After the baseline visit, patients received a 285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection. The last dose was administered on day 85, and the patients were then followed for another 91 days to monitor measures of efficacy and safety.
Baseline differences	Patient 2 had received Glybera 5 years earlier In Patients 2 and 3, measurements of LPL activity after the administration of heparin showed values that were less than 2 to 4 nmol of free fatty acids per minute per milliliter of plasma (<3% of normal levels) both before enrollment in the study
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	The patients were followed for 91 days, after the last dose has been administered on day 85, to monitor measures of efficacy and safety.
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Reduction of triglyceride levels in three patients with the familial chylomicronaemia syndrome and triglyceride levels ranging from 1406 to 2083 mg per decilitre (15.9 to 23.5 mmol per litre).
Secondary outcomes (including scoring methods and timings of assessments)	Fasting blood samples for measurement of APOC3, triglycerides, triglycerides in chylomicrons, apolipoprotein B-48, and other lipids at baseline, on day 8, and then weekly or every other week during the treatment period (until day 85) and then on days 92, 99, 127, and 176 during the safety follow-up period.

Study name	Rouis M, Dugi KA, Previato L, et al. Therapeutic Response to Medium-Chain Triglycerides and ω-3 Fatty Acids in a Patient With the Familial Chylomicronemia Syndrome
Objective	To investigate the LPL gene of a patient presenting classical features of the familial chylomicronaemia syndrome, including marked hypertriglyceridemia and recurrent episodes of pancreatitis.
Location	
Design	Case report
Duration of study	
Patient population	8-year-old black female with a history of reccurent episodes of pancreatitis requiring hospitalisation from the age of 3 with marked hypertriglyceridemia not responsive to a low-fat diet or nicotinic acid.The patient was diagnosed with LPL deficiency at 5 years old.
Sample size	1 patient
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 1) and comparator(s) (n = 17 untreated controls)	The administration (15 to 30 g/d) of an MCT oil–containing diet.
Baseline differences	NA
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	On this therapy the patient experienced no further episodes of abdominal pain or pancreatitis and the plasma lipoprotein profile remained normal for a period of 2 years
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	Analysis of lipoproteins, apolipoproteins, and plasma Lipid Analysis Quantitation of plasma HL Activity and LPL activity and mass Analysis for a circulating plasma inhibitor to rule out the presence of a potential inhibitor of the lipolytic system To determine size and abundance of LPL mRNA isolated from adipocytes as well as macrophages Sequence analysis of the LPL gene and of LPL cDNA to identify any mutations

Study name	Stroes ES, Nierman MC, Meulenberg JJ, et al. Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients.
Objective	To establish efficacy and safety of intramuscular application of this vector
Location	
Design	Open label study. LPLS447X-adeno-associated virus subtype 1(AAV1) vector was injected in the leg musculature of 8 LPL-deficient patients at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight (40 and 60 injections of 500 microliters, respectively)
Duration of study	3 months
Patient population	LPL-deficient individuals after intramuscular administration of a viral vector
Sample size	8 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 8) and comparator(s) (n =)	1(AAV1) vector was injected in the leg musculature at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	long-term follow up of triglycerides and local LPL protein and activity 31 months
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	To achieve a reduction in individual median fasting plasma TG to a level equal to or less than 10 mmol/L on top of diet, or to achieve a reduction in median fasting plasma TG equal to or more than 40% on top of diet.
Secondary outcomes (including scoring methods and timings of assessments)	Serious adverse events Median TG levels compared to baseline TG Muscle function tests and MRI-assessed fat content at the beginning versus the end of the trial.

Study name	Mingozzi F, Meulenberg JJ, Hui DJ, et al. AAV-1–mediated gene transfer to skeletal muscle in humans results in dose-dependent activation of capsid-specific T cells.
Objective	
Location	Academic Medical Center, Amsterdam
Design	8 subjects were enrolled in 2 dose cohorts (4 subjects per cohort) receiving 10^{11} gc/kg and 3×10^{11} gc/kg. Vector was administered intramuscularly into multiple sites at a dose of 1.6 to 4.2×10^{11} gc/site of injection
Duration of study	
Patient population	LPL-deficient subjects with missense mutations in both LPL alleles
Sample size	
Inclusion criteria	LPL-deficient subjects with missense mutations in both LPL alleles
Exclusion criteria	
Intervention(s) (n =8) and comparator(s) (n =)	4 patients in each cohort were administered 10^{11} gc/kg and 3×10^{11} gc/kg respectively. Vector was administered intramuscularly into multiple sites at a dose of 1.6 to 4.2×10^{11} gc/site of injection
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	Carpentier AC, Frisch F, Labbe SM, et al. Effect of Alipogene Tiparvovec (AAV1-LPLS447X) on Postprandial Chylomicron Metabolism in Lipoprotein Lipase-Deficient Patients
Objective	To determine the effect of i.m. administration of an adeno-associated viral vector (AAV1) for expression of LPL(S447X) in muscle (alipogene tiparvovec, AAV1-LPL(S447X)) on postprandial chylomicron metabolism and on nonesterified fatty acid (NEFA) and glycerol metabolism in LPLD individuals.
Location	ECOGENE 21 Clinical Research Center in Chicoutimi
Design	An open-label clinical trial (CT-AMT-011-02) Lipoprotein lipase-deficient (LPLD) subjects were administered alipogene tiparvovec at a dose of $1 \times 10^{(12)}$ genome copies per kilogram.
Duration of study	14 weeks
Patient population	LPLD subjects were diagnosed and selected based on a history of pancreatitis, fasting plasma TG greater than 10 mmol/liter, a post-heparin LPL activity 20% or less of normal, and confirmed homozygosity or compound heterozygosity for mutations in the LPL gene
Sample size	5 patients
Inclusion criteria	The LPLD subjects were diagnosed and selected based on a history of pancreatitis, fasting plasma TG greater than 10 mmol/liter, a post-heparin LPL activity 20% or less of normal, and confirmed homozygosity or compound heterozygosity for mutations in the LPL gene.
Exclusion criteria	
Intervention(s) (n = 5) and comparator(s) (n = 5)	Five overweight but otherwise healthy control subjects underwent assessment of postprandial chylomicron metabolism using similar methods except for meal fat content and tracer
Baseline differences	Two subjects had insulin-dependent diabetes mellitus (participants 1001 and 1002).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Fourteen weeks after alipogene tiparvovec administration chylomicron metabolism and plasma palmitate and glycerol appearance rates were determined
Statistical tests	Data are expressed as mean ± SD in the text and in the tables and as mean ± SEM in the figures, unless stated otherwise. Intragroup characteristics were compared by paired Student's *t* test or two-way ANOVA for repeated measures in the case of postprandial curves with pretreatment *vs.* posttreatment, postprandial time, and interaction as independent variables. A two-tailed *P*value <0.05 was considered significant.

Primary outcomes (including scoring methods and timings of assessments)	Change in chylomicron metabolism in response to treatment within the LPLD group Postprandial chylomicron TG levels and chylomicron 3^{H} excursion
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	Gaudet D, Méthot J, Déry S, et al. Efficacy and long term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open label trial.
Objective	To assess the long-term safety of alipogene tiparvovec and achieve a ≥40% reduction in fasting median plasma triglyceride (TG) at 3–12 weeks compared with baseline
Location	ECOGENE-21 Clinical Research Center, Chicoutimi, Quebec, Canada
Design	Open-label, dose-escalation clinical trial
Duration of study	
Patient population	14 LPLD patients with a history of pancreatitis and who participated in a prospective observational study (PREP-02)
Sample size	14 patients
Inclusion criteria	LPLD patients with a history of pancreatitis and who participated in a prospective observational study (PREP-02)
Exclusion criteria	
Intervention(s) (n = 14) and comparator(s) (n =)	Cohorts 1 (n=2) and 2 (n=4) received 3×10^{11}gc/kg, and cohort 3 (n=8) received 1×10^{12}gc/kg. Cohorts 2 and 3 also received immunosuppressants from the time of alipogene tiparvovec administration and continued for 12 weeks
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Biological activity and expression of LPL^{S447X} in the muscle was measured after 26 weeks,
Statistical tests	Because of intra-subject variability in TG levels, multiple data points were used to derive pre- and post-therapy values. The median of the six most recent measurements before the day of alipogene tiparvovec administration was used for pre-therapy values. All TG data from week 3 until and including week 12 were

	used for the main study post-administration TG response assessment. A linear mixed model was used to estimate the average reduction in individual TG after alipogene tiparvovec administration and whether there was a statistically significant reduction in TG calculated using median and mean values. Individual pre-therapy and post-therapy TG values until week 12, and 26, were compared using the non-parametric Wilcoxon test. A score of 0 or 1 was assigned to subject's TG levels to indicate success or failure (TG ≤10.00 mmol/L or > 10.00 mmol/L, respectively). Using a Chi-squared statistic, a Mixed Model Repeated Measures and Wilcoxon Signed Rank test, it was determined whether alipogene tiparvovec, or a specific dose, lowers TG significantly. All hypotheses were tested with an overall two-sided significance level of 0.05.
Primary outcomes (including scoring methods and timings of assessments)	Long-term safety profile of alipogene tiparvovec Reduction in fasting median plasma TG of at least 40%, 3–12 weeks after therapy compared to baseline
Secondary outcomes (including scoring methods and timings of assessments)	Reduction in fasting TG to ≤10.0 mmol/L within 12 weeks Biological activity and expression of $LPLS^{447X}$ in the muscle after 26 weeks Potential immune responses against $LPLS^{447X}$ and AAV1 capsid proteins Biodistribution and shedding of AAV1-LPLS447X vector DNA

Study name	Ferreira V, Twisk J, Kwikkers K, et al. Immune Responses to Intramuscular Administration of Alipogene Tiparvovec (AAV1-LPLS447X) in a Phase II Clinical Trial of Lipoprotein Lipase Deficiency Gene Therapy.
Objective	To analyse systemic and local immune responses against AAV1,for their impact on safety and the persistence of LPL transgene expression.
Location	ECOGENE-21 Clinical Research Center, Chicoutimi, Quebec, Canada
Design	An open-label, single-dose study evaluating the safety and efficacy of alipogene tiparvovec (AAV1-LPLS^{447X}),
Duration of study	14 weeks
Patient population	Five subjects with LPL deficiency (LPLD)
Sample size	5 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 5) and comparator(s) (n =)	Five subjects with LPLD were exposed to a fixed dose of 1×10^{12} gc/kg alipogene tiparvovec administrated as a one-time series of IM injections into the lower extremities. All subjects were treated and maintained with immune suppression starting shortly before administration until 12 weeks after administration of alipogene tiparvovec
Baseline differences	None
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Subjects were monitored at predefined intervals for various clinical parameters, including routine hematology, biochemistry, and immune parameters. No hematology and routine biochemical assessments were planned after week 12, whereas immunological parameters continued to be assessed after 12 weeks. A biopsy of the injected muscle was scheduled between 14 and 52 weeks after vector administration.
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Impact of systemic and local immune responses against AAV1 on safety and the persistence of LPL transgene expression
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	Meyers CD, Tremblay K, Amer A, et al. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome.
Objective	To assess the safety, tolerability, and effects of the DGAT1 inhibitor pradigastat on fasting and postprandial plasma TG in patients with FCS and severe hypertriglyceridemia.
Location	ECOGENE-21 clinical trial center and laboratories Chicoutimi, Canada
Design	Open-label clinical study
Duration of study	3x21 days
Patient population	Familial chylomicronaemia syndrome (FCS) patients
Sample size	Six Familial chylomicronaemia syndrome (FCS) patients
Inclusion criteria	FCS patients aged 18–75 years not on any lipid-lowering medications for ≥8 weeks prior to enrolment were eligible for the study. Patients had to meet at least two of the following criteria: fasting TG ≥890 mg/dL (>10 mmol/L); post-heparin plasma LPL activity ≤20% of normal; LPL mass >5% and/or confirmed homozygote or compound heterozygote mutations in LPL gene (null alleles) with LPL mass >5% and LPL activity ≤20%.
Exclusion criteria	Pregnant/nursing women and patients with uncontrolled diabetes or an active pancreatitis episode within 1 month of enrollment were excluded
Intervention(s) (n = 6) and comparator(s) (n =)	Patients underwent three consecutive 21 day treatment periods (pradigastat at 20, 40 & 10 mg, respectively). Treatment periods were separated by washout periods of ≥4 weeks
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Following the final 24 hour post- baseline meal tolerance test (MTT) blood sample, patients returned to their home. An end of study visit was performed at least 14 days after the final treatment period ended.
Statistical tests	A dose comparison was carried out for fasting TG data, which was analyzed using a linear mixed effect model for repeated measurements. The model included treatment, time, and treatment by time interaction as factors; baseline as a covariate; and subject as a random effect. Postprandial peak and AUC TG were analyzed for dose comparison by a linear mixed effect model, with treatment and baseline values as fixed effects and subject as a random effect; however, the

	pharmacokinetic parameters were analyzed on Day 21 using an ANOVA model with dose level as a factor, and subject as a random effect. Estimates of the treatment effect of different dose levels, together with 90% CI were obtained. Log-transformation was applied prior to the analysis and the results were back transformed and reported in the original scale. All the above analyses were repeated for secondary end points. Missing measurements for AUC were imputed by linear interpolation only if two adjacent time points had observed data and was set to missing otherwise. Missing measurements at the end of the time interval were imputed from the previous time point.
Primary outcomes (including scoring methods and timings of assessments)	Reduction in fasting triglyceride
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	An Open Label, 52-week, Safety and Tolerability Extension to a Randomized, Double-blind, Placebo Controlled Study of LCQ908 in Subjects With Familial Chylomicronemia Syndrome.
Objective	To evaluate the overall long-term safety and tolerability of LCQ908 in patients with Familial Chylomicronaemia Syndrome, who either discontinued from the CLCQ908B2302/NCT01514461 study (due to tolerability issues) or completed the CLCQ908B2302/NCT01514461 study after 52 weeks. In addition, patients who had previously completed study CLCQ908A2212/NCT01146522 were eligible to participate.
Location	United States, Washington Novartis Investigative Site Seatlle, Washington, United States, 98104 Canada, Quebec Novartis Investigative Site Chicoutimi, Quebec, Canada, G7H 7P2 Novartis Investigative Site Ste-Foy, Quebec, Canada, G1V4M6 Canada Novartis Investigative Site Ouest-Montreal, Canada, H2W1R7 France Novartis Investigative Site Nantes, France, 44093 Novartis Investigative Site Paris Cedex 13, France, 75651 Germany Novartis Investigative Site Hamburg, Germany, 20246 Netherlands Novartis Investigative Site Meibergdreef 9, Netherlands, 1105 AZ South Africa Novartis Investigative Site

	Cape Town, South Africa, 7925 United Kingdom Novartis Investigative Site Manchester, United Kingdom, M13 9NT
Design	Open-label, single arm Patients abstained from alcohol consumption for 48 hours before each study visit. After the baseline visit, patients received a 285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection. The last dose was administered on day 85, and the patients were then followed for another 91 days to monitor measures of efficacy and safety.
Duration of study	52 weeks
Patient population	38 participants
Sample size	38 participants
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Subjects that either discontinue prematurely or complete the CLCQ908B2302 study after 52 weeks or FCS subjects who have previously completed study CLCQ908A2212
Exclusion criteria	1. Subjects discontinued from the CLCQ908B2302 study for serious, potentially study drug related adverse events. 2. Subjects from the CLCQ908B2302 study who have developed any other contraindication to participation (for example, renal failure) 3. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. 4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 5. Subjects with type 1 diabetes mellitus or type 2 diabetes mellitus if HbA1C is ≥ 8.5%. 6. Treatment with fish oil preparations within 4 weeks prior to randomisation. 7. Treatment with bile acid binding resins (i.e., colesevelam, etc) within 4 weeks prior to randomisation.

	8. Treatment with fibrates within 8 weeks prior to randomisation. Washout may occur following screening if required. 9. Glybera [alipogene tiparvovec (AAV1-LPLS447X)] gene therapy exposure within the two years prior to screening. 10. eGFR <45 ml/min/1.73m2 or history of chronic renal disease. Other protocol defined inclusion/exclusion criteria may apply.
Intervention(s) (n =) and comparator(s) (n =)	Patients initiated at 10 mg/day. After at least 8 weeks of treatment with a dose, optional up-titration to the next possible dose will be allowed. One down titration allowed from the highest dose attained.
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Number of Patients With Any Adverse Events, Serious Adverse Events and Death [Time Frame: 52 weeks]
Secondary outcomes (including scoring methods and timings of assessments)	1. Changes From Baseline in Triglyceride Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52] Blood samples were collected for a fasting lipid panel, including total triglycerides. Lipid measurements were collected after a 12 hour (overnight) fast. The maintenance of effect was assessed on triglyceride levels during continued therapy with LCQ908 for up to 52 weeks. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

2. Changes From Baseline in Cholesterol Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including cholesterol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

3. Changes From Baseline in HDL and Non HDL Cholesterol Levels up to 52 Weeks
[Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including HDL and non HDL cholesterol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

4. Changes From Baseline in Glycerol Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including glycerol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212,

	baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100. 5. Changes From Baseline in Free Fatty Acid Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52] Blood samples were collected for a fasting lipid panel, including free fatty acid level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100. 6. Changes From Baseline in Apolipoprotein A1 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52] Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein A1. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

7. Changes From Baseline in Apolipoprotein B-48 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein B-48. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

8. Changes From Baseline in Apolipoprotein B-100 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein B-100. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

[redacted]

[redacted]

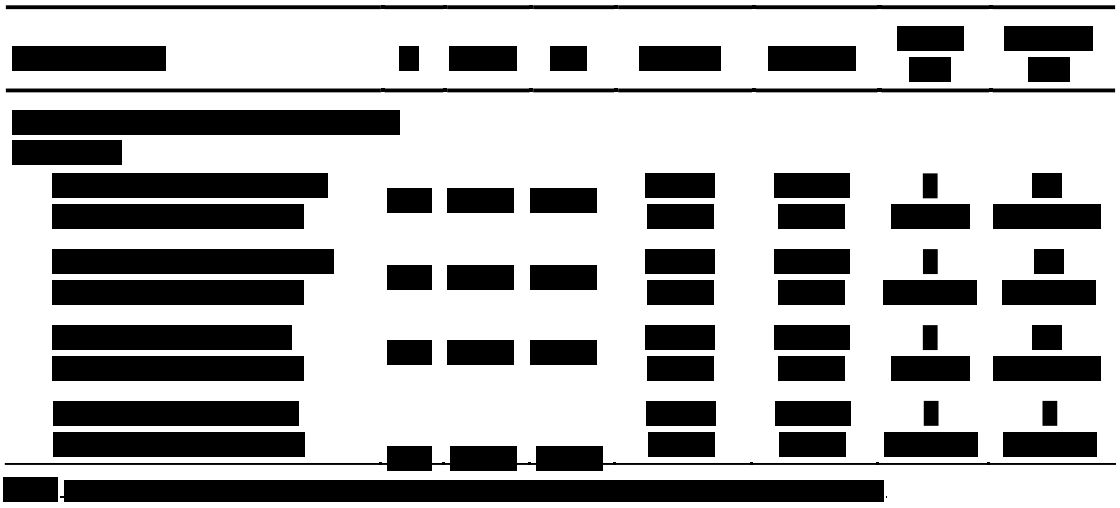
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



17.7 Appendix 7: Clinical expert survey

17.7.1 Questionnaire

CLINICAL EXPERT QUESTIONS

1) Description of Chronic Pancreatitis presentation in FCS: symptomatology and management.

For the health economic evaluation of Volanesorsen by NICE, Akcea need to assess the progression of patients with FCS over the course of an individual's lifetime. A proportion of patients with FCS will experience repeat episodes of acute pancreatitis, and some will go on to develop chronic pancreatitis (CP).

There is a lack of evidence in the literature with regard to the management and use of healthcare resources associated with these conditions. As this has significant health economic relevance, Akcea need to provide NICE with detailed insights in the absence of clear evidence.

With this in mind, please could you answer the following questions:

a) What symptoms, if any, are typical of patients with high triglyceride (HTG) related CP?

Notes:

---

b) What healthcare resources are required to manage these symptoms (circle) (drugs, outpatient appointments, tests and investigations, A&E attendances, hospital admissions including surgical intervention/s and/or ICU)?

Notes:

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c) In your experience, what proportion of these patients require hospital admission, surgical intervention, ICU admission/ nursing care at home/ palliative care?

Notes .....

2) Health related quality of life for FCS patients with Chronic Pancreatitis.

The overall health status (QoL) measure, known in health economics as the 'utility', places overall health status on a scale from 0 (dead) to 1 (perfect health).

Akcea has commissioned independent research to estimate the utilities for patients according to different combinations of disease history – including both triglyceride level and history of acute pancreatitis (see table below). For example, a patient with high triglycerides and a history of acute pancreatitis is estimated to have a utility of 0.459.

Table 1 Utility values by health state

Health State	Utility estimate
Low triglycerides, no history of acute pancreatitis	0.797
High triglycerides, no history of acute pancreatitis	0.597
Low triglycerides, history of acute pancreatitis	0.741
High triglycerides, history of acute pancreatitis	0.459

In the model, we also require an estimate for the utility associated with CP. Unfortunately, there is very little evidence in the literature about utilities for CP.

The closest approximation can be found in a paper which reported EQ5D utilities from a cohort of CP patients awaiting surgery, and at follow up.[7] However, the majority of patients in this study had an alcohol- related cause of CP which is unlikely to be comparable to an FCS population with CP. Utilities for this alcohol- related CP group at baseline were 0.335 or 0.275 (endoscopic drainage and surgery group) respectively.

[7] Laramée P, Wonderling D, Cahen DL, et al Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis BMJ Open 2013;3:e003676. doi: 10.1136/bmjopen-2013-003676

Given that the FCS population with CP may be different from a population with alcohol- related CP, is the figure 0.459 described above [for acute pancreatitis, high triglycerides] appropriate enough for the group of patients we are considering ie FCS patients with CP? Put another way, is it reasonable to assume that the utility associated with CP is at best equivalent to that for "High triglycerides, history of acute pancreatitis"? (as set out in Table 1).

Q Do you agree with this reasoning? Yes/ No

If no, please explain?

Can you also help our understanding by answering the following questions:

a) Could you give us an impression of the impact of CP on a patient in terms of the following:

	High	Med	Low
Mobility			
Usual activities			
Pain			
Anxiety/ depression			
Sleep			
Fatigue			

b) Could you please comment on the impact of CP on carers and families? High/ Med/ Low

Are there any specific patients for whom this carer burden may be particularly significant?

c) Finally, could you give us an idea of the risk of an untreated patient with FCS developing CP in the course of their lifetime? What is the proportion of FCS patients that will ultimately progress to CP at some stage during their life time? Suggest a percentage
eg 25%, 50%, 75%, other % [INSERT]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

		[redacted]
	[redacted]	[redacted]

		[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

		[redacted]
	[redacted]	[redacted]

	[redacted]	[redacted]

17.8 Appendix 8: AFT model outputs

Time to first/next Acute Pancreatitis event

	Time to first Acute Pancreatitis event				
	Coef.	Std. Error	HR	95% CI	
(Intercept)					
Age (years)					
Women vs. men					
TG [10,22.7) vs. <10					
TG 22.7+ vs. <10					
History of acute pancreatitis					
TG [10,22.7) * history of AP					
TG 22.7+ * history of AP					

Time to diagnosis of Chronic Pancreatitis

Time to diagnosis of Chronic Pancreatitis

	Coef.	Std. Error	HR	95% CI	
(Intercept)					
Age (years)					
Women vs. men					
TG [10,22.7) vs. <10					
TG 22.7+ vs. <10					
History of acute pancreatitis					
TG [10,22.7) * history of AP					
TG 22.7+ * history of AP					

Time to diagnosis of type 2 diabetes

Time to diagnosis of type 2 diabetes

	Coef.	Std. Error	HR	95% CI	
(Intercept)					
Age (years)					
Women vs. men					
TG [10,22.7) vs. <10					
TG 22.7+ vs. <10					
History of acute pancreatitis					
TG [10,22.7) * history of AP					
TG 22.7+ * history of AP					

18 Related procedures for evidence submission

18.1 Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘[redacted] and information submitted under [redacted]

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

18.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technologies (HST)

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Dear Luke

The Evidence Review Group, School of Health & Related Research Sheffield and the technical team at NICE have looked at the submission received on 20th June from Akcea Therapeutics. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **26th July 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (Orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Systematic review

A1. **Priority question:** The number of included studies for volanesorsen is stated to be 4 in the header of the final box, but then listed as 3 in subheading "Volanesorsen", and then four studies are actually listed. These are listed as 2 published RCTs, 1 open label study and 1 unpublished RCT. The submission goes on to report three of these studies, which are 2 published RCTs (APPROACH and COMPASS) and one unpublished open label study (APPROACH OLE). A fourth study appears in Table C3 (p57), which does not appear to be an unpublished RCT, and nor is a reason given for excluding it. Please clarify and provide data from the fourth study if it meets the inclusion criteria for the review.

A2. **Priority question:** No quality assessment is provided for APPROACH OLE or COMPASS. Please provide quality assessment using an appropriate tool for each study.

A3. In Table C1 ("Selection Criteria for published studies", p53) it is stated that no study type restrictions were used for the effectiveness review. It is further stated in section 9.2.2 (p54) that case reports were eligible for inclusion. However, in the appendices (17.1.4) the ERG notes that a study type filter specifically excluding case reports has been applied to both the Medline and EMBASE search strategies. Please explain the justification behind this given your stated inclusion criteria.

A4. Table C1 (p52) lists the inclusion criteria. The outcomes fatigue, neurological and psychological impact and HRQoL do not appear in the list of included outcomes, but they are part of the NICE scope. Please clarify if studies reporting these outcomes would have been excluded.

A5. The intervention is stated as "volanesorsen". However, the PRISMA flow diagram lists many other treatments. Please clarify why there is an apparent mismatch between the PRISMA and the inclusion criteria?

A6. Please clarify if any studies were excluded on the basis of language, and if so what these were?

A7. The PRISMA flow diagram (Figure 8, p54) does not appear to add up. There were 1330 studies after deduplication, and 951 abstracts were excluded. This should leave 379 citations being retrieved at full text and the reasons for exclusion of these should be reported. However, only 6 citations are listed as having been excluded. Please clarify.

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A8. The ERG notes that reference lists of relevant systematic reviews and included studies were manually checked for any additional studies. Please clarify whether any forward citation searching (of more recent papers citing those included) was conducted also.

A9. Please cite the source of the search filters used to identify included study types in the database searches for the effectiveness studies (Appendix 1).

APPROACH and **APPROACH OLE baseline characteristics**

A10. **Priority question:** Please provide data by trial arm and for the whole trial on:

- Diabetics and use of insulin
- Adherence to diet after the stabilisation period
- Numbers of patients with 0, 1 and ≥2 pancreatic attacks in the previous 5 years
- Patients who had previously been enrolled in other clinical trials, what these clinical trials were of, and whether the effects of these trials are likely to have worn off, e.g. in the case of gene therapies such as Glybera
- Genetic subgroups

APPROACH and APPROACH OLE heterogeneity

A11. The NICE scope calls for an investigation into heterogeneity of health benefits within the population. Please clarify to what extent you have considered response heterogeneity?

APPROACH and APPROACH OLE Withdrawals

A12. Throughout APPROACH and APPROACH OLE patients can withdraw voluntarily or due to adverse events or be lost to follow-up.

- Please clarify if lost to follow-up in Figure 11 refers exclusively to patients who did not enter the post-treatment evaluation phase?
- Please provide a list of all patient withdrawals and the exact reason for withdrawal (e.g. not enough time, lack of efficacy, type of AE) by treatment group and the time of withdrawal.
- If available, please provide non-enrolment reasons for all patients between APPROACH/COMPASS and APPROACH OLE.
    - Please clarify how was "satisfactory completion of APPROACH or COMPASS" judged? (Table C7, APPROACH OLE inclusion criteria). How many patients were excluded on this basis?

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- Please clarify how many patients were excluded due to unwillingness to comply with lifestyle requirements?

APPROACH trial

A13. **Priority question:** Please clarify how many pancreatitis events were there in each arm?

A14. **Priority question:** Please clarify why the data in Figure 13 (p88) do not match the data reported in Table C13 (p84)? Please provide the same figure using the data from Table C13. Is the increase in TG levels for patients on volanesorsen seen from months 3 to 12 in Figure 13 due to treatment discontinuations? i.e. Can you show that the TG levels would be stable from month 3 to 12 if patients that had discontinued treatment were taken out of this figure? Please explain why the TG levels in the placebo group initially increased and then decreased? Finally, please provide confidence intervals around the mean change from baseline.

A15. **Priority question:** Given that the submission states that patients with a history of pancreatitis have a statistically significant benefit (p89), please provide Figure 13 (p87) by the number of pancreatitis attacks in the last 5 years (0, 1, 2+).

A16. **Priority question:** Please clarify, how was the value 750mg/dL derived as a pre-specified cut-off for the responder analysis in APPROACH? How was the 40% reduction cut-off for the second responder analysis in APPROACH derived? (Table C6, p65) Please explain, why were two different definitions of responder included in the analysis plan? Why do these values not match the values used for the discontinuation rule or the values used in the model to define low, intermediate and high risk TGs?

A17. It was stated in the submission (Table C6, p66) that "[redacted]".

- Please clarify whether this is for patients for which documentation is missing, patients that have never had pancreatitis, or a combination of the two?
- If the first of the above, please explain how these patients were randomised as one of the stratification factors was history of pancreatitis.
- Please provide clarification about why this capping was applied, and what the justification for choosing 28% was.

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- Please provide the percentage of such patients who were recruited in the trial.

A18. Please specify which subgroup analyses are pre-planned? Is the analysis [redacted] pre-planned (page 89)? Please provide which covariates these are adjusted for?

A19. Clinical advisors to the ERG suggested that the patient group that they might expect to experience greater benefit would be those with high TG levels and a recent history of pancreatitis. Please comment. Please also provide a rationale for why [redacted] were excluded from the trial.

A20. In Table C6 (p66) it is stated that you use '[redacted]

i) Please clarify, why were other baseline factors not included within the adjustment for the primary analysis? Please comment on and provide the impact on the results (Table C13, p84) adjusting for baseline covariates, including where possible those stipulated in question A10 above.

ii) Please clarify whether secondary analyses were adjusted and if not please comment on and provide the impact on the results (Table C13) adjusting for baseline covariates, including where possible those stipulated in question A10 above.

A21. Please clarify if there is a difference between the FAS analyses reported in the clinical section of the report and the ITT analyses in the modelling section. Please provide definitions for both.

A22. The CSR states that the following two tertiary endpoints were investigated:

- Percent change from Baseline in fasting apolipoprotein B-48 (apoB-48) and chylomicron TG
- Percent change from Baseline in post-prandial apoB-48 and chylomicron-TG

Please provide analyses for the above endpoints.

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A23. Please explain why quality of life was higher than the same age patients in the general population? Is there any evidence to suggest only the most well patients completed the questionnaires?

A24. In the submission on page 99, it is stated that there were 12 serious adverse events, but only two are described (grade 4 thrombocytopenia). Please clarify what the other serious adverse events were in each arm, and whether these were considered to be related to treatment?

A25. In the CS (p97) it is reported that [redacted]. Please clarify, is there any clinical reason why volanesorsen might lead to diabetes mellitus?

A26. Please provide data for all adverse events that occured in 3% or more of volanesorsen patients.

APPROACH OLE

A27. **Priority question:** In Figure 14 (p93), the patient numbers at each time point do not seem to match the number of withdrawals reported in table C11 (p79). Please clarify the reason why patients are missing at each time point in Figure 14 (p92). Please, also clarify, can it be reproduced with the x-axis to scale? Finally, please could you recreate this using the December 2017 cut off? Are these results based on an adjusted analysis? If not, please also present this.

A28. **Priority question:** There are very few patients still on treatment in the APPROACH-OLE study at the January 2017 data cut and the ERG considers that it is difficult to draw any conclusions from this analysis. If possible, please use a later data cut for the efficacy data than the January 2017 analyses eg. the safety data uses a December 2017 data cut.

A29. In the submission, on p74 it is stated that "there were no differences between the patient populations in these two studies" (referring to APPROACH and APPROACH OLE). However, the baseline characteristics in Table C8 (p74) and C9 (p75) show that treatment naive patients had much lower rates of abdominal pain than treatment experienced patients in APPROACH OLE or than either group in APPROACH. Also, mean fasting TG levels were higher in the treatment naive group of APPROACH OLE and both APPROACH groups than the experienced group in APPROACH OLE.

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- Please clarify how the statement about there being no differences between patients in the two studies accurately describes these data?

A30. APPROACH OLE includes one patient not from APPROACH at the interim analysis, according to text in the submission, on page 74. Table C11 (p79) states there were no patients from COMPASS in the interim (MAA) analysis, so logically this would suggest the patient was a patient who had not been in either trial, and so would not have 12 months of data before APPROACH OLE commenced (assuming the MAA analysis and the interim analysis are the same analysis). However, Figure 14 (p92) shows all patients have 12 month data from a trial (n=11 experienced, n=18 naive) before APPROACH OLE started. Please clarify why there is an apparent mismatch?

A31. All results are presented separately for the treatment-experienced and -naive groups for APPROACH OLE. Please clarify if this subgrouping was planned or post-hoc.

Continuation rule

A32. **Priority question:** Please clarify, what proportion of patients would have discontinued treatment under the proposed treatment continuation rule in the full APPROACH and APPROACH OLE analysis sets? What proportion of patients would have discontinued under the rule in the subgroup of patients who had dose reductions from APPROACH and APPROACH OLE? Please explain, what proportion of patients do you predict would discontinue under the rule, at the proposed reduced bi-weekly dose? Please, also clarify, what impact would you expect this to have on the results?

Bi-weekly dosing

A33. **Priority question:** Please clarify how many patients across APPROACH, APPROACH OLE and COMPASS received bi-weekly doses of volanesorsen for long enough to assess TG levels within this group? Please provide TG levels in these patients, showing the change in levels from weekly to bi-weekly dosing using a more recent data cut point, e.g. December 2017.

- If this is not available, we note the following from the FDA assessment of this treatment "In the applicant's analysis of the effect of dose interval change or dose pauses in patients that completed CS6-pivotal, TG decreased from baseline by 54% at Month 12 in the 13 VLN-treated patients that completed the study with a dose adjustment compared to a 76% reduction in the 6 VLN-treated patients that maintained weekly VLN 300 mg for 52 weeks." Please provide details of this analysis and appropriate summary statistics, and any other analyses that might help to confirm the results from the PK/PD analysis.

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Exposure-adjusted discontinuations

A34. **Priority question:** Please clarify, whether years of exposure from APPROACH were included in the "total years of exposure"?

A35. **Priority question:** Please provide the equivalent of Table C19 (p106) for the treatment naive group.

A36. Please provide details about the method used for calculating the exposure adjusted discontinuation rates, see onpage 107.

A37. Please explain, is there any reason why dose adjustments occurred more quickly on average in COMPASS than in APPROACH or APPROACH OLE?

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Section B: Clarification on cost-effectiveness data

B1. **Priority question:** We asked in question A28 for you to provide a later data cut for the efficacy data than the January 2017 analyses. Please could you use this later data cut to assess the appropriateness of the transition probabilities from month 4 onwards [redacted] As stated previously, it is difficult to draw any conclusions from the APPROACH OLE data presented due to the limited number of patients on treatment at the January 2017 data cut. Please also revisit the assumption around the bi-weekly discontinuation rates based on the later data cut.

B2. **Priority question:** Please clearly describe where the figures in Table D8 (p170) are derived from to estimate the reduced efficacy associated with a bi-weekly dose compared with a weekly dose.

B3. **Priority question:** Please could you explain why you did not include patients in defining the health states for the vignette study? Please could you highlight the literature or the clinical input that led to such different symptoms for the low TG and high TG levels? The ERG's clinical experts suggest that TG level *per se* would not impact upon patient quality of life. Therefore, please also present an analysis which assumes that the utilities for low, medium and high TG levels are the same.

B4. **Priority question:** The PSA results should be presented as the base case ICER since they account for non-linearity in the model. Since they are substantially different to the deterministic results, all other scenario and sensitivity analyses should be undertaken using the PSA parameters. Please rerun all of the results using the PSA rather than the deterministic parameters.

B5. The MEDLINE and EMBASE search strategies for the cost-effectiveness review include terms relating to the UK. Please clarify, was the intention to restrict the scope of this review to results from the UK, as this does not appear explicit in the inclusion/exclusion criteria?

B6. The ERG notes that reference lists of relevant systematic reviews and included studies were manually checked for any additional studies. Please clarify whether any forward citation searching (of more recent papers citing those included) was conducted also.

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B7. Please cite the source of the search filters used to identify included study types in the database searches for the economic evidence (Appendix 3) and utilities (Appendix 4).

B8. Please could you provide further explanation about where the acute pancreatitis disutility has been derived from? Please clarify why you did not use the vignette data for the acute pancreatitis health state but instead estimated the utility based on the utilities in the other health states from the vignette study. Please also show the calculation to achieve a disutility of 0.22.

B9. It is our understanding that the transition probabilities are estimated using the formula P(TG transition)*P(dose transition)*P(AP event). In order for this to be correct, each of these must be independent. Please could you comment on this and amend the model if necessary.

B10. In the 'Trial Dose data' worksheet, it is unclear where the 12 months+ data is from (AT34: BF37). Please could you explain or amend these figures?

B11. CALIBER analysis

- Please provide the rationale that the patient's age was [redacted].
- Please provide the model equation used for the AFT model in the analysis to predict the incidence of AP, CP and diabetes.

B12. Please clarify, why did you choose a 3-month cycle length given that patients are treated and monitored every 2 weeks? Please confirm whether in the trial and in practice patients are/ would be able to discontinue treatment/ adjust their dose every 2 weeks.

B13. Whilst the submission states that a half cycle correction is not required due to the short length of the cycle, the ERG requests that this is applied because it could have a substantial impact on the model results in this case. Please apply half cycle correction.

B14. Please clarify, why was the 3 month fasting TG measurement taken as the average of week 12 and week 13, rather than using the measurement from week 13 directly? (52weeks/4=13weeks). Similarly, for the 6 and 12 month TG measurements; please explain why not use week 26 and week 52 respectively?

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B15. **Priority question:** Please explain the clinical rationale for choosing the cut-off of 22.7mmol/l for your health states in the model? Please provide supporting data to show that there is a step change in risk at this point, rather than a continuous change.

B16. **Priority question:** The impact of moving from a weekly dose as in APPROACH to a bi-weekly dose is highly uncertain, yet very little sensitivity analyses have been undertaken around the efficacy and discontinuation parameters to explore this. Please undertake a range of sensitivity analyses to explore the impact of plausible effects on these parameters.

B17. Please explain, what is the justification for using CALIBER for AP naive and AP1, but not AP2+? On page 177 in the submission, you state that 'Patients in APPROACH with a history of 2+ events in the past 5 years had a mean annual AP rate of 0.746 vs. the rate of 0.2 from the AP-experienced, 22.7+ mmol group from CALIBER.' However, no comparison is provided for patients in APPROACH with a history of <2 events and CALIBER to know whether this too is inconsistent.

B18. The cost of bi-weekly and weekly volanesorsen appears to be similar within the formula, given that both estimates use 26/4 to estimate the frequency. Please correct the cost of weekly volanesorsen.

B19. The annual cost of chronic pancreatitis taken from Hall et al, 2014, includes both direct and indirect costs. Please could you input an estimate that includes only direct costs?

B20. It is stated that the model uses a time horizon of 100 years, but in the model it is 46+50=96 years. Please could you extend the time horizon to match the text in the report?

B21. The mortality rate is calculated by multiplying the relative risk of dying from diabetes by the relative risk of dying from acute pancreatitis (Vola- Markov, SoC - Markov, column G). Are these relative risks independent? Please amend the parameters in the model if necessary.

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Section C: Textual clarifications and additional points

C1. **Priority question:** A substantial amount of text is marked as confidential. Please could you check that all of this text is confidential? For example, data that is provided on Clinicaltrials.gov is in the public domain. Please provide updated submission with correct marking.

C2. Submission, Figure 9 page 65: Please clarify the weeks of the post-treatment evaluation period. This is currently stated to be [redacted], however we think this should read [redacted] weeks.

C3. Please clarify if the sentence on page 89 "who had experienced 2 attacks in the last 5 years" should read "who had experienced ≥2 attacks in the last 5 years".

C4. Submission, page 141, "[redacted] appears to be missing the word "not" after "where absolute TG levels have". Please confirm.

C5. In the submission, in Table D6 (p167), it is stated that patients are assumed to be on reduced dose 'if patient was classed as being on once every weeks dosing or had 6 or more pauses in that cycle.' Please clarify that this should say 'if patient was classed as being on once every 2 weeks dosing…'

C6. In the submission, in Table D7 (p169) it is stated that for month 9 TG levels, in the third instance, 'Use the average of the Week 6 and Week 9 endpoints'. Should this say Month 6 and Month 10 endpoints'?

C7. Submission page 202 it is stated that "separate rapid searches using were carried out to…". This appears to contain a typo. Please confirm if "using" should be deleted, or if the sentence is incomplete.

C8. In Appendix 6 (p318), it is stated that '[redacted] Please confirm whether this should not include the word 'never' and instead read '...who had experienced acute pancreatitis.'

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C9. Submission page 319 the sentence “No participants reported a” is incomplete. Please clarify what this should say.

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Highly Specialised Technologies (HST)

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Dear Luke

The Evidence Review Group, School of Health & Related Research Sheffield and the technical team at NICE have looked at the submission received on 20th June from Akcea Therapeutics. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **26th July 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed [redacted] on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Orsolya Balogh, Technical Lead (Orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely,

Sheela Upadhyaya
Associate Director – Technology Appraisals and Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Systematic review

A1. **Priority question:** The number of included studies for volanesorsen is stated to be 4 in the header of the final box, but then listed as 3 in subheading "Volanesorsen", and then four studies are actually listed. These are listed as 2 published RCTs, 1 open label study and 1 unpublished RCT. The submission goes on to report three of these studies, which are 2 published RCTs (APPROACH and COMPASS) and one unpublished open label study (APPROACH OLE). A fourth study appears in Table C3 (p57), which does not appear to be an unpublished RCT, and nor is a reason given for excluding it. Please clarify and provide data from the fourth study if it meets the inclusion criteria for the review.

Response to A1:

A total of 4 potentially relevant clinical trials of volanesorsen were identified. These comprise two published RCTs (APPROACH[1] and COMPASS) and two open label studies (one unpublished: APPROACH OLE, and one published: Gaudet et al. 2014).

Three of these studies were written up in detail as they were considered to be directly relevant with respect to the decision problem. These were APPROACH, APPROACH OLE and COMPASS. The fourth study, Gaudet et al. 2014, identified in searches as potentially relevant, was not written up in detail in the Akcea submission as it was not considered to address the decision problem. The fourth study was a phase II, open-label, single arm study of volanesorsen in 3 patients with FCS. A summary of this study, including reported outcomes, was included in the submission appendices (Appendix 5).

[1] *Note: at this stage only baseline data from the APPROACH study has been published*

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A2. **Priority question:** No quality assessment is provided for APPROACH OLE or COMPASS. Please provide quality assessment using an appropriate tool for each study.

Table 1 Critical appraisal of APPROACH-OLE

Study name	**APPROACH OLE**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	The study was open-label. All patients received volanesorsen.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label. All patients received volanesorsen.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Data were analysed for two patient groups: those who had previously received volanesorsen in APPROACH or COMPASS and those who were treatment-naïve (i.e. received placebo in either APPROACH or COMPASS, or did not take part in either of these studies). [redacted]
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.

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Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	[redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The interim study report does not report on all outcomes, as there were insufficient data for some outcomes at the time of the analysis. However, all the outcomes measured will be fully documented in the final study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	[redacted]
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table 2 Critical appraisal of COMPASS

Study name	**COMPASS**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomised 2:1 to receive either volanesorsen or placebo using an interactive voice/web response system. Patients were stratified by: • prior history of pancreatitis; • concurrent use of fibrates and/or prescription omega-3 fatty acids.

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		A permuted block schedule was used.
Was the concealment of treatment allocation adequate?	Yes	The study was double-blind.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	As described in Section 9.4.3 of the submission, baseline characteristics and demographics were balanced between treatment groups in the subset of 7 patients with FCS, although there were no male patients in the placebo group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The sponsor, patients, monitors and study centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apoC-III and TGs, were not available to any of these individuals. An independent review committee adjudicated all SAEs that were consistent with either a major adverse cardiovascular event or acute pancreatitis. The committee members were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	All 7 patients in the FCS subset completed the study. Five of these patients received volanesorsen and 2 received placebo.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes measured are fully documented in the study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

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A3. In Table C1 ("Selection Criteria for published studies", p53) it is stated that no study type restrictions were used for the effectiveness review. It is further stated in section 9.2.2 (p54) that case reports were eligible for inclusion. However, in the appendices (17.1.4) the ERG notes that a study type filter specifically excluding case reports has been applied to both the Medline and EMBASE search strategies. Please explain the justification behind this given your stated inclusion criteria.

Response to A3:

A case report filter was applied in the search strategy and criteria should be updated to reflect this. Previous search strategies indicated that this did not reveal any further relevant studies.

A4. Table C1 (p52) lists the inclusion criteria. The outcomes fatigue, neurological and psychological impact and HRQoL do not appear in the list of included outcomes, but they are part of the NICE scope. Please clarify if studies reporting these outcomes would have been excluded.

Response to A4:

Although we have not included these in the table, they are not explicitly excluded either from the search strategy or rejected from the search results.

A5. The intervention is stated as “volanesorsen”. However, the PRISMA flow diagram lists many other treatments. Please clarify why there is an apparent mismatch between the PRISMA and the inclusion criteria?

Response to A5:

The original PRISMA in the Akcea submission was developed to list all potentially relevant comparator studies (as opposed to just the intervention, volanesorsen), reflecting the scope for the appraisal which includes a broadly defined comparator. However, none of the potential comparator studies were ultimately considered directly relevant to the decision problem and were excluded on this basis. A corrected PRISMA is presented below. Please note that, as explained above, one of the 4 volanesorsen studies listed in the PRISMA was not written up in full in the submission and was summarised in Appendix 5 of the Akcea submission. This study was an open label, single-arm study of volanesorsen in 3 patients.

A6. Please clarify if any studies were excluded on the basis of language, and if so what these were?

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Response to A6:

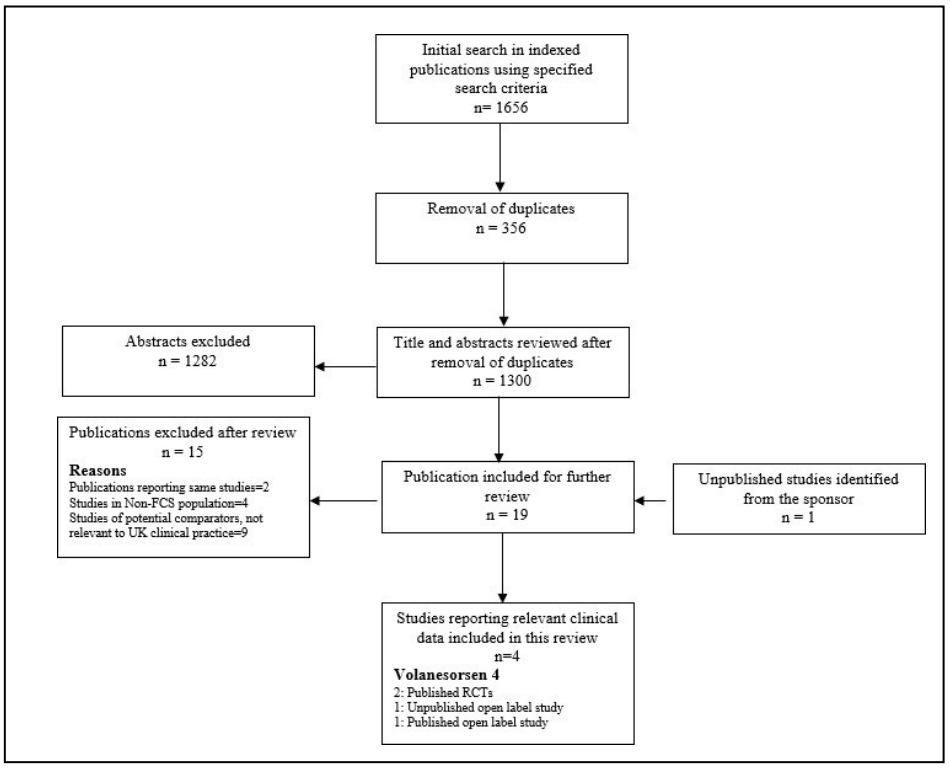
No studies were excluded on the basis of language.

A7. The PRISMA flow diagram (Figure 8, p54) does not appear to add up. There were 1330 studies after deduplication, and 951 abstracts were excluded. This should leave 379 citations being retrieved at full text and the reasons for exclusion of these should be reported. However, only 6 citations are listed as having been excluded. Please clarify.

Response to A7:

A corrected PRISMA is presented below.

Figure 1 PRISMA diagram



A8. The ERG notes that reference lists of relevant systematic reviews and included studies were manually checked for any additional studies. Please clarify whether any forward citation searching (of more recent papers citing those included) was conducted also.

Response to A8:

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Yes, forward citation searching was conducted.

A9. Please cite the source of the search filters used to identify included study types in the database searches for the effectiveness studies (Appendix 1).

Response to A9:

A database search strategy was developed using a combination of Medical Subject Headings, key disease terms along with search filters developed by the Scottish Intercollegiate Guidelines Network for searching OVID databases MEDLINE and EMBASE and search filters various other previous HTA submissions.

APPROACH and **APPROACH OLE baseline characteristics**

A10. **Priority question:** Please provide data by trial arm and for the whole trial on:

- Diabetics and use of insulin
- Adherence to diet after the stabilisation period
- Numbers of patients with 0, 1 and ≥2 pancreatic attacks in the previous 5 years
- Patients who had previously been enrolled in other clinical trials, what these clinical trials were of, and whether the effects of these trials are likely to have worn off, e.g. in the case of gene therapies such as Glybera
- Genetic subgroups

Response to A10:

- **Diabetics and use of insulin**

[redacted]

Table 3: Summary of APPROACH Patients with Medical History of Diabetes

Preferred Term	Placebo (N=33) n (%)	Volanesorsen (N=33) n (%)	All Patients (N=66) n (%)
Type 2 diabetes mellitus Diabetes mellitus	[redacted]	[redacted]	[redacted]

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Table 4: Summary of APPROACH OLE Patients with Medical History of Diabetes

Preferred Term	Treatment naive group (N=50) n (%)	APPROACH-Volanesorsen (N=14) n (%)	COMPASS-Volanesorsen (N=3) n (%)	All Patients (N=67) n (%)
Type 2 diabetes mellitus Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]

Insulin and blood glucose lowering medications were reported as prior medications as described for the APPROACH study in Table 5 and the APPROACH OLE in Table 6.

Table 5: Prior Medications for Patients in APPROACH study

ATC Class Generic Name	Placebo (N=33) n (%)	Volanesorsen (N=33) n (%)	All Patients (N=66) n (%)
Insulins and analogues for Injection, Fast-acting Insulin Aspart Insulin Lispro	[redacted]	[redacted]	[redacted]
Insulins and analogues for Injection, Long-acting Insulin Insulin Glargine	[redacted]	[redacted]	[redacted]
Other blood glucose lowering drugs, excl. insulins	[redacted]	[redacted]	[redacted]
Combinations of oral blood glucose lowering drugs Kombiglyze	[redacted]	[redacted]	[redacted]

Table 6: Prior Medications for Patients in APPROACH OLE study

ATC Class Generic Name	Treatment naive group (N=50) n (%)	APPROACH-Volanesorsen (N=14) n (%)	COMPASS-Volanesorsen (N=3) n (%)	All Patients (N=67) n (%)
Insulins and analogues for Injection, Fast-acting Insulin Aspart Insulin Lispro	[redacted]	[redacted]	[redacted]	[redacted]
Insulins and analogues for Injection, Long-acting Insulin Detemir Insulin Glargine	[redacted]	[redacted]	[redacted]	[redacted]
Other blood glucose lowering drugs, excl. insulins	[redacted]	[redacted]	[redacted]	[redacted]
Combinations of oral blood glucose lowering drugs Kombiglyze	[redacted]	[redacted]	[redacted]	[redacted]

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- **Adherence to diet after the stabilisation period**

[redacted]

- **Numbers of patients with 0, 1 and ≥2 pancreatic attacks in the previous 5 years**

[redacted]

Table 7: Number of APPROACH Patients by Number of Pancreatitis Attacks in Previous 5 Years

Number of Adjudicated Pancreatitis Events in Previous 5 Years	Placebo (N=33)	Volanesorsen (N=33)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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- **Patients who had previously been enrolled in other clinical trials, what these clinical trials were of, and whether the effects of these trials are likely to have worn off, e.g. in the case of gene therapies such as Glybera**

[redacted] To ensure that effects of the Glybera treatment had worn off, prior treatment within 2 years was an exclusion criterion. We are not aware of any patient having been excluded based on the 2-year post-treatment window, as most treatments with Glybera had occurred prior to 2010, and the APPROACH study was initiated in mid-2014. Patients in the APPROACH and APPROACH OLE studies had not previously been enrolled in any other clinical trials.

- **Genetic subgroups**

[redacted] The 51 APPROACH study patients with an identified genetic mutation were further classified by the specific mutation in Table 9.

Table 8: Number of APPROACH Patients in each Genetic Characterization Subgroup

	APPROACH Placebo (N=33)	APPROACH Volanesorsen (N=33)	APPROACH OLE All Patients (N=67)
Confirmed LPL Mutation	[redacted]	[redacted]	[redacted]
Confirmed Non-LPL Mutation	[redacted]	[redacted]	[redacted]
Non-Confirmed Genetic Mutation	[redacted]	[redacted]	[redacted]

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Table 9: Number (%) of APPROACH Study Patients with each Genetic Mutation

Type I causing gene	Placebo (N=33)	Volanesorsen (N=33)	All Patients (N=66)
LPL	[redacted]	[redacted]	[redacted]
APOA5	[redacted]	[redacted]	[redacted]
GPIHBP1	[redacted]	[redacted]	[redacted]
LMF1	[redacted]	[redacted]	[redacted]
APOC2	[redacted]	[redacted]	[redacted]
LPL/LMF1	[redacted]	[redacted]	[redacted]
LPL/APOA5	[redacted]	[redacted]	[redacted]

APPROACH and APPROACH OLE heterogeneity

A11. The NICE scope calls for an investigation into heterogeneity of health benefits within the population. Please clarify to what extent you have considered response heterogeneity?

Response to A11:

Figure 2 shows the triglyceride results, ordered based on the final triglyceride values, for the volanesorsen-treated patients in the APPROACH study at 3 months. [redacted] The data in orange represent placebo patients who had triglyceride level changes in both directions from baseline values. The notable difference between treatment groups underscores both the pronounced efficacy and the high response rate to volanesorsen.

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Figure 2: **Response to Volanesorsen Treatment by Individual Patient at Month 3 in the APPROACH study**

[redacted]

APPROACH and APPROACH OLE Withdrawals

A12. Throughout APPROACH and APPROACH OLE patients can withdraw voluntarily or due to adverse events or be lost to follow-up.

- Please clarify if lost to follow-up in Figure 11 refers exclusively to patients who did not enter the post-treatment evaluation phase?
- Please provide a list of all patient withdrawals and the exact reason for withdrawal (e.g. not enough time, lack of efficacy, type of AE) by treatment group and the time of withdrawal.
- If available, please provide non-enrolment reasons for all patients between APPROACH/COMPASS and APPROACH OLE.
    - Please clarify how was "satisfactory completion of APPROACH or COMPASS" judged? (Table C7, APPROACH OLE inclusion criteria). How many patients were excluded on this basis?
    - Please clarify how many patients were excluded due to unwillingness to comply with lifestyle requirements?

Response to A12:

- Yes, 'lost to follow-up' in the final submission Figure 11 refers exclusively to patients who did not enter or complete the full post-treatment evaluation phase.

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[redacted]

Table 10: Reasons for Voluntary Withdrawal from the APPROACH study

Treatment	Available Information on Voluntary Withdrawal
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Placebo	[redacted]

- Table 11 provides non-enrolment reasons for all patients between APPROACH/COMPASS and APPROACH OLE. [redacted]
- [redacted]

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[redacted]

Table 11: Reasons for Non-enrolment of Eligible Patients from APPROACH and COMPASS studies

Treatment	Reason for not continuing in APPROACH OLE
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Volanesorsen	[redacted]
Placebo	[redacted]
Placebo	[redacted]

APPROACH Trial

A13. **Priority question:** Please clarify how many pancreatitis events were there in each arm?

[redacted]

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[redacted]

All events of pancreatitis were adjudicated by an independent monitoring committee based on all AE and SAE events reported. On-treatment events of pancreatitis are summarised by treatment arm in Table 12.

Table 12: Overall Incidence of On-treatment Pancreatitis Events in APPROACH and COMPASS Studies

	Placebo Patients (events)	Volanesorsen Patients (events)	p-value
APPROACH	[redacted]	[redacted]	[redacted]
COMPASS	[redacted]	[redacted]	[redacted]
APPROACH + COMPASS	[redacted]	[redacted]	[redacted]

A14. **Priority question:** Please clarify why the data in Figure 13 (p88) do not match the data reported in Table C13 (p84)? Please provide the same figure using the data from Table C13. Is the increase in TG levels for patients on volanesorsen seen from months 3 to 12 in Figure 13 due to treatment discontinuations? i.e. Can you show that the TG levels would be stable from month 3 to 12 if patients that had discontinued treatment were taken out of this figure? Please explain why the TG levels in the placebo group initially increased and then decreased? Finally, please provide confidence intervals around the mean change from baseline.

Response to A14:

The data used for Figure 13 on p88 of the original submission was a subset of the FAS with non-missing endpoints. The data in Table C13 on p84 of the original submission was from the full FAS using multiple imputation method for missing data. Figure 13 from the original submission has been recreated using the data from Table 13 in Figure 3 below.

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Figure 3: **Original Submission Figure 13 'LS mean % change in fasting triglyceride levels to Month 12' Updated with Data from Original Table C13**

[redacted]

Figure 4 provides illustrates persistence of efficacy over 12 months in APPROACH taking into account dose adjustments. [redacted]

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[redacted]

[redacted] Enrolled patients were already established to have FCS at the time of screening and were generally cared for in centers with expertise in the management of the disease, including dietary instruction. As noted, diet is a preoccupation of patients with FCS and the vast majority have had pancreatitis and experience recurrent abdominal pain related to food, even when adherent to diet. Therefore, this is a highly motivated population, compliant with medical instruction and of low likelihood to deviate from dietary advice.

Figure 4: Triglycerides Over Time Including Dose Adjustments and Non-Completers in the APPROACH Study

[redacted]

Figure 5: Triglyceride Reduction Over Time for Full Analysis Set in APPROACH

[redacted]

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A15. **Priority question:** Given that the submission states that patients with a history of pancreatitis have a statistically significant benefit (p89), please provide Figure 13 (p87) by the number of pancreatitis attacks in the last 5 years (0, 1, 2+).

Response to A15:

[redacted]

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Figure 6: Original Submission Figure 13 'LS mean % change in fasting TG levels to Month 12' Subgroup of Patients with 0 Prior Pancreatitis Events in Prior 5 Years

Figure 7: Original Submission Figure 13 'LS mean % change in fasting TG levels to Month 12' Subgroup of Patients with 1 Prior Pancreatitis Event in Prior 5 Years

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Figure 8: Original Submission Figure 13 'LS mean % change in fasting TG levels to Month 12' Subgroup of Patients with 2+ Prior Pancreatitis Events in Prior 5 Years

A16. **Priority question:** Please clarify, how was the value 750mg/dL derived as a pre-specified cut-off for the responder analysis in APPROACH? How was the 40% reduction cut-off for the second responder analysis in APPROACH derived? (Table C6, p65) Please explain, why were two different definitions of responder included in the analysis plan? Why do these values not match the values used for the discontinuation rule or the values used in the model to define low, intermediate and high risk TGs?

Response to A16:

The value of 750 mg/dL (8.5 mmol/L) was the cut-off for both study entry and the level prespecified for determination of a responder threshold based on prior precedent (pradigastat; diacylglycerol acyltransferase 1 inhibitor) and also agreed as a responder threshold with the major regulatory agencies (EMA and FDA) in pre-Phase 3 consultations. This value is reported to represent a value at which serum triglycerides are predominantly found to be in the form of chylomicrons (Kjems L, Filozof C, Wright M, et al. Association Between Fasting Triglycerides and Presence of Fasting Chylomicrons in Patients with Severe Hypertriglyceridemia. Journal of Clinical Lipidology 2014; 8(3): 312-313.), the form which exacerbates risk of pancreatitis.

Additional values were added as sensitivity analyses. As a target value favoured for the prevention of pancreatitis, 1000 mg/dL (11.3 mmol/L) was also selected. EU agencies favour 880 mg/dL (10 mmol/L

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approximately) as a regulatory and as a threshold for chylomicronemia, which was therefore analysed and reported, and 500 mg/dL (5.6 mmol/L) was also analysed as a most conservative standard for responders to fully profile the potential benefit of Volanesorsen for triglyceride lowering.

A17. It was stated in the submission (Table C6, p66) that "patients without a documented history of pancreatitis were also eligible but their enrolment was capped at 28%".

- Please clarify whether this is for patients for which documentation is missing, patients that have never had pancreatitis, or a combination of the two?
- If the first of the above, please explain how these patients were randomised as one of the stratification factors was history of pancreatitis.
- Please provide clarification about why this capping was applied, and what the justification for choosing 28% was.
- Please provide the percentage of such patients who were recruited in the trial.

Response to A17:

The Applicant response is structured in bullets corresponding to the questions posed. By way of background, enrolment of patients with a high incidence of pancreatitis was requested (FDA) to identify potential beneficial impact of such events on-treatment based on a predetermined probability of such events occurring over 12 months of observation and treatment. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

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A18. Please specify which subgroup analyses are pre-planned? Is the analysis in patients with a history of pancreatitis attacks and who had abdominal pain at baseline on the effect on pancreatitis and abdominal pain pre-planned (page 89)? Please provide which covariates these are adjusted for?

Response to A18:

The following were the pre-planned analyses proposed for the APPROACH study:

- Treatment response rate, where a patient with fasting plasma triglyceride < 750 mg/dL at the primary analysis time point is defined as a responder
- Average of maximum intensity of patient reported abdominal pain during the treatment period
- Percent change from baseline in post-prandial triglyceride area under the curve
- Treatment response rate, where a patient who achieves fasting triglyceride ≥ 40% reduction from baseline at the primary analysis time point is defined as a responder
- Absolute change from baseline in fasting TG as measured at the primary analysis time point
- Frequency of composite of episodes of acute pancreatitis and patient reported abdominal pain during the on-treatment period
- Change from baseline in hepatic volume as assessed by MRI at Week 52

The subgroup analysis of patients who had pain at baseline was pre-planned as an exploratory analysis (with missing data imputed using Next Observation Carried Back (NOCB)), in addition to the overall assessment of pain in the full study population which was also planned. [redacted]

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A19. Clinical advisors to the ERG suggested that the patient group that they might expect to experience greater benefit would be those with high triglyceride levels and a recent history of pancreatitis. Please comment. Please also provide a rationale for why active pancreatitis patients within 4 weeks of screening were excluded from the trial.

Response to A19:

As stated, risk of pancreatitis rises with degree of triglyceride elevation. As published by Nawaz H. et al (Am J Gastroenterol 2015) and others, the risk appears to rise significantly above 1,000mg/dL (11.3 mmol/L) and to accelerate further between that level and 2,000 mg/dL (22.6 mmol/L). Individual patients appear to vary greatly in their thresholds for an acute event. Table 13 provides the values of triglycerides taken closest to an acute attack of pancreatitis among patients with FCS in the APPROACH study.

Table 13: Triglyceride Levels at the Closest Measurement to Pancreatitis Events in the APPROACH Study

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Prior pancreatitis is also a known risk factor for further attacks; however, being an ultra-orphan disease, there is little documentation of this risk quantitatively, but it is held as established among physicians experienced in diagnosing and managing patients with FCS. [redacted]

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[redacted]

Therefore, the opinion is that prior attacks of pancreatitis may predict the likelihood of future attacks, but not the temporality. However, for those patients not reporting prior pancreatitis, the absence of an event is not a protection against a first attack, which is often the most serious and life-threatening.

[redacted]

A20. In Table C6 (p66) it is stated that you use 'an ANCOVA model with history of pancreatitis and presence/absence of concurrent omega-3 fatty acids and/or fibrates as factors, and log-transformed baseline TG as a covariate. Secondary endpoints were only analysed if the treatment comparison of the primary endpoint was statistically significant. Analysis was carried out sequentially, i.e. an endpoint was only tested if the previous endpoint was shown to be statistically significant.'

i) Please clarify, why were other baseline factors not included within the adjustment for the primary analysis? Please comment on and provide the impact on the results (Table C13, p84) adjusting for baseline covariates, including where possible those stipulated in question A10 above.

ii) Please clarify whether secondary analyses were adjusted and if not please comment on and provide the impact on the results (Table C13) adjusting for baseline covariates, including where possible those stipulated in question A10 above.

Response to A20:

(i) [redacted]

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[redacted]

Table 14: Triglyceride Lowering at Month 3 by Presence or Absence of Diabetes in APPROACH Volanesorsen Group

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 15: Triglyceride Lowering at Month 3 by Number of Pancreatitis Events in Previous 5 Years in APPROACH Volanesorsen Group

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

(ii) [redacted]

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[redacted]

A21. Please clarify if there is a difference between the FAS analyses reported in the clinical section of the report and the ITT analyses in the modelling section. Please provide definitions for both.

Response to A21:

[redacted]

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A22. The CSR states that the following two tertiary endpoints were investigated:

- Percent change from Baseline in fasting apolipoprotein B-48 (apoB-48) and chylomicron TG
- Percent change from Baseline in post-prandial apoB-48 and chylomicron-TG

Please provide analyses for the above endpoints.

Response to A22:

[redacted]

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Table 16: Summary of Fasting ApoB-48 (mg/dL) Over Time for FAS from APPROACH Study

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Table 17: Summary of Fasting Chylomicron-TG (mg/dL) Over Time for FAS from APPROACH Study

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[redacted]

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Figure 9: Plot of On-Treatment Mean (+/- SEM) of Postprandial apoB-48 (g/L) and Chylomicron TG (mmol/L) for FAS from APPROACH Study

A23. Please explain why quality of life was higher than the same age patients in the general population? Is there any evidence to suggest only the most well patients completed the questionnaires?

Response to A23:

We are currently unable to offer an explanation as to the high HRQL reported by patients in the APPROACH trial, compared to same age patients in the general population. As noted in the Akcea submission, these values are implausible. There is no clear indication that patients completing questionnaires in the trial were 'most well'. The table below provides a summary of patient characteristics and TG outcomes according to whether HRQL data was available or missing.

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Table 18 Summary of HRQL data from APPROACH

	Volanesorsen		**Placebo**		**All patients**	
Characteristic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration (days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline TG level (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TG reduction at 3mo (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A24. In the submission on page 99, it is stated that there were 12 serious adverse events, but only two are described (grade 4 thrombocytopenia). Please clarify what the other serious adverse events were in each arm, and whether these were considered to be related to treatment?

Response to A24:

[redacted]

A25. In the CS (p97) it is reported that 12% of volanesorsen patients were diagnosed with diabetes mellitus during the course of the study, whilst 0% of placebo patients were. Please clarify, is there any clinical reason why volanesorsen might lead to diabetes mellitus?

Response to A25:

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[redacted]

In summary, treatment with volanesorsen was not associated with new onset of diabetes mellitus in any patient, while short-term treatment with glucocorticoids to correct drug-related thrombocytopenia was associated with transient hyperglycaemia, a recognized risk of glucocorticoid use and about which physicians will be alerted.

A26. Please provide data for all adverse events that occurred in 3% or more of volanesorsen patients.

Response to A26:

[redacted]

Table 19: Summary of Adverse Reactions Considered Related or Possibly Related to Volanesorsen Treatment in APPROACH Study

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]
[redacted]		[redacted]

[redacted]

APPROACH OLE

A27. **Priority question:** In Figure 14 (p93), the patient numbers at each time point do not seem to match the number of withdrawals reported in table C11 (p79). Please clarify the reason why patients are missing at each time point in Figure 14 (p92). Please, also clarify, can it be reproduced with the x-axis to scale? Finally, please could you recreate this using the December 2017 cut off? Are these results based on an adjusted analysis? If not, please also present this.

Response to A27:

In original submission Figure 14 on p93, the patient numbers reflect patients who have progressed to each timepoint as of the data cut-off date of January 2017. Also, in some cases, patients discontinued treatment and still returned for triglyceride measurements which would have been included in the observed data set. For these two reasons, including patient progression along the study timepoints and the inclusion of all observed datapoints, the number of patients in original submission Figure 14 and original submission Table C11 are different.

Original submission Figure 14 has been reproduced with data and number of patients from the December 2017 data cut-off and presented in Figure 10, below. These results are based on observed values and not adjusted by ANCOVA.

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Figure 10: Original Submission Figure 14 'Percent change in fasting TG levels over time' Updated for Dec 2017 Data Cut-off

A28. **Priority question:** There are very few patients still on treatment in the APPROACH-OLE study at the January 2017 data cut and the ERG considers that it is difficult to draw any conclusions from this analysis. If possible, please use a later data cut for the efficacy data than the January 2017 analyses eg. the safety data uses a December 2017 data cut.

Response to A28:

APPROACH OLE data from the December 2017 data cut-off has been used to update the original submission Table C14 in Table 20 below. However, abdominal pain during OLE treatment period data was not updated at the December 2017 data-cut, so the January 2017 data is retained in the table. Original submission Figure 14 has been updated using data from the APPROACH OLE December 2017 data cut-off date as shown in Figure 11 below.

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Table 20: Submission Table C14 'Outcomes from APPROACH OLE' Updated for Dec 2017 Data Cut-off

[redacted]

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Figure 11: Original Submission Figure 14 'Percent change in fasting TG levels over time' Updated for Dec 2017 Data Cut-off

A29. In the submission, on p74 it is stated that "there were no differences between the patient populations in these two studies" (referring to APPROACH and APPROACH OLE). However, the baseline characteristics in Table C8 (p74) and C9 (p75) show that treatment naive patients had much lower rates of abdominal pain than treatment experienced patients in APPROACH OLE or than either group in APPROACH. Also, mean fasting triglyceride levels were higher in the treatment naive group of APPROACH OLE and both APPROACH groups than the experienced group in APPROACH OLE.

- Please clarify how the statement about there being no differences between patients in the two studies accurately describes these data?

Response to A29:

As referenced above from the original NICE submission, patients enrolled in pivotal trial, APPROACH, are presented below for fasting triglyceride values, and for number of patients with abdominal pain during screening and Week 1 of the study. By contrast, patients entering the open label extension study, APPROACH OLE study, are made up of treatment-naïve patients and patients continuing volanesorsen. The baseline serum triglyceride values in the treatment-naïve patients are consistent with the patients entering the APPROACH study. For patients transitioning from the APPROACH study, triglycerides

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are appropriately demonstrating the positive impact of volanesorsen on baseline triglyceride values. The baseline frequency of abdominal pain is lower in the treatment naïve patients, perhaps reflecting a shorter period of observation.

Extracted from Table C8: Patient demographics and baseline characteristics in APPROACH

Extracted from Table C9: Patient demographics and baseline characteristics in APPROACH OLE

A30. APPROACH OLE includes one patient not from APPROACH at the interim analysis, according to text in the submission, on page 74. Table C11 (p79) states there were no patients from COMPASS in the interim (MAA) analysis, so logically this would suggest the patient was a patient who had not been in either trial, and so would not have 12 months of data before APPROACH OLE commenced (assuming the MAA analysis and the interim analysis are the same analysis). However, Figure 14 (p92)

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shows all patients have 12 month data from a trial (n=11 experienced, n=18 naive) before APPROACH OLE started. Please clarify why there is an apparent mismatch?

Response to A30:

[redacted]

A31. All results are presented separately for the treatment-experienced and -naive groups for APPROACH OLE. Please clarify if this subgrouping was planned or post-hoc.

Response to A31:

The subgrouping by treatment-experienced and treatment-naïve groups in APPROACH OLE was planned.

Continuation rule

A32. **Priority question:** Please clarify, what proportion of patients would have discontinued treatment under the proposed treatment continuation rule in the full APPROACH and APPROACH OLE analysis sets? What proportion of patients would have discontinued under the rule in the subgroup of patients who had dose reductions from APPROACH and APPROACH OLE? Please explain, what proportion of patients do you predict would discontinue under the rule, at the proposed reduced bi-weekly dose? Please, also clarify, what impact would you expect this to have on the results?

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Response to A32:

[redacted]

Bi-weekly dosing

A33. **Priority question:** Please clarify how many patients across APPROACH, APPROACH OLE and COMPASS received bi-weekly doses of volanesorsen for long enough to assess TG levels within this group? Please provide TG levels in these patients, showing the change in levels from weekly to bi-weekly dosing using a more recent data cut point, e.g. December 2017.

- If this is not available, we note the following from the FDA assessment of this treatment "In the applicant's analysis of the effect of dose interval change or dose pauses in patients that completed the APPROACH pivotal study, triglycerides decreased from baseline by 54% at Month 12 in the 13 VLN-treated patients that completed the study with a dose adjustment compared to a 76% reduction in the 6 VLN-treated patients that maintained weekly VLN 300 mg for 52 weeks." Please provide details of this analysis and appropriate summary statistics, and any other analyses that might help to confirm the results from the PK/PD analysis.

Response to A33:

[redacted]

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[redacted]

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Table 21: Summary of Triglycerides by Dose Regimen in APPROACH

[redacted]

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[redacted]

Table 22: Summary of Percent Change from Baseline in Triglycerides During Weekly and Bi-Weekly Treatment: Volanesorsen-treated Patients Enrolled in APPROACH and Transitioned into APPROACH OLE with Bi-weekly dose

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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[redacted]

Table 23: Summary of Triglycerides by Dose Regimen in COMPASS

	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

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In summary, triglyceride lowering effect observed for weekly and bi-weekly doses were consistent across trials and both regimens provided clinically meaningful reduction in triglycerides.

Exposure-adjusted discontinuations

A34. **Priority question:** Please clarify, whether years of exposure from APPROACH were included in the "total years of exposure"?

Response to A34:

Yes, years of exposure from APPROACH were included in the "total years of exposure".

A35. **Priority question:** Please provide the equivalent of Table C19 (p106) for the treatment naive group.

Response to A35:

The equivalent of original submission Table C19 on p106 has been provided for the treatment naïve group below in Table 24.

Table 24: Original Submission Table C19 ' Exposure-adjusted discontinuations with or without dose adjustment (APPROACH OLE)' for the Treatment Naive Group

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off: 31 December 2017

A36. Please provide details about the method used for calculating the exposure adjusted discontinuation rates, see on page 107.

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Response to A36:

Total patient year of exposure was calculated by adding up the duration of volanesorsen exposure in days (defined as date of last dose – date of first dose + 1) for individual patients and dividing by 365.25 days/year for patients with any dose adjustment and patients without any dose adjustment respectively. Then, discontinuation rate (%) per patient year of exposure was calculated as (number of patients discontinued divided by total patient year of exposure) x 100.

A37. Please explain, is there any reason why dose adjustments occurred more quickly on average in COMPASS than in APPROACH or APPROACH OLE?

Response to A37:

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[redacted]

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** We asked in question A28 for you to provide a later data cut for the efficacy data than the January 2017 analyses. Please could you use this later data cut to assess the appropriateness of the transition probabilities from month 4 onwards which take the average of the transition probabilities from months 4 - 12 on the basis that there is no evidence of treatment effect waning in either the APPROACH or APPROACH OLE trials. As stated previously, it is difficult to draw any conclusions from the APPROACH OLE data presented due to the limited number of patients on treatment at the January 2017 data cut. Please also revisit the assumption around the bi-weekly discontinuation rates based on the later data cut.

Response to B1:

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[redacted]

B2. **Priority question:** Please clearly describe where the figures in Table D8 (p170) are derived from to estimate the reduced efficacy associated with a bi-weekly dose compared with a weekly dose.

Response to B2:

[redacted]

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[redacted]

B3. **Priority question:** Please could you explain why you did not include patients in defining the health states for the vignette study? Please could you highlight the literature or the clinical input that led to such different symptoms for the low TG and high TG levels? The ERG's clinical experts suggest that TG level *per se* would not impact upon patient quality of life. Therefore, please also present an analysis which assumes that the utilities for low, medium and high TG levels are the same.

Response to B3:

[redacted]

Table 25 Akcea vignette study: Health State A. Pre-AP, Low TG

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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Table 26 Akcea vignette study: Health State B. Pre-AP, High TG

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

We would argue however that these results under-represent the true benefit to patients of TG-lowering, as this assumes that the *only* benefits in terms of health-related quality of life (HRQL) are prevention

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of infrequent episodes of acute pancreatitis, diabetes and chronic pancreatitis. Patients with FCS have a well-characterised disease burden including abdominal pain, nausea, diarrhoea, constipation, bloating, joint pain and fatigue, many of which occur daily (InFOCUS study), as well as cognitive and emotional symptoms. As the key pathology of FCS is uncontrolled TGs leading to chylomicronaemia, to suggest that lowering TGs to within normal levels would not improve day-to-day HRQL implies that either there is no chronic disease burden, that any burden is not the result of high TGs, or that these symptoms have no impact on HRQL.

B4. **Priority question:** The PSA results should be presented as the base case ICER since they account for non-linearity in the model. Since they are substantially different to the deterministic results, all other scenario and sensitivity analyses should be undertaken using the PSA parameters. Please rerun all of the results using the PSA rather than the deterministic parameters.

Response to B4:

This has been carried out; updated results are presented in Table 27 and Table 28 at the end of this document.

B5. The MEDLINE and EMBASE search strategies for the cost-effectiveness review include terms relating to the UK. Please clarify, was the intention to restrict the scope of this review to results from the UK, as this does not appear explicit in the inclusion/exclusion criteria?

Response to B5:

Studies relating to resource utilisation and costs were restricted to the UK only. However, cost-effectiveness papers (i.e. those reporting potentially relevant economic evaluations in FCS) were not restricted to the UK.

B6. The ERG notes that reference lists of relevant systematic reviews and included studies were manually checked for any additional studies. Please clarify whether any forward citation searching (of more recent papers citing those included) was conducted also.

Response to B6:

Yes, forward citation searches were conducted.

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B7. Please cite the source of the search filters used to identify included study types in the database searches for the economic evidence (Appendix 3) and utilities (Appendix 4).

Response to B7:

Search filters used to identify study types for the economic evidence were derived from previous NICE HST appraisals.

B8. Please could you provide further explanation about where the acute pancreatitis disutility has been derived from? Please clarify why you did not use the vignette data for the acute pancreatitis health state but instead estimated the utility based on the utilities in the other health states from the vignette study. Please also show the calculation to achieve a disutility of 0.22.

Response to B8:

[redacted]

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B9. It is our understanding that the transition probabilities are estimated using the formula P(TG transition)*P(dose transition)*P(AP event). In order for this to be correct, each of these must be independent. Please could you comment on this and amend the model if necessary.

Response to B9:

For the purposes of the modelling we have assumed that these events are independent as no data are available to suggest otherwise.

B10. In the 'Trial Dose data' worksheet, it is unclear where the 12 months+ data is from (AT34: BF37). Please could you explain or amend these figures?

Response to B10:

[redacted]

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[redacted]

B11. CALIBER analysis

- Please provide the rationale that the patient's age was capped to be below 40 in CALIBER analysis.
- Please provide the model equation used for the AFT model in the analysis to predict the incidence of AP, CP and diabetes.

Response to B11:

- Targeting a population aged <40 was with a view to minimising the proportion of patients with hypertriglyceridemia (HTG) caused by lifestyle or secondary factors, i.e. more similar to an FCS population with HTG presenting at an early age (Moulin, et al., 2018. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score". Atherosclerosis. 275). Consequently, the outcomes measured were also more likely to be the direct result of HTG as opposed to other secondary factors.

- The model specifications along with their coefficients and standard errors were provided within the submission in Appendix 8.

- [redacted]

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B12. Please clarify, why did you choose a 3-month cycle length given that patients are treated and monitored every 2 weeks? Please confirm whether in the trial and in practice patients are/ would be able to discontinue treatment/ adjust their dose every 2 weeks.

Response to B12:

Although in the APPROACH trial the visit schedule required biweekly TG monitoring, only the last two readings at the end of 3, 6 and 12 months were used for endpoint calculations. Therefore, in cases of missing data only the clinical endpoints had been imputed by the Akcea statisticians and these were only available to inform the economic model at 3-month intervals.

In practice, FCS patients are followed up every 6-12 months. While it is anticipated that this may be more frequent in the initial stages of treatment on volanesorsen in order to assess response, clinician follow-up is likely to become less frequent once stablished. Therefore, discontinuation due to lack of efficacy is unlikely to occur more frequently than every 3 months.

As for any medicine, in practice patients can discontinue treatment at any time if they experience an adverse event which results in urgent contact with a healthcare professional. [redacted] This is comparable to the discontinuation rates of biologics in chronic diseases such as arthropathies where a 3-month model cycle is commonly implemented.

B13. Whilst the submission states that a half cycle correction is not required due to the short length of the cycle, the ERG requests that this is applied because it could have a substantial impact on the model results in this case. Please apply half cycle correction.

Response to B13:

This correction has been made when producing the results in the updated tables (see end of this document).

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B14. Please clarify, why was the 3 month fasting TG measurement taken as the average of week 12 and week 13, rather than using the measurement from week 13 directly? (52weeks/4=13weeks). Similarly, for the 6 and 12 month TG measurements; please explain why not use week 26 and week 52 respectively?

Response to B14:

[redacted]

B15. **Priority question:** Please explain the clinical rationale for choosing the cut-off of 22.7mmol/l for your health states in the model? Please provide supporting data to show that there is a step change in risk at this point, rather than a continuous change.

Response to B15:

The relationship between TG levels and risk of acute pancreatitis (AP) is a continuous one and therefore 22.7 mmol is an approximation based on categorised results in the literature. There will undoubtedly be some heterogeneity within individuals, particularly where patients may have sustained pancreatic injury from prior events and there may be higher susceptibility to TG levels.

There are numerous publications alluding to the fact that there appears to be a step change in risk somewhere around 2000 mg/dL (22.7 mmol). In Toth et al, 2014 (see Akcea submission), risk increased markedly above 2000 mg/dL (see screen capture below). Sandhu et al 2011 (see Akcea submission) noted that acute pancreatitis as a consequence of high TGs occurred rarely if ever unless TG levels were greater than 20 mmol (1772 mg/dl). In the Endocrine Society's 2012 Clinical Guidelines a risk category of 'very severe hypertriglyceridemia' has been defined for levels above 2000 mg/dl, indicative of "a risk of acute pancreatitis". 'Severe hypertriglyceridemia', defined as 1000-1999 mg/dL (11.2–22.4

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mmol), "carries a susceptibility for intermittent increases in levels above 2000 mg/dl and subsequent risk of pancreatitis." (Berglund et al., 2012, Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline).

Screenshot from Toth et al., 2014

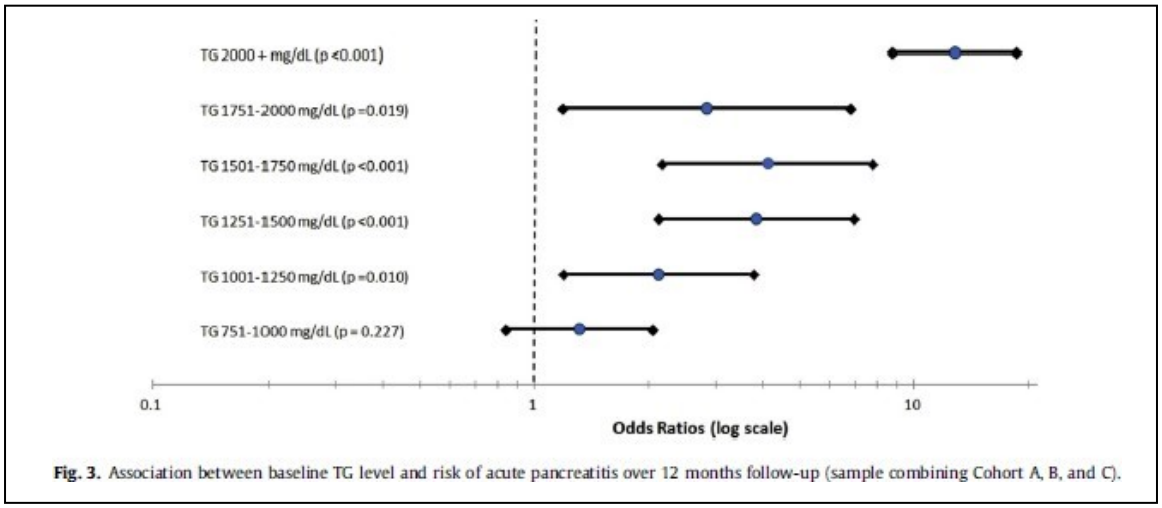

Fig. 3. Association between baseline TG level and risk of acute pancreatitis over 12 months follow-up (sample combining Cohort A, B, and C).

B16. **Priority question:** The impact of moving from a weekly dose as in APPROACH to a bi-weekly dose is highly uncertain, yet very little sensitivity analyses have been undertaken around the efficacy and discontinuation parameters to explore this. Please undertake a range of sensitivity analyses to explore the impact of plausible effects on these parameters.

Response to B16:

[redacted]

B17. Please explain, what is the justification for using CALIBER for AP naive and AP1, but not AP2+? On page 177 in the submission, you state that 'Patients in APPROACH with a history of 2+ events in the past 5 years had a mean annual AP rate of 0.746 vs. the rate of 0.2 from the AP-experienced, 22.7+

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mmol group from CALIBER.' However, no comparison is provided for patients in APPROACH with a history of <2 events and CALIBER to know whether this too is inconsistent.

Response to B17:

[redacted]

B18. The cost of bi-weekly and weekly volanesorsen appears to be similar within the formula, given that both estimates use 26/4 to estimate the frequency. Please correct the cost of weekly volanesorsen.

Response to B18:

[redacted]

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[redacted]

B19. The annual cost of chronic pancreatitis taken from Hall et al, 2014, includes both direct and indirect costs. Please could you input an estimate that includes only direct costs?

Response to B19:

The reporting of direct and indirect costs within the Hall et al paper is unfortunately very ambiguous, and it is not at all clear how to separate out these elements in a reliable way. However, we have attempted to produce an indicative estimate for the direct costs only in line with the ERG request. Assuming that all the costs associated with pain in Hall's analysis are indirect (*note*: this is not clearly stated), the remaining costs for admissions, endocrine and exocrine insufficiency, total £155.3m. For the reported number of cases (3,600/annum) this equates to approximately £45,000 per patient per annum (inflated to current prices). This value has been incorporated in the updated results tables (see end of this document).

B20. It is stated that the model uses a time horizon of 100 years, but in the model it is 46+50=96 years. Please could you extend the time horizon to match the text in the report?

Response to B20:

This has been corrected and has been incorporated in the updated tables (see end of this document).

B21. The mortality rate is calculated by multiplying the relative risk of dying from diabetes by the relative risk of dying from acute pancreatitis (Vola- Markov, SoC - Markov, column G). Are these relative risks independent? Please amend the parameters in the model if necessary.

Response to B21:

The relative risk of mortality due to prior pancreatitis has been amended to 1 in the model (no additional risk) and has been incorporated in the updated tables (see end of this document).

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Section C: Textual clarifications and additional points

C1. **Priority question:** A substantial amount of text is marked as confidential. Please could you check that all of this text is confidential? For example, data that is provided on Clinicaltrials.gov is in the public domain. Please provide updated submission with correct marking.

Response to C1:
We have now reviewed the original submission and a copy with revised marked up text has been provided.

C2. Submission, Figure 9 page 65: Please clarify the weeks of the post-treatment evaluation period. This is currently stated to be [redacted] weeks, however we think this should read [redacted] weeks.

Response to C2:
The figure contains a typo and should state [redacted]. Following the Week 52 visit, those patients not participating in the expanded access program entered a 13-week post-treatment evaluation period.

C3. Please clarify if the sentence on page 89 "who had experienced 2 attacks in the last 5 years" should read "who had experienced ≥2 attacks in the last 5 years".

Response to C3:
Yes, this statement should be "who had experienced ≥2 attacks in the last 5 years".

C4. Submission, page 141, [redacted] appears to be missing the word "not" after "where absolute TG levels have". Please confirm.

Response to C4:
Yes, the word 'not' is missing.

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C5. In the submission, in Table D6 (p167), it is stated that patients are assumed to be on reduced dose 'if patient was classed as being on once every weeks dosing or had 6 or more pauses in that cycle.' Please clarify that this should say 'if patient was classed as being on once every 2 weeks dosing…'

Response to C5:

Yes, the correction is appropriate.

C6. In the submission, in Table D7 (p169) it is stated that for month 9 TG levels, in the third instance, 'Use the average of the Week 6 and Week 9 endpoints'. Should this say Month 6 and Month 10 endpoints'?

Response to C6:

This should read 'Use the average of the Month 6 and Month 12 endpoints.' There was no Month 10 endpoint.

C7. Submission page 202 it is stated that "separate rapid searches using were carried out to…". This appears to contain a typo. Please confirm if "using" should be deleted, or if the sentence is incomplete.

Response to C7:

Yes, the word using should be removed.

C8. In Appendix 6 (p318), it is stated that [redacted] Please confirm whether this should not include the word 'never' and instead read '...who had experienced acute pancreatitis.'

Response to C8:

Yes, the correction is appropriate.

C9. Submission page 319 the sentence "No participants reported a" is incomplete. Please clarify what this should say.

Response to C9:

This statement should read: "No participants reported a diagnosis of FCS."

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Updated results

Please find below updated base case results and structural sensitivity analyses (Table 27 and Table 28) from the Akcea submission (as per Tables D31 and D32 in the original submission), having incorporated the half-cycle correction (question B13), chronic pancreatitis direct costs only (B19), 54-year time horizon (question B20), and relative risk of mortality with history of acute pancreatitis set to 1 (question B21).

The base case results table has been updated using the PSA results (question B4). Additional scenarios have been added to the table (using PSA results), including setting all utilities equal (question B3), and exploration of different discontinuation rates and efficacy of biweekly dosing (question B16).

Note that while implementing the additional analyses a minor error was identified in the STATA code to convert from weekly to biweekly efficacy, which has also been corrected.

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Table 27 Probabilistic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	-
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 28 Results of structural sensitivity analyses

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
	Base case (PSA)		[redacted]	[redacted]	[redacted]
Dosing schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		[redacted]			
Continuation rule	No continuation rule	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

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Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Transitions for patients on volanesorsen who discontinue	Patients follow the actual TG transitions observed in APPROACH	Patients follow the transitions of placebo arm patients	[redacted]	[redacted]	[redacted]
Extrapolation beyond year 1	Assume that patients discontinue at the same rate in later years as in APPROACH OLE (conditional on dose) and that patients follow the grouped month 4-12 TG transitions conditional on dose.	Assume that patients remain in the same dose category and also the same TG category (based on the grouped 4-12 months transitions) after year 1	[redacted]	[redacted]	[redacted]
Choice of HRU inputs	HRU from Manchester study (using CALIBER inputs where data unavailable)	HRU from CALIBER study	[redacted]	[redacted]	[redacted]
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level	[redacted]	[redacted]	[redacted]

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Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		Assuming that HRQoL is the same at all TG levels [redacted]	[redacted]	[redacted]	[redacted]
Missing data imputations	Imputed via bootstrap imputation	Imputed via multiple imputation	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Volanesorsen for the treatment of familial chylomicronaemia syndrome (FCS)

Company submission of evidence

30th August 2019

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested

in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with ‘see appendix X’. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

List of tables and figures

List of tables

List of figures

Glossary of terms

Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
AP	Acute pancreatitis
apoC-III	Apolipoprotein C-III
ASO	Antisense oligonucleotide
CI	Confidence interval
CP	Chronic pancreatitis
CPRD	Clinical Practice Research Database
DM	Diabetes mellitus
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EQ-5D	EuroQol 5 dimensions questionnaire
FCS	Familial chylomicronaemia syndrome
GLMM	Generalised Linear Mixed Model
HES	Hospital episode statistics
HRQL	Health-related quality of life
HTG	Patients with high triglycerides, including non-familial hypertriglyceridemia
ICER	Incremental cost-effectiveness ratio
ISM	Individual simulation model
ISR	Injection-site reaction
LPL	Lipoprotein lipase
LPLD	Lipoprotein lipase deficiency
LS	Least squares
NHS	National Health Service
OLE	Open-label extension
ONS	Office for National Statistics
PSS	Personal social services
QoL	Quality of life
RCT	Randomised controlled trial
SC	Subcutaneous
SD	Standard deviation
SF-36	36-item short-form health survey
SoC	Standard of care
TG	Triglyceride

Triglyceride conversion table

mmol/L	mg/dL
750	8.5
885	10
1000	11.3
2000	22.6

1 mg/dL = 88.495575 mmol/L

Foreword to submission

Akcea originally submitted a dossier for volanesorsen via the HST process in June 2018, with an expectation of a positive opinion from the committee for human medicinal products (CHMP) in July 2018, in time for a September 2018 NICE committee meeting. During regulatory review, changes to the draft SmPC led to the submission of an addendum to NICE in November 2018. Volanesorsen received conditional marketing authorisation on the 20th May 2019. The final summary of product characteristics (SmPC) was different from the version that underpinned the original HST dossier and the addendum submitted in November 2018 in the following ways:

- The indication is for adults with genetically confirmed FCS at high risk for pancreatitis
- Treatment should be discontinued at 3 months in patients with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L
- The posology now consists of three months of weekly dosing, followed by down-titration to a maintenance dosing schedule of once every 2 weeks for those after 3 months
- Platelet monitoring rules have been introduced, with clear indications for dose pausing or discontinuation

These changes in the elements critical to an economic analysis: patient population, dose and continuation on treatment render the previous economic analysis invalid and have required amendment prior to resubmitting this dossier to NICE. This updated submission reflects both the approved labelling and the benefit of volanesorsen in a patient population with significant unmet need.

The model that underpins the economic analysis is structurally the same with inputs and assumptions amended to meet the final SmPC. This submission reports not only the clinical efficacy and safety of volanesorsen under the new

posology and monitoring rules, but also updates the economic analysis as follows:

- The population evaluated in the economic analysis is one with a documented history of acute pancreatitis. Clinicians have stated this is the population that they consider ‘at risk of acute pancreatitis’, meeting this new label requirement. The increased risk of sequelae associated with having both high triglycerides *and* prior pancreatitis supported by the available literature and the CALIBER observational study: chronic pancreatitis and type 2 and 3C diabetes, is also incorporated into the model.

- Genetic confirmation, while explicit in the indication, is not known to impact other baseline characteristics such as fasting triglycerides or likelihood of acute pancreatitis. The majority of patients diagnosed with FCS via the clinical algorithm described in Section 6.1 (Figure 3) will have familial disease. Genetic confirmation is therefore assumed not to affect the generalisability of the available clinical data to clinical practice nor to the economic analysis.

- The model implements a patient review at 3 months to evaluate if the individual patients in the APPROACH trial achieved ≥25% reduction or triglycerides beneath 22.6 mmol/L. The model is also able to consider a more restrictive stopping rule requiring ≥25% reduction *and* triglycerides beneath 22.6 mmol/L. Patients who do not achieve these thresholds discontinue treatment in the economic model.

- Treatment effect of every 2 weeks volanesorsen for patients in APPROACH who continue treatment after 3 months is informed by a robust statistical analysis of all available triglyceride measurements in the APPROACH and APPROACH open-label extension (OLE) trials

- Treatment discontinuation on volanesorsen is modelled using the closest available patient population to the final SmPC indication and

monitoring requirements: treatment-naïve patients commencing treatment in the APPROACH open-label extension (OLE) study

- Treatment effect of volanesorsen on incidence of acute pancreatitis is informed by historical vs. on treatment adjudicated acute pancreatitis rates captured in the APPROACH OLE study

The population restriction, additional stopping rules and more robust modelling methodology results in a significantly lower ICER than presented in the previous submission and submission addendum.

Executive Summary

Nature of the condition

FCS is an ultra-rare, genetic disease characterised by extremely high levels of plasma triglycerides (TG), between 10 and 100 times normal values, and a build-up of lipoprotein particles called chylomicrons (Ahmad and Wilson, 2014, Brunzell, 1999 Oct 12 [Updated 2011 Dec 15], Chokshi et al., 2014). Patients with FCS have inherited mutations that reduce the activity of lipoprotein lipase (LPL), an enzyme that hydrolyses TGs and breaks down chylomicrons (Blom, 2010, NORD, 2016). This results in severe hypertriglyceridemia, the hallmark feature of the disease.

Severe hypertriglyceridemia places patients with FCS at an increased risk of acute pancreatitis, which can be fatal. A recent survey of international lipidologists with experience of managing patients with FCS report that 67% of FCS patients have been admitted to hospital for confirmed acute pancreatitis (Gaudet et al., 2016a) and have a mortality rate of 6% (due to acute pancreatitis or its long-term consequences). This aligns with research describing clinical outcomes in patients admitted to hospital with acute pancreatitis and severe hypertriglyceridemia which reported an in-hospital mortality of 8% (Nawaz et al., 2015). Recurrent episodes of acute pancreatitis, which occur if the severe hypertriglyceridemia is not reduced, exposes the patient to long term complications, including chronic pancreatitis and diabetes. FCS is also associated with a breadth of cognitive impairments, significant emotional burden and poor mental health.

FCS prevalence is estimated to be 2 people per million (Stroes et al., 2017). This suggests there are 130 FCS patients in the UK, of whom 120 are in England. It is estimated that 65-80% of FCS patients have a history of acute pancreatitis (Gaudet et al., 2016a; The Manchester study, Akcea data on file 2018d), and are therefore at high risk of pancreatitis. This indicates that between 80 and 100 people in England are likely to be eligible for treatment with volanesorsen.

The daily burden imposed by FCS is considerable for patients and their families. It affects their physical and emotional health, employment status, relationships and social life. Symptoms such as nausea and abdominal pain occur daily and can quickly worsen and become debilitating (Gelrud et al., 2017). Patients report anxiety, worry and fear relating to the food they can eat and the consequences of the disease. They also report being angry and frustrated due to the burden of the disease and the social isolation it leads to (Davidson et al., 2018). Families and carers report finding it hard to adjust to a reduced social life and not always understanding the seriousness of FCS (Gelrud et al., 2017). It is telling that 44% of patients felt FCS impacted their decision on whether to have children or how many children to have (Davidson et al., 2018).

Current treatments

There are currently no approved treatments for FCS. The standard of care is strict dietary control where fat intake is restricted to 10 – 15 g/day (equivalent to one tablespoon of olive oil) (Valdivielso et al., 2014). However, for most patients even a severely restricted low-fat diet will not be sufficient to reduce the risk of a potentially fatal episode of acute pancreatitis (Bruno, 2010, Gaudet et al., 2010, Stroes et al., 2017).

Some patients also receive lipid-lowering agents, such as fibrates, fish oils or niacin. However, these are generally ineffective as they act, at least in part, on the LPL-dependent metabolic pathway, which is absent in patients with FCS (Brahm and Hegele, 2015, Brisson et al., 2010, McCrindle et al., 2007). The risk of severe symptoms remains high in FCS patients despite receiving lipid-lowering drugs (Ahmad and Wilson, 2014). Evidence from a French data set and the volanesorsen clinical trial programme also indicates that patients are on a cocktail of drugs to control the pain and other symptoms of FCS, including steroids, analgesics, anxiolytics, antidepressants, diabetes treatments, and antithrombotics (Moulin et al., 2018, APPROACH clinical study report, 23rd June 2017).

The technology

Volanesorsen (Waylivra®) is an antisense oligonucleotide that inhibits the production of apolipoprotein C-III (apoC-III), a key regulator of plasma triglyceride (TG) levels.

Marketing authorisation

In May 2019, volanesorsen received a conditional marketing authorisation from the European Commission as an adjunct to diet in adult patients with genetically confirmed familial chylomicronaemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The marketing authorisation is conditional on the implementation of a registry study investigating the effectiveness of the platelet monitoring and dosing adjustments in the prevention of thrombocytopenia.

Dosing/posology

The recommended starting dose is 285 mg in 1.5 ml injected subcutaneously once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks. Treatment should be discontinued at 3 months in patients with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L (Volanesorsen SmPC).

After 6 months of treatment with volanesorsen, increase of dose frequency to 285 mg weekly should be considered if response has been inadequate in terms of serum triglyceride reduction as evaluated by the supervising experienced specialist and in the condition that platelet counts are in the normal range. Dosing may also change at 9 months and thereafter depending on response to treatment and platelet levels.

Presentation

Volanesorsen is supplied in pre-filled syringes containing 285 mg in 1.5 mL solution (each mL contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen). These are available as individual single-use syringes. The NHS list price is £11,394 per pre-filled syringe. Dosing, as specified in the summary of product characteristics (SmPC) is by subcutaneous (SC) injection

once-weekly for the first 3 months, after which the dose should be given once every 2 weeks.

Clinical trial – APPROACH trial programme

Efficacy endpoints

In the pivotal Phase 3 randomised, double-blind, placebo-controlled APPROACH study (n = 66), treatment with volanesorsen led to a marked reduction in plasma triglycerides versus placebo (-77% vs. +18%, respectively; 94% treatment effect, *P*<0.0001) at 13 weeks, with reductions continuing throughout the 12-month study period: mean -40.2% vs. +8.9% (patients completing study on both none reduced dose [n = 6] and reduced dose [n = 12]). All secondary and tertiary outcomes relating to triglyceride levels, cholesterol, chylomicron triglycerides and apolipoproteins B, B-48, A-1 and C-III were statistically significant in favour of volanesorsen. Health related quality of life and pain outcomes were not statistically significant, but the trial was not powered for these outcomes and this is not an unexpected finding given patient numbers. The number of acute pancreatitis (AP) events numerically favoured volanesorsen: 1 vs 4. Similarly, an exploratory analysis investigating the number of adjudicated acute pancreatitis events within the 12-month study period in patients at high risk for acute pancreatitis, relative to the 5-year pre-randomisation period, numerically favoured volanesorsen compared with placebo with 0 vs 4 events reported in each arm respectively. As AP is an event that severely impact patients' daily activities, quality of life and can be life-threatening, this is a significant outcome.

APPROACH open-label extension (OLE) study (planned enrolment n = 70) reports interim data that suggest the reduction in TG levels are sustained over the longer-term. [redacted]

Adverse events

In APPROACH, the most common adverse event reported with volanesorsen treatment was injection site reactions (n = 20; 61%), the majority of which were mild in intensity, and reductions in platelet levels (n = 11; 33%). A

reduction in platelet count to <50 x 10^9/L was observed in 3 patients prior to the initiation of enhanced platelet monitoring (Witztum et al., 2019). Thereafter, thrombocytopenia was manageable with monitoring and dose adjustment when required, as specified in the SmPC. [redacted]

The trials clearly demonstrate the efficacy of volanesorsen, representing a step-change in the management of FCS. Platelet count can be managed with the SmPC monitoring requirements which will be implemented by an expansion of the Akcea Connect Patient Support Programme, funded by the company.

Quality of life

Twenty-two of the volanesorsen treated patients in the APPROACH OLE study also took part in a quality of life study that reported significantly reduced number of symptoms per patient across physical, emotional and cognitive domains. Significant reductions from baseline were reported for steatorrhea (fatty stools), pancreatic pain and worry about an attack of pain/AP. Benefits were also reported relating to work responsibilities and the impact to personal, social and professional life (Arca et al., 2018).

Early Access to Medicines Scheme

The benefit of treatment conferred by volanesorsen and the significant unmet need faced by FCS patients was recognised in the award of a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) and participating in the EAM scheme. The company has provided volanesorsen free of charge to EAMS patients since March 2018.

Twenty-five patients have been identified as eligible, of whom 20 were on treatment as of 31 July 2019. EAMS uses a similar platelet monitoring and dose adjustment schedule as that in the SmPC. No EAMS patient has had a platelet level < 50 x 10^9/L with the monitoring and dosing programme in place. TG and other available data are currently being collected for the EAMS

cohort. With the NICE Committee's permission Akcea will provide this information in advance of the November Committee Meeting. Anecdotal feedback from EAMS supports that value of this product to patients with clinicians reporting patients getting and keeping jobs, going on holiday and forming partnerships, all for the first-time as adults, since starting treatment.

Value for money

A formal cost-effectiveness analysis from the perspective of the NHS in England is presented that demonstrates volanesorsen offers value for money to the NHS compared with the standard of care.

The model structure captures the key aspects of FCS including TG levels, acute pancreatitis events, chronic pancreatitis, diabetes and death. The model has a lifetime time horizon and assumes a discount rate of 3.5% for both costs and efficacy outcomes. The population in the model is adults with genetically confirmed FCS at high risk of acute pancreatitis in whom response to diet and triglyceride lowering therapy has been inadequate (the licensed indication). The model can also test other populations based on AP risk and prior pancreatitis events. The model is populated with efficacy data from APPROACH and APPROACH open label extension (OLE) clinical trials, the literature and real-world evidence; healthcare resource utilisation data is derived from literature and real-world evidence and utilities from an FCS-specific vignette study with data from the trial EQ-5D-5L presented in a scenario analysis. The model follows the SmPC dosing regimen with a treatment review at 3 months. Patients not meeting the required response discontinue treatment.

The model base case uses the previously accepted simple patient access scheme (PAS) with a per syringe price of [redacted] The base case model also assumes [redacted]

Observed trial data and statistical models have been used to estimate the treatment efficacy likely with the SmPC dosing schedule (as the trial dose

protocols do not exactly align with the SmPC). Similarly, treatment continuation (not including the 3-month review) is estimated based on the trial population that best reflects the SmPC in terms of dosing regimen and platelet monitoring: APPROACH OLE treatment-naïve patients.

The submitted base case reports an incremental cost effectiveness ratio of £213,755 per quality adjusted life year gained. Using trial discontinuation rates an incremental (undiscounted) QALY gain of [redacted] is estimated. Using EAMS treatment-related discontinuation, the model predicts [redacted] undiscounted QALYs could be gained. Under this scenario the model estimates an ICER of [redacted] or £78,664 with the QALY weighting of [redacted] applied, demonstrating that volanesorsen would be a good use of NHS resources.

The economic model is a robust representation of critical aspects of FCS and uses appropriate methodological approaches to address data uncertainties. Limitations include datasets falling below a sample size of n=30, a size at which standard economic and statistical techniques are limited, and the omission of eating disorders, fatty liver disease and hepatosplenomegaly due to insufficient data and limitations in the economic model. These challenges should be taken into consideration when making decisions based on the presented evidence.

Budget impact

Based on the prevalence estimates stated above, 120 FCS patients are estimated for England. Akcea is aware of approximately [redacted] patients who have a genetically confirmed diagnosis of FCS. Not every FCS patient will be considered high risk for AP and with shared treatment decision making between patients and clinicians it is likely that not all eligible patients will be prescribed volanesorsen. We estimate that a total of [redacted] patients would receive treatment with volanesorsen in Year 1, including those transitioning from the EAMS programme. By Year 5, a total of [redacted] patients will have started treatment cumulatively. Taking into account the current approved simple PAS we estimate a budget impact of [redacted] (year 1) and [redacted] (year 5) (undiscounted).

Volanesorsen's benefits beyond health

Available research indicates that FCS is likely to have a substantial impact on work productivity. The In-FOCUS study supports this with almost all FCS patients who were unemployed or employed on a part-time basis (94%) reporting that their employment status was a result of having FCS (Davidson et al., 2018). This is supported by evidence in the literature that pancreatitis has a negative impact on work productivity: in a multicentre study authors observed a profound impact on the ability to work and on interpersonal relationships for patients who experienced chronic pancreatitis (Gardner et al., 2010).

A published report from an advisory board (Gelrud et al., 2017) indicates that carer time may relate closely with the complications of FCS. The authors report carers using their own holiday time to provide care for patients during FCS complications. It is likely that over the lifetime of an FCS patient, carer time burden will be substantial, particularly in patients developing comorbidities such as diabetes or chronic pancreatitis.

The trial data demonstrate volanesorsen to be a step-change in the treatment of FCS - a chronic, intrusive disease with severe complications, some of which can be fatal. The relief that volanesorsen can offer patients and their family is profound. Based on this, and the formal economic evaluation, volanesorsen represents good value for money with a manageable budget impact due to the very low patient numbers.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults with familial chylomicronaemia syndrome	The population is patients with genetically confirmed FCS and at high risk for pancreatitis in whom response to diet and triglyceride-lowering therapy has been inadequate.	In line with the final indication.
Intervention	Volanesorsen in combination with established clinical management (including dietary fat restrictions)	None	
Comparator(s)	Established clinical management without volanesorsen (including dietary fat restrictions)	None	
Outcomes	The outcome measures to be considered include: • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability) • incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular	Data gaps and limitations, and concerns regarding double counting mean that some outcomes are not explicitly considered in the model: e.g. pancreatic necrosis and fatty liver disease. Cardiovascular disease is not in the economic model as there is no clinical	

	disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions) • mortality (including all-cause and pancreatitis related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers).	consensus regarding the impact of FCS on CVD outcomes. Chylomicrons are not considered to be involved in the atherosclerotic process due to their large particle size. Data relating FCS and CVD are limited.	

Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options	None	
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)	None	
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used	None	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise	None	
Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into	None	

	account any Managed Access Arrangements • The evaluation will include consideration of the costs and implications of genetic testing and measurement of enzyme level but will not make recommendations on specific diagnostic tests. • Consideration should be given to the precise definition and clinical diagnosis of familial chylomicronaemia syndrome. • If evidence allows, consideration will be given to the subgroup of patients with comorbid diabetes • If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues. • If appropriate, consideration may be given to whether factors contributing to, or exacerbating hypertriglyceridemia are associated with characteristics that are protected under equality legislation (for example, but not limited to, women using oral contraceptives).		

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name: Waylivra®

Approved name: volanesorsen

Therapeutic class: other lipid modifying agents (ATC code: C10AX)

2.2 What is the principal mechanism of action of the technology?

Metabolism of triglycerides (TGs) occurs primarily through the action of lipoprotein lipase (LPL) and via an LPL-independent pathway involving the LDL, low density lipoprotein (LDL) receptor (LDLR)/LDL receptor-related protein-1 (LRP1) axis. Both metabolic pathways are inhibited by the glycoprotein apolipoprotein C-III (apoC-III).

Volanesorsen is an antisense oligonucleotide (ASO) inhibitor of apoC-III. It selectively binds to apoC-III mRNA, preventing production of the apoC-III protein thereby removing the inhibitory regulation of triglyceride metabolism. Patients with FCS do not have functional LPL, hence the mechanism of volanesorsen in this patient group occurs primarily via the LPL-independent pathway.

2.3 Please complete the table below.

Table A2 Dosing Information of technology being evaluated

Pharmaceutical formulation	Solution for subcutaneous (SC) injection. Supplied in pre-filled syringes containing 285 mg volanesorsen in 1.5 mL solution
Method of administration	SC injection
Doses	285 mg in 1.5 mL
Dosing frequency	The recommended starting dose is 285 mg once-weekly for 3 months. After 3 months, the dosing frequency should be reduced to 285 mg once every 2 weeks. However, if the patient has not achieved a >25% reduction in triglyceride levels, or if triglyceride levels remain above 22.6 mmol/L at 3 months, treatment should be discontinued. If the patient's response is considered inadequate (in terms of serum triglyceride reduction) after 6 months of treatment, an increase in dosing frequency to 285 mg once-weekly should be considered (provided the patient's platelet levels are in the normal range). If this does not provide significant additional triglyceride reduction after 9 months of treatment, the dose should be reduced back to 285 mg once every 2 weeks. The potential for a dose frequency increase, while recommended in the label, has not been advocated by UK clinicians in a number of advisory boards conducted by Akcea. In EAMS, in which patients initiate on every 2 weeks dosing, no patients have increased dosing frequency.
Average length of a course of treatment	Chronic
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	Please see volanesorsen monitoring and treatment recommendations in Table A3

	below. No dose adjustments are needed for elderly patients, or for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment. With respect to hepatic impairment, evidence is not available. However, volanesorsen is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment.

Source: Volanesorsen SmPC

In the SmPC, the dose of volanesorsen is given as 285 mg. However, in the CSRs for the studies included in this submission, this dose is given as 300 mg, which relates to its formulation as volanesorsen sodium. Please note that in this submission, the dose is referred to as 285 mg throughout to reflect the SmPC.

Table A3 Volanesorsen monitoring and treatment recommendations

Platelet count (x10^9/L)	Dose (285 mg prefilled syringe)	Monitoring frequency
Normal (>140)	Starting dose: weekly After 3 months: every 2 weeks	Every 2 weeks
100 to 139	Every 2 weeks	Weekly
75 to 99	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Weekly
50 to 74[a]	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Every 2-3 days
Less than 50[a,b]	Discontinue treatment Glucocorticoids recommended	Daily

[a]Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels <75 x 10^9/L. Treatment with these medicinal products must be discontinued at platelet levels <50 x 10^9/L. [b]Consultation with a haematologist is required to consider the benefit/risk of possible further treatment with volanesorsen.

Source: Volanesorsen SmPC

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes, a conditional marketing authorisation was granted by the EMEA on 8th May 2019.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that volanesorsen will be commercially available in the UK in Q2 2020. Volanesorsen has been available to eligible patients via the Early Access to Medicines Scheme (EAMS) since March 2018.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Volanesorsen has a conditional marketing authorisation in the EU.

3.4 If the technology has been launched in the UK provide information on the use in England.

Although volanesorsen is not yet commercially available in the UK, it has had the benefit of being part of the EAMS with Akcea providing the treatment free of charge since March 2018. To date, 25 patients have been identified as being eligible for treatment, of whom 20 were on treatment as of 31 July 2019. Of those treated there have been no treatment-related discontinuations (1 patient did cease treatment due to a recurrence of cancer). With the monitoring and EAMS support programme in place there have been no platelet counts <50 x 10^9/L. Clinicians have reported anecdotally that patients are holding down jobs, travelling with work and going on holiday for the first time due to improvements in their disease while on volanesorsen.

Triglyceride and other available outcomes are currently being collected, and with the NICE Committee's permission will be submitted as part of this assessment when available (October 2019).

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table A4 shows completed and ongoing studies of volanesorsen in patients with FCS.

Table A4 List of completed and ongoing studies

Trial no. (Acronym) Phase	Interventions	Population	Treatment duration	Primary outcome	Status	Publications
NCT02211209 APPROACH Phase III	• Volanesorsen (285 mg) by SC injection, once weekly • Placebo by SC injection	Adult patients with FCS (n=66)	52 weeks	Percent change in TG at Month 3, defined as average of Week 12 and Week 13 assessments	Completed	Trial results published: (Witztum et al., 2019). Baseline data: (Blom et al., 2018b).
NCT02300233 COMPASS Phase III	• Volanesorsen (285 mg) by SC injection, once weekly* • Placebo by SC injection	Adult patients with hypertriglyceridemia (including FCS, n=7)	26 weeks	Percent change in TG at Month 3, defined as average of Week 12 and Week 13 assessments	Completed	Manuscript in preparation
NCT02658175 APPROACH OLE Phase III	• Volanesorsen (285 mg) by SC injection, once weekly	Adult patients with FCS who: • rolled over from APPROACH • rolled over from COMPASS • did not take part in APPROACH or COMPASS (planned enrolment n=70)	ongoing	Percent change and absolute change from baseline in fasting TG†	Study is ongoing. Patients are transferring out of the study and onto commercial product as their country of residence gains marketing authorisation. Interim data cuts are ongoing.	Unpublished

*All patients had dose frequency reduced to 285 mg every 2 weeks after 13 weeks of treatment with exemptions given to patients who had completed ≥5 months of dosing as of 27 May 2016. †No formal designation of outcomes as 'primary' or 'secondary' in APPROACH OLE; see Section 9.4.1 for a full list of study outcomes
OLE, open-label extension; SC, subcutaneous; TG, triglycerides
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file; COMPASS clinical study report, 2nd June 2017, Akcea data on file; APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

APPROACH and APPROACH OLE provide the pivotal evidence for this submission. In COMPASS, only 7 of the 113 patients enrolled had FCS; this study provides supportive evidence and is discussed briefly where information specific to these 7 patients is available.

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

An SMC submission will be made in Q3 2019. AWMSG have not requested a submission as they have confirmed they will follow this NICE assessment. It is anticipated that Northern Ireland will also follow this NICE assessment.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

We do not believe that this evaluation will result in any of these scenarios.

5.2 How will the submission address these issues and any equality issues raised in the scope?

While we do not anticipate any specific equality issues will be raised as a result of this assessment, it is important that the NICE committee is aware of a higher prevalence in South Asian communities.

Consideration should also be given to women with FCS who may wish to become pregnant. There is increased risk of FCS during pregnancy. In the IN-FOCUS study, 44% of respondents reported that having FCS impacted their decision on whether to have children, or how many children to have (Davidson et al., 2018). Although there are no data available regarding the use of volanesorsen in pregnant women, it is not contra-indicated and the biochemistry would suggest that it doesn’t cross the blood placenta barrier.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

FCS is an ultra-rare, genetic disease with an estimated prevalent of 2 per million people, equivalent to 120 people in England. It is estimated that 65 – 80% of patients with FCS will experience acute pancreatitis (Blom et al., 2018b, Gaudet et al., 2016a).

FCS is characterised by markedly elevated levels of triglycerides in the plasma (>8.4 mmol/L was the threshold in APPROACH, the pivotal phase 3 APPROACH trial) and a build-up of chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body) (Gaudet et al., 2014, NORD, 2016). The disease is autosomal recessive and caused by homozygous (or compound or double heterozygous) mutations in the LPL gene or in genes which code for proteins governing LPL function (Table B1), rendering the patient deficient in functioning LPL. The disease was previously known by the terms type 1 hyperlipidaemia lipoprotein lipase deficiency, or LPLD.

Table B1 Known mutations responsible for FCS

Gene (gene product)	Gene product function	Molecular features	% of monogenic mutations
LPL *(LPL)*	Hydrolysis of TGs and peripheral uptake of FFA	Severely reduced or absent LPL enzyme activity	95.0
APOC2 *(apoC-II)*	Required cofactor of LPL	Absent of nonfunctional ApoC-II	2.0
GPIHBP1 *(GPI-HBP1)*	Stabilises the binding of chylomicrons near LPL	Absent or defective GPI-HBP1	2.0
APOA5 *(apoA-V)*	Enhancer of LPL activity	Absent or defective apoA-V	0.6
LMF1 *(LMF1)*	Chaperone molecule required for proper LPL folding	Absent or defective LMF1	0.4

ApoC-II, apolipoprotein C-II; FCS, familial chylomicronaemia syndrome; FFA, free fatty acids; LPL, lipoprotein lipase; TG, triglyceride

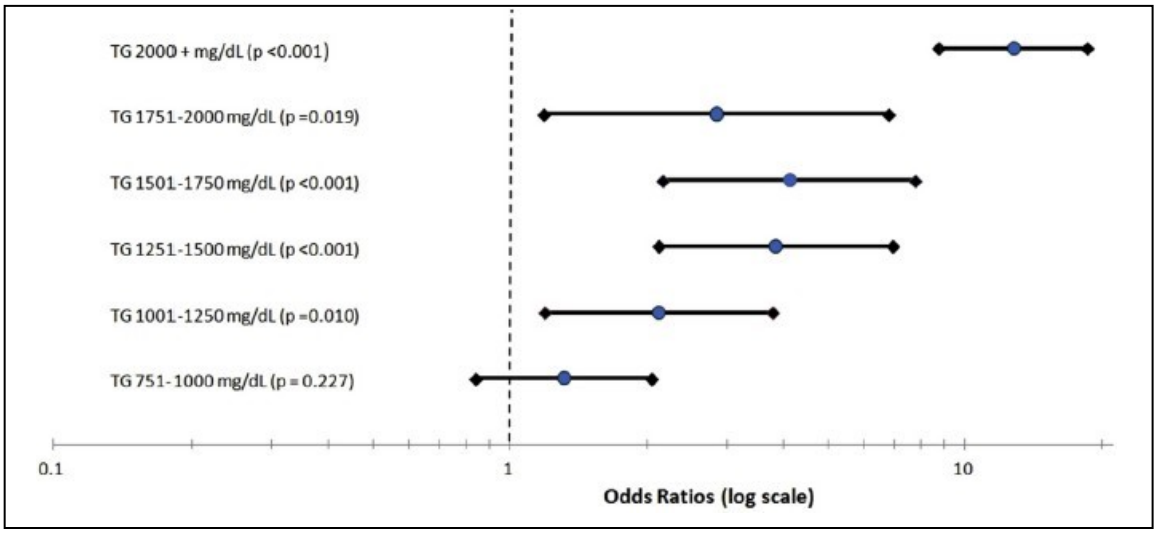
Source: Stroes et al, 2017; Brahm and Hegele, 2015.

These genetic mutations and the resulting elevated TG and chylomicron levels are associated with a broad range of negative consequences. This includes abdominal pain, ranging from mild to incapacitating (Chait et al., 1981), risk of acute pancreatitis, which is unpredictable and often recurrent (Blom, 2010, Gan et al., 2006, Gaudet et al., 2016a, Khokhar and Seidner, 2004, Valdivielso et al., 2014), the frequently reported symptoms of brain fog and confusion (Davidson et al., 2018), chronic pancreatitis, pancreatic necrosis, fatty liver disease and diabetes. These are all thought to be a

consequence of a build-up of chylomicron particles that reduce blood flow through organs microcirculation (Valdivielso et al., 2014).

A ‘dose/response’ relationship is observed between TG level and disease: poorer outcomes are observed at higher TG levels (Adiamah et al., 2017). The risk of acute pancreatitis increases with increasing TG levels (Valdivielso et al., 2014, Pedersen et al., 2016, Rashid et al., 2016, Murphy et al., 2013; Toth et al., 2014; Akcea data on file, 2018a). Toth et al. (2014) found a pronounced increase in risk for patients with TG levels >2000 mg/dL (22.7 mmol/L; Figure 1).

Figure 1 Relationship between TG levels and acute pancreatitis



Source: Toth et al., 2014

A retrospective analysis of UK observational data in the CALIBER database indicated that higher TG levels were associated with a higher incidence of acute pancreatitis (Figure 2). [redacted]

[redacted]

Source: Akcea data on file, 2018a

Additional studies have also reported patients with acute pancreatitis and TG levels >1000 mg/dL (11.4 mmol/L) experience more severe pancreatitis with worse outcomes than those with normal TG levels (i.e. <150 mg/dL, 1.7 mmol/L), including increased need for intensive care, higher rates of pancreatic necrosis, more frequent persistent organ failure, and higher mortality rates (Nawaz et al., 2015, Wang et al., 2016).

Women with FCS have additional risks, as increases in oestrogen can further increase TG levels. TG-induced acute pancreatitis during pregnancy can lead to pre-term delivery, loss of the foetus, or even death for the mother (Amin et al., 2015, Tang et al., 2010).

Patients who have experienced acute pancreatitis are at higher risk of future events, and those with recurrent events are particularly at risk of developing long-term complications including chronic pancreatitis, type 2 and type 3C diabetes, pancreatic insufficiency, and their attendant burdens (Das et al., 2014, Makhija and Kingsnorth, 2002, Sankaran et al., 2015, Symersky et al., 2006). The literature is supported by the hazard ratios (HRs) from CALIBER:

for the effect of prior acute pancreatitis on future incidence the HR was [redacted] (Akcea data on file, 2018a). Pancreatitis can be fatal, as a result of necrosis, sepsis and multi-organ failure caused by local inflammation in the pancreas (Makhija and Kingsnorth, 2002). Mortality rates are higher in patients with pancreatitis caused by raised TG levels than in those with pancreatitis due to other causes (Bardia and Garg, 2015). Results of a survey of lipidologists found that patients with FCS have a high risk of developing recurrent acute pancreatitis and that death from pancreatitis-related complications is not uncommon despite modern medical care (Gaudet et al., 2016a).

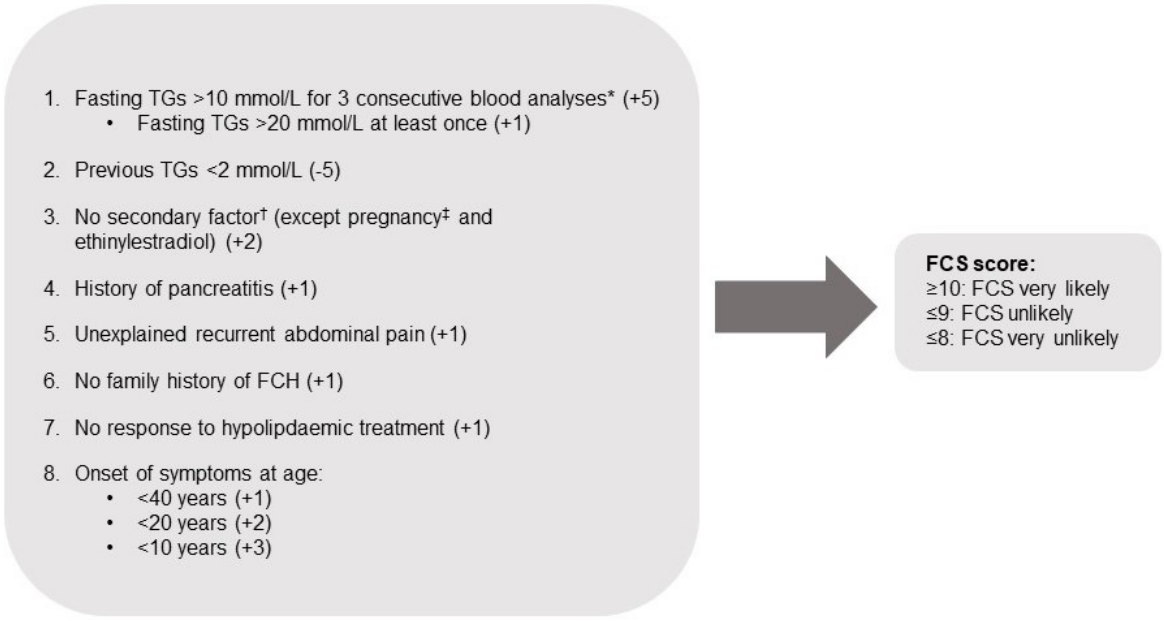
Other characteristics of FCS include (Brahm and Hegele, 2015, Brunzell, 1999 Oct 12 [Updated 2011 Dec 15], Tremblay et al., 2011, Yuan et al., 2007) eruptive cutaneous xanthomata (yellow papules that generally appear on the trunk, buttocks or extremities); lipemia retinalis (milky appearance of the retinal vessels and pink retina); lipemic blood (caused by the sustained presence of serum chylomicrons, even in the fasting state); and hepatosplenomegaly (enlarged liver and spleen).

Patients with FCS may also experience episodes of fatigue, a lack of energy (asthenia), impaired cognition, and a numbness or tingling sensation (dysthesia) and well a poor mental health, demonstrating the broad and negative impact this disease has (Brown et al., 2016, Chait et al., 1981, Davidson et al., 2018).

Diagnosis

Traditionally, patients have been diagnosed by assessment of several criteria, including recurrent raised TG levels that are refractory to current lipid-lowering therapies and are not due to other causes (e.g. type 2 diabetes, hypothyroidism), plus a history of acute pancreatitis and abdominal pain. Recently a panel of European clinical experts convened to review the diagnostic criteria for FCS and derived an FCS Score which can clinically discriminate with a high level of specify and sensitivity patients with FCS from those with severe hypertriglyceridaemia due to secondary causes. (Figure 3) (Moulin et al., 2018).

Figure 3 FCS score

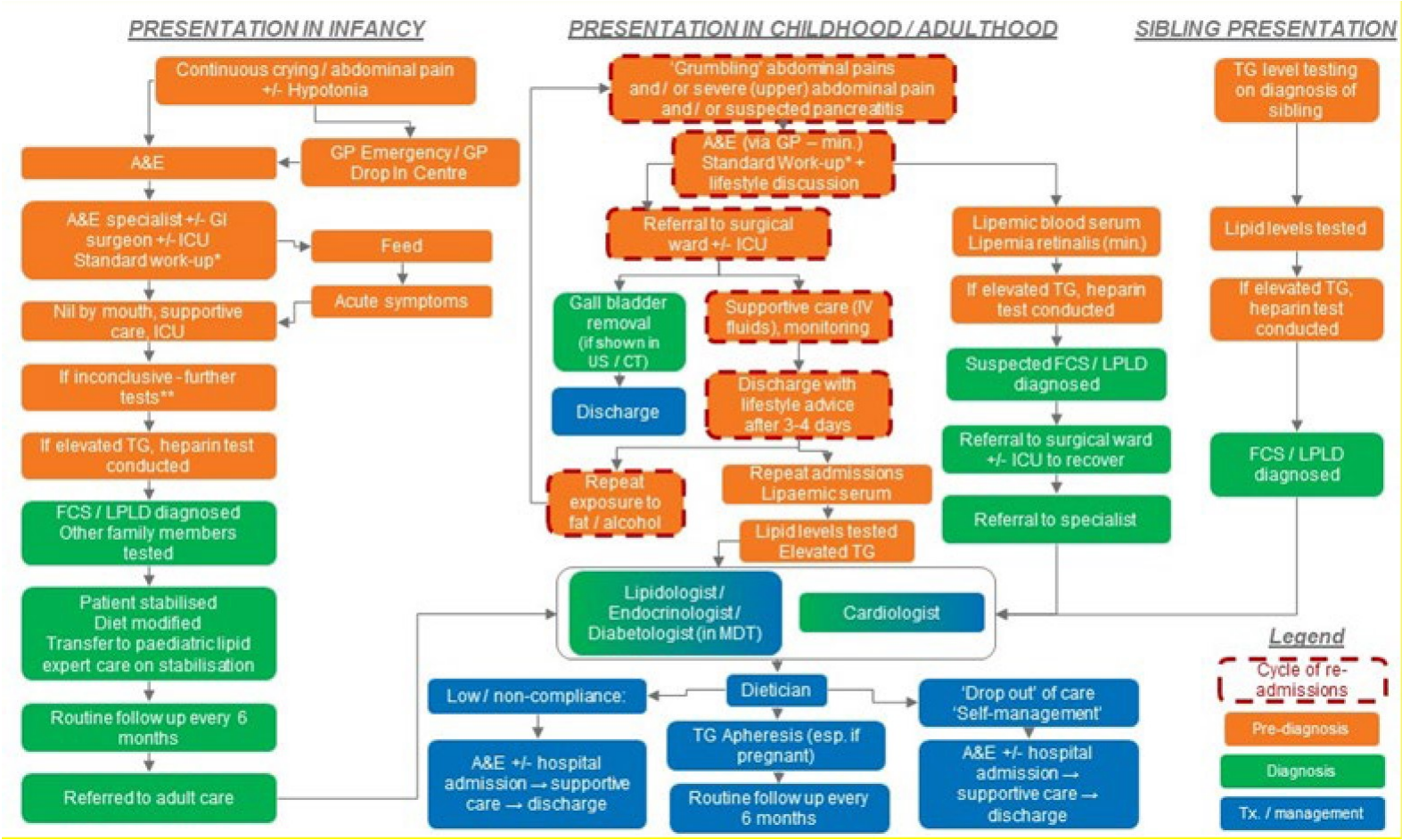


Numbers in parentheses = weighting given to each item. FCS score = sum of all items present. FCH, familial combined hyperlipidaemia. *Eruptive xanthoma may be used as a surrogate for high TG levels (rare). †Secondary factors include alcohol, uncontrolled diabetes, metabolic syndrome, hypothyroidism, corticotherapy. ‡If diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis post-partum.
Source: Moulin et al., 2018

Volanesorsen is indicated for adults with genetically confirmed FCS. Clinicians currently define 'genetically confirmed' FCS as patients exhibiting homozygous (or compound or double heterozygous) mutations in the LPL, APOC2, APOA5, LMF1 or GPIHPB1 genes, which code for proteins governing lipoprotein lipase activity (see Table B1) (Brahm and Hegele, 2015).

Some patients are diagnosed in infancy but those who are not are at risk of being caught in a cycle of misdiagnosis and diagnostic delay. Awareness of FCS is low among general practitioners and emergency physicians, and adult patients often find that healthcare professionals assume their attacks of acute pancreatitis are caused by an alcohol or drug problem. Consequently, it can take several years before a patient is correctly diagnosed. This puts patients at greater risk of complications. Figure 4 shows how the patient journey differs depending on the time of first presentation.

Figure 4 The patient journey in FCS



A&E, accident and emergency; CT, computed tomography; GI, gastrointestinal; GP, general practitioner; ICU, intensive care unit; TG, triglycerides; US, ultrasound
Source: Akcea data on file, 2017

Current treatment options

There are currently no treatment options for FCS, so patients rely on a highly restrictive-low fat diet to control their plasma TG levels (see Section 8 for further details). In most patients this is not sufficient to reduce TGs to a low enough level to reduce the risk of acute pancreatitis (Stroes et al., 2017). Some patients may receive lipid-lowering agents; however, these are generally ineffective because they operate via LPL, which is functionally impaired in FCS. Plasmapheresis, a procedure that rapidly lowers TG levels, is rarely used in the UK as the reductions seen in TGs are transient, lasting only a few days (Diakoumakou et al., 2014, Ewald and Kloer, 2012).

The burden of FCS is driven by extremely high plasma TGs. Volanesorsen offers patients a treatment option that significantly reduces TG levels which, in turn, reduces the risk of acute pancreatitis. In doing so, the risk of chronic pancreatitis, diabetes, pain, cognitive impairment, and social isolation should be improved.

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

FCS is an ultra-rare condition with a prevalence of 2 per million (Stroes et al., 2017). Estimates for England are 120 people, of whom approximately 60 patients have a genetically confirmed diagnosis.

The indication requires patients to be both genetically confirmed and at high risk of pancreatitis to be eligible for treatment. Expert clinicians in the UK have advised Akcea that patients ‘at high risk for pancreatitis’ are likely to be those with a history of acute pancreatitis. Approximately 65-80% of FCS patients have a documented history of acute pancreatitis (Gaudet et al., 2016a; The Manchester study, Akcea data on file 2018d), indicating that around 80-100 patients would be eligible according to the indication.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

There is no reliable information on life expectancy for patients with FCS. As described in Section 6.1, acute pancreatitis, a complication of FCS, can be life-threatening. A proportion of patients will also develop comorbid diabetes or chronic pancreatitis, both having an impact on life expectancy.

7 Impact of the disease on quality of life

7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

FCS imposes a significant burden on patients and their carers, adversely affecting their physical and emotional health, employment status, relationships and social life.

Physical and emotional health

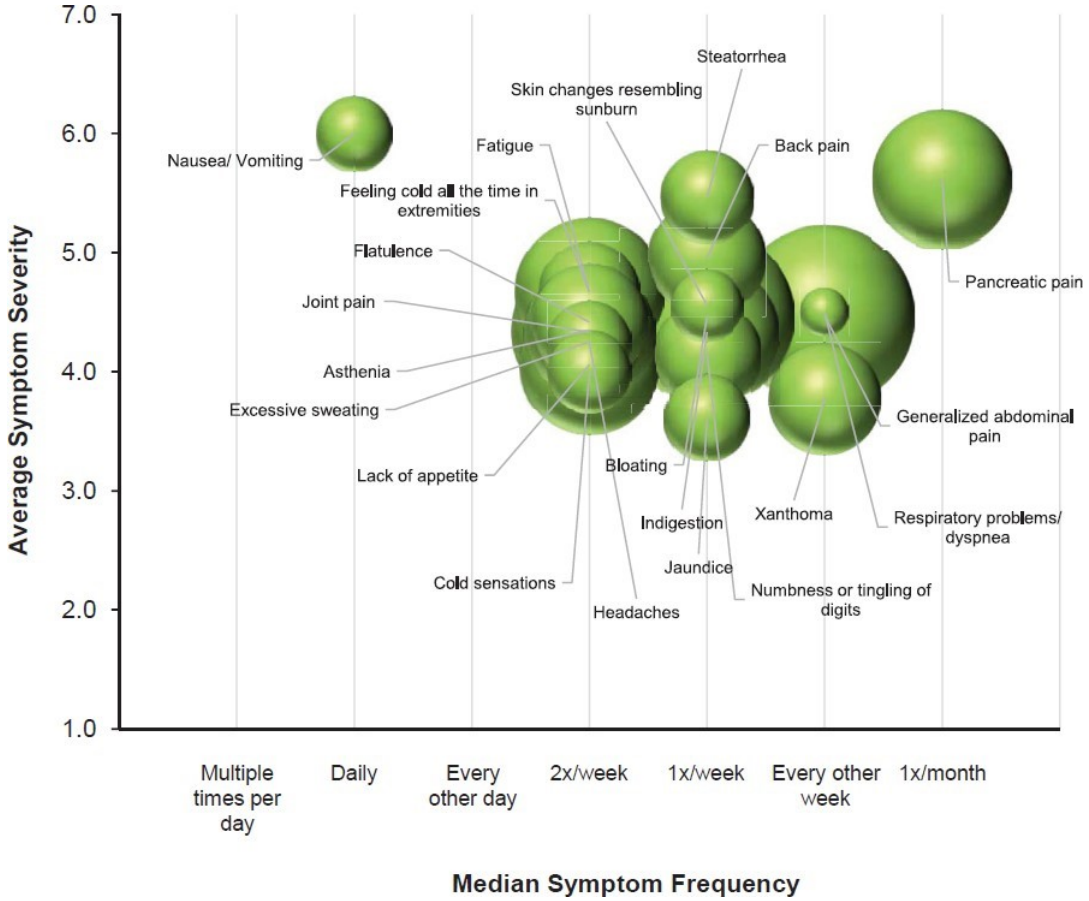
Patients with FCS often have multiple comorbidities and symptoms which span physical, emotional and cognitive domains.

In a recent survey of 166 patients with FCS from 10 countries (Davidson et al., 2018), at least one-third of the patients reported 2 or more comorbidities, including AP (40%), eating disorders (23%), diabetes (16%), chronic pancreatitis (11%), hepatomegaly (11%), splenomegaly (10%), hypertension (10%), lipemia retinalis (9%), peripheral neuropathy (7%), addiction to pain medication such as opioids (5%), other conditions (5%), and pancreatic calcification (2%).

Figure 5 shows the incidence, frequency and severity of physical symptoms. The most common symptom was nausea vomiting which was severe and daily for those affected. Other very common symptoms were generalised

abdominal pain (41%), bloating (37%), asthenia (weakness, 30%), indigestion (27%) and fatigue (23%); these symptoms were experienced between twice a week and once every 2 weeks (Davidson et al., 2018).

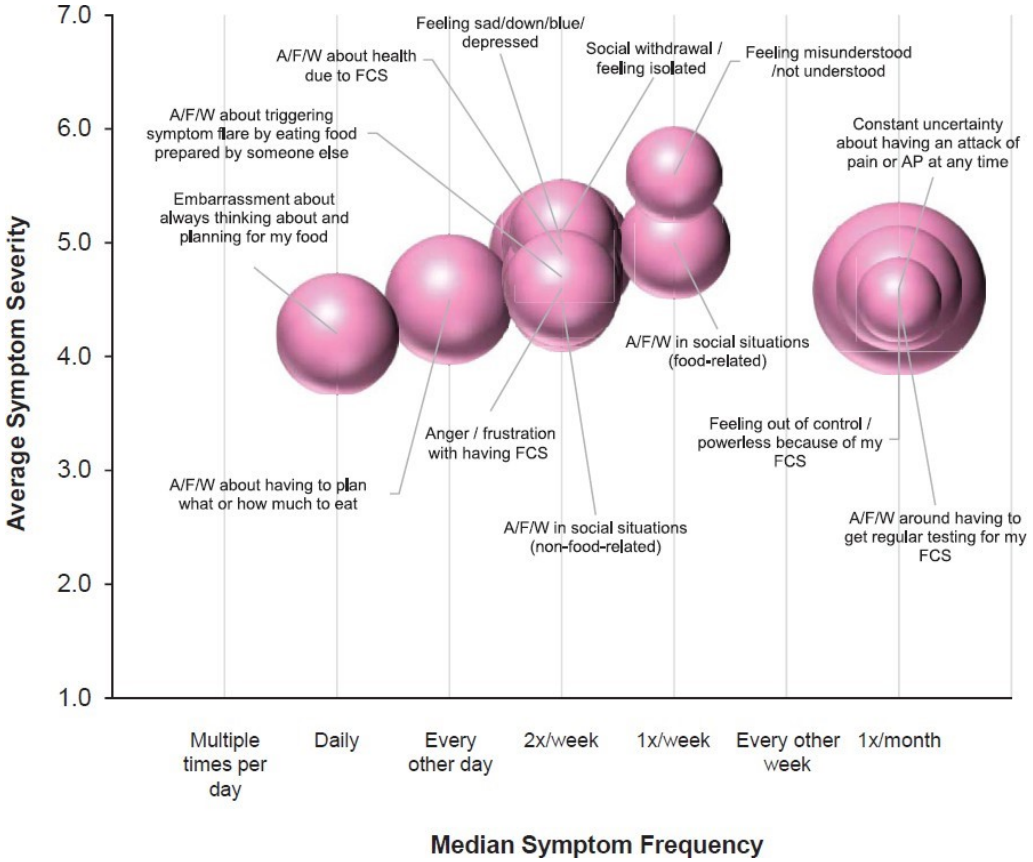
Figure 5 Physical symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
Source: Davidson et al., 2018

Figure 6 shows the results of this study for emotional symptoms. Patients reported feeling uncertainty about having pain or acute pancreatitis at any time, and that they were worried about their health and meal planning. They also said that they felt helpless or out of control.

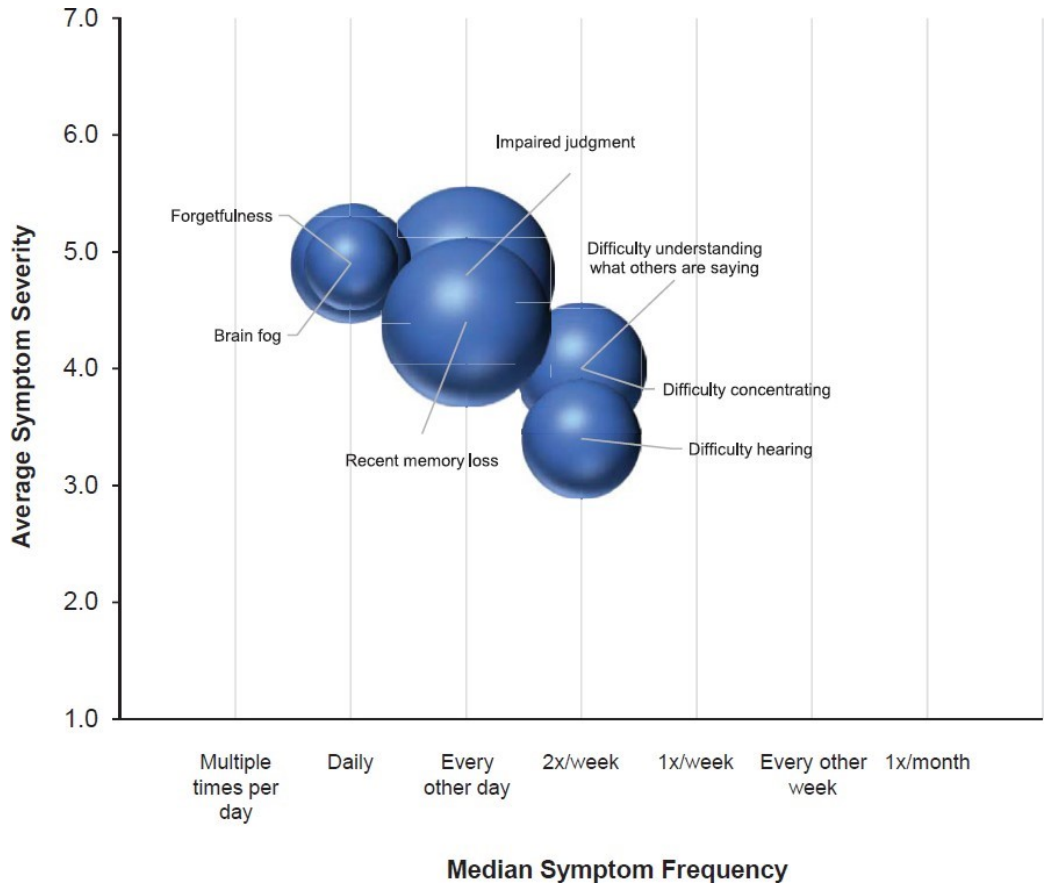
Figure 6 Emotional symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
A/F/W, anxiety, fear/worry; AP, acute pancreatitis
Source: Davidson et al., 2018

Figure 7 shows the study results for cognitive symptoms. The most common symptoms were difficulty concentrating (16%), impaired judgement (11%), ‘brain fog’ (8%) and forgetfulness (8%); patients experienced these symptoms daily or every other day.

Figure 7 Cognitive symptoms experienced by patients with FCS: frequency and severity



Severity was recorded on a scale of 1-7, where 1 = very mild and 7 = very severe. Frequency was recorded as multiple times per day, daily, every other day, twice a week, once a week, or every other week. Sphere size is proportional to the percentage of patients who selected the symptom.
Source: Davidson et al., 2018

Data from UK patients (n = 20) who took part in the survey support the overall findings. Patients reported a diverse range of symptoms, including generalised abdominal pain, fatigue, and anxiety/fear/worry about their health. Forty-five percent of UK respondents reported experiencing acute pancreatitis, averaging one episode in the last 12 months and 13 over the course of their lives so far. All patients said they had been hospitalised during their episodes of acute pancreatitis (Soran et al., 2018).

In a study of patients with FCS by Gelrud et al., all 10 patients interviewed reported daily nausea and low-level abdominal pain that could quickly worsen and become debilitating. Patients also reported that their symptoms increased in frequency as they got older (Gelrud et al., 2017).

As yet, there is no specific tool to measure quality of life (QoL) in patients with FCS. Johnson et al. (2015) evaluated 11 patients with LPLD using the European Organisation for Research and Treatment of Cancer's quality of life questionnaires QLQ-C30 (all cancers) and QLQ-PAN26 (pancreatic cancer). They found that the most relevant QoL domains for patients with LPLD were pain, fatigue and sleeping problems, digestive and dietary factors, work, daily and social activity restrictions, impact on emotional functioning, and satisfaction with healthcare professionals, all consistent with the IN-FOCUS findings.

Employment status

In the IN-FOCUS study (Davidson et al., 2018), only 60% of patients with FCS were employed full- or part-time (37% part-time, 23% full-time). Most of those who were unemployed had been employed in the past and many attributed their unemployment to FCS. Forty percent of homemakers felt their lack of employment opportunities was due to FCS. Data from UK respondents were similar: 65% of patients were employed (15% full-time). Of the UK patients who worked part-time or were unemployed, 80% said that FCS had an impact on their employment status, and 90% said it impacted their choice of career (Soran et al., 2018).

The symptoms of FCS can limit patients' ability to train for or perform work in their preferred career, and patients find that they may miss out on promotion because of frequent absences from work (Gelrud et al., 2017). Patients report that fatigue and an inability to concentrate limit performance at work (Gelrud et al., 2017).

Relationships and social life

Patients' social lives can be limited by fatigue and dietary considerations (Davidson et al., 2018, Gelrud et al., 2017). This also has an impact on carers, with some finding it hard to adjust to a reduced social life (Gelrud et al., 2017). Friends and family may not always understand the seriousness of FCS, which can be difficult for the patient (Gelrud et al., 2017). Importantly, 44% of patients felt FCS impacted their decision on whether to have children, or how many children to have (Davidson et al., 2018).

Impact of restricted diet

Following a strict low-fat diet places a burden on patients in terms of the time required to research and prepare fat-free meals, and the cost of buying fat-free food (Gelrud et al., 2017). There is also a considerable psychosocial burden as a result of following a strict low-fat diet. Patients report that they find it difficult to comply with their diet, particularly when not at home, that their satisfaction with the diet is low, and that it causes anxiety for both themselves and their carers. Having to comply with a strict diet also limits socialization and affects other members of the household who have no such dietary restrictions.

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

The introduction of volanesorsen will have a considerable impact on patients, their families and carers. The current standard of care (strict restriction of dietary fat) is ineffective, leaving patients with dangerously-elevated TG levels (Blom et al., 2018b, Stroes et al., 2017). APPROACH and APPROACH OLE demonstrate that patients treated with volanesorsen experienced robust and sustained reductions in TG levels. In many patients, TG levels fell below thresholds that are known to be associated with an increased risk of pancreatitis.

Reductions in TGs translate into benefits in terms of reductions in the incidence of acute pancreatitis, which will have a considerable impact on patients' QoL. Volanesorsen will not only improve patients' physical wellbeing by reducing the number of episodes of pancreatitis and abdominal pain, but also to improve their emotional wellbeing (and that of their families and carers) by reducing the anxiety and uncertainty caused by the prospect of experiencing these events.

In addition, reducing the frequency of acute pancreatitis and abdominal pain is expected to reduce the number of associated hospitalisations and time lost from work, which will remove some of the restrictions that FCS patients feel in terms of employment prospects and in their ability to contribute to their family income.

8 Extent and nature of current treatment options

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

There are currently no NICE, NHS England or other national guidelines for the treatment of FCS. A clinical diagnostic scoring system has recently been developed that is sensitive enough to discriminate between FCS and severe hypertriglyceridaemia arising due to secondary causes/multifactorial chylomicronaemia (Moulin et al., 2018), see Section 6.1. There is not however any comprehensive treatment algorithms or guidelines for FCS. Unfortunately, FCS was not included in the recent revision of the NICE Pancreatitis Guidelines (NICE, 2018a).

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Patients are currently managed in a small number of lipid clinics, mainly in a tertiary referral setting. Management requires specialist services (a consultant-led service plus dietician and nurse support). Patients may also need to access other NHS services to receive treatment for complications of FCS, such as abdominal pain and acute pancreatitis.

The current standard of care is strict restriction of dietary fat intake together with lifestyle changes, such as avoidance of alcohol. Volanesorsen will be used alongside dietary control, not as an alternative to it.

Some patients may receive lipid-lowering drugs (including fibrates and statins). However, these are generally ineffective (Brahm and Hegele, 2015, Brisson et al., 2010, McCrindle et al., 2007). The risk of severe symptoms, such as pancreatitis, remains high, even in patients with FCS who receive lipid-lowering drugs (Ahmad and Wilson, 2014).

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Diet alone is not sufficient to reduce the risk of acute pancreatitis (Bruno, 2010, Gaudet et al., 2010, Stroes et al., 2017), and TG levels are difficult to control, even in those patients who manage to adhere to the low-fat regimen (Brisson et al 2010). The recommended fat intake for patients with FCS is approximately 10 to 15 g/day (Valdivielso et al., 2014), which is equivalent to around one tablespoon of olive oil. Patients find this regimen hard to adhere to and need close monitoring by a dietician or nutritionist, with regular assessment of their lipid profiles. However, access to expert dietary advice is limited outside the secondary/tertiary care setting, with only a few centres having access routinely to dieticians and nutritionists.

Due to the rarity of FCS, only a limited number of clinicians in England in specialist centres have sufficient expertise to adequately manage patients with FCS and to oversee the clinical aspects of introducing a novel class of therapy such as volanesorsen to the small patient cohort in England. In addition, FCS is associated with many comorbidities, and affected patients frequently require access to other NHS services. Optimal multi-disciplinary management of FCS patients is therefore likely to be only available in a few expert centres. This, in addition to the lack of a national clinical guideline for FCS, is likely to result in geographic variations of clinical practice. Support and training on injection technique, monitoring requirements and use of volanesorsen will be provided to specialist centres by the UK Akcea medical team. Akcea is also planning to put in place a nurse service, via a third-party provider.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

Volanesorsen is expected to be used in patients with a genetically confirmed diagnosis of FCS and at high risk of pancreatitis as an adjunct to diet and not as an alternative treatment. It is anticipated that genetic confirmation will have been obtained under the NHS England genetic testing program, prior to and independently of assessment of eligibility for volanesorsen (see Section 8.7). As described in Section 8.7, patients receiving volanesorsen will require regular platelet monitoring and training on how to self-administer the drug; Akcea intends to support this via a nurse and homecare service.

Due to the uncertainty about current best practice highlighted in Section 8.3, we would anticipate that volanesorsen is prescribed and patients are monitored by clinicians with an expertise in FCS, via a nationally commissioned service.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Volanesorsen represent a 'step-change' in the management of FCS. Receiving the PIM designation for the product indicates that the MHRA recognises the value of the product, the significant unmet for treatment and the burden FCS places on patients and their families.

Volanesorsen is an innovative treatment with demonstrated significant and sustainable TG lowering effect and reduction in pancreatitis events Therefore alleviating the broad and negative impact that FCS has physical, psychosocial, cognitive and economic aspects of patients' lives.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

At an advisory board held by Akcea, there was a consensus that a networked (hub and spoke) service could improve the current service, ensuring that there

is an optimal broader service provision associated with the centres prescribing volanesorsen (for example access to expert dieticians and specialist nurse services) to provide adequate disease management and long-term patient support.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

Genetic testing

Volanesorsen is indicated for patient with genetically confirmed FCS. From October 2018, the genomic testing programme within England is being restructured and will ultimately be delivered through a network of 7 regional genomic laboratory hubs (GLHs). These 7 centres will provide reimbursed (from April 2020) genomic analysis for over 450 prespecified indications, including FCS (labelled as lipoprotein lipase deficiency (LPLD), a previous nomenclature for FCS). The National Genomic Test Directory specifies which genomic tests will be commissioned by the NHS in England and can be found online at: https://www.england.nhs.uk/publication/national-genomic-test-directories/. Genetic testing will therefore not be additional to usual practice as it is anticipated that patients will seek genetic confirmation independently of any decision to initiate volanesorsen.

Monitoring

Reductions in platelet occur in patients with FCS during treatment with volanesorsen; these reductions may result in thrombocytopenia. Careful monitoring is therefore important. Before starting treatment, patients should have a platelet count. Patients with a platelet count <140 x 10^9/L should have a second measurement approximately one week later. If the count remains below 140 x 10^9/L upon second measurement, treatment with volanesorsen should not be initiated.

Once treatment has started, platelet counts should be routinely carried out every 2 weeks. Table B2 shows the recommended dosing and monitoring

adjustments for patients who experience a reduction in platelet count. If treatment is paused or discontinued because of severe thrombocytopenia, the benefits and risks of returning to treatment once the platelet count recovers to ≥140 x 10^9/L should be carefully considered. For discontinued patients, a haematologist should be consulted before resuming treatment.

Akcea Therapeutics will support the monitoring requirements of volanesorsen with an extension to its Akcea Connect Patient Support Programme, thereby absorbing the majority of costs associated with the monitoring.

Table B2 Recommended dosing and monitoring adjustments following reduction in platelet count

Platelet count (x10^9/L)	Dose (285 mg prefilled syringe)	Monitoring frequency
Normal (>140)	Starting dose: weekly After 3 months: every 2 weeks	Every 2 weeks
100 to 139	Every 2 weeks	Weekly
75 to 99	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Weekly
50 to 74[a]	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Every 2-3 days
Less than 50[a,b]	Discontinue treatment Glucocorticoids recommended	Daily

[a]Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels <75 x 10^9/L. Treatment with these medicinal products must be discontinued at platelet levels <50 x 10^9/L. [b]Consultation with a haematologist is required to consider the benefit/risk of possible further treatment with volanesorsen.
Source: Volanesorsen SmPC

There is also a requirement in the SmPC relating to renal and liver function:

Renal toxicity has been observed after SC and IV administration of other antisense oligonucleotides. It is therefore recommended that a urine dipstick test is carried out on a quarterly basis during treatment with volanesorsen. If the test is positive, a wider assessment of renal function should be performed and treatment stopped if any of the following are observed:

- Proteinuria ≥500 mg/24 hours
- Increase in serum creatinine ≥0.3 mg/dL (26.5 µmol/L) that is greater than the upper limit of normal (ULN)

- Creatinine clearance ≤30 mL/min/1.73 m^2 (as estimated by the CKD-EPI equation)

Elevation of liver enzymes has also been observed after SC and IV administration of other antisense oligonucleotides. It is therefore recommended that serum liver enzymes and bilirubin are monitored on a quarterly basis during treatment with volanesorsen. Treatment should be stopped if any of the following are observed:

- A single increase in ALT or AST >8 x ULN
- An increase in ALT or AST >5 x ULN that lasts for ≥2 weeks
- Lesser increases in ALT or AST that are associated with total bilirubin >2 x ULN or INR >1.5
- Any clinical signs or symptoms of hepatic impairment or hepatitis

Administration

There will be a requirement to educate patients in best practice for self-administration- and rotation of injection sites. This will be provided by Akcea through home visits from a nurse along with educational material for both patients and physicians.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

It is anticipated that the current tertiary service will evolve slightly, if volanesorsen is recommended, to ensure that treatment continues in the few expert-consultant-led services with dietician and specialist nurse support available. No substantial facilities, technologies or infrastructure are needed. EAMS has provided a useful pilot for the current service and care appears to be very effective in the current EAMS centres.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

The introduction of volanesorsen has the potential to reduce the number of accident and emergency visits and hospital admissions due to abdominal

pain and acute pancreatitis. There is also the potential that utilisation of other services (e.g. blood tests, surgery) related to treatment of other comorbidities and complications of FCS (such as pancreatic dysfunction leading to diabetes and malabsorption) will be reduced.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

Akcea conducted a systematic literature review of the published English language literature to identify and summarise outcomes related to the treatment of FCS. Searches were conducted in the following databases to identify literature published from database inception to 7 June 2019: MEDLINE (via Ovid), Embase, the Cochrane National Health Service Economic Evaluation Database (NHS EED), the Cochrane Health Technology Assessment (HTA) Database, the Database of Abstracts of Reviews of Effects (DARE). The search strategy used is presented in Appendix 1.

The literature search was broad in scope to include all the interventions for FCS. Studies which did not involve the patient population specified in the scope were subsequently excluded after reading the abstract and title (level 1 screening) and reading the full text (level 2 screening).

In addition, reference lists of all accepted studies, and all relevant systematic reviews and meta-analyses were screened manually to identify any relevant

studies that were not identified using the above electronic search strategy. Moreover, grey literature (material not published in peer-reviewed or indexed medical journals) was also searched for relevant conference abstracts and posters reporting interventional or observational studies in FCS.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Publication database searches were supplemented with unpublished data from completed and ongoing Akcea studies of volanesorsen. In addition to Ovid and EMBASE searches for published literature relevant to the decision problem and relevant to the NICE scope, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), the UK Clinical Trials Gateway, the EU Clinical Trials Register, and the World Health Organization International Clinical Trials Registry Platform were searched from inception to 7 June 2019. Details of the search strategy used are presented in Appendix 1.

9.2 Study selection

Published studies

9.2.1 Complete table C1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for published studies

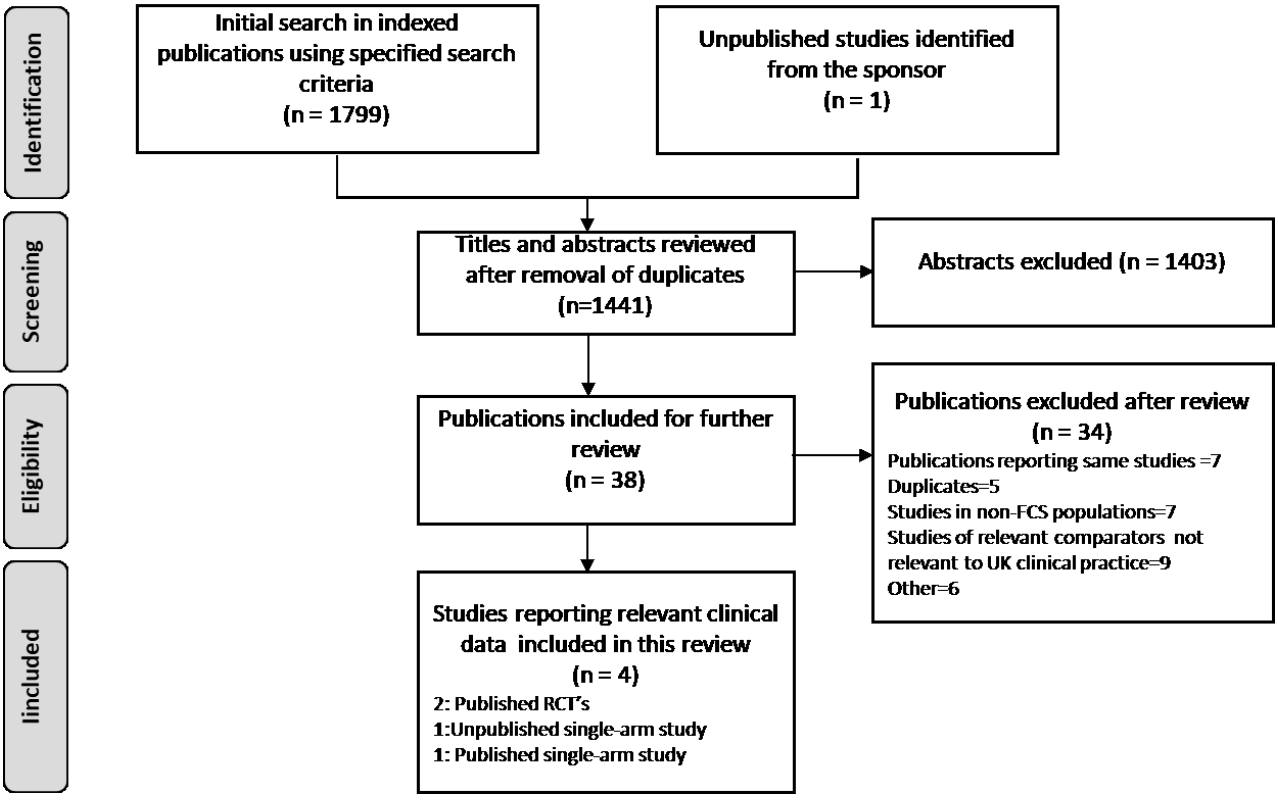
Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

As FCS is extremely rare, we included all sources of information (including case-reports and case-series) in our literature search.

The result of the search and subsequent screening is shown in Figure 8. No relevant clinical studies were identified other than the core studies comprising the volanesorsen clinical programme. Information on other clinical studies involving other potential treatment options for FCS are summarised from the available literature to provide context. Sections 9.3 to 9.7 include information from the volanesorsen clinical programme only.

Figure 8 PRISMA diagram of clinical studies



FCS, familial chylomicronaemia syndrome; RCT, randomised controlled trial

Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

One unpublished study was identified from the sponsor – the APPROACH OLE clinical trial. No unpublished studies were excluded from the SLR.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

The comparators in the scope are broadly defined as “Established clinical management without volanesorsen (including dietary fat restrictions)”. Tables C3 and C4 show four clinical trials of volanesorsen that were identified in the searches as being potentially relevant. Three of these (APPROACH, APPROACH OLE and COMPASS) were ultimately considered to be directly relevant to the decision problem and are described in detail in this submission. The fourth (a Phase II, open-label, single-arm study in three patients by Gaudet et al) is not described further in this submission as it is not considered to address the decision problem.

Given the paucity of clinical data, we have also provided an overview of studies that have investigated other technologies in FCS. These studies are included in Table C5 but are not discussed further as they either do not compare with volanesorsen, and/or they investigate technologies that are not currently available as a treatment for FCS and so cannot be considered as appropriate comparators.

Table C3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
1. Gaudet, et al. Targeting APOC3 in the familial chylomicronemia syndrome. N Engl J Med. 2014 Dec 4;371(23):2200-6. doi: 10.1056/NEJMoa1400284		Patients with the familial chylomicronaemia syndrome and LPL deficiency (single-arm trial)	285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection	None
2. Gaudet et al. The APPROACH study: a randomized, double-blind, placebo-controlled, phase 3 study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome (FCS). J Clin Lipidol 2017;11 (3):814-5.	The APPROACH study NCT02211209	FCS patients with fasting triglycerides >=8.4 mmol/L (>=750 mg/dL)	Participants were randomised 1:1 to 52 weeks of weekly subcutaneous volanesorsen (285 mg) or placebo	Placebo
3. Gouni-Berthold et al. Apolipoprotein C-III inhibition with volanesorsen in patients with hypertriglyceridemia (COMPASS): A randomized, double-blind, placebo-controlled trial. J Clin Lipidol 2017;11 (3):794-5) .	The COMPASS study NCT02300233	Patients with Hypertriglyceridemia including FCS with fasting triglycerides +/- 500 mg/dL	Patients were randomised 2:1 to receive 285 mg volanesorsen SC once a week or placebo, respectively for 26 weeks.	Placebo

Table C4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
The APPROACH open label study: a study of volanesorsen (formerly IONIS-APOCIIIRx) in patients with familial chylomicronaemia syndrome	The Approach Open Label Study (APPROACH OLE) NCT02658175	Patients with FCS	Volanesorsen (IONIS 304801) 285 mg administered subcutaneously to patients with familial chylomicronaemia Syndrome (FCS)	None (Phase 3 study)

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

Studies identified but not included either do not compare with volanesorsen, and/or they investigate technologies that are not currently available as a treatment for FCS and so cannot be considered standard of care comparators.

Table C5 List of excluded (published) studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Rouis M, Dugi KA, Previato L, et al. Therapeutic Response to Medium-Chain Triglycerides and ω-3 Fatty Acids in a Patient With the Familial Chylomicronemia Syndrome Arteriosclerosis, Thrombosis, and Vascular Biology. 1997; 17:1400-1406		8-year-old black female patient (case report)	(15 to 30 g/d) of an MCT oil - containing diet or (15 to 30 g/d) of an MCT oil–containing diet	None	Triglyceride levels Abdominal pain
Stroes ES, Nierman MC, Meulenberg JJ, et al. Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients. Arterioscler Thromb Vasc Biol. 2008 Dec; 28(12):2303-4.	CT-AMT-010-01	8 LPL-deficient patients (open - label)	LPLS447X-adeno-associated virus subtype 1(AAV1) vector injected in the leg musculature at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight (40 and 60 injections of 500 microliters, respectively)	None	Reduction in individual median fasting plasma TG
Mingozzi F, Meulenberg JJ, Hui DJ, et al. AAV-1–mediated gene transfer to skeletal muscle in humans results in dose-dependent activation of capsid-specific T cells. Blood. 2009;114(10):2077-2086		8 LPL-deficient subjects with missense mutations in both LPL alleles (Cohort study)	Intramuscular administration of the AAV-1 vector encoding LPL (AAV-1-LPLS447X) at a dose of 10^{11} gc/kg (n=4) and 3×10^{11} gc/kg (n=4).	None	Immune response (B- and T-cell responses) to both vector capsid and transgene product

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Carpentier AC, Frisch F, Labbe SM, et al. Effect of Alipogene Tiparvovec (AAV1-LPLS447X) on Postprandial Chylomicron Metabolism in Lipoprotein Lipase-Deficient Patients, The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 5, 1 May 2012, Pages 1635–1644,	CT-AMT-011-02	5 LPLD subjects (Open-label trial)	1×10^{12} genome copies (gc)/kg	None	Triglyceride (TG) content of the chylomicron fraction Chylomicron-TG/total plasma TG ratio
Gaudet D, Méthot J, Déry S, et al. Efficacy and long term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open label trial. Gene Therapy. 2013;20(4): 361-369. doi:10.1038/gt.2012.43.	CT-AMT-011-01 (ClinicalTrials.gov NCT01109498)	14 adult LPLD patients (Open-label trial)	Cohorts 1 (n=2) and 2 (n=4) received 3×10^{11} gc/kg, and cohort 3 (n=8) received 1×10^{12} gc/kg. Cohorts 2 and 3 also received immunosuppressants from the time of alipogene tiparvovec administration and continued for 12 weeks	None	Long-term safety of alipogene tiparvovec Reduction in fasting median plasma triglyceride
Ferreira V, Twisk J, Kwikkers K, et al. Immune Responses to Intramuscular Administration of Alipogene Tiparvovec (AAV1-LPLS447X) in a Phase II Clinical Trial of Lipoprotein Lipase Deficiency Gene Therapy. Human Gene Therapy. 2014;25(3): 180-188	CT-AMT-011-02 (ClinicalTrial.gov #CT00891306)	Five subjects with LPL deficiency (Open-label trial)	1×10^{12} gc/kg alipogene tiparvovec administered intramuscularly	None	Impact of systemic and local immune responses against AAV1 on safety and the persistence of LPL transgene expression.

Primary study reference	Study name (acronym)	Population	Intervention	Comparator	Outcome
Meyers CD, Tremblay K, Amer A, et al. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome. Lipids Health Dis. 2015 Feb 18;14:8	NCT01146522	6 patients with FCS (open-label trial)	Pradigastat orally once daily for three weeks in each of the three periods in a non-randomised sequence at 20 (period 1), 40 (period 2), and 10 mg (period 3) in patients on the low-fat diet.	None	Changes in fasting and postprandial plasma triglycerides
Extension to a Randomized, Double-blind, Placebo Controlled Study of LCQ908 in Subjects With Familial Chylomicronemia Syndrome. Novartis Pharmaceuticals (ClinicalTrials.gov)	NCT01589237 CLCQ908B2305 2012-000802-32 (EudraCT Number)	Subjects with FCS	Patients initiated on LCQ908 at 10 mg/day. After at least 8 weeks of treatment with a dose, optional up-titration to the next possible dose will be allowed. One down titration allowed from the highest dose attained.	Placebo (Phase 3 study)	Adverse events, serious adverse events and death Changes from baseline in triglyceride, cholesterol HDL and non HDL cholesterol, free fatty acids, apolipoprotein A1, B-48 and B-100 levels up to 52 weeks
A Randomized, Double-blind, Placebo Controlled Study to Assess Efficacy, Safety and Tolerability of LCQ908 in Subjects With Familial Chylomicronemia Syndrome Novartis Pharmaceuticals (ClinicalTrials.gov)	NCT01514461 CLCQ908B2302 2011-005535-68 (EudraCT Number)	Subjects with FCS	Patients were randomised (1:1:1) to receive once daily oral pradigastat, 20 mg, 40 mg or placebo. An optional down titration was allowed for safety and tolerability reasons after week 12.	Placebo (Phase 3 study)	Percent change in fasting triglycerides from baseline to 12 weeks

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using the tables provided as appropriate. A separate table should be completed for each study.

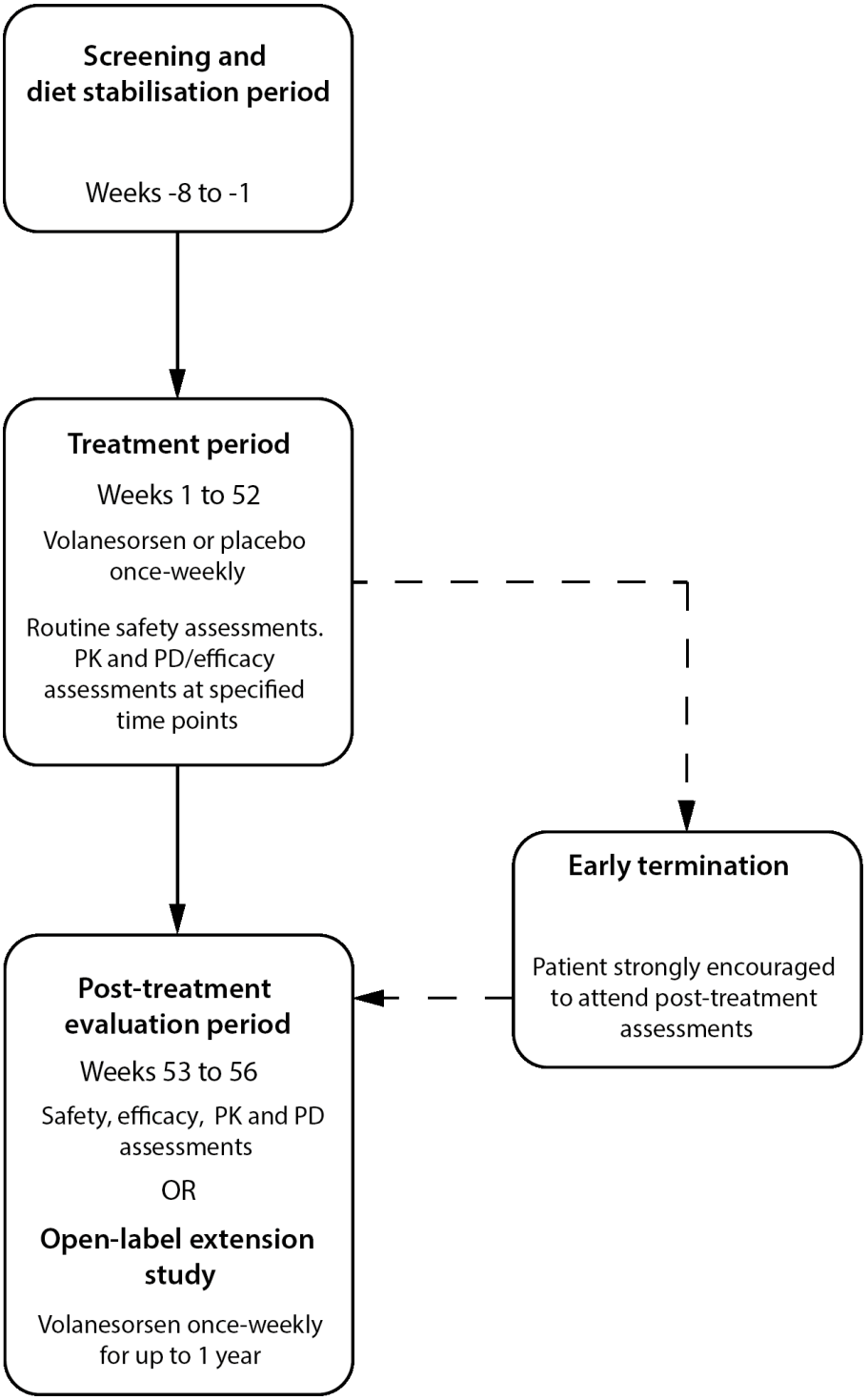
Sections 9.4 to 9.7 describe the methodology and results of the studies from the volanesorsen clinical development programme. The methodology of other studies identified in the literature search is described in Appendix 5.

APPROACH

APPROACH was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 52-week study in patients with FCS. The study design is shown in Figure 9. Briefly, the study consisted of three periods:

- Screening: up to 8 weeks, including a 6-week diet stabilization period. Baseline assessments were performed in the final 2 weeks of the screening period
- Treatment period: 52 weeks
- Follow-up: 13 weeks **or** entry into an open-label extension study (APPROACH OLE)

Figure 9 APPROACH study design



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C6 summarises the study methodology.

Table C6 Summary of methodology for APPROACH

Study name	**The APPROACH Study: a randomised, double-blind, placebo-controlled, phase 3 study of ISIS 304801 administered subcutaneously to patients with familial chylomicronemia syndrome (FCS)**
Objectives	To evaluate the efficacy and safety of volanesorsen administered subcutaneously to patients with FCS. The primary hypothesis was that volanesorsen would show superior efficacy over placebo in the treatment of adult patients with FCS
Location	40 study centres worldwide (US: 12; Spain: 5; UK: 4; Canada: 4; France: 3; Italy: 3; Netherlands: 1; Germany: 2; Israel: 2; Brazil: 2; Hungary: 1; South Africa: 1)
Design	Randomised, double-blind, placebo-controlled study
Duration of study	• Screening/diet stabilization: 8 weeks • Treatment: 52 weeks • Follow-up: 13 weeks
Sample size	66 patients Sample size calculations were based on results of previous clinical trials with volanesorsen. It was estimated that the SD of the percent change in total TG is approximately 46%. With 22 patients in each group, there would be approximately 80% power to detect a 50% difference in TG levels between treatment groups at the 0.01 significance level, assuming a 60% reduction in the volanesorsen group and a 10% reduction in the placebo group. The sample size was therefore calculated as 70 patients in total.
Key inclusion criteria	• ≥18 years of age • Diagnosis of FCS by documentation of at least one of: (a) Confirmed homozygote, compound heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1) or (b) Post heparin plasma LPL activity of ≤20% of normal • Fasting TG ≥750 mg/dL (8.4 mmol/L) at screening • Documented history of chylomicronaemia • Agreed to follow a diet comprising ≤20 g fat per day

	• History of pancreatitis (defined as a documented diagnosis of acute pancreatitis or hospitalisation for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made). Patients without a documented history of pancreatitis were also eligible but their enrolment was capped at 28% (i.e. ≤20 of the 70 patients) to enrich for patients with a history of pancreatitis
Key exclusion criteria	• Diabetes mellitus if newly diagnosed or if HbA1c ≥9.0% • Other types of severe hypertriglyceridemia • Active pancreatitis within 4 weeks of screening • Acute or unstable cardiac ischaemia within 6 months of screening • Major surgery within 3 months of screening • Treatment with Glybera® therapy within 2 years of screening • Previous treatment with volanesorsen • Any other conditions that, in the opinion of the investigator, could interfere with the patient participating in or completing the study
Method of randomisation	1:1, stratified by prior history of pancreatitis and concurrent treatment with fibrates and/or prescription omega-3 fatty acid. Patients were allocated to treatment using an Interactive Voice/Web-Response System.
Method of blinding	Double-blind. Patients and study personnel were blinded until all patients had completed treatment and the database was locked. To maintain the blind, study personnel were not allowed access to any lipid panel results, including apoC-III.
Intervention(s) (n =) and comparator(s) (n =)	Volanesorsen 285 mg, given as a single 1.5 mL subcutaneous injection, once a week (n = 33) Placebo, given as a single 1.5 mL subcutaneous injection, once a week (n = 33)
Baseline differences	None (see Section 9.4.3)
Duration of follow-up, lost to follow-up information	13 weeks. Not all patients entered the 13-week follow-up period, as at the end of the treatment period they could choose to enter the APPROACH OLE instead.

Statistical tests	The primary endpoint (see below) was analysed using an ANCOVA model with history of pancreatitis and presence/absence of concurrent omega-3 fatty acids and/or fibrates as factors, and log-transformed baseline TG as a covariate. Secondary endpoints were only analysed if the treatment comparison of the primary endpoint was statistically significant. Analysis was carried out sequentially, i.e. an endpoint was only tested if the previous endpoint was shown to be statistically significant.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the percentage change in fasting TG levels between baseline and the end of Month 3. The value at the end of Month 3 was defined as the average of the Week 12 (Day 78) and Week 13 (Day 85) fasting assessments.
Secondary outcomes (including scoring methods and timings of assessments)	• Treatment response rate (responders were defined as patients with a fasting TG level <750 mg/mL at 3 months. Only patients with baseline TG >750 mg/mL were included). • Percentage change in fasting TG between baseline and Month 6 • Percentage change in fasting TG from baseline to Month 12 • Average maximum intensity of patient-reported abdominal pain • Change in postprandial TG area under the curve (0-9h) between baseline and on-treatment measures (i.e. between Weeks 13 and 19) • Treatment response rate, where responders were defined as patients who achieved a 40% reduction in fasting TG between baseline and Month 3. • Absolute change in fasting TG from baseline to Month 3 • Frequency of composite of episode of acute pancreatitis and patient-reported abdominal pain during the treatment period. • Change in hepatic volume from baseline, as assessed by MRI at Week 52.

ANCOVA, analysis of covariance; APOC2, apolipoprotein C2; GPIHBP1, glycophosphatidylinositol-anchored high density lipoprotein binding protein 1; HbA1c, glycated haemoglobin; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase; MRI, magnetic resonance imaging; TG, triglycerides
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

COMPASS

COMPASS was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 26-week study in patients with hypertriglyceridemia, including FCS. It comprised 3 study periods:

- Screening: 8 weeks, including a 6-week diet stabilisation period
- Treatment: 26 weeks
- Follow-up: 13 weeks **or** entry into APPROACH OLE (NB only patients with FCS were eligible to enter APPROACH OLE)

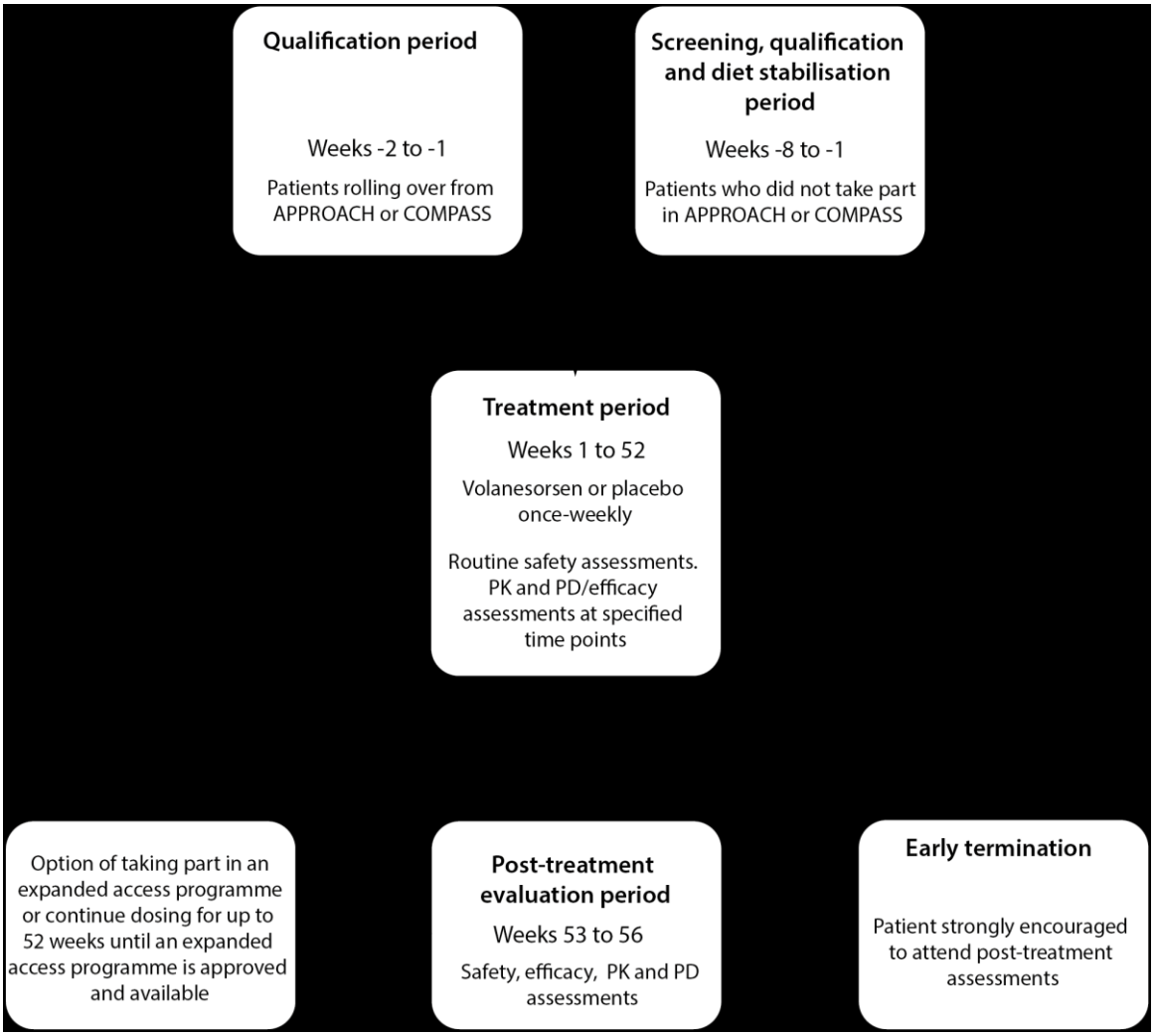
Following screening, patients were randomised 2:1 to SC volanesorsen 285 mg once-weekly or placebo. However, a protocol amendment saw the dose of volanesorsen adjusted to 285 mg every 2 weeks at or after 13 weeks of treatment (patients, who had already received at least 5 months of dosing when this amendment came into effect, were exempt).

As for APPROACH, the primary efficacy outcome was the percent change from baseline in fasting TG levels at Month 3, defined as the average of the Week 12 and Week 13 assessments.

APPROACH OLE

APPROACH OLE is an ongoing, Phase 3 open-label study in patients with FCS. It includes patients who have previously received volanesorsen in the double-blind APPROACH and COMPASS studies (N.B. only FCS patients), and patients who are treatment naïve (i.e. received placebo in either APPROACH or COMPASS, or did not take part in either of these studies). Figure 10 shows the study design.

Figure 10 APPROACH OLE study design



Adapted from: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

Table C7 summarises the methodology for APPROACH OLE.

Table C7 Summary of methodology for APPROACH OLE

Study name	**APPROACH OLE: an open-label study of volanesorsen administered subcutaneously to patients with familial chylomicronemia syndrome (FCS)**
Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen administered subcutaneously to patients with FCS
Location	19 study centres worldwide (US: 5; Canada: 4; UK: 3; Spain: 3; France: 1; Italy: 1; Netherlands: 1; South Africa: 1)
Design	Open-label. Three patient groups are being enrolled: • Group 1: FCS patients rolling over from APPROACH • Group 2: FCS patients rolling over from COMPASS • Group 3: Patients who did not take part in either APPROACH or COMPASS
Duration of study	Groups 1 & 2: • Qualification period of up to 2 weeks Group 3: • 8-week screening and qualification period, including a 6-week diet stabilisation period All patients: • Patients will receive treatment for 52 weeks. Following this, they will have the option to take part in an expanded access program (where available) or continue dosing until an expanded access program becomes available (for a maximum of 52 additional weeks). Patients not taking part in an expanded access program will enter a 13-week follow-up period.
Sample size	Approximately 70 patients (planned)
Key inclusion criteria	• ≥18 years of age • Able and willing to take part in a 65-week study Groups 1 & 2: • Satisfactory completion of APPROACH or COMPASS Groups 2 & 3: • Documented history of chylomicronaemia • Diagnosis of FCS by documentation of the following: confirmed homozygote, compound

	heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1) • Group 2: fasting TG ≥750 mg/dL (8.4 mmol/L) at screening for double-blind APPROACH study • Group 3: fasting TG ≥750 mg/dL at screening for APPROACH OLE
Key exclusion criteria	• Unwilling to comply with lifestyle requirements for the duration of the study Groups 1 & 2: • Any new condition or worsening of existing condition that made the patient unsuitable for participation in the study Group 3: • Diabetes mellitus if newly diagnosed or if HbA1c ≥9.0% • Other types of severe hypertriglyceridemia • Active pancreatitis within 4 weeks of screening • Acute or unstable cardiac ischaemia within 6 months of screening • Major surgery within 3 months of screening • Treatment with Glybera® therapy within 2 years of screening • Previous treatment with volanesorsen • Any other conditions that, in the opinion of the investigator, could interfere with the patient participating in or completing the study
Method of randomisation	N/A: volanesorsen was the only intervention in this study
Method of blinding	N/A: this is an open-label study
Intervention(s) (n =) and comparator(s) (n =)	Volanesorsen 285 mg, given as a single 1.5 mL subcutaneous injection, once a week (n = 29)
Baseline differences	Baseline characteristics and demographics were broadly similar between treatment groups. As would be expected, patients in the treatment-naïve group had higher TG levels at study entry (2288 mg/dL) than those who had previously taken volanesorsen during APPROACH (1469 mg/dL)
Duration of follow-up, lost to follow-up information	13 weeks

Statistical tests	No p values were generated in the interim analysis. Data were summarised using descriptive statistics.
Efficacy outcomes (including scoring methods and timings of assessments)	• Percent and absolute change from baseline in fasting TG levels at Months 3, 6 and 12 • Treatment response rates at Months 3, 6 and 12 • Frequency and severity of patient-reported abdominal pain during the treatment period • Percent change from baseline in other fasting lipid measures at Months 3, 6 and 12 • Percent change from baseline in fasting total apoC-III at Months 3, 6 and 12 • Change from baseline in QoL questionnaires (EQ-5D, SF-36) at Months 3, 6 and 12 • Independently adjudicated acute pancreatitis event rate • Frequency of other symptoms, e.g. eruptive xanthoma, lipemia retinalis
Safety outcomes (including scoring methods and timings of assessments)	• Incidence of AEs, including independently adjudicated pancreatitis and major CV events, local cutaneous reactions at the injection site, flu-like reactions and platelet reductions • Change from baseline in vital signs and weight • Physical examination • Change from baseline in clinical laboratory tests (serum chemistry, haematology, urinalysis) • Echocardiography • ECG • Use of concomitant medications • Change from baseline in MRI scans

Missing data were imputed via a multiple imputation analysis under the assumption of Missing at Random. A post-hoc analysis was also carried out using a bootstrap imputation (see Section 12.2.1 for further details)
APOC2, apolipoprotein C2; apoC-III, apolipoprotein C3; ECG, electrocardiogram; GPIHBP1, glycophosphatidylinositol-anchored high density lipoprotein binding protein 1; HbA1c, glycated haemoglobin; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase; MRI, magnetic resonance imaging; N/A, not applicable; QoL, quality of life; SF-36, short-form 36; TG, triglycerides
Source: APPROACH OLE interim clinical study report, 2nd June 2017, Akcea data on file

Data presented in this submission are from an interim analysis with a cut-off date of 28 February 2019.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Unless otherwise stated data included in this submission are from the clinical study reports. The APPROACH study was published in the New England Journal of Medicine (Witztum et al., 2019) but too late to be a core reference for this submission. Baseline data for patients enrolled in APPROACH have been published in The Journal of Clinical Lipidology (Blom et al., 2018b). Efficacy data were also presented at the National Lipid Association 2017 Scientific Sessions (Gaudet et al., 2017b), the 85th Annual Congress of the European Atherosclerosis Society 2017 (Gaudet et al., 2017a), the 50th Jubilee Meeting of the European Pancreatic Club 2018 (Blom et al., 2018a) and the National Lipid Association 2018 Scientific Sessions (Gelrud et al., 2018). Very limited data from the seven patients in COMPASS who had FCS were presented at the National Lipid Association 2017 Scientific Sessions (Gouni-Berthold et al., 2017) and the International Symposium on Atherosclerosis 2018 (Gouni-Berthold et al., 2018).

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

APPROACH was a randomised, double-blind trial that compared volanesorsen with placebo, whereas APPROACH-OLE was an open-label trial in which all patients received volanesorsen. COMPASS was also a randomised double-blind trial that compared volanesorsen with placebo; however the population included patients with various types of hypertriglyceridemia (not just FCS), patient were randomised 2:1 (volanesorsen:placebo) and treatment lasted 26 weeks, not 52. As described in Section 4.1, COMPASS is therefore not considered pivotal to this submission, but provides some supportive evidence in a subset of patients with FCS (n = 7).

Baseline characteristics and demographics are described below for each study.

APPROACH

There were no differences in baseline characteristics and demographics between the treatment groups in APPROACH (see Table C8).

Table C8 Patient demographics and baseline characteristics in APPROACH

	Volanesorsen (n = 33)	Placebo (n = 33)
Age, mean (range) years	47 (22 – 75)	46 (20 – 68)
Gender, % M/F	48.5/51.5	42.4/57.6
FCS mutation, n (%)		
LPL	16 (48.5)	24 (72.7)
APOA5	1 (3.0)	1 (3.0)
GPIHBP1	5 (15.2)	0 (0.0)
LMF1	1 (3.0)	0 (0.0)
APOC2	1 (3.0)	0 (0.0)
LPL/LMF1	1 (3.0)	0 (0.0)
LPL/APOA5	0 (0.0)	1 (3.0)
Fasting TG, mean (range) mg/dL	2267 (347 – 5660)	2152 (631 – 5475)
Documented history of acute pancreatitis, n (%)		
Yes	24 (72.7)	26 (78.8)
No	9 (27.3)	7 (21.2)
Pancreatitis attacks in the last 5		

	Volanesorsen (n = 33)	Placebo (n = 33)
years, n		
None	20	23
1 attack	6	6
≥2 attacks	7	4
Abdominal pain during screening and Week 1, n (%)	7 (21.2)	10 (30.3)
Lipid lowering therapies, n (%)*		
Fibrates	17 (51.5)	15 (45.5)
HMG-CoA reductase inhibitors	9 (27.3)	4 (12.1)
Fish oils	3 (9.1)	1 (3.0)
Platelet aggregation inhibitors*	8 (24.2)	5 (15.2)
History of type II diabetes, n (%)	6 (18.2)	4 (12.1)
History of diabetes mellitus, n (%)	1 (3.0)	0 (0.0)
Blood glucose lowering therapies, n (%)*		
Fast-acting insulin	4 (12.1)	0 (0.0)
Long-acting insulin	5 (15.2)	1 (3.0)
Other	1 (3.0)	0 (0.0)
Combinations of oral blood glucose lowering drugs	0 (0.0)	1 (3.0)

*Concomitant medications include those that patients were exposed on or after the first dose of study medication.
HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-coenzyme A; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file; ID1326 volanesorsen ERG clarification responses, July 2018, Akcea data on file

COMPASS

In the subset of patients with FCS, baseline characteristics and demographics were balanced between treatment groups, although there were no male patients in the placebo group (Table C9).

Table C9 Patient demographics and baseline characteristics in COMPASS

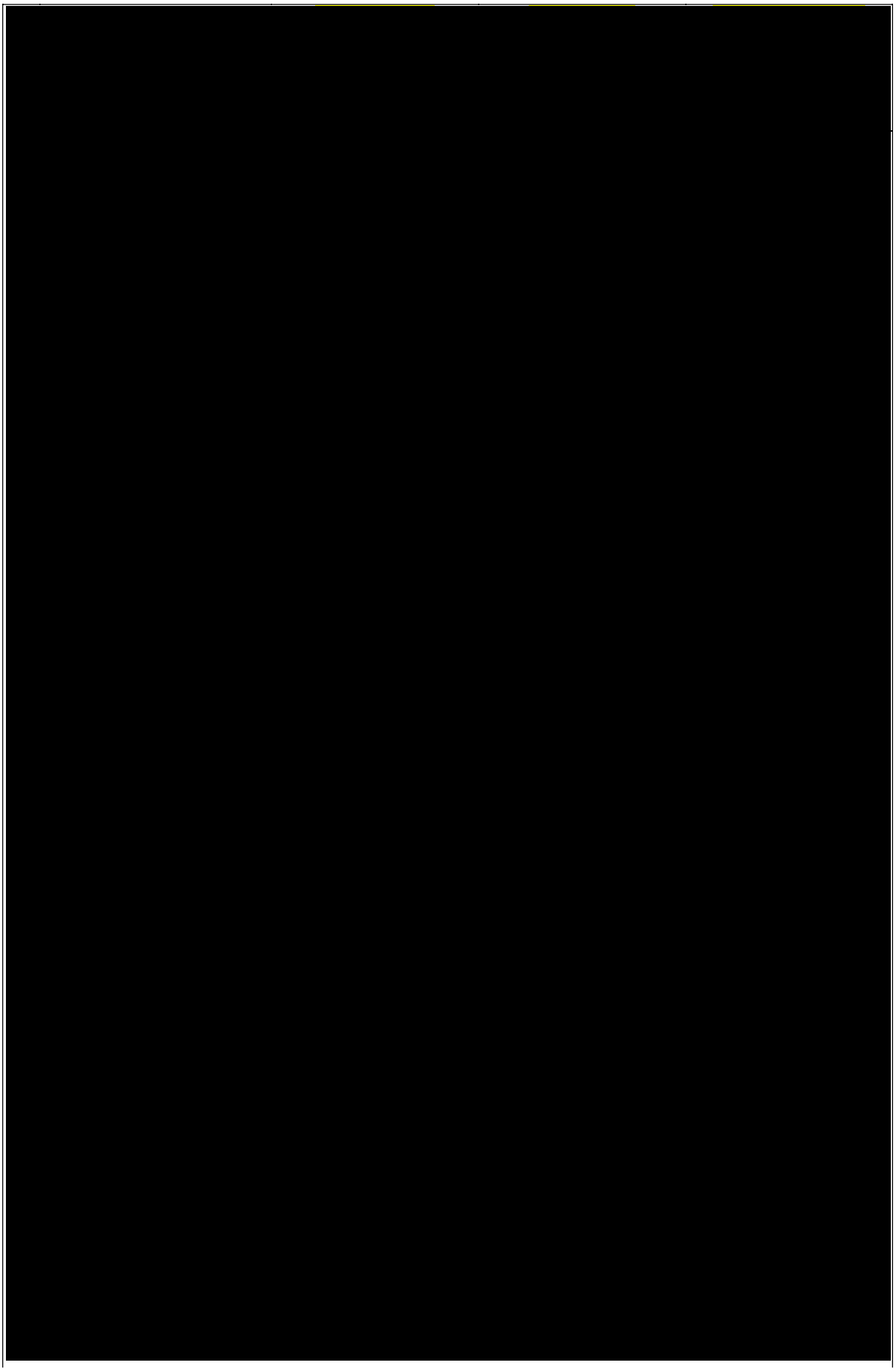
	Volanesorsen (n = 5)	Placebo (n = 2)
Age, mean (range) years	47 (33 – 54)	51 (43 – 58)
Gender, % M/F	40.0/60.0	0.0/100.0
Fasting TG, mean (range) mg/dL	2134 (1074 – 3998)	2644 (2422 – 2867)

TG, triglyceride
Source: COMPASS clinical study report, 2nd June 2017, Akcea data on file

APPROACH OLE (data cut off: 28 February 2019)

Table C10 shows baseline characteristics and demographics for patients enrolled in APPROACH OLE. As would be expected, patients in the treatment-naïve group had higher TG levels at study entry than those who had previously taken volanesorsen.

[redacted]



*Concomitant medications include those that patients were exposed on or after the first dose of study medication.
HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-coenzyme A; TG, triglyceride
Source: Table 14.1.1.1, Table 14.1.4.1b, Table 14.1.4.3adhoc, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In APPROACH, the percent change from baseline in TG levels was evaluated by gender, race, age, ethnicity and region. These analyses were pre-planned and were designed to investigate any potential effect of these factors on response to treatment with volanesorsen.

Post-hoc analysis of TG for the following subgroups was undertaken to consider the impact of dose on the primary endpoint:

- Patients who completed treatment and had a dose adjustment or a pause in dosing (n = 6 at baseline)
- Patients who completed treatment without dose adjustment or a pause in dosing (n = 13 at baseline)
- Patients who withdrew early (n = 14 at baseline)

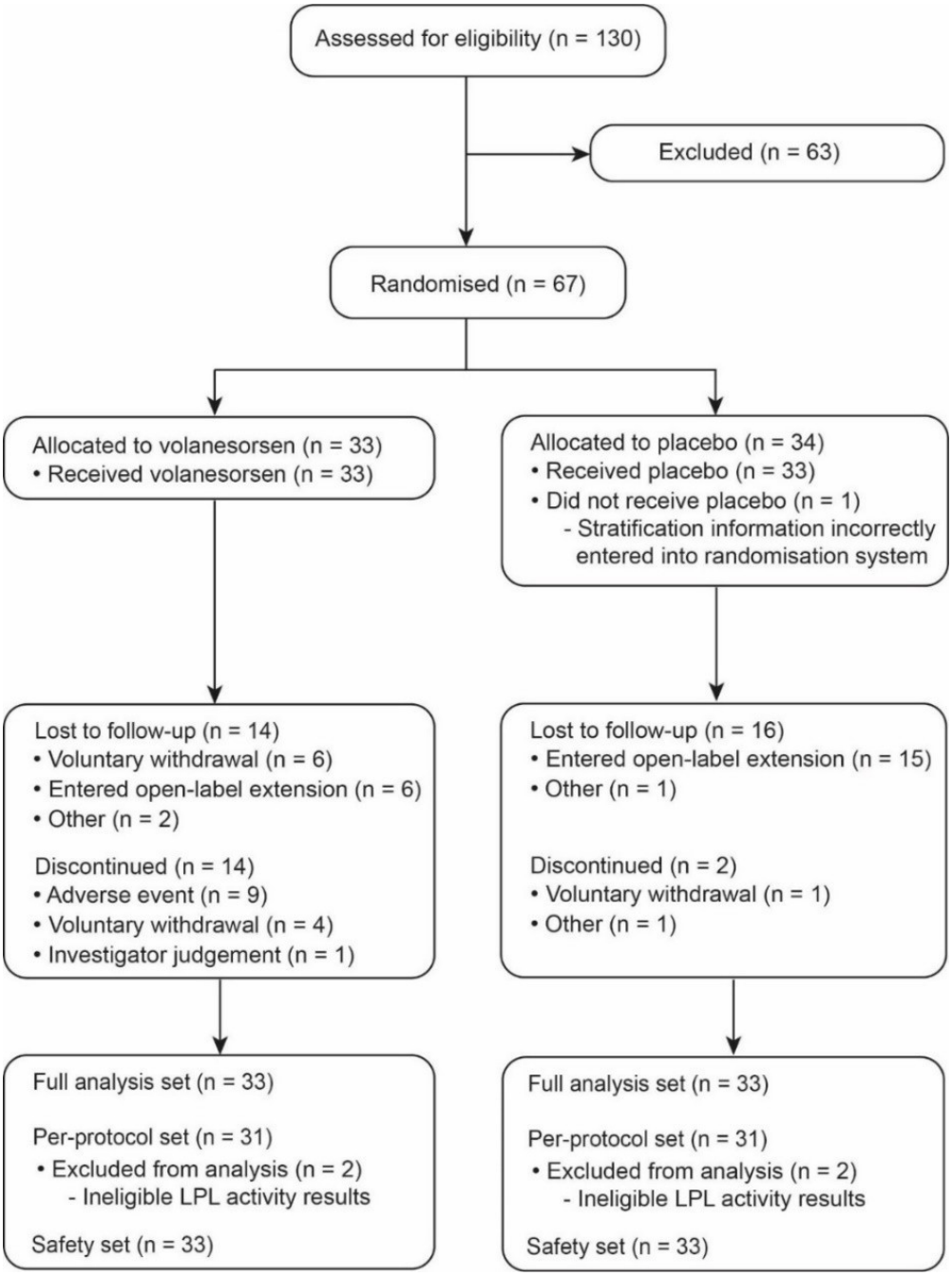
In APPROACH OLE, the change from baseline in TG levels and other lipid parameters, and response rate were evaluated by age. The change from baseline in TG levels were also evaluated by history of acute pancreatitis. Some limited analyses on the subgroup of patients who reduced dosing frequency ('mixed dose' analyses) were also carried out (Section 9.9.4). These analyses were *post-hoc*.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

APPROACH

Figure 11 shows patient flow in the APPROACH study.

Figure 11 CONSORT flow diagram: APPROACH



Lost to follow-up refers exclusively to patients who did not enter or complete the full post-treatment evaluation phase. LPL, lipoprotein lipase
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

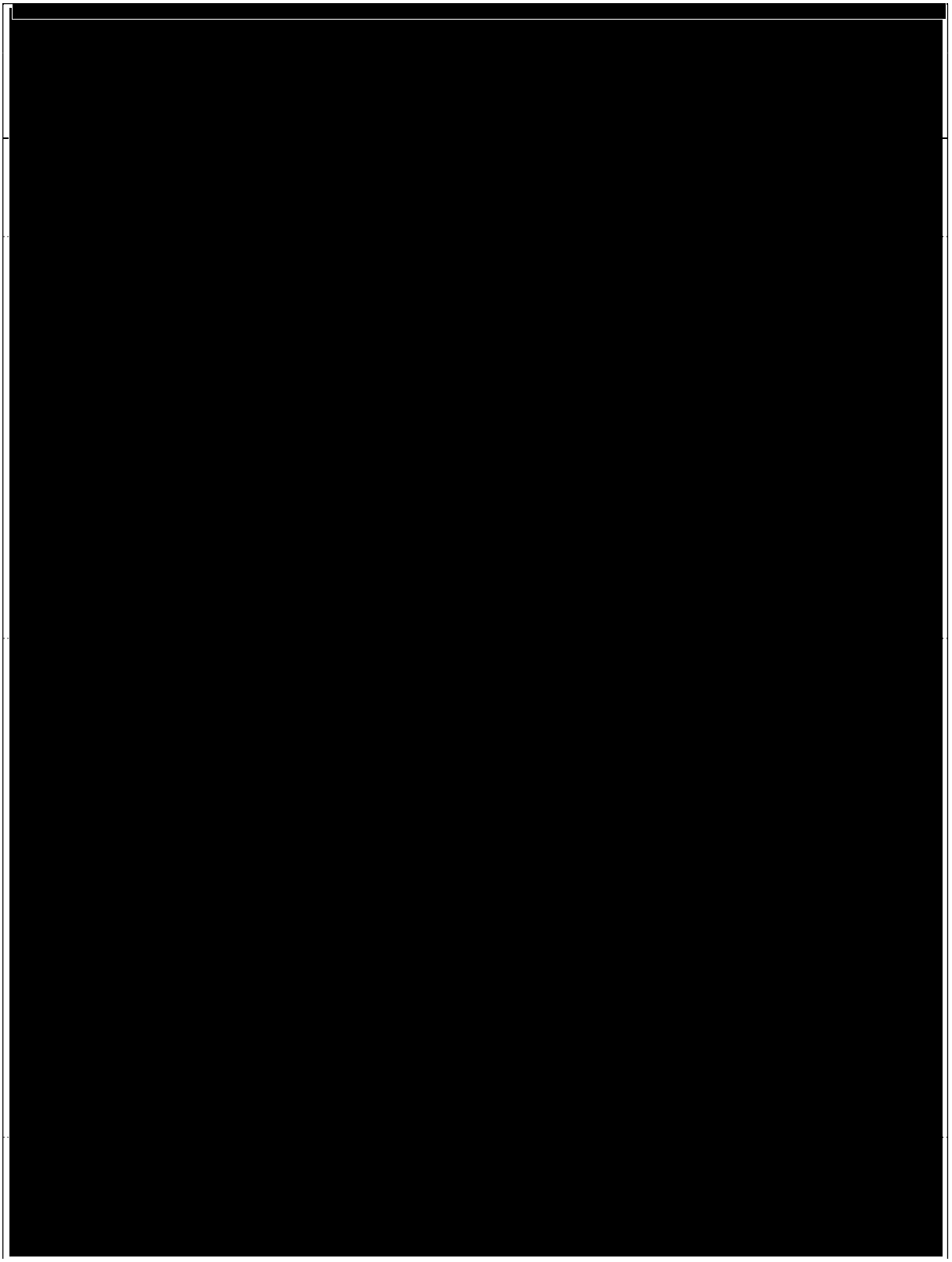
COMPASS

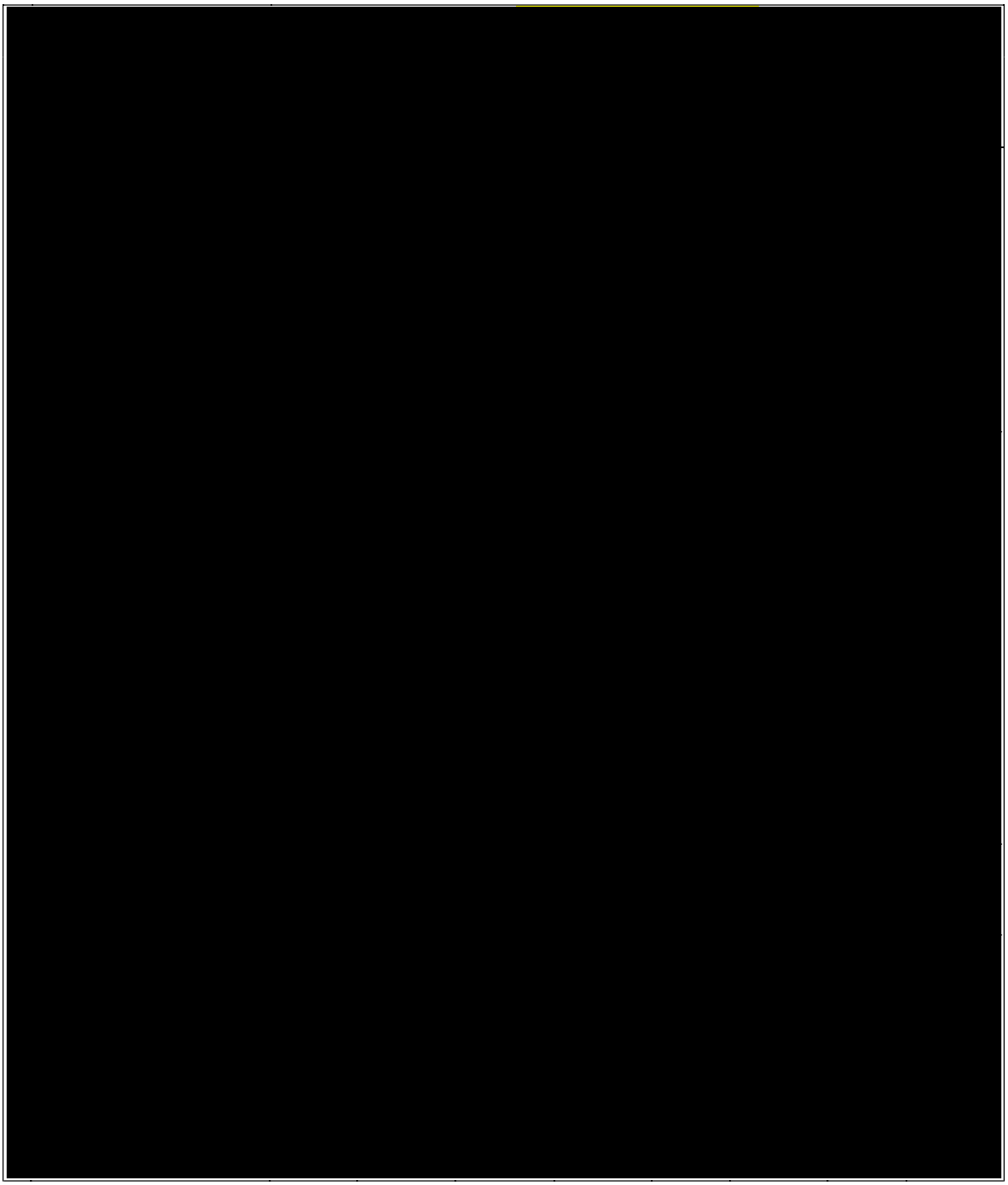
In total, 7 patients with FCS were enrolled in COMPASS: 5 in the volanesorsen group and 2 in the placebo group. All 7 patients completed study treatment.

APPROACH OLE

Table C11 shows the disposition of patients enrolled at the data cut-off of 28 February 2019.

Table C11 Patient disposition: APPROACH OLE





AE, adverse event; SAE, serious adverse event.
Source: Table 14.1.2, Table 14.3.1.1.1, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

APPROACH

In total, 58 patients (87%) entered the post-treatment follow-up. Of these, 30 were lost to follow-up, as shown in the diagram in Section 9.4.5. The most common reason for loss to follow-up was entry into the APPROACH OLE.

Fourteen patients (42%) in the volanesorsen group discontinued the study. Of these, 2 (6%) discontinued before Week 13, 7 (21%) discontinued between Weeks 13 and 26, and 5 (15%) discontinued after Week 26. The most common reason for discontinuation was adverse events (AEs; n = 9). Decreased platelet count and thrombocytopenia were the most common AEs leading to discontinuation (n = 5). Other AEs leading to discontinuation were injection site reaction and fatigue (n = 1), fatigue (n = 1), chills and sweating (n = 1) and generalised erythema (n = 1). Four patients withdrew voluntarily from the study, and one was withdrawn owing to investigator judgement. Reasons for voluntary withdrawal were: withdrawal of consent owing to dehydration caused by diarrhoea; complaints about duration of study visits; patient became aware of information suggesting volanesorsen does not work and needs redeveloping; patient wished to go travelling.

In the placebo group, one patient voluntarily withdrew from the study. This patient had chronic ferropenic anaemia and a low body weight, and could not support giving blood samples every two weeks owing to fatigue.

Four patients from the volanesorsen group did not enter APPROACH OLE: three chose to withdraw from further study participation and one was withdrawn by the study medical monitor owing to low platelet counts while on the every 2 week dosing regimen. Another patient in the volanesorsen group was not enrolled in APPROACH OLE because of prolonged regulatory delays in approval of the study. Among eligible patients in the placebo group, two did not continue into APPROACH OLE. Of these, one made a joint decision with study personnel not to continue because of low platelet counts in a sibling, and the other withdrew owing to the burden of study participation.

APPROACH OLE

Details of patients who withdrew from the study are given in Table C11 (Section 9.4.5). [redacted]

Figure 12 shows treatment persistence up to Week 104 for the APPROACH-volanesorsen group compared with the treatment-naïve group.

[redacted]

Source: Figure 14.3.10.adhoc3, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

[redacted]

[redacted]

[redacted]

Source: Figure 14.3.10.adhoc4, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown below.

Tables C12 to C14 show the critical appraisals of APPROACH, COMPASS and APPROACH OLE.

Table C12 Critical appraisal of APPROACH

Study name	APPROACH	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomised to treatment using an interactive voice/web response system. Patients were stratified by: • prior history of pancreatitis; • concurrent use of fibrates and/or prescription omega-3 fatty acids. A permuted block schedule was used.
Was the concealment of treatment allocation adequate?	Yes	The study was double-blind.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	As described in Section 9.4.3, patients' baseline characteristics were well balanced between the treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The sponsor, patients, monitors and study centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apoC-III, were not available to any of these individuals. An independent review committee adjudicated all SAEs that were consistent with a major cardiovascular event, and all AEs and SAEs that were consistent with acute pancreatitis. The committee members were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Yes	Fourteen patients (42.4%) in the volanesorsen group withdrew from the study, compared with 2 (5.9%) in the placebo group. The most common reason for withdrawal from the study in the volanesorsen group was AEs: 9 patients (27.3) withdrew for this reason. No patients in the placebo group withdrew because of AEs. 5 patients who discontinued because of thrombocytopenia did so before an enhanced monitoring system was put in place.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes measured are fully documented in the study report.
Did the analysis include an intention-to-treat analysis? If so, was this	Yes	The primary analysis was carried out on the FAS, which represents the practically-

appropriate and were appropriate methods used to account for missing data?		feasible intent-to-treat population as defined in ICH Guidelines.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C13 Critical appraisal of COMPASS

Study name	**COMPASS**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomised 2:1 to receive either volanesorsen or placebo using an interactive voice/web response system. Patients were stratified by: • prior history of pancreatitis; • concurrent use of fibrates and/or prescription omega-3 fatty acids. A permuted block schedule was used.
Was the concealment of treatment allocation adequate?	Yes	The study was double-blind.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	As described in Section 9.4.3 of the submission, baseline characteristics and demographics were balanced between treatment groups in the subset of 7 patients with FCS, although there were no male patients in the placebo group.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The sponsor, patients, monitors and study centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apoC-III and TGs, were not available to any of these individuals. An independent review committee adjudicated all SAEs that were consistent with either a major adverse cardiovascular event or acute pancreatitis. The committee members were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	All 7 patients in the FCS subset completed the study. Five of these patients received volanesorsen and 2 received placebo.

Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes measured are fully documented in the study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table C14 Critical appraisal of APPROACH OLE

Study name	**APPROACH OLE**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	The study was open-label. All patients received volanesorsen.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label. All patients received volanesorsen.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Data were analysed for two patient groups: those who had previously received volanesorsen in APPROACH or COMPASS and those who were treatment-naïve (i.e. received placebo in either APPROACH or COMPASS, or did not take part in either of these studies). As described in Section 9.4.3, at the interim analysis, patients' baseline characteristics were broadly similar between the two groups. However, as would be expected, patients in the treatment-naïve group had higher TG levels at study entry than those who had previously taken volanesorsen.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	At data cut off on 6th January 2017, [redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The interim study report does not report on all outcomes, as there were insufficient data for some outcomes at the time of the analysis. However, all the outcomes measured will be fully documented in the final study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

The primary endpoint of the APPROACH was met: at 3 months the % difference in change from baseline in TG was -94.1% (95% CI -121.7, -66.6) *P*<0.0001): a statistically significant and clinically meaningful benefit associated with volanesorsen treatment.

APPROACH

Table C15 shows the results of the APPROACH study. Data are presented for the full analysis set (FAS), which included 33 patients in each group.

Table C15 Outcomes from APPROACH

Study name		APPROACH	
Size of study groups	**Treatment (volanesorsen)**	N = 33	
	Control (placebo)	N = 33	
Study duration	**Time unit**	52 weeks	
Type of analysis	**Intention-to-treat/per protocol**	Full analysis set (all patients who received at least one dose of study drug and had a baseline TG assessment)	
Primary outcome: % change from baseline in fasting TG (mg/dL) at Month 3			
		Volanesorsen	Placebo
% change, LS mean		-76.5	17.6
Relative difference in % change		-94.1 (95% CI: -121.7, -66.6)	
p value		<0.0001 (ANCOVA)	
Secondary outcome 1: responder analysis (endpoint fasting TG <750 mg/dL at Month 3)			
		Volanesorsen	Placebo
n (%) of patients		23 (76.7)	3 (9.7)
Odds ratio		186.16 (95% CI: 12.86, N/A)	
p value		0.0001 (logistic regression model)	
Secondary outcome 2: % change from baseline in fasting TG (mg/dL) at Month 6*			
		Volanesorsen	Placebo
% change, LS mean		-52.5	25.3
Relative difference in % change		-77.8 (95% CI: -106.4, -49.1)	
p value		<0.0001 (ANCOVA)	
Secondary outcome 3: % change from baseline in fasting TG (mg/dL) at Month 12*			
		Volanesorsen	Placebo
% change, LS mean		-40.2	8.9
Relative difference in % change		-49.1 (95% CI: -94.7, -3.5)	
p value		0.0347 (ANCOVA)	
Secondary outcome 4: Average maximum intensity of abdominal pain during on-treatment period			
		Volanesorsen	Placebo
Mean (SD)		0.38 (0.83)	0.36 (0.79)
p value		0.8959 (two-sample t-test)	
		As the treatment comparison for this endpoint was not statistically significant, all subsequent planned secondary analyses were considered exploratory	

Outcome: % change from baseline in postprandial TG $AUC_{(0\text{-}9h)}$		
	Volanesorsen	Placebo
% change, mean	-76.6	29.9
LS mean treatment difference	-91.1 (95% CI: -131.5, -50.6)	
p value	0.0002 (ANCOVA)	
Outcome: responder analysis (≥40% reduction in fasting TG at Month 3)		
	Volanesorsen	Placebo
n (%) of patients	29 (87.9)	3 (9.1)
Odds ratio	99.69 (95% CI: 15.75, 631.06)	
p value	<0.0001 (logistic regression model)	
Outcome: absolute change from baseline in fasting TG (mg/dL) at Month 3		
	Volanesorsen	Placebo
Change from baseline, LS mean	-1712	92
LS mean treatment difference	-1804 (95% CI: -2306, -1302)	
p value	<0.0001 (ANCOVA)	
Outcome: incidence of acute pancreatitis and/or moderate/severe abdominal pain		
	Volanesorsen	Placebo
n (%) of patients	12 (36)	13 (39%)
Mean (SD) number of events, per patient per year	2.73 (6.57)	2.04 (4.28)
p value	0.6131 (two-sample t-test)	
Outcome: change from baseline in hepatic fat volume (cm^3) at Week 52*		
	Volanesorsen	Placebo
Change from baseline, LS mean	113	-25
Relative treatment difference	138 (95% CI: -36, 312)	
p value	0.1206 (ANCOVA)	

*Using a multiple imputation model for missing data that was stratified by treatment and contained the following variables: baseline fasting TG levels, post baseline fasting TG levels, randomisation stratification factors. ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; N/A, not applicable; SD, standard deviation; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Primary endpoint

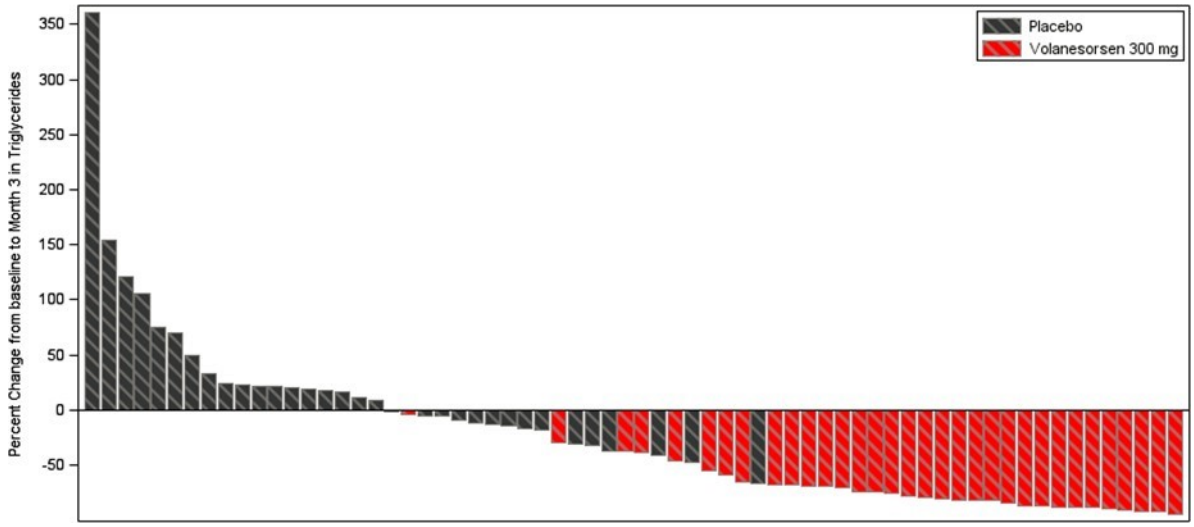
There was a 94.1% difference (95% CI: -121.7, -66.6; *P*<0.0001) between treatment groups in % change from baseline in fasting TGs at Month 3. This demonstrated a statistically and clinically significant benefit associated with volanesorsen treatment.

Secondary & tertiary triglyceride endpoints

Volanesorsen-treated patients achieved robust reductions in TG levels. In the volanesorsen group, there was a mean reduction in fasting TG levels of 77% at Month 3, compared with an 18% increase in the placebo group (*P*<0.0001) (Table C15). The mean absolute reduction at Month 3 was 1712 mg/dL, compared with a mean absolute increase of 92 mg/dL in the placebo group (Table C15).

All patients who received volanesorsen had a reduction in their fasting TG levels at Month 3, with most achieving a reduction of >50% (Figure 14).

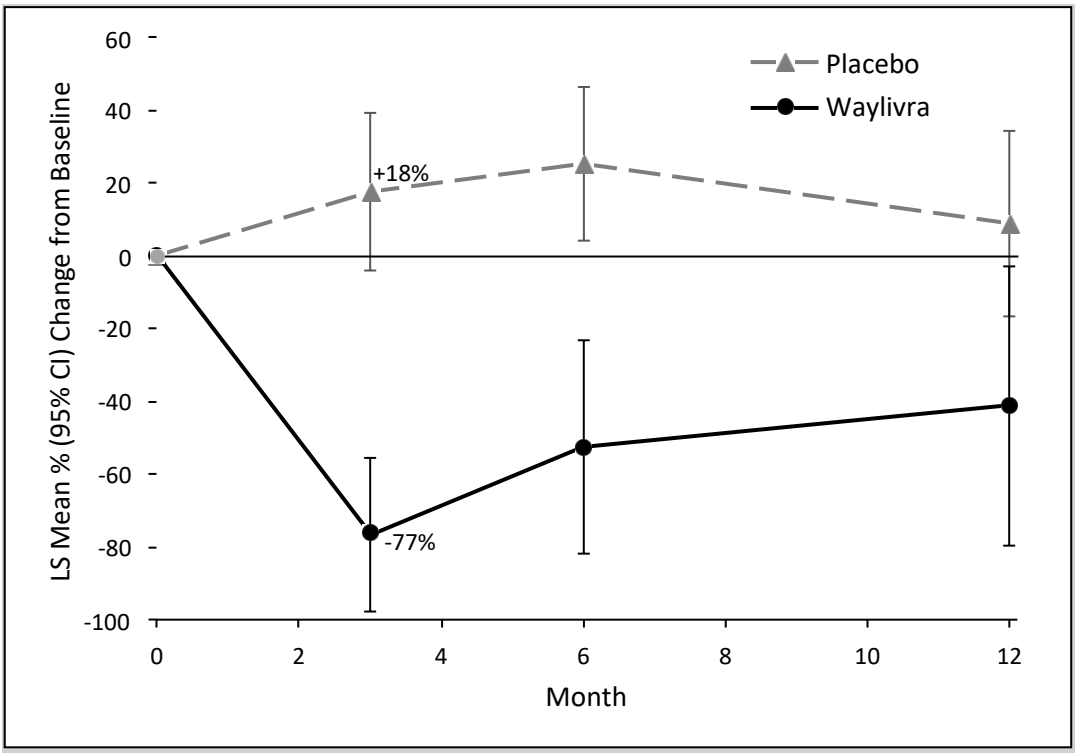
Figure 14 Waterfall plot of % change in fasting TG levels from baseline to Month 3



Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Onset of the reduction in fasting TG levels was rapid with separation from placebo seen as early as Week 4. Maximum response was seen at Month 3. Clinically and statistically significant reductions in fasting TG levels were maintained with volanesorsen over the 52-week treatment period (Figure 15).

Figure 15 LS mean % change in fasting TG levels to Month 12

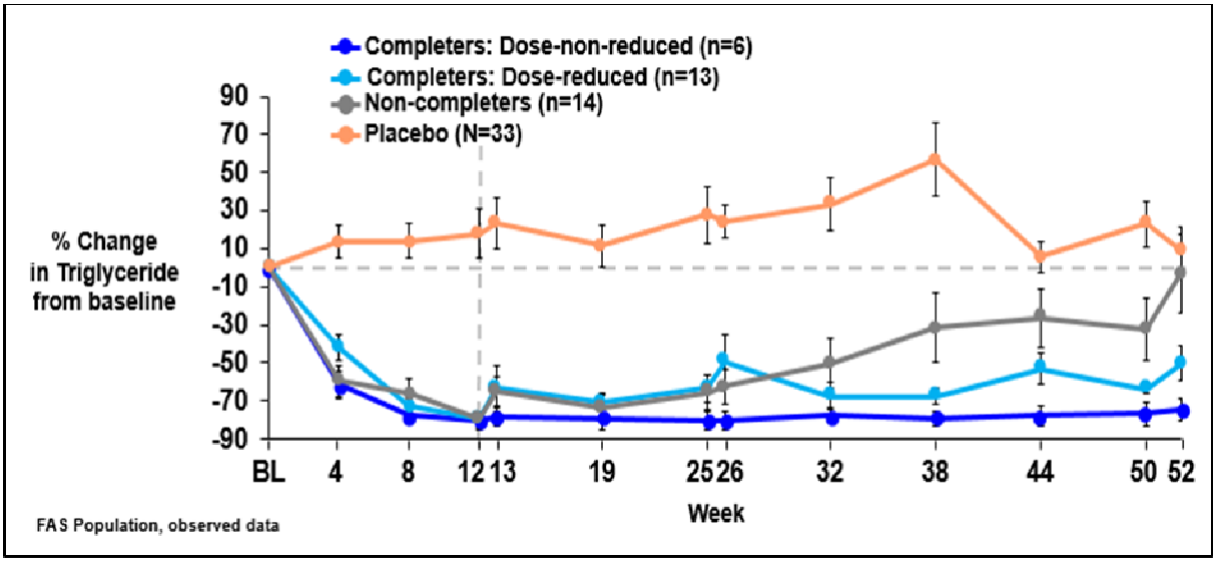


Difference = LS mean of volanesorsen % change – placebo % change (ANCOVA model)
P value at Month 3 < 0.0001, at Month 6 < 0.0001, at Month 12 = 0.0116
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

The slight increase in TG levels seen in the placebo group was no greater than would be expected in patients in a TG-lowering trial and indicates that, in general, patients adhered to the strict dietary regimen.

As shown in Figure 16, patients who received volanesorsen once-weekly throughout the study had a consistent, sustained response. Patients who had their dose adjusted to once every 2 weeks had a smaller percent reduction in their fasting TG levels at Months 6 and 12 than those who did not. However, the mean percent reduction at these time points were clinically meaningful regardless of dose adjustment. In patients receiving volanesorsen who discontinued from the study, TG levels gradually returned to baseline.

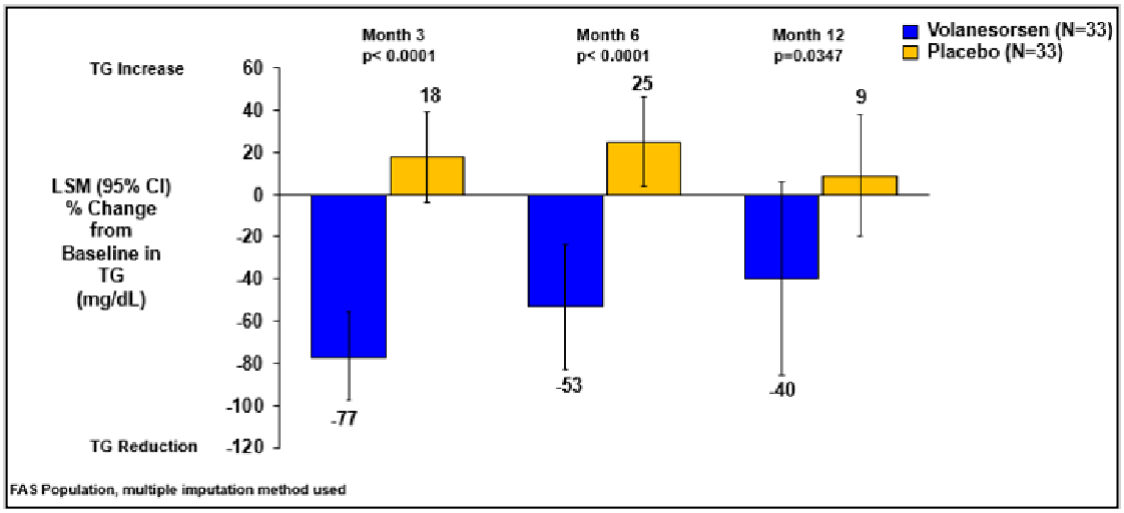
Figure 16 TG levels over time, including dose adjustments and non-completers



Source: ID1326 volanesorsen ERG clarification responses, July 2018, Akcea data on file

Figure 17 shows the 95% CIs associated with the mean change from baseline in TG levels over time.

Figure 17 95% CIs for mean change in TGs over time



CI, confidence interval; LSM, least squares mean; TG, triglyceride
Source: ID1326 volanesorsen ERG clarification responses, July 2018, Akcea data on file

Pre-planned subgroup analyses of percent change in fasting TG levels showed that gender, age race, ethnicity and region had no clinically meaningful effect on the response to volanesorsen.

Among patients who had baseline fasting TG levels ≥750 mg/dL, significantly more volanesorsen-treated patients achieved TG levels <750 mg/dL at Month

3 (Table C15). In total, 50% of patients in the volanesorsen group who had baseline fasting TG levels ≥750 mg/dL achieved TG levels <500 mg/dL at Month 3, compared with no patients in the placebo group (*P* = 0.003).

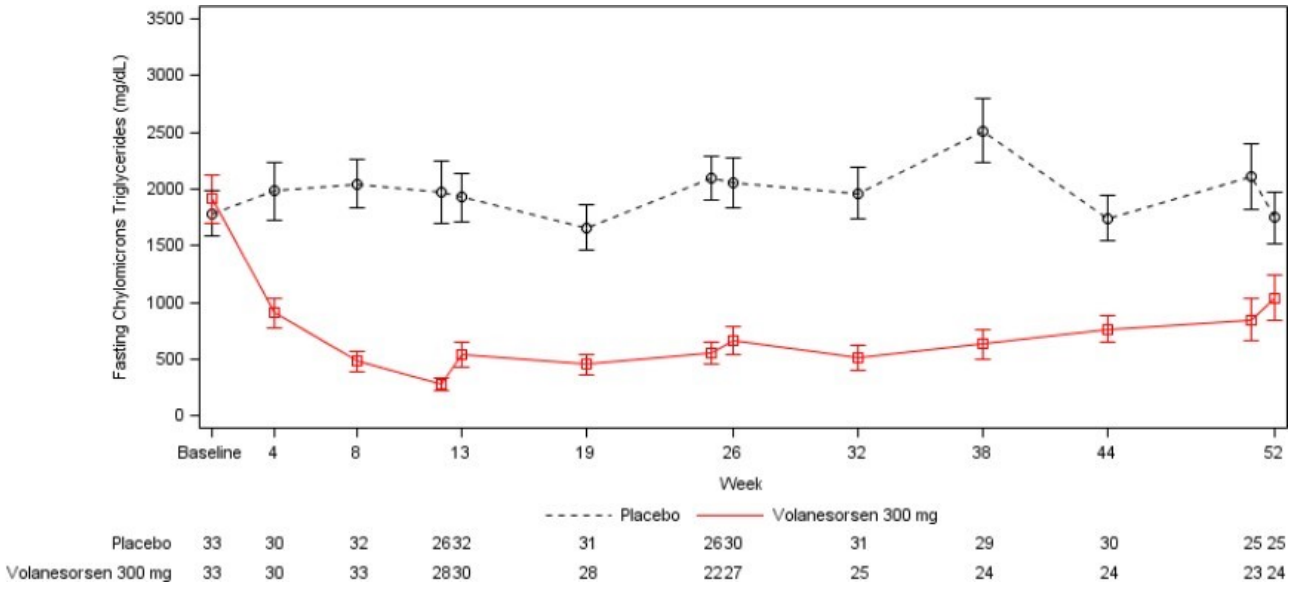
When TG levels exceed 750 – 880 mg/dL, they are predominantly found in chylomicrons, larger particles that are associated with specific restrictions in organ microvasculature. As expected, treatment with volanesorsen significantly reduced levels of chylomicron TGs. Table C16 shows the percent reduction in fasting chylomicron TG levels. Figure 18 shows the mean level of fasting chylomicron TGs over time.

Table C16 Percent change in fasting chylomicron TG levels over time

	% change from baseline, mean (SD)		
	Volanesorsen (n = 33)	**Placebo (n = 33)**	**P value**
Fasting chylomicron TG (mg/dL)			
Month 3	-76.6 (22.1)	+37.7 (112.4)	<0.0001
Month 6	-65.3 (39.1)	+37.7 (75.3)	<0.0001
Month 12	-52.3 (44.9)	+21.9 (79.4)	<0.0001

The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. If one visit was missing, then the other visit was used as the endpoint. The Month 6 endpoint was defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments. If one visit was missing, then the other visit was used as the endpoint. The Month 12 endpoint was defined as the average of Week 50 (Day 344)/Week 51 (Day 351) and Week 52 (Day 358) fasting assessments. If one visit was missing, then the other visit was used as the endpoint.
SD, standard deviation; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

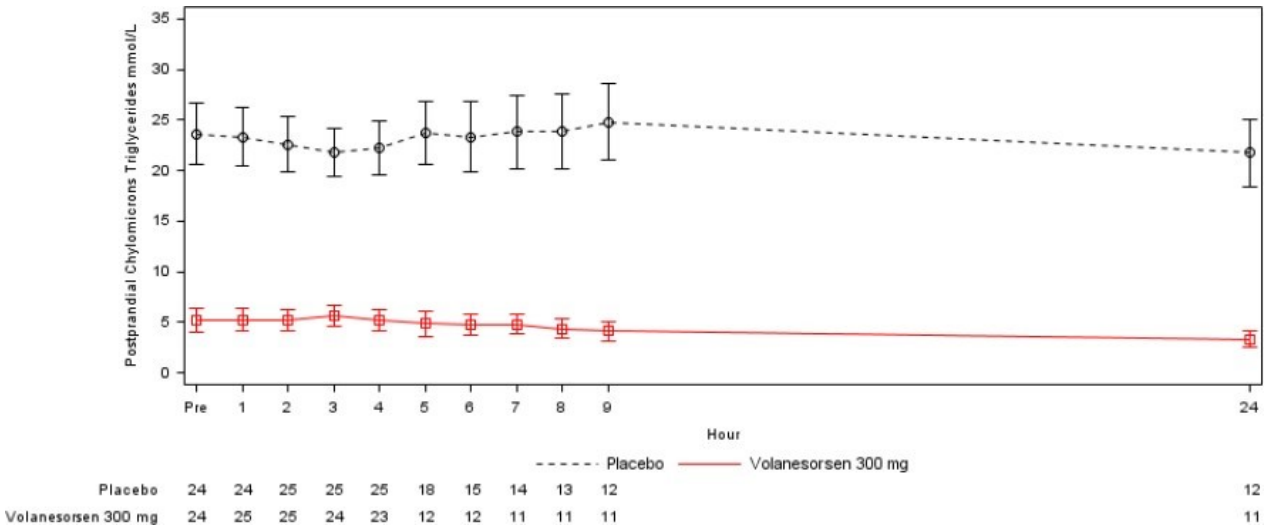
Figure 18 Mean (SEM) fasting chylomicron TG levels over time



SEM, standard error of the mean; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Postprandial TG AUC measurements suggested that volanesorsen provides a sustained reduction in plasma TG levels throughout the 24 hours between doses. The mean percent change from baseline in postprandial TG $AUC_{(0\text{-}9h)}$ was -91.1% (P = 0.0002) and the corresponding value for $AUC_{(0\text{-}4h)}$ was -75.3% (P<0.0001). There was also a statistically significant decrease from baseline in postprandial chylomicron TG $AUC_{(0\text{-}9h)}$ of 81% (P = 0.002) in the volanesorsen group. Figure 19 shows mean (SEM) postprandial chylomicron TG levels over time.

Figure 19 Mean (SEM) postprandial chylomicron TG levels over time



SEM, standard error of the mean; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

In addition to lowering TG levels, volanesorsen had an effect on other lipid parameters. Volanesorsen reduced total cholesterol (-39%), non-HDL cholesterol (-45%), apoC-III (-84%), apoB-48 (-75%), and VLDL cholesterol (-65%), and increased LDL cholesterol (139%), HDL cholesterol (45%), and apoB (20%), as measured by mean percent change from baseline at Month 3. The reduction in apoC-III confirms the action of volanesorsen on its target.

Secondary endpoints: effect on acute pancreatitis

Two separate analyses of the effect of volanesorsen on acute pancreatitis were undertaken within the APPROACH study.

The first, a pre-specified analysis, investigated the number of adjudicated acute pancreatitis events (adjudicated by a blinded, independent review committee) within the 12m study period. In the placebo arm, 3 patients experienced 4 adjudicated acute pancreatitis events, compared to 1 patient in the volanesorsen arm who experienced 1 adjudicated acute pancreatitis event (after discontinuation of study medication) (P = 0.6132) (Table C17).

Table C17 Patients experiencing pancreatitis attacks and pancreatic attack events in the 12 months of the APPROACH study

Volanesorsen (n = 33)		Placebo (n = 33)	
Patients	**Events**	**Patients**	**Events**
1	1	3	4
	P = 0.6132		

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

The second, *post-hoc*, analysis investigated the number of adjudicated acute pancreatitis events within the 12-month study period in patients at high risk for acute pancreatitis (defined as having at least 2 adjudicated pancreatitis events in the 5 years preceding randomisation), relative to the 5-year pre-randomisation period. In the placebo group, 4 patients experienced 17 adjudicated acute pancreatitis events in the 5 year pre-randomisation period, 3 of whom experienced 4 adjudicated acute pancreatitis events in the 12-month study period, compared with 7 patients in the volanesorsen group who experienced 24 adjudicated acute pancreatitis events during the 5 year pre-randomisation period, none of whom experienced an event during the 12-month study (*P* = 0.0242) (Table C18).

Table C18 Pancreatitis in patients at high risk of recurrent attacks (≥2 adjudicated pancreatic events in the past 5 years)

	Volanesorsen (n = 33)		Placebo (n = 33)	
	Patients	**Events**	**Patients**	**Events**
Patients with multiple (2 or more) adjudicated events in the past 5 years	7	3	4	17
Events during study	0	0	3	4
		P = 0.0242		

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Given the high level of treatment discontinuation, there is potential bias in the proportions experiencing acute pancreatitis due to differential time at risk. However, reduced acute pancreatitis rates [redacted] per patient year) were also observed on-treatment in the APPROACH OLE study (see APPROACH OLE reporting and Section 12.2.1) [redacted]

Secondary endpoints: pain

During the treatment period, 15 patients (46%) in the volanesorsen group and 14 (42%) in the placebo group reported abdominal pain. There was no significant treatment difference in the average maximum intensity of the reported abdominal pain events (Table C15). Fewer patients in the volanesorsen group reported severe abdominal pain during the treatment period: 5 patients (15%) reported weekly severe abdominal pain, compared with 8 (24%) in the placebo group.

A pre-planned exploratory analysis showed that volanesorsen-treated patients who had abdominal pain at baseline had a statistically significant reduction in the average maximum intensity of abdominal pain, compared with the same subset of patients in the placebo group (P = 0.0227).

Treatment with volanesorsen also showed a trend towards reduction in the:

- frequency of abdominal pain after 7 to 12 months treatment (3 events per patient per year *vs*. 11 in the placebo group);
- frequency of episodes of moderate to severe abdominal pain during 4 to 12 months (2 events per patient per year *vs*. 5 in the placebo group) and 7 to 12 months of treatment (2 events per patient per year *vs*. 7 in the placebo group);
- worst abdominal pain intensity during 4 to 12 months (3.14 *vs*. 5.4 in the placebo group) and 7 to 12 months of treatment (2.4 *vs*. 5.4 in the placebo group).

Secondary endpoints: Quality of life

Health-related quality of life (HRQL) was assessed as an exploratory endpoint in the APPROACH study using the EQ-5D-5L and SF-36 questionnaires. These tools have limited sensitivity to pick up QoL differences in slow-progressing chronic /episodic diseases and are therefore not ideal for FCS (Cubí-Mollá et al., 2017). A brief study commissioned by Akcea noted that aspects of the trial, the disease and the instruments used may explain why HRQL reported in the study is difficult to reconcile with the disease impact that patients describe. As noted in the report discussion, patients with chronic diseases develop coping mechanisms, generic instruments are not adapted nor as sensitive as disease-specific ones and may not sufficiently capture the effects of many symptoms, and EQ5D enquires about how patients feel on that specific day, therefore episodic symptoms may not be captured (FCS QOL manuscript, Akcea data on file 2019). There is currently no specific, validated QoL tool for FCS although Akcea is currently evaluating the potential to develop a validated FCS questionnaire based on the IN-FOCUS study.

Both SF-36 and EQ-5D-5L scores were comparable across the volanesorsen and placebo groups; there were no significant differences in SF-36 or EQ-5D-5L scores when assessed as change from baseline to Months 3 (P = 0.6627 and P = 0.2920, respectively), 6 (P = 0.9226 and P = 0.5923, respectively), and 12 (P = 0.7912 and P = 0.4079, respectively). Similar results were also obtained when the scores were analysed in a subset of patients who reported abdominal pain >0 or in subset of patients who had pre-dose adjudicated pancreatitis. However, baseline scores were higher than those generally seen in the general population, which makes it unlikely that any change would have been detected. HRQL data are discussed further in Section 10.1.3.

COMPASS

In the subset of 7 patients with FCS, the mean absolute reduction in fasting TG levels at Month 3 was 1,511 mg/dL in the volanesorsen group (n = 5). This correlated with a mean percent reduction of -73%, compared with a mean increase of +70% in patients who received placebo. At Month 6, the mean

percent reduction was -78% in those patients receiving weekly doses of volanesorsen (n = 2).

Three of the patients with FCS who received volanesorsen achieved fasting TG levels <500 mg/dL after 3 months of treatment.

Three patients with FCS had their dosing changed from once-weekly to once every 2 weeks after 13 weeks of treatment. For these patients, the mean percent reduction in fasting TG levels at Month 6 was -69%, compared with -78% for the two patients who remained on once-weekly dosing. The implications of dosing once every 2 weeks are discussed in Section 9.9.

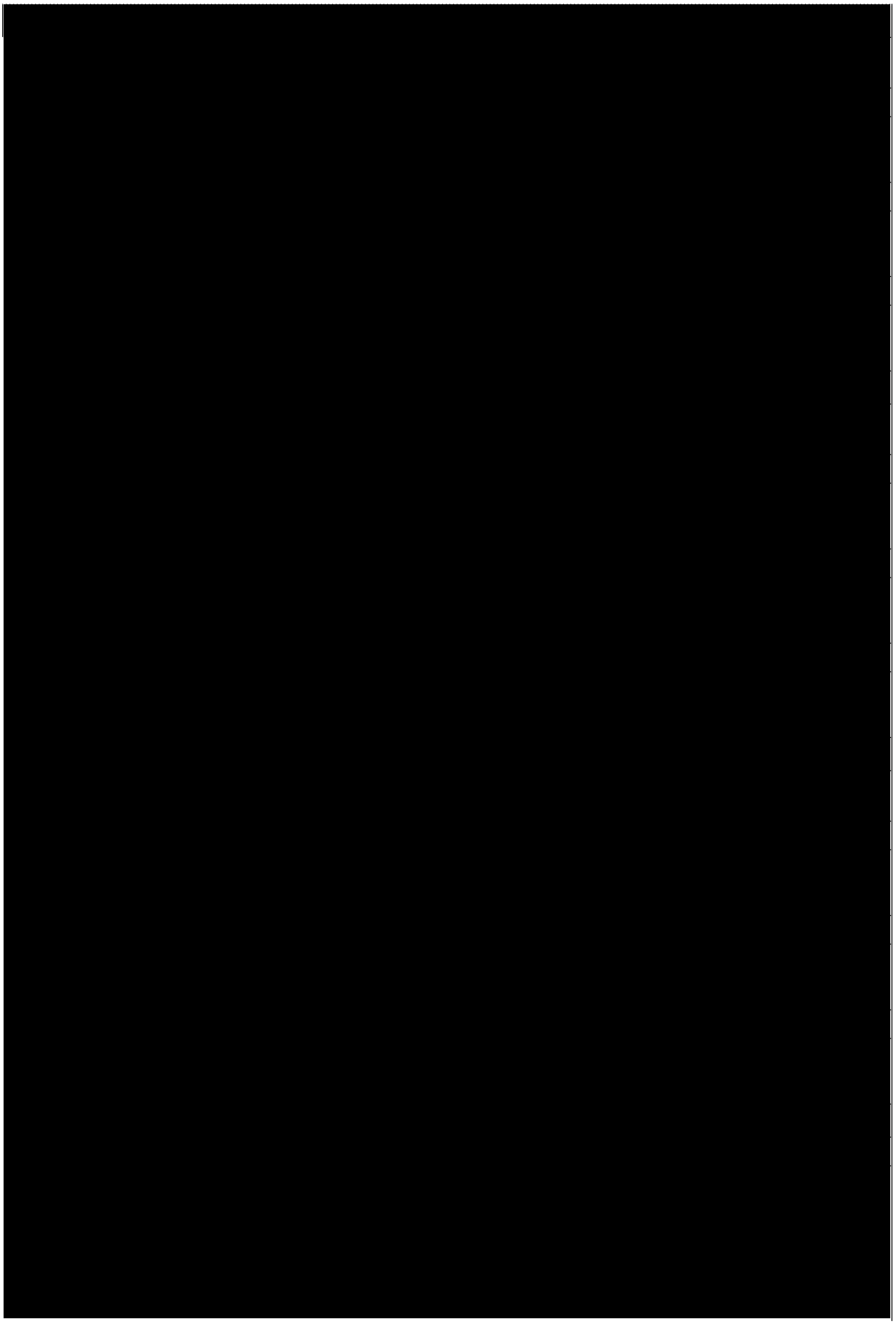
APPROACH OLE (interim results)

It is planned that approximately 70 patients will be enrolled into this study. Data presented below are from an interim analysis with a cut-off date of 28 February 2019.

Table C19 shows efficacy data from APPROACH OLE. Data are presented for the FAS.

[redacted]

[redacted]

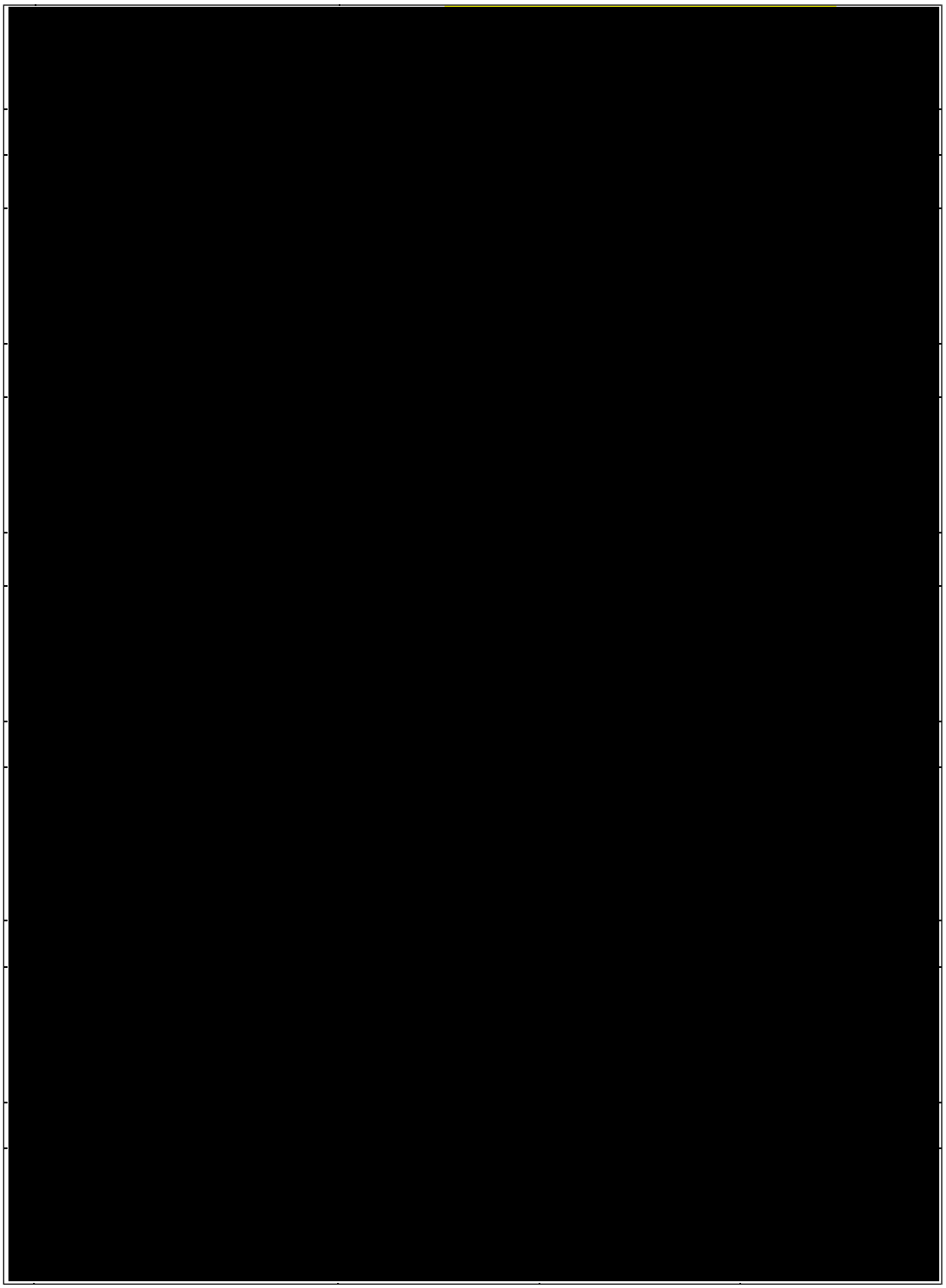


[redacted]

[redacted]

Effect on TG levels

[redacted]



Other outcomes

The frequency of other symptoms (eruptive xanthoma and lipemia retinalis) was not included in the interim analysis.

Effect on burden of disease – the ReFOCUS study

Patients who received volanesorsen for at least 3 months in APPROACH OLE took part in a retrospective web-based survey to assess the burden of disease (Arca et al., 2018). They were asked about their experiences during the 3 months before starting treatment and the most recent 3-month period while on treatment. Twenty-two patients completed the survey.

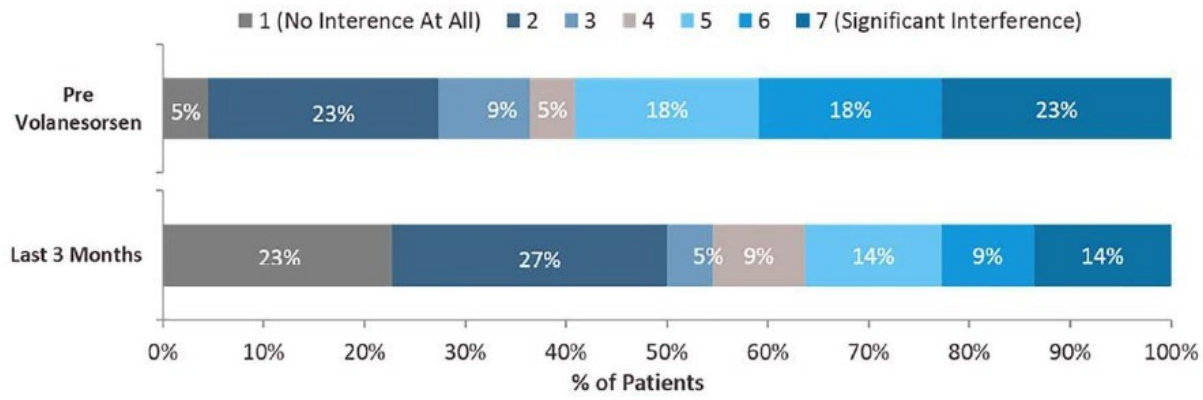
Overall, patients reported that they believed their FCS was more effectively managed with volanesorsen than with their previous regimen. After volanesorsen treatment, more patients said that strategies for managing their symptoms were effective (40% *vs*. 19% before treatment) and that their symptoms were controlled with adherence to diet (90% *vs.* 55% before treatment).

The mean number of symptoms experienced decreased from 9 before starting volanesorsen to 5 after at least 3 months of treatment. This represents a 44% reduction ($P<0.05$). There were significant decreases from baseline for steatorrhea, pancreatic pain, and constant worry about an attack of pain or acute pancreatitis.

When considering the overall impact of FCS on their lives, the proportion of respondents who reported “no interference” increased from 5% prior to volanesorsen to 23% while on therapy, whereas those reporting a high level of interference (levels 5 to 7 on a 7-point scale) decreased from 59% prior to treatment to 37% while on volanesorsen (Figure 22). Symptoms of FCS had a significantly lower impact on respondents’ lives during volanesorsen treatment, with a 22% reduction in mean score from baseline ($P<0.05$). The proportion of respondents who reported no interference of FCS with work or school increased from 36% before starting volanesorsen to 64% during treatment. In addition, treatment with volanesorsen improved patients’ ability to socialise and engage with others. Patients reported reduced stress over

managing diet and less difficulty planning meals while on volanesorsen treatment.

Figure 22 Overall impact of FCS on patients' lives before and during volanesorsen treatment (n = 22)



Source: Arca et al., 2018

Several aspects of emotional and mental well-being, including stress and anxiety, feelings of self-worth, and sleep quality also improved significantly after treatment with volanesorsen.

9.6.2 Justify the inclusion of outcomes in the tables above from any analyses other than intention-to-treat.

All outcomes in Tables C15 and C19 are presented for the FAS population, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

N/A. There are no studies that were designed to primarily assess safety outcomes.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown below.

APPROACH

Table C21 shows the treatment-emergent AEs (TEAEs) that were considered to be related or possibly related to volanesorsen in APPROACH.

Table C21 TEAEs considered related or possibly related to volanesorsen: APPROACH

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)
General disorders and administration site conditions	Administration-related reactions* Injection site reactions† Asthenia Fatigue	Chills Malaise Feeling hot Influenza-like illness Oedema
Investigations	Platelet count decreased	Blood creatinine increased Blood urea increased Creatinine renal clearance decreased Transaminases increased White blood cell count decreased
Skin and subcutaneous tissue disorders		Erythema Pruritus Urticaria Hyperhidrosis Rash Petechiae
Musculoskeletal and connective tissue disorders	Myalgia	Pain in extremity Arthralgia Arthritis Back pain Muscle spasms Musculoskeletal pain

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)
Nervous system disorders	Headache	Hypoaesthesia Presyncope Retinal migraine Syncope
Blood and lymphatic system disorders	Thrombocytopenia	Eosinophilia Immune thrombocytopenic purpura Spontaneous haematoma
Gastrointestinal disorders		Nausea Diarrhoea Dry mouth Gingival bleeding Mouth haemorrhage Parotid gland enlargement Vomiting
Respiratory, thoracic and mediastinal disorders		Epistaxis Cough Dyspnoea Nasal congestion Pharyngeal oedema Wheezing
Vascular disorders		Haematoma Hypertension Hot flush
Eye disorders		Conjunctival haemorrhage
Injury, poisoning and procedural complications		Contusion
Metabolism and nutrition disorders		Diabetes mellitus

*Any reaction on the day of injection with a missing resolution date is also included. †An on-treatment local cutaneous reaction is defined as any treatment emergent local cutaneous reactions occurred from the first dose of the study drug through 28 days post the last dose of study drug. Local cutaneous reactions at injection site are erythema, swelling, pruritus, pain, or tenderness started on the day of injection and persisted for at least 2 days, i.e., event onset date on the day of injection and resolution date not on the day of injection or the day after injection. The most common manifestations associated with reports of local cutaneous reactions at the injection site were injection site erythema, injection site pain, injection site pruritus, and injection site swelling.
Source: ID1326 volanesorsen ERG clarification responses, July 2018, Akcea data on file

The most common events with volanesorsen were related to local tolerability, i.e. TEAEs at the injection site or local cutaneous injection site reactions (any cutaneous reaction at the injection site that lasted more than two days). Local cutaneous injection site reactions occurred following 12% of injections in the volanesorsen group. Sixty-one percent of patients in the volanesorsen group

experienced at least one local cutaneous injection site reaction. These reactions included erythema, pain, pruritus and local swelling. Most were mild and most resolved. One patient discontinued treatment because of a local cutaneous injection site reaction. There were no local cutaneous injection site reactions in the placebo group.

Reductions in platelet counts to below normal (140 x 10^9/L) were observed in 75% of patients treated with volanesorsen and 24% who received placebo. Reductions to below 100 x 10^9/L were seen in 47% of patients treated with volanesorsen and none who received placebo. The reductions in platelet counts were generally well managed with dose adjustments. Two patients in the volanesorsen group experienced Grade 4 thrombocytopenia (platelet count <25 x 10^9/L) and were withdrawn from the study. There were no major or severe bleeding events.

Most TEAEs were mild in severity. Five patients (15%) in the volanesorsen group had severe TEAEs; four of these events were considered to be related to treatment: severe thrombocytopenia (two patients), fatigue (one patient) and musculoskeletal pain (one patient). Three patients in the placebo group had severe TEAEs; none were considered potentially related to treatment.

Twelve patients had serious AEs (SAEs): 7 (21%) in the volanesorsen group had a total of 8 events and 5 (15%) in the placebo group had a total of 6 events. Two patients in the volanesorsen group had SAEs of Grade 4 thrombocytopenia that were considered potentially related to treatment and led to discontinuation. No other SAEs in the volanesorsen group were considered related to treatment and all resolved (abdominal pain (n = 1), cyst (n = 1), cholangitis and drug-induced liver injury (n = 1), ankle fracture (n = 1) and dehydration (n = 1)). None of the SAEs in the placebo group were considered related to treatment.

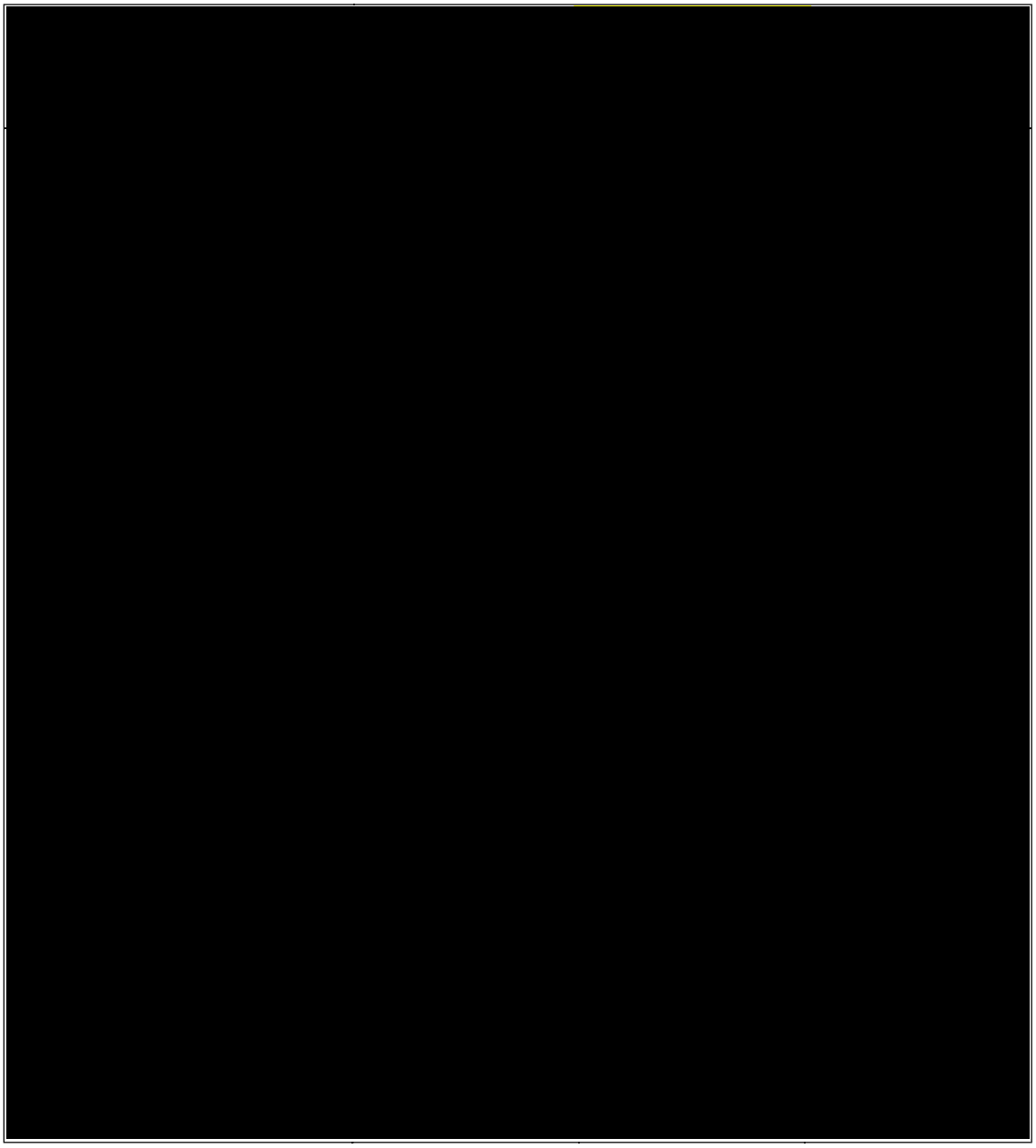
Nine patients (27%) in the volanesorsen group withdrew from the study because of TEAEs. The most frequent events leading to withdrawal from the study were thrombocytopenia, decreased platelet count and fatigue.

There were no hepatic, renal or cardiac safety signals, and no increase in liver fat. There were no deaths during the study.

Ten patients in the volanesorsen group had their dosing changed from once-weekly to once every 2 weeks. These dose adjustments all occurred between Weeks 26 and 42. Two patients had their dose adjusted in response to AEs: thrombocytopenia (n = 1) and injection site induration and discolouration (n = 1). Eight patients had dose adjustments because of low platelets that were not reported as AEs. The implications of dosing every 2 weeks is discussed in Section 9.9.

APPROACH OLE

At the data cut-off of 28 February 2019, the safety population included 68 patients [redacted]



[redacted]

[redacted]

[redacted]

COMPASS

In COMPASS, only local cutaneous injection site reactions and flu-like reactions were analysed separately for the subset of FCS patients.

Three patients (60%) in the volanesorsen group had local cutaneous injection site reactions. There were no local cutaneous injection site reactions in the placebo group.

No patients in the FCS subset reported flu-like reactions.

Three patients in the subset of FCS patients had their dosing of volanesorsen changed from once-weekly to every other week during the study. However, the reasons for the adjustments were not reported separately for these patients.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Volanesorsen was generally well tolerated during APPROACH and APPROACH OLE. The mean duration of treatment with volanesorsen was 267 days in APPROACH. [redacted]

The most common TEAEs were related to local tolerability at the injection site (as would be expected given the SC administration) and reductions in platelet counts. With appropriate monitoring (i.e. every two weeks), any reduction in platelet counts should be detected in a timely manner and can be managed with dose adjustment.

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

N/A: an indirect treatment comparison is not appropriate.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The studies identified in the SLR comprised:

- Studies of volanesorsen, which have been discussed already within this submission
- Studies of tiparvovec, which has been withdrawn from the UK and is therefore not a relevant comparator as it is not available for use in FCS patients
- Studies of pradigastat, an unlicensed experimental treatment developed by Novartis, which is not a relevant comparator as it is not available for use in FCS patients
- One case report of the use of medium chain triglycerides in an FCS patient

The identified studies do not therefore provide sufficient evidence to justify either quantitative or qualitative evidence syntheses, as the treatments are either unavailable in the UK or were in a single patient.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

In the pivotal Phase 3 randomised, double-blind, placebo-controlled APPROACH study (n = 66), treatment with volanesorsen led to a marked reduction in plasma TGs versus placebo (-77% vs +18% respectively; 94% treatment effect, $p<0.0001$) at 13 weeks, with reductions continuing throughout the 12-month study period: mean -40.2% vs +8.9% (patients

completing study on both none reduced dose (n = 6) and reduced dose (n = 12)). All secondary and tertiary outcomes relating to TG levels, cholesterol, chylomicron triglycerides and apolipoproteins B, B-48, A-1 and C-III were statistically significant in favour of volanesorsen. Health related quality of life and pain outcomes were not statistically significant, but the trial was not powered for these outcomes and this is not an unexpected finding given patient numbers. In contrast, the number of acute pancreatitis events numerically favoured volanesorsen: 1 vs 4. Similarly, an exploratory analysis investigating the number of adjudicated acute pancreatitis events within the 12-month study period in patients at high risk for acute pancreatitis, relative to the 5-year pre-randomisation period, numerically favoured volanesorsen compared with placebo with 0 vs 4 events reported in each arm respectively. As AP is an event that severely impact patients' daily activities, quality of life and can be life-threatening, this is a significant outcome

APPROACH open-label extension (OLE) study (planned enrolment n = 70) reports interim data that suggest the reduction in TG levels are sustained over the longer-term. [redacted]

In APPROACH the most common adverse event reported in associated with volanesorsen treatment was injection site reactions n=20 (61%), the majority of which were mild in intensity, and reductions in platelet levels n=11 (33%). A reduction in platelet count to <50 x 10^9/L was observed in 3 patients prior to the initiation of enhanced platelet monitoring (Witztum et al., 2019). Thereafter, thrombocytopenia was manageable with monitoring and dose adjustment when required, as specified in the SmPC.

Through its effectiveness at lowering TG levels, volanesorsen has the potential to transform patients' lives. It has a manageable safety profile, and with the support of the Patient Support Programme that is designed to make the blood monitoring as convenient as possible for the patient, the safe use of the product can be maintained with minimal burden to patients.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

APPROACH was a randomised, controlled trial in the patient population under consideration. It included more than 60 patients from across the world, which is remarkable considering that FCS is an ultra-rare disease. The trial results (in terms of the benefits offered by volanesorsen) are impressive and unprecedented in this patient population. The significant decrease in TGs observed in response to volanesorsen translated to a decreased risk of acute pancreatitis and abdominal pain. In turn, it is anticipated that this would result in improved QoL for both patients and their families.

The study included clinically relevant endpoints. Reductions in acute pancreatitis and abdominal pain are particularly important to patients as they are extremely debilitating manifestations of the disease.

Limitations

In the studies in the clinical development program, the initial dose of volanesorsen was 285 mg once-weekly. However, volanesorsen has received conditional marketing authorisation at an initial dose of 285 mg once-weekly for 3 months followed by dose adjustment to once every 2 weeks. Analyses have shown that the reduced dosing frequency still produces clinically relevant decreases in TG levels with stabilization of platelet levels. These are discussed in Section 9.9.4.

APPROACH was not powered to detect differences in patients' HRQL; this was only included as an exploratory endpoint. There is currently no specific, validated QoL tool for FCS. Tools such as the EQ-5D and SF-36 have limited sensitivity to pick up QoL differences in slow-progressing chronic diseases and are therefore not ideal for FCS.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The clinical evidence base described in this submission is derived principally from the APPROACH and APPROACH OLE clinical trial. Data from these trials are centrally relevant to the scope for this appraisal, capturing evidence on TG reduction, acute pancreatitis episodes, and rates of important AEs such as thrombocytopenia, all of which feature in the final scope.

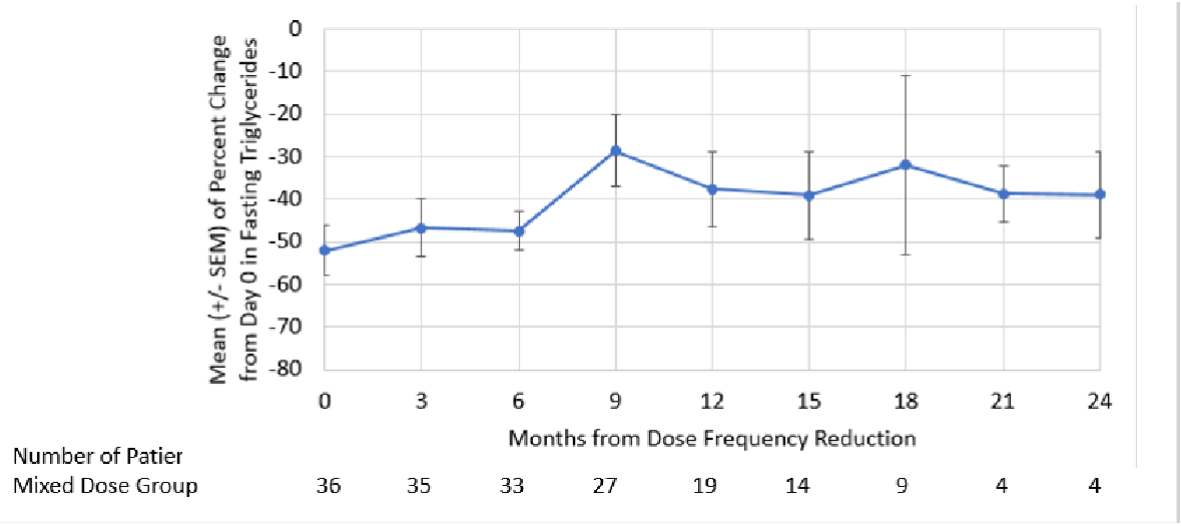
9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Dosing

In the clinical development programme, the dose of volanesorsen was 285 mg once-weekly. Some patients had their dose adjusted to once every 2 weeks which could affect the external validity of the data with respect to modelling outcomes versus the indicated dosing posology (see Section 9.7.2). In order to asses the impact of changing the dosing frequency from once-weekly to once every 2 weeks, Akcea has analysed data from patients in APPROACH and APPROACH OLE who were on a mixed dose regimen, defined as patients who started on once-weekly treatment, had their dose reduced at some point during the study to once every 2 weeks and remained on this dose for more than 3 months. Note that the APPROACH OLE data are from an interim analysis with a cut-off date of 20 June 2018.

Overall, 36 (44.4%) of 81 patients were on a mixed dose regimen at 20 June 2018. Of these 36 patients, 14 conformed to the approved dosing regimen (i.e. an initial dose of 285 mg once-weekly for the first 3 months, followed by an adjustment to once every 2 weeks). The reduction from baseline in fasting TG levels, in these patients, was sustained at approximately 40% following adjustment to once every 2-weekly dosing (Figure 24).

Figure 24 Change in TG levels over time after dose adjustment in APPROACH and APPROACH OLE



Day 0 is defined as the last TG assessment before or on the date of first dose adjustment. SEM, standard error of the mean
Source: Volanesorsen Type A briefing book, November 2018, Akcea data on file

Because of small patient numbers, using the above data in the economic model resulted in unstable ICER estimates. To address this a *post-hoc* analysis of pooled APPROACH and APPROACH OLE data was carried out (see Section 12.2.1 and Appendix 8). In this analysis, a generalized linear mixed model (GLMM) was fitted to all available TG readings from APPROACH and APPROACH OLE with the objective of characterizing response to once every 2 weeks volanesorsen after Month 3. The results of this analysis estimated that the mean % reduction in TG levels of patients on once every 2 weeks dosing is between 43.2% and 45.0%, so substantiating the trial results, presented in Figure 24.

Treatment discontinuation rate

It is reported that 3 out of the 33 patients (9%) on the volanesorsen treatment arm in APPROACH were withdrawn from the study due to investigator concerns (Witztum et al., 2019). In contrast we are not aware of any EAMS patients stopping volanesorsen for any disease-or treatment-related reasons (one patient had to stop due to the recurrence of cancer). Therefore, it is likely that the treatment continuation reported in the trial is not the same as will be seen in routine clinical practice. Therefore, this is explored in sensitivity analyses in the economic model.

Population

The APPROACH trial population aligns with the therapeutic indication and with patients treated in the EAMS. As such it is a valid population, reflective of that likely to be seen in routine clinical practice.

Baseline TG levels in APPROACH did not vary according to 5-year history of adjudicated acute pancreatitis. The mean baseline TG levels of patients with 0, 1 or more, or 2 or more episodes in the past five years were 25.3, 24.4 and 25.3 mmol/L respectively. A *post-hoc* analysis showed that patients with a history of pancreatitis attacks achieved similar reductions in TG levels during volanesorsen treatment to the overall FAS population.

Together, these results demonstrate that the efficacy of volanesorsen with respect to both relative and absolute reduction in TG levels is generalisable to a patient population restricted to those at high risk of acute pancreatitis.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

Patients that meet the criteria specified in the SmPC:

> *adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate*

are likely to be those that are selected for treatment in clinical practice. We do not anticipate any other criteria being required.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

FCS imposes a significant burden on patients and their carers, adversely affecting their physical and emotional health, employment status, relationships and social life. Patients with FCS often have multiple comorbidities and symptoms which span physical, emotional and cognitive domains.

In a recent survey of 166 patients with FCS from 10 countries (Davidson et al., 2018), at least one-third of the patients reported 2 or more comorbidities, including AP (40%), eating disorders (23%), diabetes (16%), chronic pancreatitis (11%), hepatomegaly (11%), splenomegaly (10%), hypertension (10%), lipemia retinalis (9%), peripheral neuropathy (7%), addiction to pain medication such as opioids (5%), other conditions (5%), and pancreatic calcification (2%).

The same survey highlighted the elements that patients reported impacted them which included daily severe nausea and vomiting, fatigue, weakness and feeling cold more frequently than once a week. A large number of respondents reported abdominal pain and pancreatic pain as severe on a fortnightly or monthly basis. (see Section 7.1, Figure 5).

While the TG level in itself may not be something the patient is aware of, the impact it has on patients day-to-day life appears to be severe and chronic for a substantial proportion of patients.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

FCS does not follow a clear disease trajectory, likely in part due to the dietary control required to manage the disease. People's ability to control their diet differs at different stages in life.

The literature reports a poorer quality of life for acute pancreatitis (Pendharkar et al., 2014), an event that FCS patients are particularly susceptible to, and which carries a mortality risk of 6%. Recurrent AP increases the risk of chronic pancreatitis (Symersky et al., 2006), while the evidence is scarce, chronic pancreatitis is associated with very poor quality of life (Guarner et al., 2009, Laramee et al., 2013).

Diabetes is common in this population (around 16% at diagnosis). The negative impact of diabetes on QoL is well researched as is the impact of diabetic complications (Sullivan et al., 2011). It is not known how FCS and diabetes interact with each other. Anecdotally, patients with both FCS and diabetes find it harder to manage both diseases (i.e. they are worse than the sum of their parts).

Patients do report worsening symptoms with age (Davidson et al., 2018) however, some younger patients can have a terrible quality of life associated with very frequent acute pancreatitis events or, for example, eating disorders.

Unfortunately, there is not a robust HRQoL tool available to measure the broad impact of FCS at the current time.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

In both APPROACH and APPROACH OLE, HRQL was measured using the EQ-5D-5L and SF-36 questionnaires. However, it should be noted that as these are not disease-specific tools, it is unlikely that they were sensitive enough to detect changes in a population of patients with FCS, especially given the small sample size. HRQL was not assessed in COMPASS.

APPROACH

HRQL was an exploratory outcome in APPROACH. Patients completed the EQ-5D and SF-36 questionnaires at baseline, Week 13 (Month 3), Week 26 (Month 6) and Week 52 (Month 12). The results are shown in Tables C24 (ED-5D-5L) and C25 (SF-36). EQ-5D-5L index scores at baseline were notably very high in both treatment groups (in the volanesorsen and placebo arms respectively; Table C24). These index scores are implausible in the context of the reported burden of FCS on patients (Davidson et al., 2018). Given the impact of this disease is experienced at every meal, measuring HRQL four times in one year is unlikely to detect important changes in quality of life.

Similar results were seen in the subgroup of patients who reported abdominal pain >0 and in the patients who had pre-dose adjudicated pancreatitis.

Table C24 EQ-5D-5L scores (FAS, n = 66)

Dimensions Mean (SD)	Baseline		3 months		6 months		12 months	
	Volanesorsen	Placebo	Volanesorsen	Placebo	Volanesorsen	Placebo	Volanesorsen	Placebo
Overall health status VAS	[redacted]							
Mobility	[redacted]							
Self-care	[redacted]							
Usual activities	[redacted]							
Pain/discomfort	[redacted]							
Anxiety/depression	[redacted]							

Overall health status VAS scored on a 100 mm scale, where 0 = worst health imaginable and 100 = best health imaginable. Individual domains scored on a scale of 1 to 5, where 1 = no problem and 5 = extreme problems. VAS, visual analogue scale
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C25 EQ-5D-5L index scores (95% CI) by treatment arm and study period

Treatment Group (n)	Baseline
Volanesorsen (24)	[redacted]
Placebo (26)	[redacted]
	Month 3
Volanesorsen (30)	[redacted]
Placebo (32)	[redacted]
	Month 6
Volanesorsen (23)	[redacted]
Placebo (23)	[redacted]
	Month 12
Volanesorsen (16)	[redacted]
Placebo (22)	[redacted]

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

Table C26 SF-36 weighted sum scores (FAS, n = 66)

Weighted scores Mean (SD)	Baseline		3 months		6 months		12 months	
	Volanesorsen	Placebo	Volanesorsen	Placebo	Volanesorsen	Placebo	Volanesorsen	Placebo
Physical Functioning	[redacted]							
Role Physical	[redacted]							
Bodily Pain	[redacted]							
General Health	[redacted]							
Vitality	[redacted]							
Social Functioning	[redacted]							
Role-Emotional	[redacted]							
Mental health	[redacted]							

Weighted scores are on a scale of 0 to 100, where 0 = maximum disability and 100 = no disability.
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

APPROACH OLE (data cut off: 28 February 2019)

[redacted]

Table C27 EQ-5D-5L scores (FAS): APPROACH OLE

	Mean (SD) score			
Dimensions	**Baseline***	**Week 13**	**Week 26**	**Week 52**
Overall health status VAS	[redacted]	[redacted]	[redacted]	[redacted]
Index score	[redacted]	[redacted]	[redacted]	[redacted]
Mobility	[redacted]	[redacted]	[redacted]	[redacted]
Self-care	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	[redacted]	[redacted]	[redacted]	[redacted]
Pain/discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/ depression	[redacted]	[redacted]	[redacted]	[redacted]

*Baseline is defined as the last non-missing measurement on Week 1 of the double-blind study for the APPROACH-volanesorsen group and the last non-missing measurement on Week 1 of the OLE study baseline for the treatment-naïve group. Overall health status VAS scored on a 100 mm scale, where 0 = worst health imaginable and 100 = best health imaginable. Individual domains scored on a scale of 1 to 5, where 1 = no problems and 5 = extreme problems. VAS, visual analogue scale
Source: Table 14.2.8.2.1, Table 14.2.8.2.2, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file.

Table C28 SF-36 weighted sum scores (FAS): APPROACH OLE

	Mean (SD) weighted score							
	Baseline*		Week 13		Week 26		Week 52	
	[redacted]							
Physical Functioning	[redacted]							
Role Physical	[redacted]							
Bodily Pain	[redacted]							
General Health	[redacted]							
Vitality	[redacted]							
Social Functioning	[redacted]							
Role-Emotional	[redacted]							
Mental health	[redacted]							

*Baseline is defined as the last non-missing measurement on Week 1 of the double-blind study for the APPROACH-volanesorsen group and the last non-missing measurement on Week 1 of the OLE study for the treatment-naïve group. Weighted scores are on a scale of 0 to 100, where 0 = maximum disability and 100 = no disability.
Source: Table 14.2.9.1, Table 14.2.9.2, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file.

HRQL data derived from clinical trials: summary

The EQ-5D-5L index values collected in the APPROACH study were very high across groups at baseline. The mean index scores were 0.971 and 0.982 in the volanesorsen and placebo arms respectively. These are notably higher than the average UK index value – which is approximately 0.85 for an adult in their mid-40s (Szende et al., 2014). In light of the detailed information with respect to how FCS impacts on different health domains, as described in the In-FOCUS study (Davidson et al., 2018), the baseline values appear implausible.

EQ-5D-5L data collected at follow-up visits remained similar to baseline and did not reveal any significant differences between treatment arms. Given the high baseline values, it is perhaps not surprising that the EQ-5D-5L was unable to capture any benefit of treatment; in other words a ceiling effect was observed. This supports our conclusion that the EQ-5D data from the APPROACH study are not the preferred source of utility data for the cost-effectiveness analysis. We present an alternative source of utility data from a large, well-designed vignette study, EVA-22200 (Matza et al., 2018; Akcea data on file, 2018c) in the cost-effectiveness base case and include the APPROACH data as a sensitivity analysis.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

A mapping study was not undertaken.

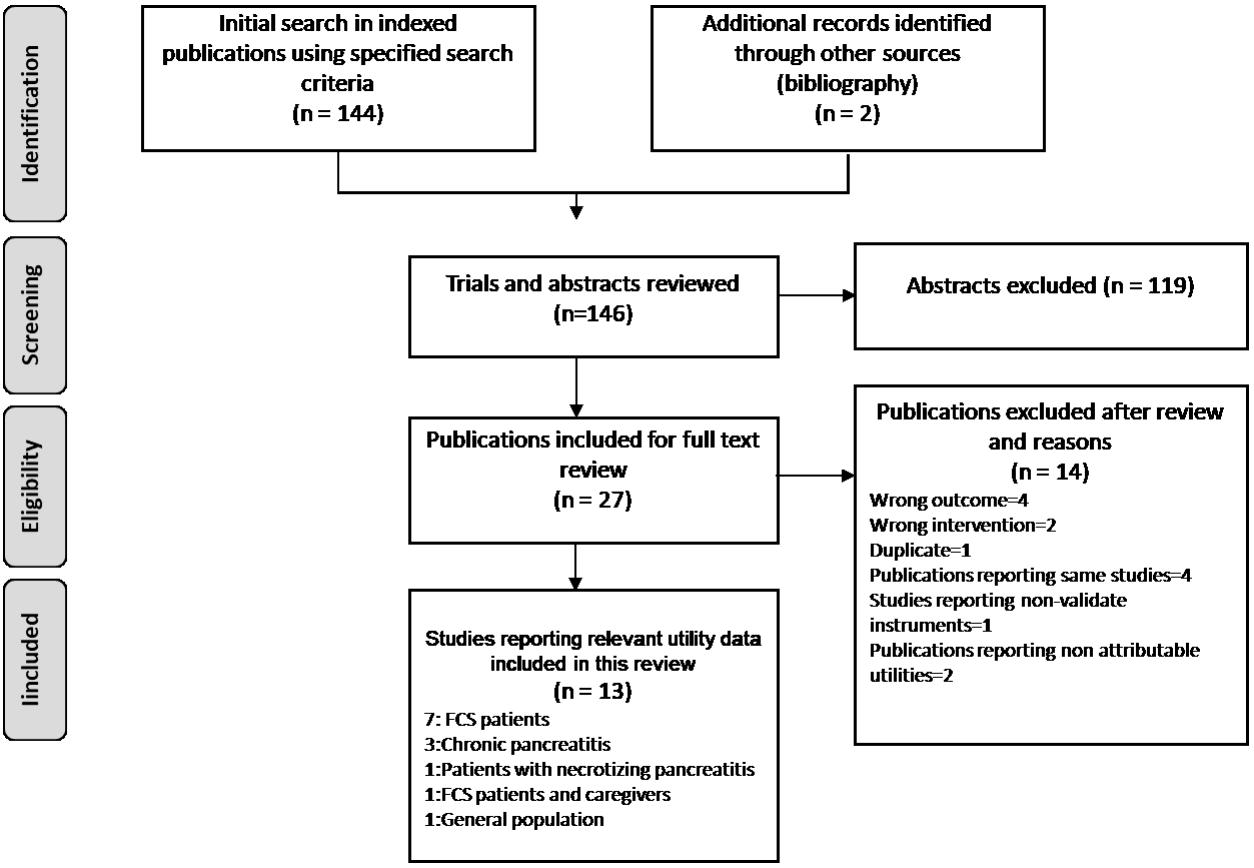
HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic search of published literature was conducted using the bibliographic databases, EMBASE via Ovid®; MEDLINE via Ovid® (1973 to 7th June 2019); Cochrane Database of Systematic Reviews via the Cochrane Library; Database of Abstracts of Reviews of Effects via the Cochrane Community; Health Technology Assessment Database via the Cochrane Library; NHS Economic Evaluation Database via the Cochrane Community. In addition, PubMed and Google were searched separately using key words related to the main search strategy.

A systematic search for HRQL was performed simultaneously with a systematic search for economic studies and resource use in FCS and hypertriglyceridemia (Section 11.1.1). Since FCS predisposes to acute pancreatitis, the search strategy was broadened to include MESH terms as well as key words to represent pancreatitis. No date restriction was applied, however, the search was limited to publications in English language. Details of the search strategy are provided in Appendix 4. The search yielded 13 results. These studies are reported in Appendix 4.

Figure 25 PRISMA diagram for HRQL systematic review



10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.

- Consistency with reference case.
- Results with confidence intervals.

A total of 13 studies were included and are summarised in Appendix 4.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Values derived from the literature searches are not comparable to HRQL data collected in the APPROACH clinical trial in an FCS population. The literature searches emphasise the lack of evidence available on HRQL in FCS. Some data are available in patients with chronic pancreatitis, though these are likely non-FCS populations with a different aetiology.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

The effect of specific AEs on patients' HRQL was not captured during the clinical trials of volanesorsen. Although the trial measures of HRQL were similar across treatment groups, we have included utility decrements to reflect the impact of severe AEs (Grade III or above) that were observed in patients in either treatment group in the APPROACH study. Utility decrements for these AEs were derived from targeted literature searching.

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

As described earlier in Section 10.1.3, data collected in the APPROACH study is not suitable as a source of utility data for the base case cost-effectiveness modelling. These data are, however, used in a sensitivity analysis. Following extensive literature searches which revealed that suitable alternative utility data were not available in published form, a vignette study, EVA-22200, was commissioned by Akcea, in order to derive appropriate utility values to inform

cost-effectiveness modelling. A summary of the vignette study is presented in Appendix 6. A full study report describing the methods and results of the vignette study is available on request.

Based on the substantial reduction in TGs observed in patients receiving volanesorsen (from a mean of 26.2 mmol/L to a predicted mean of 12.1 mmol/L on every 2 weeks), accompanied by the improvement in quality of life reported in the ReFOCUS study, patients on treatment in the cost effectiveness analysis are assumed to have the utility of the ‘low TG’ health states from the EVA-22200 vignette study and those off treatment have the utility of the ‘high TG’ health states. Due to the stopping rules, no patients on volanesorsen are anticipated to have ‘high TGs’. This is in line with estimates of mean fasting triglycerides on standard of care vs. volanesorsen in the clinical trials as well as those predicted in the economic analysis; patients on standard of care have mean TGs of 26 mmol (‘high TG’ utilities) and patients on every 2 weeks volanesorsen have mean TGs of 12.1 mmol (‘low TG’ utilities).

Table C29 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Justification
Low TG[1], AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
High TG[2], AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
Low TG[1], historical AP	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
High TG[2], historical AP	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
Low TG[1], recurrent AP	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
High TG[2], recurrent AP	[redacted]	[redacted]	EVA-22200 vignette study. See section 10.1.3
Chronic Pancreatitis	0.42	0.37-0.48	Assumption: same as state High TG and recurrent AP, with additional monthly decrements of AP representing disease 'flares'
Carer of volanesorsen-treated patient	0.02	*NA*	Utilities of carers in diseases that do not cause physical disability are absent in the literature. A nominal annual QALY gain of 0.1 has been assumed for carers of patients with volanesorsen to reflect the psychological benefit of knowing that patients are on an effective treatment that improves their day-to-day symptoms and prevents acute pancreatitis.

Key: SoC, standard of care
1, assigned to patients on volanesorsen in the model
2, assigned to patients on SoC in the model

Events	Utility decrement, annualised	Confidence interval	Justification
Acute Pancreatitis	[redacted]	NA – calculated from other vignette health states, see below.	Adjusted for duration of AP before applying to each AP event in model. Please see calculation below, referring to vignette values in Appendix 6.
Diabetes	0.23	Uncertainty not available	Diabetes is a well-described comorbidity associated with FCS. Having FCS makes it particularly difficult to manage diabetes, therefore 50% of patients are assumed to have the complications of diabetes. Sullivan et al., 2011.
Thrombocytopenia, Grade 3 (25,000-50,000/μL)	0.18	Uncertainty not available	See section 10.1.8
Thrombocytopenia, Grade 4 (< 25,000/μL)	0.18	Uncertainty not available	See section 10.1.8
Fatigue	0.12	Uncertainty not available	See section 10.1.8
Injection site reaction	0.08	Uncertainty not available	See section 10.1.8

[1]Calculation of the disutility of pancreatitis based on the vignette is reported in Appendix 6b

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were asked to address the issue of HRQL for patients with CP. Very limited evidence was identified in the SLR with respect to CP, which is an important long-term, chronic complication, expected to affect a substantial proportion of patients with FCS. Specifically, for the economic evaluation of volanesorsen, we required an estimate of the utility associated with CP. Advice was sought from a small number of experts who were engaged either in a face to face interview, or on the telephone.

A total of 8 clinical experts were approached and 7 participated. The one respondent who did not participate did not feel they had sufficient, relevant expertise to address the specific questions in the survey. Akcea invited clinical experts to participate on the basis of clinical expertise in the field of FCS. The number of clinical experts in the UK fitting this description is limited and Akcea relied upon the existing clinical expert network. The focus of the survey related to the impact of chronic pancreatitis on patients with FCS and this influenced the selection of experts to approach.

Included in the sample of clinical experts who participated in the survey were Consultants in Diabetology, Endocrinology, Chemical Pathologist and Metabolic Medicine. Two broad areas of questioning were included – firstly with regard to the symptoms associated with CP for patients with FCS and the NHS resources associated with management of CP. Secondly, the impact of CP in terms of HRQL and the likely incidence of CP in patients with FCS. A copy of the survey questions and a summary of the participant responses is included in Appendix 7.

Specifically regarding HRQL for patients with CP, we explored the rationale for assuming the same utility for CP as for those patients with a history of

acute pancreatitis (AP) and high TG levels. The latter had been derived from the vignette study. All clinical experts who participated in the survey agreed with the rationale – i.e. that it was reasonable to assume HRQL for patients with CP would be 'at best equivalent' to that for "High triglycerides, history of acute pancreatitis".

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The characteristics of the model health states in terms of HRQL experience were described in the vignette study (Akcea data on file, 2018c). High TG and low TG health states were supported by a vignette, developed with clinical and patient experts. Vignettes were also developed to explore the HRQL impact of acute pancreatitis. Further details are provided in Appendix 6. The HRQL of patients with FCS is expected to vary significantly according to TG level and history of pancreatitis. This is supported by the findings in the vignette study. Within the model, we therefore capture the way in which HRQL is expected to vary for patients over time, according to their TG levels and associated risks of AP. In addition, patients with FCS may experience comorbidities. In the model, we capture the impact of comorbid diabetes as an annual utility decrement. Finally, the HRQL of patients is impacted by the adverse effects of treatment, and in the model we capture this as utility decrements associated with the more severe (grade III and above) adverse events observed in the APPROACH study.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Eating disorders, fatty liver disease, problems sleeping, being cold are commonly described elements of FCS that are not included in the model. Akcea made the decision to focus on what appear to be the most critical elements associated with FCS: TG level, AP, CP and diabetes. The vignettes allow a little more breadth of impact to be considered, including worry, cognitive impairment and social isolation. Adding in more health effects would have increased the risk of double counting and increased the complexity of the model potentially with limited value.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to be constant over time, this is a limitation in the model as patients report worsening of symptoms over time (Davidson et al., 2018).

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

According to the SmPC, after the initial three months of weekly treatment, patients who have not achieved a reduction in serum TGs of >25% or still have serum TG levels above 22.6 mmol/L should be taken off treatment with volanesorsen.

While the SmPC recommends re-uptitration after 6 months of treatment in cases of insufficient TG-lowering, insight from EAMS suggests that this is unlikely. To date, one patient in EAMS has had their dose increased to weekly dosing. Of the 4 patients in APPROACH OLE who re-uptitrated to weekly treatment, 2 re-downtitrated to once every 2 weeks treatment. If patients fail to maintain TG levels consistently below 22.6 mmol/, they should cease treatment with volanesorsen. It is critical that they are supported in maintaining their diet to ensure that relaxation of the diet is not driving high TG levels.

In discussion with clinical experts it seems likely that in the UK patients who experience multiple AP events or develop chronic pancreatitis would be removed from treatment on the basis that the treatment is not efficacious for that patient. The effect of this stopping rule is tested in the economic model.

These treatment discontinuation rules ensure that patients are not maintained on a treatment that is no longer efficacious for them. We anticipate that there would be negligible costs associated with implementing a 3-month stopping rule as this aligns with real world evidence from a UK cohort of FCS patients (The Manchester study, Akcea data on file 2018d), suggesting TG levels are routinely measured once every 3 months. Accordingly, a 3-month decision point on the basis of the TG levels over the would not be expected to incur additional healthcare resources.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

Akcea conducted a systematic literature review of the published English language literature to identify relevant published studies reporting the cost-effectiveness of volanesorsen or any other intervention for the management of FCS. Searches were conducted in the following databases to identify literature published from database inception to 7 June 2019: MEDLINE (via Ovid), Embase, the Cochrane National Health Service Economic Evaluation Database (NHS EED), the Cochrane Health Technology Assessment (HTA) Database, the Database of Abstracts of Reviews of Effects (DARE). The search strategy used is presented in Appendix 1.

The literature search was broad in scope to include any intervention (including volanesorsen) evaluated for the management of FCS. Studies which did not involve the patient population specified in the scope were subsequently excluded after reading the abstract and title (level 1 screening) and reading the full text (level 2 screening).

In addition, reference lists of all accepted studies, and all relevant systematic reviews and meta-analyses were screened manually to identify any relevant studies that were not identified using the above electronic search strategy. Moreover, grey literature (material not published in peer-reviewed or indexed

medical journals) was also searched for relevant conference abstracts and posters reporting interventional or observational studies in FCS

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

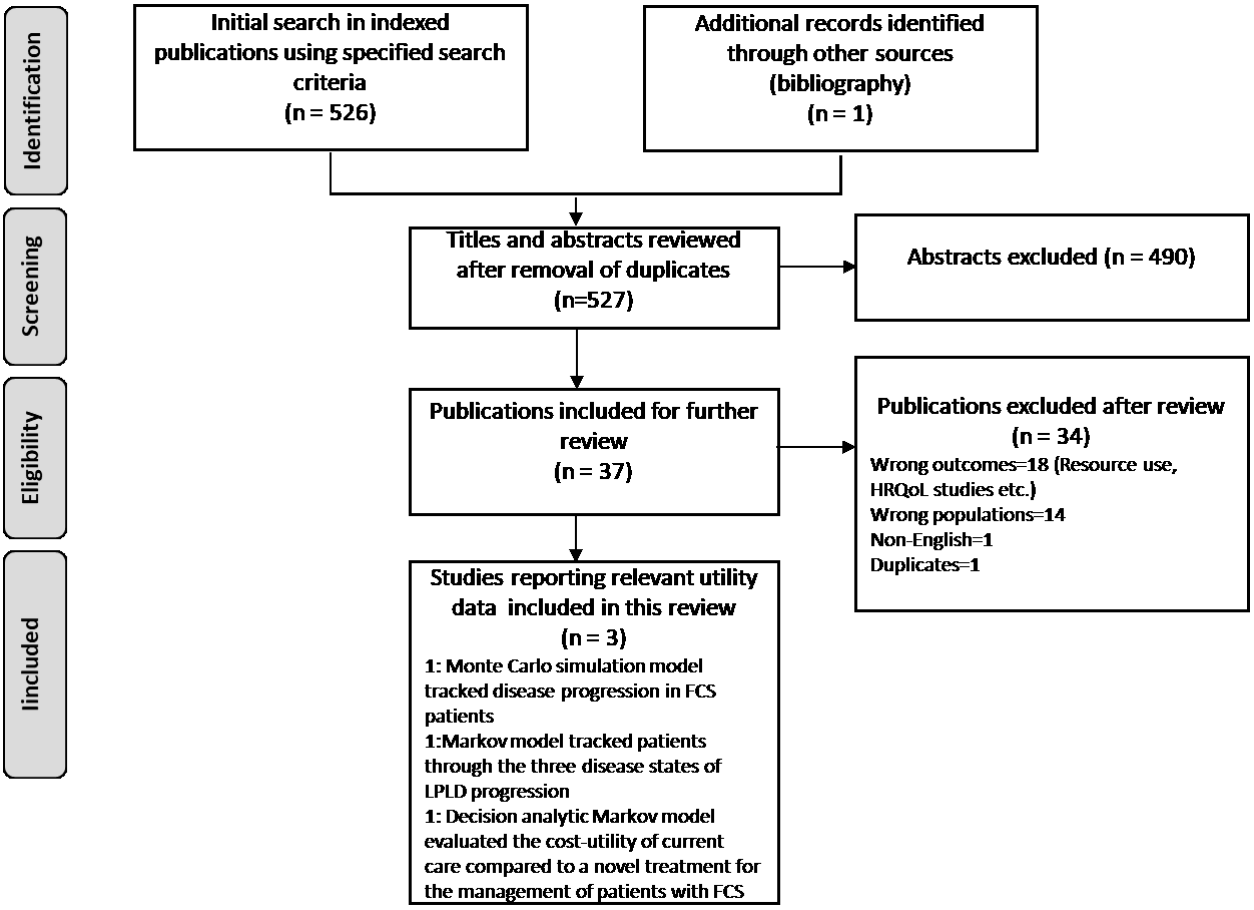
Table D1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with familial chylomicronaemia, lipoprotein lipase deficiency and hypertriglyceridemia
Interventions	Volanesorsen or usual care
Outcomes	• Direct and indirect costs • Cost-effectiveness • Resource utilisation
Study design	In the review, studies of the following study designs are eligible: • Systematic reviews • Randomised controlled trials (RCTs) • Prospective comparative studies - such as cohort studies • Retrospective comparative studies - such as case-control studies • Prospective case series/registry studies • Non-randomised non-control studies • Non-randomised non-concurrent control trials • Natural history epidemiological studies • Studies must include more than 2 participants for inclusion Studies with any duration of follow up are eligible for inclusion. Eligible systematic reviews must meet the same inclusion criteria as the RCTs. Abstracts or conference presentations for clinical studies are eligible for inclusion, providing sufficient detail is available to allow appraisal and assessment of results to be undertaken and thereby inform the review. Systematic reviews are used as a source of references only
Language restrictions	Only publications in English will be included
Search dates	No date limits applied to the searches.
Exclusion criteria	
Population	Other than those described above
Interventions	Other than those described above
Outcomes	No restrictions
Study design	No restrictions
Language restrictions	Restricted to publications in English language only
Search dates	No date limits applied to the searches

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Three studies were identified for economic studies in FCS, potentially relevant to the decision problem. Specifics of the search are provided in Appendix 3.

Figure 26 PRISMA diagram for economic systematic review



11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

No studies specifically assessing the cost-effectiveness of volanesorsen for FCS were identified, but three studies reported economic models for assessing interventions in FCS (one specifically for Glybera). Two studies reported a Markov structure and one an individual simulation (ISM) model. All studies included acute pancreatitis and associated sequelae as part of model outcomes. The paucity of publications identified reflects the limited evidence base in FCS, and highlights the lack of treatment options and innovation in this disease area.

Given the limitations in the reporting of previous studies and the lack of any published evaluation of volanesorsen, a *de-novo* model was developed.

Table D2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Lin F et al. 2014	USA	An individual Monte Carlo simulation model was built to track disease progression of a cohort of FCS patients. The model projected	A cohort of FCS patients with a mean age of 37.8 years, 60% male, and a mean triglyceride level of 2,741 mg/dL.	The discounted lifetime cost of acute pancreatitis was projected to be $154,126 per patient.	With standard diet control, the average life expectancy of the studied cohort was estimated to be 16.45 years. These patients were expected to experience 10.16 episodes of acute pancreatitis during their lifetime, resulting in 80.7 inpatient days.	The discounted lifetime cost of acute pancreatitis was projected to be $154,126 per patient. The cumulative mortality due to acute pancreatitis was estimated to be 54.3%. Should an intervention

		the number of acute pancreatitis events, mortality and medical costs. Benefits of a hypothetical triglyceride reduction intervention were assessed.				reduce triglyceride levels by 50% in FCS patients, the life expectancy would be increased by 3.16 years and 7.72 fewer episodes of acute pancreatitis would occur, preventing 61.21 inpatient days and saving $118,594 in medical cost.
Han et al. 2015	USA	Markov model tracked patients through the three disease states of LPLD progression, defined by the symptoms of pancreatitis. The effectiveness of the novel gene therapy based on published clinical trial data was evaluated. QoL, utility scores and cost data for each disease state was derived from the published literature. We estimated the discounted costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) was estimated. Univariate	Markov model was used to track patients through disease states. No other information on patient characteristics is presented	The cost data for each disease state was derived from the published literature; and the discounted costs were estimated. However, the actual data is not presented for these parameters.	Not available	The incremental cost-effective ratio (ICER) of Glybera was € 51,789/QALY gained when compared with no intervention. The net monetary benefit (NMB) is €667,478, given the willingness-to-pay (WTP) is €114,875.

		sensitivity analyses were conducted to assess the impact of parameter uncertainty on the results.				
Priedane et al. 2018a	UK	A decision analytic Markov model was developed to evaluate the cost-utility of current standard of care compared to a novel treatment for the management of patients with FCS. The model included five health states: high-risk TG level, low-risk TG level, acute pancreatitis (event-tunnel state), post-high-risk TG level, and post-low-risk TG level. A cycle length of 3 months and the perspective of the UK healthcare system were used. The model structure was developed to adjust for a potential dose adjustment/pause. Clinical outcomes, costs and utilities	A decision analytic Markov model was used to evaluate the cost-utility of current SoC compared to a novel treatment for the management of patients with FCS. The model included five health states. No other information on patient characteristics is presented	Clinical outcomes, costs and utilities were obtained from publicly available sources and through discussions with clinical experts	Not available	Not available

		were obtained from publicly available sources and through discussions with clinical experts.				

11.3 **Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.**

Table D3 – not applicable due to abstracts only

All three studies were in abstract form only and therefore no qualitative assessment has been carried out.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The patients included in the model are those in line with the indication: adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

The cohort in the model has a mean age of 41. Patients are assumed to be high risk based on prior AP experience: patients with no AP history are low risk of AP, while those with 2 prior APs in the last 5 years are considered the most high risk. Given the limited data this is a pragmatic way of identifying the patients we consider the regulators deemed most able to benefit from volanesorsen.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The comparison ‘standard of care’ (SoC) is no active treatment. The placebo arm in APPROACH is considered a good reflection of UK clinical practice in

which clinicians manage symptoms of FCS and its sequelae (diabetes) but there is no treatment for the underlying FCS.

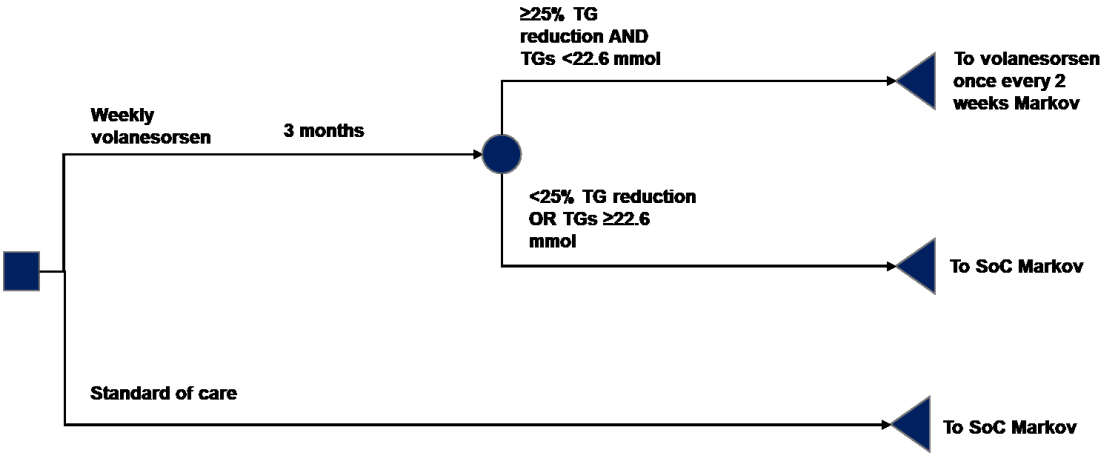
The lack of comparator highlights the significant need for treatment in this disease. Importantly, a zero-cost comparator penalises innovative treatments for diseases with unmet need in cost-effectiveness analysis.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

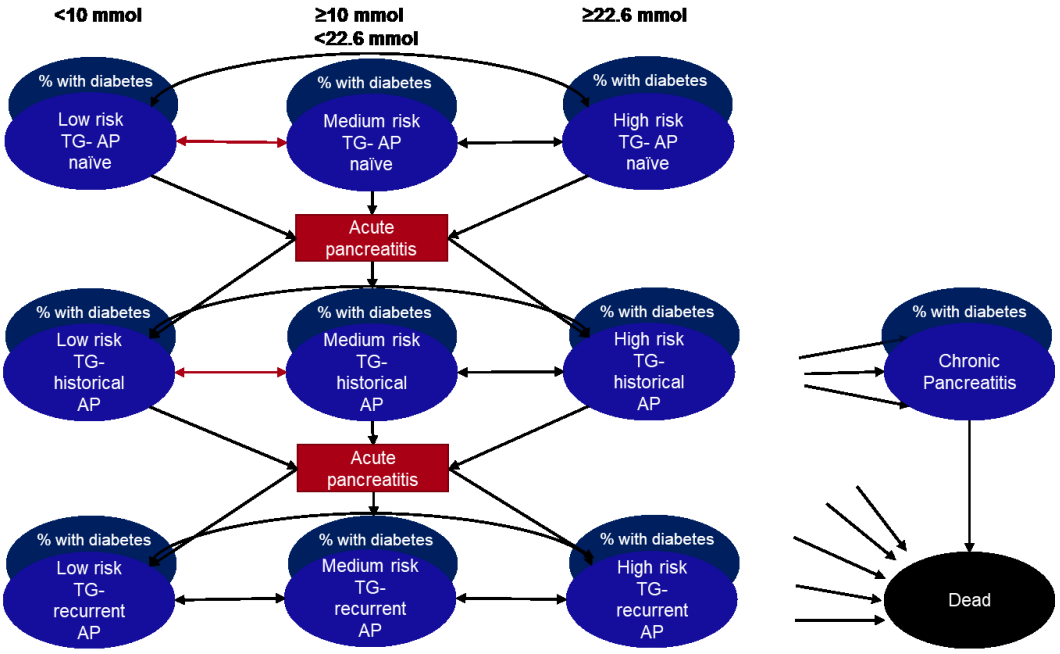
Figure 27 Model structure

A. 3-month decision tree



Note: Patients also have a risk of mortality and chronic pancreatitis in the first 3 months, but numbers are small and similar between arms.

B. Long-term Markov



Key: TG, triglyceride; AP, acute pancreatitis; Low risk TG is <10 mmol, Medium risk TG is ≥10 mmol and <22.6 mmol and High risk TG is ≥ 22.6 mmol.

Note: There are separate Markov traces for weekly dosing, every 2 weeks dosing and off treatment (SoC) in the volanesorsen arm of the model, to capture the clinical impact of dose. The SoC arm of the model has one trace for SoC.

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The *de novo* economic model structure is reflective of FCS the disease, in the absence of a well-defined clinical pathway of care. The model enables the estimation of the relative cost-effectiveness of volanesorsen in the treatment of FCS from the perspective of the NHS in England. The model adopts a lifetime time horizon, in line with the NICE reference case and the experience of patients in this life long disease.

The model captures the critical health consequences: AP, CP and diabetes with patients transitioning through the model based on TG levels. This is a valid reflection of how patients with FCS and its consequent elevated trigylceride levels experience FCS. The impact of volanesorsen within this disease is estimated based on the available evidence.

The model combines a short-term decision tree (initial 3 months) informed by an individual patient simulation and a longer-term cohort Markov structure (3-month cycles). Patients enter the model on weekly volanesorsen and are assessed for response after 3 months of treatment using the decision tree, according to the SmPC stopping rules (which were not a feature of either the APPROACH or APPROACH OLE trials). The decision tree evaluates patients for a reduction in their TGs of ≥25% and absolute TGs <22.6 mmol/L at 3 months. Patients passing the stopping rule enter the long-term Markov for once every 2 weeks maintenance treatment. Those failing enter the Markov for SoC. There is also a Markov to capture patients on weekly dosing over the longer term, but this is only relevant to a scenario that reflects the ITT results of the APPROACH trial (see section 9.6.1). In the base case analysis intended to reflect a clinical pathway in line with the SmPC, no weekly dosing is assumed after the first 3 months (see section 10.1.16).

The long-term Markov model captures immediate and longer-term clinical events that affect FCS patients. The model captures the immediate impact of volanesorsen on TG levels, categorising patients into 3 levels (increasing horizontally in Figure 27B): low-risk (<10 mmol/L), medium-risk (10-22.6 mmol/L) and high risk (≥22.6 mmol/L). Occupancy of these categories is determined by whether the patient is on weekly treatment, every 2 weeks treatment or on SoC and is directly informed by the APPROACH and APPROACH OLE clinical trial data (see section 9.6.1). As the APPROACH protocol did not reflect the posology and monitoring requirements within the SmPC, the efficacy of every 2 weeks dosing is modelled using regression analysis (see section 12.2.1).

The TG health state occupied by patients determines their ongoing risk of acute pancreatitis, with higher TG categories incurring higher risks. AP is modelled as an event as opposed to a distinct health state, due to its short disease course relative to the 3-month model cycle. Modelling AP as an event is similar to the approach used by Faria et al. (2014) to model asthma exacerbations *vs*. everyday asthma symptoms. Risk of acute pancreatitis (AP) increases with higher TG levels but risk is also greatly increased when

patients have a history of AP. Hence the model also captures whether the patient is AP naïve, has had an event sometime in the past, or has recurrent AP (history increasing vertically in Figure 27B), as this has an impact on their ongoing risk of AP in a particular TG category. The absolute risk of AP in each health state is obtained from either the CALIBER observational study, or directly from the APPROACH medical history, depending on the health state. The model captures the effect of volanesorsen on risk of AP using a treatment effect estimated from the available clinical trial data (see section 9.6.1).

Longer-term sequelae of FCS such as chronic pancreatitis, diabetes and mortality, arise as a result of both ultra-high TG levels and the damage caused by AP. Incidence of these sequelae in the model is extrapolated from TG levels and AP history using the available literature and the CALIBER observational study. Diabetes is included as a co-morbidity, with prevalence determined by both the TG category and the patient's AP history, as both higher TG levels and past AP events are known to increase risk (Scherer et al., 2014). Development of chronic pancreatitis (CP), a state where patients have irreversible damage that may result in chronic abdominal pain, exocrine and endocrine dysfunction, is extrapolated from the rate of AP events in each individual health state. The number of past AP events is a major factor determining risk of CP (Sankaran et al., 2015). No treatment effect of volanesorsen is applied directly on risk of developing diabetes or CP; the risk of longer-term sequelae in the model is determined purely by the health state that patients are occupying (representing the combination of daily TG levels and AP history).

In addition to death from natural causes, excess mortality from FCS is estimated using the available literature on the mortality from acute pancreatitis, chronic pancreatitis and diabetes. Volanesorsen is assumed to have a treatment effect on the mortality risk from AP, as risk is much higher in the presence of high TGs (Nawaz et al., 2015) and volanesorsen reduces spiking of TGs to ultra-high levels (see Figure 39 in Appendix 8).

In addition to treatment discontinuation after 3 months for those patients failing the stopping rule, patients can also discontinue volanesorsen at any

point due to lack of adherence to the treatment or monitoring regimen or toxicity issues. Discontinuation is modelled using APPROACH OLE data, which is more representative of the SmPC in terms of posology, monitoring and treatment discontinuation rules relating to platelets. Patients who discontinue volanesorsen go back onto SoC.

The adverse events of volanesorsen are captured while patients are on treatment, including injection site reactions and thrombocytopenia.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table D4 List of model assumptions

Assumption	Rationale
Patients will have received genetic confirmation of FCS independently from and prior to being considered eligible for volanesorsen.	The NHS England genetic testing program, which includes FCS, will be implemented from April 2020, which will likely precede any NICE recommendation for volanesorsen (see section 8.7).
Volanesorsen is assumed to be discontinued in patients if they develop chronic pancreatitis (CP)	There is no evidence for clinical benefit in CP, where patients have sustained irreversible pancreatic damage. Following treatment with volanesorsen, and taking into account the proposed continuation rule, the majority of patients who develop CP will have come from the 22.6+ mmol health states and will already be off treatment. A scenario has been included whereby patients with CP remain on treatment.
The baseline distribution of patients in the SmPC analysis is based on the subgroup of patients in APPROACH	In APPROACH, patients with a history of AP were more likely to have higher TGs at baseline. As volanesorsen is indicated in patients at high risk of AP,

who had a history of AP (Table C8)	the baseline TG distribution is reweighted to be more representative of this patient population. Note that all the patient TG data is still used, it is simply reweighted at model entry.
Distribution of patients across TG health states is conditional on dosing frequency and baseline TGs only.	No significant treatment effect modifiers of response to volanesorsen have been identified other than dosing frequency.
Treatment effect of volanesorsen on TG levels from the APPROACH OLE study, conditional on dose, is assumed to be generalisable to APPROACH patients	No significant treatment effect modifiers of response to volanesorsen have been identified other than dosing frequency.
Other than following implementation of the 3-month stopping rule, patients are at continued risk of discontinuation for other reasons, which is assumed to be at random.	Although discontinuation due to platelet issues on weekly dosing was more likely in patients with lower body weight, this effect is greatly reduced on every 2 weeks dosing (see section 9.9.4) and patients may discontinue for a variety of other reasons.
Other than following implementation of the 3-month stopping rule, patients who discontinue return to the baseline TG distribution of patients on SoC in the following and later cycles.	Following discontinuation, there may be some residual treatment effect in the following cycle. The assumption that patients return immediately to the TG levels on SoC is therefore a conservative assumption.
Only TEAEs experienced by 10% or more patients in the treatment arm were retained in the model.	These were judged to be common (~10%) by Akcea's clinical advisors; lower incidences are likely to be due to random variation.
TEAEs judged as mild in the APPROACH trial were excluded in the	Mild events would be unlikely to impact HRQL or incur a treatment cost.

analysis.	
Model takes a lifetime horizon (up to age 100 years)	FCS is a chronic condition with sequelae that develop over the longer term. Volanesorsen can potentially reduce these long-term sequelae
All-cause mortality is subtracted uniformly from all states in the transition matrices, with the Relative Risk (RR) of death related to health states applied to the all-cause mortality for that state.	The same underlying risk of all-cause mortality is applied to all health states. State-specific differences in mortality are then represented using separate standardised mortality ratios (SMRs) or a RR applied to this risk
Excess risk of mortality due to AP events is assumed to be additional to any health state risks.	AP is an infrequent event with a small acute mortality risk, therefore any SMR or RR applied to health states will likely be reflective of other causes of mortality.
Constant TG transitions across the 3 to 12-month period are assumed to inform health state transitions for the volanesorsen arm in the APPROACH ITT modelling.	The mean TG levels of patients were relatively stable in the 3-month cycles between 3 and 12 months, conditional on dose.
Constant TG transitions across the 0 to 12-month period are assumed to inform health state transitions on SoC in the APPROACH ITT modelling.	The mean TG levels of patients on SoC were relatively stable in the 3-month cycles between 0 and 12 months
The risk of AP stratified by peak TG and AP history from CALIBER is assumed to be generalisable to FCS patients in the 'historical AP' and 'AP naïve' health states.	It was not possible to estimate an absolute risk of AP for patients who have never had an AP event using the APPROACH clinical data or any available FCS natural history data. The same is true for patients who had, experienced AP sometime in the past but not in the 5-year window in which history was captured in APPROACH. For these patients, the only source of

	data to predict absolute risk of AP on SoC is CALIBER.
The risk of AP in the 'recurrent AP' health state is assumed to be the same as the average rate of those patients in APPROACH with an event in the past 5 years.	The assumption has been made that, for those patients in APPROACH who had an AP event in the past 5 years, these were recurrent events and not their first.
Patients on once every 2 weeks dosing are assumed to remain on this dose over their lifetime if they do not discontinue.	The SmPC permits dose escalation in patients after 6-months of treatment *if* platelet counts are in the normal range *and* if their TGs do not reach the desired target. No patients to date in EAMS have uptitrated to weekly dosing and clinician feedback is that uptitration is unlikely (see section 10.1.16). [redacted]
Dose pauses or discontinuations (for the SmPC scenario) are assumed to follow the pattern of treatment-naïve APPROACH OLE patients who reduced dosing frequency to every 2 weeks	The enhanced monitoring and dose adjustment requirements implemented during APPROACH OLE are more generalisable to the SmPC. An option to assume no ongoing discontinuations is provided in the model.
The risk of diabetes increases at higher TG levels and with more frequent AP or in presence of CP.	CALIBER and the literature (Scherer et al., 2014) suggests that both affect risk of diabetes.
The costs and utility decrement of diabetes are halved while receiving volanesorsen	Volanesorsen increases insulin sensitivity by 56% along with markers of glucose control (Digenio et al., 2016) Interventions that control diabetes are known to reduce the complications of diabetes, and their costs and disutilities, particularly in younger patients (Li et al., 2010).

The utility of chronic pancreatitis is equal to the utility of the high-risk TG state for AP-experienced patients, minus a monthly disutility of monthly AP.	No suitable utility values for CP were identified in the literature. Patients with chronic pancreatitis are assumed in the base case not to receive volanesorsen and their TGs will be high, therefore they will be experiencing frequent pancreatic symptoms as well as ongoing chronic symptoms of uncontrolled FCS. Utility in the chronic pancreatitis state was therefore assumed to be the same as that in the high TG state with a history of AP from the vignette study, with an additional monthly utility decrement of AP (of 4-5 days duration).
The chronic pancreatitis health state incurs an incremental utility decrement for presence of diabetes, but not the incremental mortality or costs	Chronic pancreatitis costs and mortality were obtained from the literature, which includes patients who have developed diabetes as part of their CP. However, the utility of CP is an assumption based on a combination of the vignette utilities and disutility of acute pancreatitis, therefore diabetes would be incremental to this
Treatment emergent adverse events (TEAE) are assumed to have their cost and QoL impact within the same cycle	No moderate or severe adverse events lasted more than 3 months in APPROACH.
Platelet monitoring that occurs more frequently than every two weeks will not incur any costs.	Akcea will provide a home-monitoring service, which it is anticipated to be used by the majority of patients. Occasional use of NHS resources for monitoring would have minimal impact on the ICER.

Resource use (excluding that for managing acute pancreatitis, chronic pancreatitis and diabetes) is assumed to be the same in the High-risk and Medium-risk TG health states	No evidence is available to suggest that resource use is different between the medium-risk and high-risk TG levels other than that associated with managing pancreatitis and diabetes. This is likely to be a conservative assumption due to the impact TGs appear to have on patients' day to day quality of life.
HRU other than that associated with platelet monitoring and AEs is determined by TG levels and not by treatment type.	All of volanesorsen's clinical effect is assumed to be achieved via TG - lowering.
Patients on volanesorsen experience the day-to-day utility of the 'Low TGs' vignette state and patients on SoC experience the day-to-day utility of the 'High TGs' vignette state.	The vignette study only stratified health state descriptions into 'high TG' and 'low TG'. At least 50% of patients in APPROACH had TG >22.6 mmol/L at baseline, whereas the majority of patients on volanesorsen have levels substantially below this. The ReFOCUS study demonstrated significant improvements in QoL while on volanesorsen (section 9.6.1).

12.1.6 Define what the model's health states are intended to capture.

As described in Section 6.1, elevated TG levels are associated with an increased risk of AP. Risk has been shown to increase in a dose-response relationship in both in the published literature (Pedersen et al., 2016, Toth et al., 2014) and in the CALIBER study (Akcea data on file, 2018a). TG levels below 10 mmol are associated with a low risk of AP. Risk increases above 10 mmol and becomes particularly high at levels ≥2000 mg/dL (22.7 mmol) (Toth et al., 2014). These published AP risk categories underpinned the choice of TG health states of low risk (<10 mmol), medium (10<22.7 mmol) and high risk (≥22.7 mmol).

Patients who have had prior AP are at increased risk of further AP, with recurrent events increasing the risk of developing CP. The risk of CP has been shown to be greatest in patients with recurrent AP (defined as 2 or more episodes) than those with 1 prior AP, which is greater than that in the general population (Sankaran et al., 2015). Hence the TG states are further stratified by AP history, as the presence of prior AP would be expected to further increase the risk of AP in a patient who already has high TGs. One of the limitations of the Markovian model is that it is memoryless, therefore this feature of FCS cannot be fully explored.

Higher TG states with a history of prior pancreatitis are predicted to have a high risk of developing CP due to the much higher frequency of AP. By inference, there is great potential benefit in not only lowering TG levels in patients who are at high risk of AP, but also in lowering TG levels sufficiently to prevent patients from developing AP in the first place. The model is designed to capture these beneficial aspects of volanesorsen.

The presence of high triglycerides is an independent risk factor for development of type 2 diabetes (Hjellvik et al., 2012), even in the absence of acute pancreatitis. As the pancreas plays a major role in glucose homeostasis, damage to the pancreas following AP is independently thought to contribute to development of diabetes. Patients with AP often develop prediabetes and/or diabetes mellitus (DM) after discharge from hospital and have a greater than twofold increased risk of DM over 5 years (Das et al., 2014). The model therefore captures the increased incidence of DM in the health states conditional on fasting TG levels and history of AP.

Setting aside the risks of pancreatitis and its sequelae, the TG health states also represent different day-to-day HRQL and resource use associated with higher TGs. Patients with FCS have a variety of physical symptoms including generalised abdominal pain, bloating, asthenia, indigestion and fatigue. Cognitive and emotional symptoms include difficulty concentrating, impaired judgement, ‘brain fog’, forgetfulness, depression and anxiety (Davidson et al., 2018). FCS has an impact on patients’ ability to work as well as their family life (see section 7.1). Reduced disease burden was demonstrated in the

ReFOCUS study, where respondents reported that volanesorsen improved overall management of symptoms and reduced interference of FCS with work/school responsibilities (Arca et al., 2018). Reductions in the negative impact of FCS on personal, social, and professional life were also reported.

In a chart review of FCS patients and patients with high triglycerides (HTG) (Akcea data on file, 2018d), HTG patients with higher peak TG levels had higher resource use, including resource unrelated to pancreatitis (FCS patients could not be stratified by peak TG level in this study as all patients had at some point had TGs above 22.7 mmol).

The model TG health states are intended to capture the positive impact of volanesorsen on patients' daily lives and the reduction in healthcare resource utilisation.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below.

Table D5 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Discount of 3.5% for costs	3.5%	As per reference case	NICE guide to the Methods of Technology Appraisal
Discount of 3.5% for outcomes	3.5%	As per reference case.	NICE guide to the Methods of Technology Appraisal
Perspective (NHS/PSS)	NHS	As per NICE reference case – the impact on PSS is not included and not thought to be significant	
Cycle length	3 months	a) Endpoints in APPROACH were captured every 3 months. b) Changes in dosing take at least 3 months for full effect. a 3-month cycle length offers the necessary granularity to account for discontinuation and dose adjustment rates (the latter being relevant to the ITT analysis) as well as health benefits and health care resource use.	APPROACH study
Half-cycle correcton	Included from 3 months onwards	A half-cycle correction was requested by the ERG in the previous submission. To ensure appropriate implementation of the SmPC stopping rule, which has a specified evaluation timepoint at exactly 3 months, the half-cycle correction is only applied after this point.	ERG clarification questions, July 2018
NHS, National Health Service; PSS, Personal Social Services			

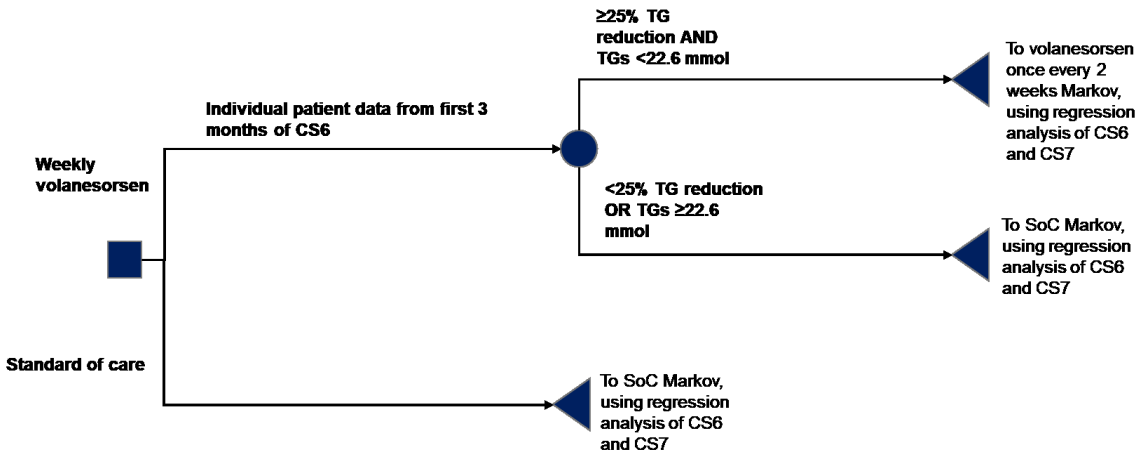
12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

A summary of how the TG data from APPROACH and APPROACH OLE is implemented in the model is shown in Figure 28.

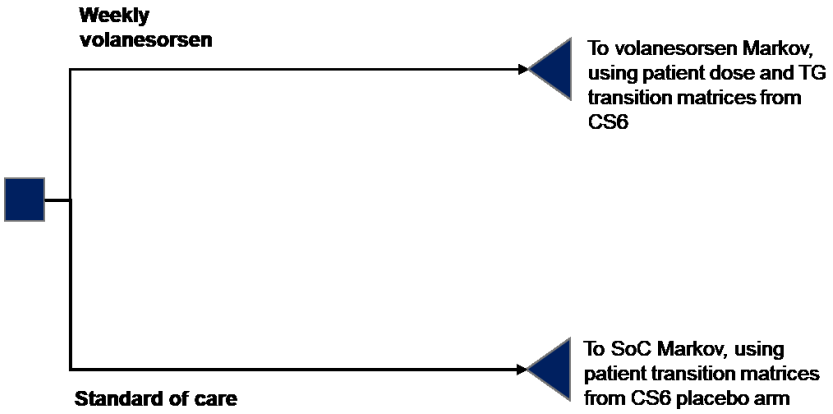
Figure 28 Source of clinical efficacy data in model

A. SmPC base case



Key: CS6 is the APPROACH RCT, whereas CS7 is the APPROACH OLE trial

B. APPROACH ITT scenario



Key: CS6 is the APPROACH RCT, whereas CS7 is the APPROACH OLE trial

The posology in the SmPC recommends initiation on weekly volanesorsen for a period of 3 months, followed by an assessment of response and frequency reduction to every 2 weeks dosing in responders. The APPROACH trial is not generalisable to the SmPC posology as patients were initiated on weekly dose and the ability to reduce dosing frequency was not implemented until relatively late in the trial. Furthermore, the trial protocol was paused and amended due

to safety signals, which makes interpreting the trial data more complex. In APPROACH OLE, treatment-naïve patients were also initiated on weekly dosing and frequency reduction was only implemented in patients experiencing AEs, notably platelet reduction.

In line with NICE's request during the decision problem meeting, the economic model is set up to present both the SmPC analysis (base case) and the APPROACH ITT analysis (scenario). The scenarios differ in that health state allocation under the ITT analysis is determined purely by patient transition matrices extracted directly from APPROACH (Figure 28A), whereas in the SmPC analysis the first 3 months include a response assessment, and health state allocation thereafter is informed by regression analysis using a Generalised Linear Mixed Model (GLMM) that, while not informed by the ITT data, attempts to maintain randomisation (Figure 28B). TG health state occupancy in the SmPC analysis is determined by the mean TG value of the cohort, whereas in the ITT analysis it is determined by the proportions of patients in each TG health state over time in APPROACH.

Both analyses include two different dosing regimens, which have different effects on TGs, therefore the model includes one set of transition matrices that determines what dose patients are on during a particular cycle, while another set informs what TG health state patients are in during a particular cycle, conditional on dose. Examples of these two interacting transition matrices is provided in Figure 29 below. Note that the 'Stop' state in Figure 29A is only used in the first cycle of the SmPC analysis for the purposes of the stopping rule. Discontinuation for all other reasons is captured directly within the Markov traces using survival curves.

Figure 29 Example model transition matrices

A. Example dose transition matrix

		3 months			
		Full dose	**Reduced Dose**	**Stop**	
Baseline	**Full dose**	0.00	0.94	0.06	1.00
	Reduced Dose	0.00	0.94	0.06	1.00
	Stop	0.00	0.00	1.00	1.00

B. Example TG transition matrix

0 to 3 months		tgcat_3m			
		<10	**10-22.6**	**>22.6**	**Total**
tgcat_base	**<10**	1.00	0.00	0.00	1.00
	10-22.6	0.93	0.07	0.00	1.00
	>22.6	0.67	0.27	0.07	1.00

The high discontinuation rate within a short follow-up time in APPROACH introduces bias into the estimates of treatment effect of volanesorsen on rate of AP, and treatment effect is better estimated using the APPROACH OLE data, which has a longer follow-up time and includes a significant number of patients who reduced dosing frequency to every 2 weeks dosing. In a *post-hoc* analysis carried out for the economic model, the AP rate per patient year of APPROACH OLE patients was calculated from their 5-year medical history (77 events in 340 patient-years; 0.226 per patient year). The treatment effect of volanesorsen on rate of AP (expressed as a rate ratio) was estimated by dividing the AP rate for these patients while on volanesorsen in APPPROACH OLE (0.0297, section 9.6.1, CSR Table 14.3.2.adhoc2) by their 0.226 medical history rate to yield a rate ratio of 0.13. This treatment effect is applied to the absolute risk of AP on SoC (informed by natural history, see section 12.2.3) in all health states to obtain a risk of AP for a patient on volanesorsen. Note that this will almost certainly underestimate the treatment effect of volanesorsen on AP as 38% of patients had missing AP history (see Table C10).

Modelling of SmPC base case

Dose transition matrices

In the model patients can move both between dose categories and between TG categories conditional on the dose received in the previous quarter. To capture dose changes, patients were categorised into one of the three mutually exclusive dose categories in each quarter, as per Figure 29A. Only discontinuation due to the stopping rule is implemented via the dose matrix in the first 3 months. All-cause discontinuation is captured separately in the Markov trace using survival curves. In the SmPC analysis, all patients are assumed to be on weekly dosing in the first quarter, and thereafter on either every 2 weeks dosing or on standard of care. Weekly dosing is not modelled after the first 3 months, as both data from EAMS and clinician feedback suggest that weekly maintenance dosing is unlikely to be implemented in the UK (see section 10.1.16).

Dose pauses were not categorised into a separate dosing category and were instead applied as a dose intensity reduction to drug costs. To calculate the dose intensity of every 2 weeks dosing, the average number of missed doses per patient year of exposure for patients who were on 3 or more months of every 2 weeks dosing was obtained from APPROACH OLE treatment naïve patients (the platelet monitoring rules in this cohort being closest to the SmPC) and divided by 26. For the dose intensity during the first 3 months of weekly therapy, the average number of missed doses during the first 3 months of weekly dosing was obtained from APPROACH OLE treatment naïve patients and divided by 13.

Starting population

During the first 3 months, response to volanesorsen is captured via an individual patient simulation in the '*Start and stop populations*' sheet. In this sheet, the eligible starting population is identified, as well as the population passing or failing the 3-month stopping rule.

In APPROACH, patients with a history of AP tended to have higher TG levels at baseline. However, when considering only those patients with a history of AP, the annual rate of AP was if anything *higher* in those patients with lower TGs at baseline. This observation may be spurious and may simply reflect the very low patient numbers in APPROACH. Alternative explanations may be that (1) patients with a history of frequent AP may go to greater efforts to control their TGs (2) patients who have had many events in the past are at higher risk of events in the future, regardless of TG levels. The model assumes that patients with higher TGs are more likely to have a history of AP, but that the 5-year rate of AP, conditional on having a history of AP, is equal across the three TG baseline categories.

The model is therefore capable of distributing the starting population via the '*Controls'* sheet as follows:

- By TG category (it is possible to prevent a particular baseline category from starting altogether)
- By AP history. Patients with higher TGs at baseline are assumed to be more likely to have a history of AP. However, conditional on having a history of AP, the frequency of events in the past 5 years is assumed to be equal across baseline TG categories.

Stratifying the patient population in the model using the '*Controls*' sheet has two effects:

- Individual patients are *flagged as starting treatment* based on whether their baseline TG category is eligible (as AP history is not a treatment effect modifier, this ensures that the maximum number of patients from APPROACH are included in the analysis regardless of their AP history)
- The proportion of patients in each starting TG category in the Markov is *reweighted* according to whether their baseline TG category is eligible, whether they have a history of AP, and minimum AP frequency (no minimum, ≥1 APs or ≥2 APs in the past 5 years)

Volanesorsen is indicated in patients with genetically confirmed FCS at high risk of acute pancreatitis. Akcea proposes that only patients with a history of AP are initiated on volanesorsen, as these patients are at high risk of further AP. Low TG measurements at a particular time does not necessarily reflect consistently low TGs and even patients with baseline measurements <10 mmol readily see their TGs spike to high levels.

The base case starting population is therefore any patient who has experienced an AP event in the past.

3-month response assessment

In the base case, all patients in APPROACH are included in the analysis as all TG categories are eligible. In the second cycle of the model (3-month decision tree phase), patients who receive volanesorsen are allocated to TG health states according to their 3-month TG endpoints captured in the APPROACH trial (the average of the Week 12 and Week 13 assessments). At this point, patients are individually assessed for response ('*Start and stop populations'* sheet) in accordance with the SmPC to determine whether they remain on maintenance treatment.

The SmPC stopping rule states that "*treatment should be discontinued in patients with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L after 3 months on volanesorsen 285 mg weekly*." In the base case, any patient in APPROACH who did not achieve a 25% reduction and absolute levels below 22.6 mmol at 3 months is assumed to discontinue treatment. All other patients are assumed to remain on treatment but down-titrate to every 2 weeks dosing.

The transition from baseline to 3-months is implemented in the model as follows:

- A TG transition matrix captures the change in TG category from baseline to month 3 (as per the example in Figure 29B).

- A dose transition matrix captures proportions of patients who continue to every 2 weeks treatment or stop treatment, conditional on starting on weekly dose and passing or failing the stopping rule (as per the example in Figure 29A). The patients then proceed into their respective Markov trace (every 2 weeks dosing or off treatment) thereafter.

Ongoing response to once every 2 weeks treatment

Neither the posology in APPROACH nor that in APPROACH OLE are generalisable to the posology in the SmPC, which recommends 3 months of weekly dosing followed by every 2 weeks dosing. APPROACH OLE permits down-titration to every 2 weeks dosing due to AEs (namely low platelet levels), but only 14 patients conformed closely to the SmPC posology (initiated treatment on weekly and then reduced every 2 weeks within 3 months for platelet count <140,000/mm^3 or at 3 months ±2 weeks).

In order to allocate APPROACH patients who passed the stopping rule to a health state on every 2 weeks dosing (from 6 months), the patients are linked with their respective predictions of TG value on every 2 weeks dosing from a post-hoc individual patient regression analysis (GLMM, see Appendix 8). The same is done for patients who fail the stopping rule (and subsequently discontinue), except that these patients are linked with their predictions of TG value off treatment. Mean TG values for each cohort of patients either continuing or stopping treatment are calculated, stratified by the patients' TGs at baseline (found in the '*GLMM TG model'* sheet), Figure 30.

Figure 30 Predicted mean TG values (mmol/L) by dose and by baseline TG category from the GLMM

A. Patients who pass the stopping rule (Every 2 weeks is used going forward)

	<10mmol	10-22.6	>=22.6
Untreated	6	16	34
Every 2 weeks	**2.8**	**7.8**	**17.0**
Every week	1.8	4.9	10.7

B. Patients who fail the stopping rule (Untreated is used in next cycle)

	<10mmol	10-22.6	>=22.6
Untreated	**0**	**0**	**47**
Every 2 weeks	0.0	0.0	26.4
Every week	0.0	0.0	14.6

Key: rows denote which dose the prediction represents; columns denote the baseline TG category of the predictions

For patients passing the stopping rule, the mean TG per baseline category on every 2 weeks dosing in Figure 30A is re-weighted by the proportions of patients in each baseline category who pass the stopping rule in Figure 31A (in the *'TG distributions'* sheet) This produces an estimate of mean TGs on every 2 weeks dosing for the cohort and its respective TG category as per Figure 31C.

Figure 31 Baseline TG distributions of patients passing/failing the 3-month stopping rule

A. For patients who pass the stopping rule

	< 10	10 > x < 22.6	> 22.6	Total
Baseline cats	4.0%	39.2%	50.4%	93.6%

B. For patients who fail the stopping rule

	< 10	0 > x < 22.	> 22.6	Total
Baseline cats	0.0%	2.8%	3.6%	6.4%

C. Re-weighted mean TGs for patients who pass the stopping rule

	Pass	TG cat
No Treatment	25.3	2
Every Two Weeks	12.6	1
Every Week	7.9	0

Key: TG cats are 0, <10 mmol, 1,10-22.6 mmol and 2, ≥22.6 mmol.

D. Re-weighted mean TGs for patients who fail the stopping rule

	Fail	TG cat
No Treatment	26.1	2
Every Two Weeks	13.0	1
Every Week	8.2	0

Key: TG cats are 0, <10 mmol, 1,10-22.6 mmol and 2, ≥22.6 mmol.

Patients who pass the stopping rule are allocated to the TG health state associated with this mean TG value on every 2 weeks dosing (Figure 31C) from the following cycle (month 6) until they discontinue treatment.

Patients who fail the stopping rule are handled using the same methodology, but are allocated to the mean TG health state for No Treatment (Figure 31D) in the following cycle only (months 3-6), as discontinuation in that cycle is assumed to be dominated by patients discontinuing due to the stopping rule.

Treatment discontinuation for reasons other than the month 3 SmPC stopping rule

Aside from the 3-month stopping rule, patients are assumed to discontinue at random in the model for a variety of reasons including AEs, tolerability and unwillingness to comply with the treatment and monitoring regimen. Discontinuing patients are allocated to the same TG health states as the SoC arm during all subsequent model cycles (see below).

Health state allocation for the SoC arm

For the SoC arm, patients in APPROACH who met the starting rules at baseline are linked with their respective predictions of TG value when off treatment from the *post-hoc* individual patient regression analysis. The mean predicted TG value stratified by baseline TG category is calculated, then reweighted by the proportion of patients in each TG category who initiated treatment to calculate the mean TG value when off treatment for the cohort.

In general, in the SmPC modelling, the TG and AP health states to which patients are allocated in the model drive ongoing costs and HRQL. Allocating

costs and utilities based on a mean score for the cohort (as opposed to using a distribution, as per the ITT) is a method that has been accepted in other models submitted to NICE, notably in biologics for the treatment of psoriasis where models are frequently based on the York assessment group model used in TA103. In psoriasis, patients begin with a baseline Psoriasis Area and Severity Index (PASI) score, are assessed for response after an initial trial period, and a new lower mean PASI score is calculated in responders from which costs and utilities are derived. Unlike in psoriasis, no algorithm is available in FCS to calculate costs and utilities, and costs and utilities are derived from the TG categories.

Retention on treatment

Aside from the 3-month stopping rule, patients are assumed to discontinue at random in the model for a variety of reasons. The rate of all-cause discontinuation was captured by fitting parametric survival functions to the time on treatment of volanesorsen-naïve mixed dose patients in APPROACH OLE (CS7), n = 32. ‘Mixed dose’ patients denote patients who reduced dosing frequency to every 2 weeks dosing during CS7. Only this population was included, as the posology, platelet monitoring protocol and platelet-related stopping rules are more generalisable to those in the SmPC than those in APPROACH (CS6). Patients who completed treatment or rolled over into early access programs were censored.

Fitted survival curves included exponential, Weibull, Gompertz, lognormal, loglogistic and generalised gamma. The exponential, Weibull, lognormal and loglogistic were selected for inclusion in the model based on goodness of fit statistics (Table D6) and visual fit (Figure 32). Together, these different curve types also largely captured the range in longer-term retention observed across the range of survival curves. The lognormal curve was selected in the base case, as this is a curve with a long tail that best represents a proportion of patients remaining on treatment over the longer term.

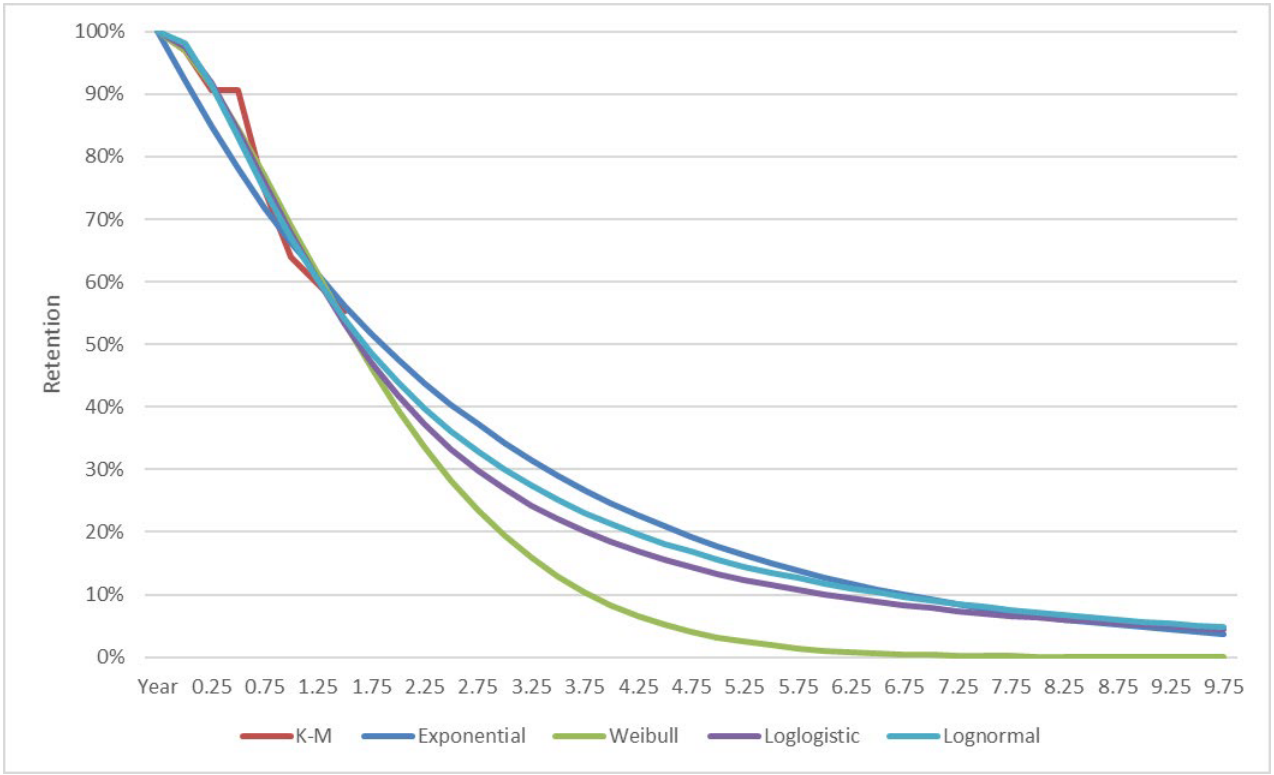
To date, discontinuation in EAMS has been low (1 patient) and for medical reasons unrelated to treatment with volanesorsen and it is possible that

discontinuation in EAMS might be lower than observed in the approach ole study. To provide a simple comparison between the discontinuation observed in APPROACH OLE and a patient who is adherent over the longer term, a curve assuming no treatment discontinuation has also been included as a scenario.

Table D6 Goodness of fit statistics for parametric survival functions

	AIC	BIC
exponential	66.60	68.07
Weibull	65.73	68.66
Gompertz	66.93	69.87
lognormal	65.27	68.21
loglogistic	65.36	68.29
generalised gamma	67.25	71.65

Figure 32 Parametric survival functions of retention in SmPC analysis



12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

TG health state occupancy

SmPC base case

The regression analysis informing TG health state allocation on every 2 weeks dosing was carried out on TG observations collected during up to 3 years of follow-up. It therefore intrinsically captures any effect of diet or dose pauses on steady state TG levels over the longer term. The estimated mean TG value on every 2 weeks treatment for patients passing the stopping rule was 12.1 mmol/L. For patients to change to a worse health state, mean TG values would need to increase to above 22.6 mmol, which is not supported by the available clinical data (Table C17), which suggests a sustained % reduction from baseline of above 40% over the longer term. The TG health state distribution for patients retained on every 2 weeks dosing is therefore assumed to remain constant over the model time horizon.

ITT scenario

In the ITT analysis, patients in the volanesorsen arm are assumed to follow the average of the grouped 4 to 12-month TG category transitions from APPROACH, conditional on dose category (as described in Section 12.2.1) for the remainder of the model time horizon. Patients in the SoC are assumed to follow the average of the grouped baseline to month 12 transitions from APPROACH.

Long-term dosing and retention on treatment

SmPC base case

In the base case it is assumed that patients on once every 2 weeks dosing continue on this dose unless they discontinue at random according to the lognormal survival curve fitted to the APPROACH OLE data. This curve has a

longer tail, which would support a population of patients that remains on longer term treatment as observed for other chronic disease therapies.

ITT analysis

In the ITT analysis, patient dose transitions from 4-12 months in APPROACH were grouped and extrapolated to reflect a constant probability of dose frequency reduction to every 2 weeks dosing. Patients in the ITT scenario are assumed to discontinue at random according to the lognormal survival curve fitted to the APPROACH data

Given the many timepoints and dosing matrices, the transition matrices are too numerous to be provided within the submission. These can be found within the model sheets *'TG transitions'* and '*Dose transitions*.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

APPROACH and APPROACH OLE's primary endpoint was % change in fasting TG levels from baseline to 3 months. Data on AP are also reported. Patients QoL with FCS is driven by the more tangible endpoints of AP, CP, diabetes as well as brain fog, social isolation and worry and anxiety. As such, the model has to link evidence from the trial (TG level and AP) to CP and diabetes. Because the AP events in the trials are very few we also substantiated trial AP evidence with evidence from the literature. We consider brain fog, social isolation and the mental health consequences of the disease to be addressed in the utility measures derived from the vignette study.

Where possible TG or AP evidence from the trial was linked to CP and diabetes via the literature. Because of insufficient data in the literature Akcea also commissioned a retrospective analysis of observational data using the CALIBER database.

CALIBER Study

CALIBER contains linked electronic health records in England between the Clinical Practice Research Datalink (CPRD - primary care data, including records for patient demographics, diagnoses, clinical biomarkers, prescribed drugs, procedures), Hospital Episode Statistics (HES - hospital admissions including records for diagnoses and procedures) and Office for National Statistics (ONS - cause specific cause of death, and patient level deprivation quintiles). The CALIBER 1997-2016 data used for the analysis included ~1.8million patients with at least 1 triglyceride (TG) record in CPRD.

In the CALIBER analysis cohorts were stratified by highest TG level and plots of cumulative (first) incidence of AP, CP and diabetes over time obtained (Akcea data on file, 2018a).

AP outcomes

Increasing levels of TGs lead to increased risk of AP via a causal dose-response mechanism (Pedersen et al., 2016, Toth et al., 2014). The CALIBER study supports this finding with a clear dose response relationship seen for the three categories <10mmol/L, 10-20mmol/L and >20mmol/L, [redacted],. (The study looked at smaller 5mmol/L increments, but patient numbers for the higher TG levels would make these narrower categories more uncertain therefore the three categories above are used).

Source: Akcea data on file, 2018a

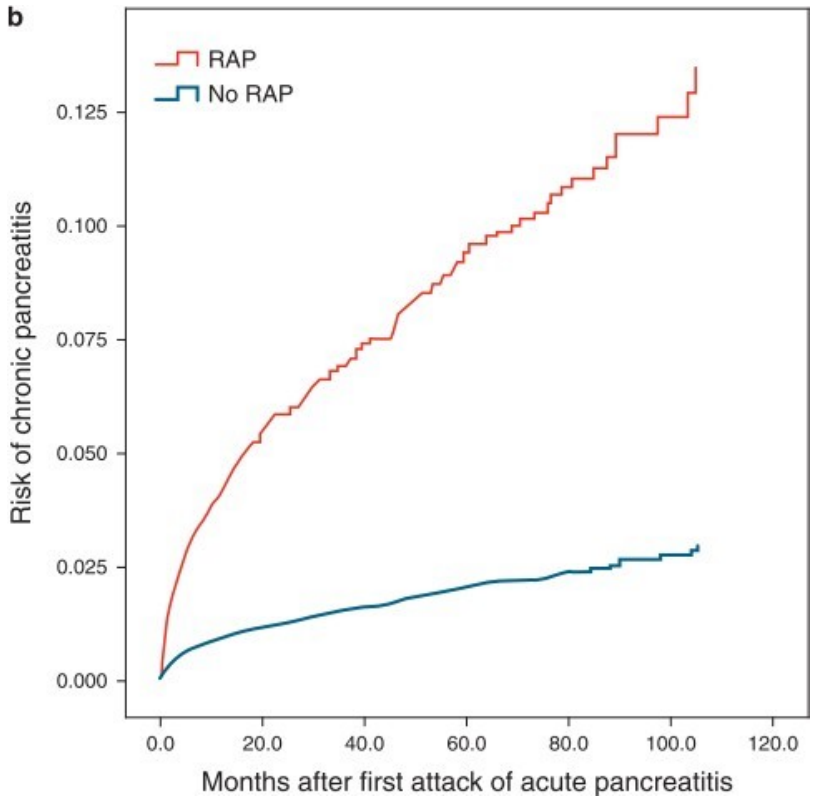
CP outcomes

CP is known to be more common with higher TG levels (Hjellvik et al., 2012) and following AP events (Das et al., 2014, Sankaran et al., 2015).

In the model frequency of CP is conditional on the incidence of AP based on evidence from the literature (Yadav et al., 2012). Therefore, probability of transition to CP in the model is conditional on the incidence of AP in each health state according to the time to CP data reported by Yadav et al. They report time to development of CP following the first AP event and following recurrent AP (Figure 34). Probabilities were derived from the 100-week timepoint assuming a constant risk. The probability following the first AP event was applied to the AP rates in the AP naïve health states, and the probability following recurrent AP was applied to the AP rates in the AP experienced health states. However, the hazard rate of the curves in Yadav notably decreased over time, and using the probabilities predicted only a 16%

maximum prevalence of CP in the model. The model was therefore calibrated so that the maximum prevalence was ~60%, which represents the peak prevalence of CP in FCS estimated by the clinicians in the clinical expert survey (Appendix 7). Given the uncertainty, this calibration is explored in a sensitivity analysis (see section 12.4.2).

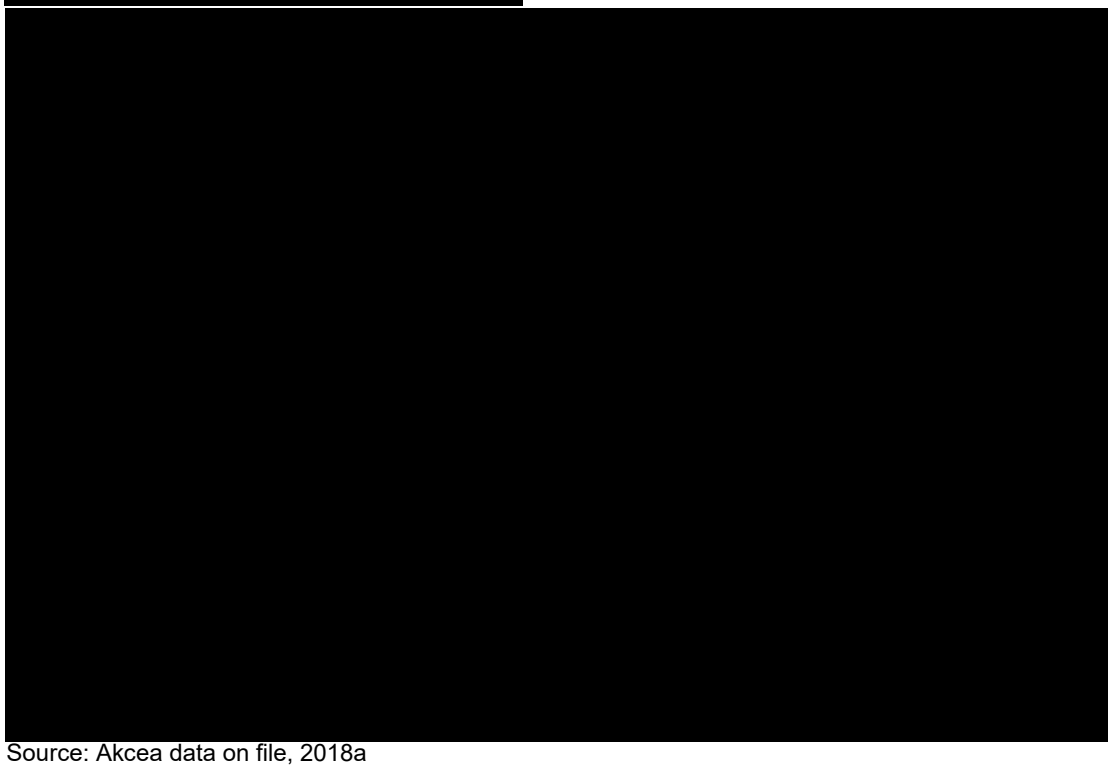
Figure 34 Yadav et al. figure 3, time to development of CP



Key: RAP. Recurrent acute pancreatitis

The CALIBER data provides supporting evidence for the association of CP with elevated TG levels, see [redacted]

[redacted]



Source: Akcea data on file, 2018a

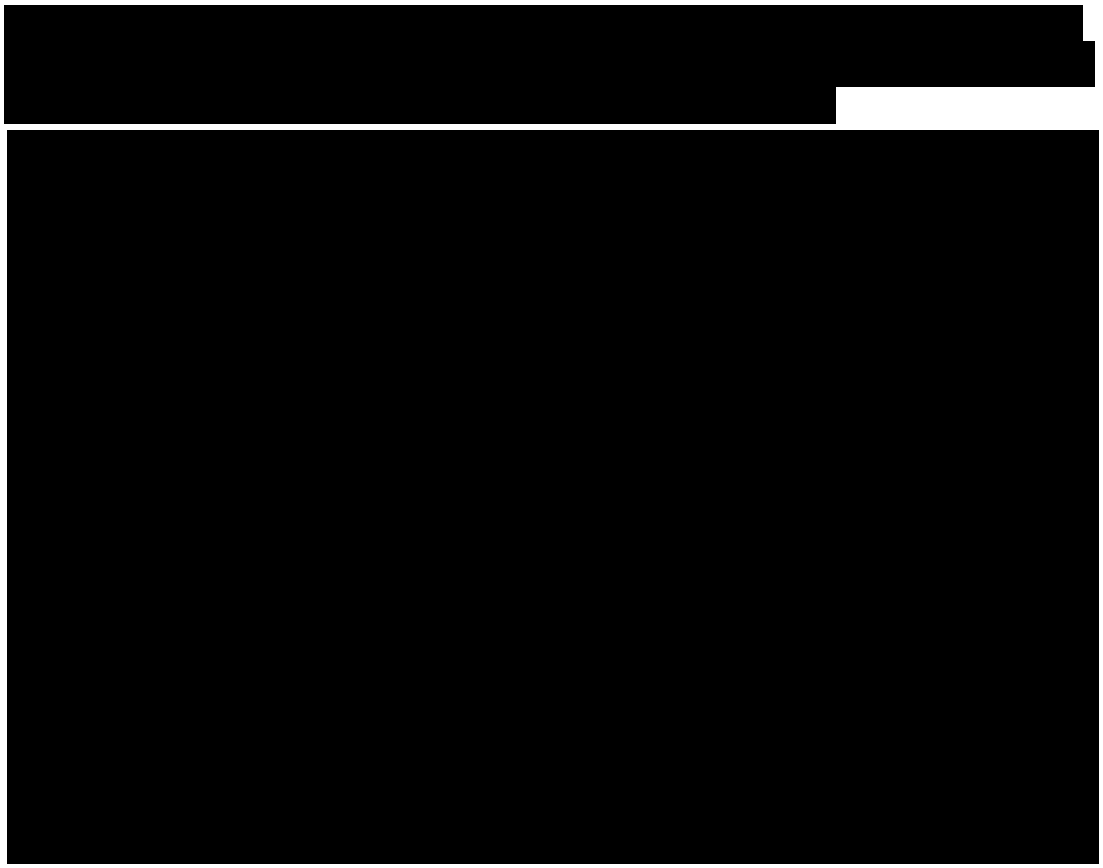
Further analysis

To inform the incidences of AP and diabetes in selected health states, accelerated failure time (AFT) models were fitted to the CALIBER data including covariates for history of AP (binary variable), highest TG level (categorical, using the TG categories in the health states) and interaction terms for TG level * history of AP.

The coefficients from the AFT models were used to predict the incidence of AP in the AP naïve and historical AP health states only (as 5-year medical history from APPROACH was available for the 'recurrent AP' health states). The coefficients from the AFT models were used to predict the incidence of diabetes in all model health states. Due to Akcea not owning the CALIBER data, only constant AFT models could be fitted and used in the model. While this is a limitation, assuming a constant AFT was appropriate given the possibility for movement between health states over time and the Markovian memory limitation.

Diabetes

The Kaplan-Meier plot for the association between TG and diabetes is shown in Figure 36.



Source: Akcea data on file, 2018a

As the diabetes event rate generated by the AFT model resulted in implausibly high levels of diabetes in the model, the prevalence in each health state was capped based on the available literature (Scherer et al., 2014, Das et al., 2014, Fortson et al., 1995). In the AP naive health states, prevalence was capped at 5.2%, 14.6% and 20.0% for low risk, medium risk and high-risk TGs respectively (20% is an assumption as no data was available for patients with TG>22.6 mmol). In the historical AP health states, prevalence was capped at 5.2%, 14.6% and 23.0% for low risk, medium risk and high-risk TGs respectively. In the recurrent AP health states, prevalence was capped at 5.2%, 14.6% and 72.0% for low risk, medium risk and high-risk TGs respectively. The cap was set at 80% for CP (NICE, 2018b).

Linking of data to final outcomes for the risk of clinical events is summarised in Table D7 below.

Table D7 Linking of TG levels to risk of clinical events

Health state	Outcome	Source of link
AP-naïve, low-risk TG	Risk of AP	CALIBER regressions, highest TG <10 mmol without a history of AP
	Risk of CP	Yadav et al., 2012, time from first attack (no RAP). Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG <10 mmol without a history of AP. Capped at 5.2% prevalence
AP-naïve, medium-risk TG	Risk of AP	CALIBER regressions, highest TG 10-22.7 mmol without a history of AP
	Risk of CP	Yadav et al., 2012, time from first attack (no RAP). Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG 10-22.7 mmol without a history of AP. Capped at 14.6% prevalence
AP-naïve, high-risk TG	Risk of AP	CALIBER regressions, highest TG ≥22.7 mmol

		without a history of AP
	Risk of CP	Yadav et al., 2012, time from first attack (no RAP). Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG ≥22.7 mmol without a history of AP. Capped at 20% prevalence
Historical AP, low-risk TG	Risk of AP	CALIBER regressions, highest TG <10 mmol with a history of AP
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG <10 mmol with a history of AP. Capped at 5.2% prevalence
Historical AP, medium-risk TG	Risk of AP	CALIBER regressions, highest TG 10-22.7 mmol with a history of AP
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG 10-22.7 mmol with a history of AP.

		Capped at 14.6% prevalence
Historical AP, high-risk TG	Risk of AP	CALIBER regressions, highest TG ≥22.7 mmol with a history of AP
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event rate in this health state
	Risk of diabetes	CALIBER regressions, highest TG ≥22.7 mmol with a history of AP. Capped at 23% prevalence
Recurrent AP, low-risk TG	Risk of AP	The event rate of patients in APPROACH with a history of 1 or more events in 5 years (2 or more events if this population is selected)
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event in this health state
	Risk of diabetes	CALIBER regressions, highest TG <10 mmol with a history of AP. Capped at 5.2% prevalence
Recurrent AP, medium-risk TG	Risk of AP	The event rate of patients in APPROACH with a history of 1 or more events in 5 years (2 or

		more events if this population is selected)
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event in this health state
	Risk of diabetes	CALIBER regressions, highest TG 10-22.7 mmol with a history of AP. Capped at 14.6% prevalence
Recurrent AP, high-risk TG	Risk of AP	The event rate of patients in APPROACH with a history of 1 or more events in 5 years (2 or more events if this population is selected)
	Risk of CP	Yadav et al., 2012, time from recurrent attack, Conditional on AP event in this health state
	Risk of diabetes	CALIBER regressions, highest TG ≥22.7 mmol with a history of AP. Capped at 72% prevalence

Health states were survival adjusted for the mortality from CP and diabetes. These were obtained from the literature, with parameters and sources described in Table D8. The mortality risk associated with AP while on volanesorsen was assumed to be 17% of that off treatment, as high TGs

increase severity of pancreatitis and the risk of death (Nawaz et al., 2015, Wang et al., 2016). The majority of AP events experienced by patients while on treatment in APPROACH and APPROACH OLE have been mild, with only 1 event of moderate severity (*post-hoc* analysis of APPROACH OLE AP events for economic evaluation). This is supported by the longer-term follow up data of patients who received Glybera (Gaudet et al., 2016b).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The APPROACH trial is the only trial that can provide adverse events (AEs) for both arms in FCS as APPROACH OLE was a single-arm study. Use of AEs from the APPROACH study is hampered by the fact that the posology and monitoring rules were not generalisable to the SmPC. Therefore, for the SmPC analysis AE frequency for volanesorsen was sourced from the APPROACH OLE study. As AEs were sourced from the entire study population, this includes AEs experienced by patients on long-term weekly dosing and thus may overestimate AE frequency.

The model includes only moderate to severe AEs affecting >10% of patients and assessed as being treatment-related. Mild events are assumed not to incur any cost or disutility and are not included, the exception being platelet lowering where counts remained above $50x10^9$/L, as this may incur some communication with a clinician. There are no AEs included in the comparator arm.

In the SmPC analysis, only injection site reactions (ISRs) and thrombocytopenia met these criteria. For the ISRs, the number of events per patient year of exposure was converted to a quarterly rate for the model (Table 14.3.1.3.6b APPROACH OLE interim analysis, data cut off 28 Feb 2019). For platelet lowering where platelet counts were >50 x 10^9/L the number of events per patient year of exposure was converted to a quarterly rate. For thrombocytopenia where platelet counts were <50 x 10^9/L, the number of events per patient year of exposure was converted to a quarterly rate and then a probability, as these can only be experienced once by a

patient on volanesorsen due to the requirement to discontinue treatment (Table 14.3.4.1.8a APPROACH OLE interim analysis, data cut off 28 Feb 2019).

Note that in the SmPC analysis, adverse event data was obtained from the entire APPROACH OLE cohort (for the ISRs, n = 68) or, for thrombocytopenia, from any patient that had platelet levels >140 x 10^9 at baseline (n = 50, a starting requirement in the SmPC). Thus, event rates include patients on weekly dosing and may be overestimated. No analysis was available for every 2 weeks dosing other than that reported in Section 9.9.4 (which reported lower thrombocytopenia), therefore all rates and probabilities for the SmPC analysis were halved. Although a strong assumption, the model results are not sensitive to AEs. We also present an 'EAMS scenario' in which we anticipate, under every 2 weeks dosing and regular platelet monitoring, no patients will experience severe thrombocytopenia.

In the APPROACH ITT analysis, the only moderate to severe adverse events affecting >10% of patients were injection-site reactions (21% of patients) and fatigue (12% of patients).

Event rate for the ITT scenario was estimated in a *post-hoc* analysis for the economic evaluation. The event rate for the patients experiencing fatigue and injection-site reactions was calculated by dividing the number of events experienced by each patient by their exposure time. The annual event rates were summarised, and the means applied to % of patients experiencing the event in the model, adjusted to the 3-month cycle time. The duration of AEs was determined from individual patient reports contained within the appendix of the CSR.

For thrombocytopenia, the event rate for all patients was calculated by dividing the number of relevant grade events experienced by each patient by their exposure time and converted to quarterly rates. For thrombocytopenia where platelet counts were <50x10^9/L, the event rates were converted to cycle probabilities. The duration of thrombocytopenia was calculated as the

number of days between the last normal platelet count and the next normal platelet count. A normal platelet count was defined as 140 x 10^9/L or above, as per the SmPC.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

None of the parameters used in the model were obtained via expert elicitation. All were obtained either from the APPROACH trial, the published literature, or the CALIBER study. Agreement on the general model structure and applicability of parameters regarding impact of TGs on incidence of AP, CP and diabetes was sought via an advisory board. Here the model structure was presented along with evidence from the literature used to inform the model (see Section 12.7 for further details).

The clinical expert survey described earlier in Section 10.1.10 and summarised in Appendix 7 was used to explore a number of model assumptions and parameters. Specifically, clinical experts were asked to comment on the HRQL impact and utility estimate for patients with chronic pancreatitis, the symptomatology and resource use profile of patients with CP and the risk of CP for patients with FCS. Model assumptions or parameters were not derived directly from the survey. Rather the survey was used to check assumptions where these had been derived from the literature or real-world evidence.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided below.

Where no confidence interval has been provided, no uncertainty values were available. Where that variable has been included in the probabilistic sensitivity analysis (which included the vast majority of parameters) a standard error of 10% of the mean has been assumed.

Table D8 Summary of variables applied in the cost-effectiveness model

Variable	Value	Range or 95% CI (distribution)	Source
Age	41 years		EAMS registry
% male	45.50%	N/A	APPROACH study
Cost of volanesorsen	[redacted]	N/A	Akcea
Number of missed doses in the first 3 months of weekly dosing (due to dose frequency reduction/pauses)	[redacted]	[redacted]	APPROACH OLE study treatment naïve subgroup, *post-hoc* analysis
Number of missed doses on every 2 weeks dosing (due to pauses) for patients with >3 months of every 2 weeks dosing exposure	[redacted]	[redacted]	APPROACH OLE study treatment naïve subgroup, post-hoc analysis
Relative risk of mortality with chronic pancreatitis	5.83	(4.21, 8.09)	Nojgaard et al., 2011
Probability of death with acute pancreatitis	4.78%	(2.5%, 7.74%)	Gaudet et al., 2016a
Relative risk of mortality with diabetes	1.28	(1.27, 1.29)	NHS Digital, 2017
Relative risk of mortality from AP with low TGs vs high TGs	0.17	(0.02, 1.34)	Wang et al., 2016
Cycle probability of acute pancreatitis when off treatment			
Low risk TG AP naïve, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP naïve)
Medium risk TG AP naïve, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP naïve)

High risk TG AP naïve, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP naïve)
Low risk TG historical AP, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP experienced)
Medium risk TG historical AP, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP experienced)
High risk TG historical AP, risk of AP event	[redacted]	N/A	AFT model for time to first pancreatitis fitted to CALIBER data (AP experienced)
Low risk TG recurrent AP, risk of AP event	[redacted]	[redacted]	APPROACH historical 5-year AP rate
Medium risk TG recurrent AP, risk of AP event	[redacted]	[redacted]	APPROACH historical 5-year AP rate
High risk TG recurrent AP, risk of AP event	[redacted]	[redacted]	APPROACH historical 5-year AP rate
Probability of transitioning to chronic pancreatitis after 100 weeks (conditional on acute pancreatitis event)			
Probability of chronic pancreatitis after first AP	2.5%	(2.1%, 2.9%)	2.5% prevalence after 100 weeks in 6010 patients. Yadav et al., 2012
Probability of chronic pancreatitis after recurrent AP	12.5%	(11.0%, 14.1%)	12.5% prevalence after 100 weeks in 1752 patients. Yadav et al., 2012
Treatment effect of volanesorsen on incidence of acute pancreatitis			
Treatment effect on incidence of AP, low risk TG states	[redacted]	[redacted]	Rate ratio of adjudicated medical history AP rate in CS7 vs. rate on treatment
Treatment effect on incidence of AP, medium to high-risk TG states	[redacted]	[redacted]	Rate ratio of the rate of AP while on treatment in CS7 vs. their recorded medical history AP rate
Annual Incidence of diabetes (lambda from AFT model			

Lambda for diabetes in low risk TG AP naïve	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in ledium risk TG AP naïve	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in high risk TG AP naïve	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in low risk TG historical AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in medium risk TG historical AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in high risk TG historical AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in low risk TG recurrent AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in medium risk TG recurrent AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in high risk TG recurrent AP	[redacted]	N/A	AFT model for time to first diagnosis of type 2 diabetes fitted to CALIBER data
Lambda for diabetes in chronic pancreatitis	[redacted]	N/A	Assumed the same as high risk recurrent AP state
HRU per year (regardless of whether on volanesorsen or not)			
All low risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in ‘Normal TG’ cohort from CALIBER (see section 12.3.2).

Specialist visit	[redacted]	[redacted]	Rates of resource use in 'Normal TG' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Rates of resource use in 'Normal TG' cohort from CALIBER (see section 12.3.2).
All medium risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Specialist visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
All high-risk TG states - CALIBER data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
GP visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Specialist visit	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption

General hospital admission	[redacted]	[redacted]	Rates of resource use in 'FCS-like' cohort from CALIBER (see section 12.3.2).
All low risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	0		None assumed, as per the HTG patients with peak TG<10mmol, Manchester study
Specialist visit	2.41	(1.66, 3.16)	Assumes only routine visits, as the HTG patients with peak TG<10mmol had no urgent visits, Manchester study
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	[redacted]	[redacted]	Assumes the rate of low TG patients in CALIBER
A&E visits	0		None assumed, as per the HTG patients with peak TG<10mmol, Manchester study
All medium risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	0.07	(0, 0.13)	Manchester study
Specialist visit	2.47	(1.72, 3.22)	Sum of urgent and routine visits, Manchester study
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	0.35	(0.07, 0.64)	Manchester study
A&E visits	0.49	(0.12, 0.86)	Manchester study

All high-risk TG states - Manchester data			
Nurse visit (TG blood test)	4		For TG blood tests, Assumption
Urgent GP visit	0.07	(0, 0.13)	Manchester study
Specialist visit	2.47	(1.72, 3.22)	Sum of urgent and routine visits, Manchester study
Triglyceride blood test	4		Clinical biochem - Quarterly TG measurements, Assumption
General hospital admission	0.35	(0.07, 0.64)	Manchester study
A&E visits	0.49	(0.12, 0.86)	Manchester study
HRU per cycle for regular platelet monitoring			
SmPC analysis			
Nurse (GP practice)	0		Platelet monitoring service provided by Akcea
Thrombocyte test	0		
ITT analysis			
Nurse (GP practice)	0		Platelet monitoring service provided by Akcea
Thrombocyte test	0		
Platelet count drop 100-140k/mm^3 management			

Specialist phone call	1		SmPC advises increased monitoring
Supplemental thrombocyte test	0		Platelet monitoring service provided by Akcea
Platelet count drop 75-100k/mm^3 management (Grade 1)			
Specialist phone call	1		SmPC advises increased monitoring and dose pause
Supplemental thrombocyte test	0.00		Platelet monitoring service provided by Akcea
Platelet count drop 50-75k/mm^3 management (Grade 2)			
Specialist phone call	1		SmPC advises increased monitoring and dose pause
Supplemental thrombocyte test	0.00		Platelet monitoring service provided by Akcea
Platelet count drop 25-50k/mm^3 management (Grade 3)			
Specialist phone call	1		SmPC advises discontinuation
Supplemental thrombocyte test	0.00		Platelet monitoring service provided by Akcea
Platelet count drop <25/mm^3 management (Grade 4)			
Specialist phone call	0.00		Assumption
Supplemental thrombocyte test	0		Platelet monitoring service provided by Akcea
Admission (thrombocytopenia)	1		SmPC recommends discontinuation. Hospitalisation would be required for any grade 4 thrombocytopenia

Haematologist visit	0		Included in admission HRG
Steroids	1		SmPC recommends steroid prescription
Monitoring and management costs (SE of 0.1 assumed for costs)			
Nurse (GP practice)	£7.00	(£5.70, £8.44)	Unit costs for 10 mins nurse time at GP practice (£42 per hour). Curtis, 2018
GP visit	£37.00	(£30.10, £44.60)	Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit). Curtis, 2018
Lipidologist visit	£128.00	(£104.15, £154.28)	WF01A - cardiology non-admitted face to face appointment. NHS Reference Costs 2018
Triglyceride blood test	£1.00	(£0.81, £1.21)	Unit cost for NHS pathology services - Clinical biochemistry DAPS04. NHS Reference Costs 2018
Thrombocyte test	£0.00	£0.00	Mobile phlebotomy service includes thrombocyte testing. Assumption
Dose administration training	£0.00		Will be provided as part of Akcea-funded home healthcare service. Akcea
Chronic pancreatitis management per year	£50,671	(£41,228, £61,073)	The costs of admissions, endocrine and exocrine insufficiency divided by the total number of patients, 2012 cost £44,060/patient, Hall et al., 2014. Inflated to 2018 values using the CPI health index.
General hospital admission	£3,026	(£2,462, £3,647)	Unit costs for n on-elective inpatient stays (long stays). Curtis, 2018
A&E Attendance	£197	(£160, £237)	Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z. NHS Reference Costs 2018
Specialist phone call (for non-grade 4 platelet events)	£70	(£57, £84)	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up.

			NHS Reference Costs 2018
Admission (thrombocytopenia)	£581.00	(£473, £700)	Non-elective short stay, Thrombocytopenia with CC Score 8+. NHS Reference Costs 2018
Steroid cost/dose	£0.03		QD dosing - 1.25mg/kg (midpoint of recommended range 0.5-2 mg/kg/d) for a 75kg person. BNF Drug tariff price of 28-pack of 5mg gastro-resistant tablets is £1.15.
Steroids	£12.48		Includes pack wastage. Calculated using above
Acute pancreatitis admission	£4,505	(£3,665, £5,430)	Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities). NHS Reference Costs 2018
Diabetes management	£3,137	(£2,552, £3,781)	Calculated - the total cost of screening, treatment and management of complications in the UK per diagnosed type 2 diabetes patient (£2,564 in 2010). Inflated to 2018 values using the CPI health index, Hex et al., 2012.
Diabetes management on volanesorsen	Half of that off treatment		Volanesorsen increases insulin sensitivity by 56% along with markers of glucose control (Digenio et al., 2016). Assumed that this reduces costs by half.
Health state utilities			
Vignette study data			
Low TG, AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, AP-naive

High TG, AP-naïve	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, AP-naïve
Low TG, historical AP	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, history of AP
High TG, historical AP	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, history of AP
Low TG, recurrent AP	[redacted]	[redacted]	EVA-22200 vignette study - low TG state, history of AP
High TG, recurrent AP	[redacted]	[redacted]	EVA-22200 vignette study - high TG state, history of AP
APPROACH study data			
Low TG level- AP naive (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Med TG level- AP naive (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- AP naive (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Low TG level- Historical AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Med TG level- Historical AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- Historical AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Low TG level- recurrent AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Med TG level- recurrent AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- recurrent AP (volanesorsen)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Low TG level- AP naïve (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR

Med TG level- AP naïve (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- AP naïve (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Low TG level- Historical AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Med TG level- Historical AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- Historical AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Low TG level- recurrent AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Med TG level- recurrent AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
High TG level- recurrent AP (off treatment)	[redacted]	[redacted]	Table 14.2.3.3.2, APPROACH CSR
Chronic pancreatitis (off treatment)	[redacted]	[redacted]	Assumed to be same as high TG state with history of AP from vignette plus disutility of monthly AP flares
Chronic pancreatitis (on treatment – scenario only)	[redacted]	[redacted]	Assumed to be same as low TG state with history of AP from vignette plus disutility of monthly AP flares
Disutilities (annual decrement)			
Acute pancreatitis (value used with APPROACH EQ-5D dataset)	[redacted]	N/A - calculated value	Calculated as difference between the mean EQ-5D score from APPROACH (all TG levels) and the HRQL of acute pancreatitis (Morris et al., 2014).
Acute pancreatitis (used with vignette utility dataset)	[redacted]	N/A - calculated value	Average of the difference between utility in the low TG AP-naïve state with vs. without active AP, and the difference between utility in the high TG AP-naïve state with vs. without active AP

			from vignette study. Duration calculated from APPROACH data
Duration of acute pancreatitis	[redacted]	[redacted]	Duration calculated from APPROACH data. In the IN-FOCUS survey (Davidson et al., 2018), approximately 50% of patients reported that they visited the hospital for every AP episode. Duration is doubled to account for those that do not contact healthcare services.
Grade 1 thrombocytopenia (75,000-100,000/μL)	0		Gauer R.L., 2012
Grade 2 thrombocytopenia (50,000-75,000/μL)	0		Gauer R.L., 2012
Grade 3 thrombocytopenia (25,000-50,000/μL)	0.184	(0.15, 0.22)	Attard et al., 2014
Grade 4 thrombocytopenia (< 25,000/μL)	0.184	(0.15, 0.22)	Attard et al., 2014
Fatigue	0.115	(0.09, 0.14)	Attard et al., 2014
Injection site reaction	0.08	(0.07, 0.1)	Shabaruddin et al., 2013
Diabetes, assuming 50% with complications	0.23	(0.18, 0.27)	Sullivan et al., 2011
Diabetes while on volanesorsen	Half of that when off treatment		Volanesorsen increases insulin sensitivity by 56% along with markers of glucose control (Digenio et al., 2016). Assumed that this reduces disutility by half.
Frequency of moderate to severe AEs (volanesorsen arm)			
SmPC analysis			

Annual rate of injection site reaction	[redacted]	[redacted]	Analysis of APPROACH OLE patient data – mild and moderate treatment-related AEs only
Annual rate of grade 1 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH OLE patient data – mild and moderate treatment-related AEs only
Annual rate of grade 2 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH OLE patient data – mild and moderate treatment-related AEs only
Annual probability of grade 3 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH OLE patient data – mild and moderate treatment-related AEs only
Annual probability of grade 4 thrombocytopenia/cycle	[redacted]	[redacted]	Analysis of APPROACH OLE patient data – mild and moderate treatment-related AEs only
ITT analysis			
% patients experiencing fatigue	12.12%	(3.51%, 25.02%)	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
% patients experiencing injection-site reaction	21.21%	(9.28%, 36.44%)	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Annual rate of fatigue for affected patients	14.24	(0.74, 27.74)	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Annual rate of injection site reaction for affected patients	19.33	(14.54, 24.11)	Analysis of APPROACH patient data – mild and moderate treatment-related AEs only
Annual rate of grade 1 thrombocytopenia/cycle	0.42	(0.20, 0.64)	Analysis of APPROACH patient data
Annual rate of grade 2 thrombocytopenia/cycle	0.23	(0.07, 0.40)	Analysis of APPROACH patient data
Annual probability of grade 3 thrombocytopenia/cycle	2.8%	(0.06%, 10.49%)	Analysis of APPROACH patient data
Annual probability of grade 4 thrombocytopenia/cycle	10.5%	(2.66%, 22.81%)	Analysis of APPROACH patient data

Duration of fatigue (days)	12.78	(3.03, 29.39)	Analysis of APPROACH patient data
Duration of injection site reaction (days)	15.97	(11.55, 21.1)	Analysis of APPROACH patient data
Duration of grade 1 thrombocytopenia/cycle (days)	73.5	(39.08, 118.62)	Analysis of APPROACH patient data
Duration of grade 2 thrombocytopenia/cycle (days)	142	(21.13, 375.58)	Analysis of APPROACH patient data
Duration of grade 3 thrombocytopenia/cycle (days)	60	(60, 60)	Analysis of APPROACH patient data
Duration of grade 4 thrombocytopenia/cycle (days)	75	(18.18, 171.32)	Analysis of APPROACH patient data

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

There are currently no specific NHS reference costs or healthcare resource group (HRG) codes applicable to management of FCS patients. Patients will have regular appointments with a clinical endocrinologist/lipidologist (the latter usually in cardiology) to monitor their triglyceride status and manage TG-lowering medications. Regular medical appointments with diabetologists will be required by patients with diabetes. Pancreatitis is managed based on need via a multidisciplinary team of surgeons, gastroenterologists, radiologists, critical care specialists and therapists. There are no pancreatitis-specific HRG codes available in NICE reference costs (NICE, 2018b). Therefore, we have constructed bottom-up costings as thoroughly and completely as possible.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

Given the lack of published data on the healthcare resource use for UK FCS patients, the search criteria for the systematic literature review were revised to include resource use in pancreatitis and diabetes. The search strategy for the resource use is summarised in Appendix 4.

Table D9 List of relevant published studies

Primary study reference	Study title
Diabetes	
Gerard et al. 1989	The cost of diabetes
Laing and Williams. 1989	Diabetes
Fenton-Lee et al. 1993	Pancreatic necrosis: Assessment of outcome related to QoL and cost of management
Neoptolemos et al. 1998	Acute pancreatitis: the substantial human and financial costs.
Govan et al. 2011	Inpatient costs for people with type 1 and type 2 diabetes in Scotland: a study from the Scottish Diabetes Research Network epidemiology group
Hex et al. 2012	Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs.
Prescribing and Medicines Team, NHS Digital (2017)	Prescribing for Diabetes - England 2006/07 to 2016/17
Pancreatitis	
Fenton-Lee et al. 1993	Pancreatic necrosis: Assessment of outcome related to QoL and cost of management
Garcea et al. 2013	Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis
Laramée et al. 2013	Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis.
Morris et al. 2014	Cost-effectiveness of early laparoscopic cholecystectomy for mild acute gallstone pancreatitis.
Hall et al. 2014	The socio-economic impact of chronic pancreatitis: a systematic review
Dennison et al. 2015	Economic Burden of Chronic Pancreatitis and Implications of Total Pancreatectomy and Autologous Islet Cell Transplantation

Table D10 Summary of cost and resource use studies

Study	Country	Population	Study type	Resource use and costs	
				Direct cost	**Indirect cost**
Diabetes					
Gerard et al. 1989	England and Wales	Diabetes	Estimation of the cost of diabetes using 'cost of illness' framework in England and Wales in 1984	£259.5-£602.5 million	£86 million
Laing and Williams. 1989	England and Wales.	Diabetes	Report-estimation for the year 1986/7	£484 million	
Govan et al. 2011	Scotland	Diabetes	Cost estimation using 2007/08 Scottish National Tariff and national register of people with diagnosed diabetes in Scotland—The Scottish Care Information – Diabetes Collaboration	Type 1 diabetes: £26million Type 2 diabetes: £275million	Not included

			(SCI-DC)		
Hex et al. 2012	UK	Diabetes	A top-down approach to estimate costs (direct and indirect) for 2010/2011 from aggregated data sets and literature.	£9.8bn (Type 1 diabetes: £1bn; Type 2 diabetes: £8.8bn)	£13.9bn (Type 1 diabetes: £0.9bn Type 2 diabetes: £13bn)
Prescribing and Medicines Team, NHS Digital (2017)	England	Diabetes	Prescribing trends on medicines prescribed in primary care in England for the treatment and monitoring of diabetes during the period April 2006 to March 2017	Cost of prescribing drugs in diabetes in 2016/17: £983.7 million	
Pancreatitis					
Fenton-Lee et al. 1993	UK	Patients with necrotizing pancreatitis	Study of the cost of management of patients with necrotizing pancreatitis admitted consecutively between August 1990 and	£9296 to £33,796	

			August 1991	
Garcea et al. 2013	UK	Chronic Pancreatitis patients	Costs estimation on the prospective database of patients undergoing total pancreatectomy (TP) + islet cell autotransplantation (IAT)	TP + IAT (admission and analgesia costs) over the 16-year period: £110,445 No TP + IAT (admission and analgesia costs) over the 16-year period: £101,608
Laramée et al. 2013	UK	Obstructive chronic pancreatitis patients	Trial-based (ISRCTN04572410) cost-utility analysis combining the frequency of each diagnostic and therapeutic procedure performed during the trial with UK unit costs from the 2010 to 2011 National Schedule of Reference Costs.	Total cost (mean) of endoscopic drainage: £22443 Total cost (mean) of surgical drainage: £15410
Morris et al. 2014	UK	Mild acute gallstone pancreatitis	A model-based cost–utility analysis. Costs are based on 2011–2012	Cost of laparoscopic cholecystectomy performed within 3 days of admission: £2748

		patients	prices	Laparoscopic cholecystectomy performed beyond 3 days but in the same admission: £3543 Laparoscopic cholecystectomy performed electively in a subsequent admission: £3752
Hall et al. 2014	UK	Chronic pancreatitis	Literature review	£285.3 million per year
Dennison et al. 2015	UK	Chronic pancreatitis	Estimates of direct and indirect costs as a result of CP are calculated from the available data from the USA and extrapolated to UK setting	£454 million per year

The search strategy for the cost-effectiveness evidence carried out in Section 11.1.1 included search terms for resource use and costs of managing FCS. Limited information relevant to the UK or England was identified during this search, which was part of the rationale for initiating two studies with the objective of gaining more data on the resource use of FCS patients: a chart review ("Manchester study") and the CALIBER study already discussed. Given that the Manchester study provided data from "true" FCS patients, the Manchester data, where available, has been chosen as the base case.

Manchester study

In the Manchester study, a chart review of patients with FCS (n = 15) and non-familial hypertriglyceridaemia (HTG; n = 16) was carried out which included, where available, highest and lowest TG readings as well as resource use. In this dataset all FCS patients had had peak TG readings above 22.7 mmol, therefore it was not possible to stratify patients by peak TG. Patients with HTG could be stratified by peak TG, with resource use shown in Table D13.

Table D11 Resource use of patients with FCS and HTG by highest TG level in Manchester study

Resource	Mean annual per patient rate by peak TG (SE)			
	HTG, <10 mmol (n=2)	HTG, 10-22.7 mmol (n=7)	HTG, ≥22.7 mmol (n=6)	FCS, ≥22.7 mmol (n=14)
Urgent GP visits	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.07 (0.03)
Routine outpatient visits	3.00 (1.00)	1.46 (0.43)	1.89 (0.23)	2.41 (0.38)
Urgent outpatient visits	0.00 (0.00)	0.00 (0.00)	0.11 (0.11)	0.06 (0.03)
A & E visits	0.00 (0.00)	0.03 (0.03)	0.89 (0.59)	0.49 (0.19)

Hospital admissions	0.00 (0.00)	0.00 (0.00)	0.69 (0.42)	0.35 (0.15)
General ward LOS/ admission	0.00 (0.00)	0.00 (0.00)	3.14 (1.76)	6.50 (2.33)
HDU LOS/ admission	0.00 (0.00)	0.00 (0.00)	0.50 (0.50)	1.17 (0.87)
ICU LOS/ admission	0.00 (0.00)	0.00 (0.00)	0.33 (0.33)	2.47 (0.38)

CALIBER study

In the CALIBER study, a cohort of 'FCS-like' patients was created, defined as follows:

- at least 1 TG >10mmol/L at age <40y AND an acute pancreatitis record at any time
    - OR at least 2 TG >10mmol/L at age <40y
- no gall bladder disease record at any time
- no alcohol abuse record at any time
- no BMI≥ 30 at any time
- no type 2 diabetes diagnosis prior to qualifying TG

Information on resource use was collected including GP appointments, outpatient appointments and hospitalisations for AP. ICD-10 codes and OPCS procedure codes were also extracted where available. The 'FCS-like' cohort was compared with a 'high triglyceride' (HTG) cohort, with the TG cut-off as per the FCS-like cohort but without exclusion of co-morbidities. A third cohort of 'normal TG' patients, with no record of TG>1.7mmol/l by the age of 40, was also used as a control. Resource use for these populations is shown in Table D14, which were used as inputs for

the model. Resource use was assumed to be driven by the patient's TG levels and not whether they were on volanesorsen or not.

[redacted]

Separate rapid searches using were carried out to identify costs and resource use involved in the management of FCS-related co-morbidities, including AP, CP and diabetes. No UK-specific information was found for the costs of managing AP or CP, as confirmed in the recent pancreatitis draft guidelines (NICE, 2018b). One publication was identified which provided the cost of diagnosis and management of type 2 diabetes in the UK.

The cost of diabetes management was assumed to be halved in the volanesorsen arm, as an RCT of the effect of volanesorsen in type 2 diabetes patients demonstrated that volanesorsen significantly improved whole-body insulin sensitivity by 57% along with clinical markers of glucose handling

(Digenio et al., 2016). Interventions that control diabetes are known to reduce the complications of diabetes, and their costs and disutilities, particularly in younger patients (Li et al., 2010).

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

General resource use assumptions were explored with clinical experts during an advisory board meeting convened in November 2017 as described elsewhere (Section 12.7.1). Resource use is an area of significant uncertainty in FCS, particularly with respect to the resources associated with longer term outcomes such as Chronic Pancreatitis. Clinical expert input was sought to gain a clearer understanding of the type of resource use associated with managing CP in FCS patients.

The clinical expert survey described earlier in Section 10.1.10 and summarised in Appendix 7 was used to explore the likely resource use associated with chronic pancreatitis. In summary, the clinical experts agreed that CP was a very varied syndrome and it was difficult to give precise information on management and resource use. They listed a variety of resource items that would be expected to be associated with CP including attendance at HPB clinics, CT/MRI scans of the pancreas, investigations for cause of chronic abdominal pain, hospitalisation for pain control, hospital admission for diabetes and referral to HPB surgeon.

The economic model presented in this submission relies on a bottom up costing estimate for the annual cost of CP. This assumption was tested in sensitivity analyses. The information gathered from the survey supports our understanding that CP management is complex and varied and that CP is likely to be associated with significant resource utilisation including hospitalisation and surgical intervention for some patients

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price is £11,394 per syringe.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A simple discount PAS has been approved with a discounted price of £[redacted] per single-use syringe. [redacted]

Base case modelling assumes a maintenance schedule of once every 2 weeks dosing. The SmPC allows for the possibility of an increase in dosing frequency to a weekly dose in certain circumstances. Specifically, the SmPC states: "After 6 months of treatment with volanesorsen, increase of dose frequency to 285 mg weekly should be considered if response has been inadequate in terms of serum triglyceride reduction as evaluated by the supervising experienced specialist and in the condition that platelet counts are in the normal range." Current feedback from clinicians is that dosing frequency is unlikely to be increased. In clinical practice it is possible, but unlikely, that a small number of patients may be moved onto a weekly dose.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables below. Table D16 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The only incremental resource use anticipated to be required for treatment with volanesorsen are platelet monitoring tests and a single session with a nurse to teach self-injection. No costs to the NHS are expected to be incurred as both administration training and platelet monitoring will be provided by Akcea via mobile phlebotomy services and home healthcare, respectively.

Otherwise, no incremental healthcare provider appointments will be required in addition to current standard of care.

No additional cost for genetic confirmation of patients is assumed, as a genetic diagnosis is assumed to have been received via the separately commissioned genetic testing program (see section 8.7).

Table D13 Costs per treatment/patient associated with the technology in the cost- effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	[redacted]	Akcea
Administration cost	None	Self-administered
Training cost	Training in drug self-administration will be provided by Akcea-funded home healthcare service and support provided to specialist centres via the Akcea medical team	Akcea
Other costs (monitoring, tests etc)	Platelet monitoring costs will be borne by Akcea, via a mobile platelet monitoring service	Akcea
Total cost per treatment/patient	[redacted]	Akcea

Table D14 Costs per treatment/patient associated with the comparator technology in the cost- effectiveness model

Not applicable, as any resource use for the comparator of dietary management and any standard of care medication will also apply to patients receiving volanesorsen, as it is licensed as an adjunct to current SoC. An *ad hoc* analysis of the costs of the most common lipid-modifying medications used at baseline in APPROACH OLE suggests costs for fibrates and statins of the order of £33-£400/patient/year for those patients prescribed them.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The

health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Health state costs were calculated by applying the resource use estimates provided in Section 12.3.2 to NHS or PSSRU unit costs in the references in Table D17. Note that the ICER was insensitive to the source of resource use, therefore health state costs for the CALIBER resource use scenario are not provided. Diabetes is not included in table D15 as costs vary according to prevalence over time.

Table D15 List of health states and associated costs in the cost-effectiveness model (per 3-month cycle)

Additional volanesorsen costs apply to all health states bar the chronic pancreatitis state but vary according to the % of patients on and off treatment.

Health states	Items	Value	Reference
Low-risk TG, AP naive	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£308.23	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£717.16	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018

Health states	Items	Value	Reference
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£0.46	CALIBRE probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
Medium-risk TG, AP naive	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£2.44	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£315.89	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£1,070.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£96.69	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018

Health states	Items	Value	Reference
	acute pancreatitis hospitalisations	£4.23	CALIBER probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
High-risk TG, AP naive	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£2.44	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£315.89	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£1,070.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£96.69	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£8.80	CALIBRE probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)

Health states	Items	Value	Reference
	TOTAL	[redacted]	
Low-risk TG, historical AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£308.23	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£717.16	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£39.50	CALIBRE probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
Medium-risk TG, historical AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	CALIBER study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018

Health states	Items	Value	Reference
	Urgent GP visit	£2.44	CALIBER study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£315.89	CALIBER study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	CALIBER study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£1,070.00	CALIBER study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£96.69	CALIBER study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£95.97	CALIBRE probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
High-risk TG, historical AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£2.44	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018

Health states	Items	Value	Reference
	Specialist visit	£315.89	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£1,070.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£96.69	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£234.43	CALIBRE probability *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
Low-risk TG, recurrent AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£0.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£308.23	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018

Health states	Items	Value	Reference
	General hospital admission	£717.16	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£0.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	acute pancreatitis hospitalisations	£67.99	Average quarterly rate of APPROACH patients with 5-year history *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
Medium-risk TG, recurrent AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for 10 mins nurse time at GP practice (£42 per hour), Curtis, 2018
	Urgent GP visit	£2.44	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Specialist visit	£315.89	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	General hospital admission	£1,070.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	A & E admission	£96.69	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference

Health states	Items	Value	Reference
			Costs 2018
	acute pancreatitis hospitalisations	£67.99	Average quarterly rate of APPROACH patients with 5-year history *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
High-risk TG, recurrent AP	**volanesorsen costs**	[redacted]	Quarterly cost of volanesorsen adjusted for dose pauses
	Nurse (GP practice)	£28.00	Manchester study, Unit costs for an average surgery consultation of 9.22 minutes including direct care staff costs (per visit), Curtis, 2018
	Urgent GP visit	£2.44	Manchester study, WF01A - cardiology non-admitted face to face appointment, NHS Reference Costs 2018
	Specialist visit	£315.89	Manchester study, Unit cost for NHS pathology services - Clinical biochemistry DAPS04, NHS Reference Costs 2018
	Triglyceride blood test	£4.00	Manchester study, Unit costs for Non-elective inpatient stays (long stays), Curtis, 2018
	General hospital admission	£1,070.00	Manchester study, Average of Emergency Medicine HRGs VB01Z to VB09Z and VB011Z, NHS Reference Costs 2018
	A & E admission	£96.69	Manchester study, Mobile phlebotomy service includes thrombocyte testing, Assumption

Health states	Items	Value	Reference
	acute pancreatitis hospitalisations	£67.99	Average quarterly rate of APPROACH patients with 5-year history *, Average of HRG costs of Non-Malignant, Hepatobiliary or Pancreatic Disorders GC17A, GC17B, GC17D, GC17E, GC17G and GC17H (codes with higher CC scores to reflect FCS-related comorbidities)
	TOTAL	[redacted]	
Chronic pancreatitis	**Total cost of health state/cycle**	[redacted]	0.25*the costs of admissions, endocrine and exocrine insufficiency divided by the total number of patients, 2012 cost £44,060/patient. Inflated to 2018 values using the CPI health index, Hall et al., 2014

Adverse-event costs

12.3.8 Complete table below with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

The model includes moderate to severe AEs affecting >10% of patients and assessed as being related to treatment only. There are therefore no AEs included in the comparator arm.

Other than thrombocytopenia, the only moderate to severe adverse events that are definitely attributable to volanesorsen is injection-site reactions. Given the nature of these AEs, and the fact that patients on volanesorsen are likely to receive advice concerning treatment of common AEs during specialist appointments, it is difficult to predict how often patients would seek medical help. Injection site reactions (ISRs) might for example require a single visit for a prescription of steroid cream which thereafter could be used for multiple ISRs. Therefore, neither fatigue nor ISRs were assumed to incur any resource use costs.

Platelet reductions below 100 x 10^9/L and above 25 x 10^9/L were assumed to require a phone call to the specialist service and would incur additional healthcare provider costs as detailed in Table D18; grade 4 thrombocytopenia (platelets <25 x 10^9/L) would require hospitalisation. Additional platelet monitoring following a platelet-lowering event is anticipated to be covered by the Akcea-funded mobile phlebotomy service.

A drop in platelet count to 100-140 x 10^9 range was assumed not to incur any resource use as the patient would simply be advised by Akcea's monitoring service that additional blood tests were needed as well as dose frequency reduction.

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Table D16 List of adverse events and summary of costs included in the cost- effectiveness model

Adverse events	Items	Value	Reference
Fatigue	No costs are assumed as advice will be provided via home healthcare service and there is no specific treatment for fatigue.		
Injection-site reaction	No costs are assumed as advice will be provided via home healthcare service. ISRs requiring medical treatment will be rare, and topical steroid treatment inexpensive.		
Grade 1 thrombocytopenia (75-100 x10^9/L)	Specialist phone call	£70.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up. NHS reference costs, 2018
Grade 2 thrombocytopenia (50-75 x10^9/L)	Specialist phone call	£70.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up. NHS reference costs, 2018

Grade 3 thrombocytopenia (25-50 x10^9/L)	Specialist phone call	£70.00	WF01C - cardiology Non-Admitted Non-Face to Face Attendance, Follow-Up. NHS reference costs, 2018
Grade 4 thrombocytopenia (<25 x10^9/L)	Hospital admission	£581	Non-elective short stay, Thrombocytopenia with CC Score 8+, NHS Reference Costs 2018
	Steroids	£12.48	QD dosing - 1.25mg/kg (midpoint of recommended range 0.5-2 mg/kg/d) for a 75kg person. BNF Drug tariff price of 28-pack of 5mg gastro-resistant tablets is £1.15. Average duration from APPROACH.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None foreseen.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None foreseen.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Uncertainty around structural assumptions has been explored as summarised in Table D17.1. One structural assumption explored is treatment discontinuation. At present, the only data to inform discontinuation that is generalisable to the SmPC is the APPROACH OLE study. Discontinuation may be much lower in practice however, and the EAMS study is expected to

provide some indication. A no discontinuation scenario has been included to provide an indication of cost effectiveness in a cohort that shows 100% adherence to treatment. An additional scenario has been provided whereby the base case lognormal curve is 'lifted' upwards using a hazard ratio of 0.3, in line with early evidence that discontinuation in EAMS will be extremely low.

The structural sensitivity analysis included using the SoC arm transition probabilities from APPROACH to inform TG category occupancy on SoC as a validation exercise vs the regression predictions. Note that this option distributes SoC patients across TG health states as observed in the APPROACH trial, rather than calculating mean TG for the cohort and placing in one health state, so a slight difference in results is to be expected.

Table D17.1 Uncertainty around structural assumptions

Structural assumption	**Base case**	**Other scenarios considered**
Treatment discontinuation	Lognormal curve	Lognormal curve with 0.3 'hazard ratio' applied at all points
		Loglogistic curve
		Exponential curve
		Weibull curve
		No discontinuation
Data informing SoC health states	Regressions	APPROACH SoC arm patient transitions

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what

was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Both one-way deterministic and probabilistic sensitivity analyses (PSA) were carried out. For the deterministic analysis, parameters were varied between their confidence intervals where available, or by +/- 10% of the mean (Table D17.2).

A number of deterministic scenarios were also explored as per Table D17.3. The first of these is an 'EAMS scenario' in which we explore the impact of no discontinuation, no severe thrombocytopenia and no AP events while on volanesorsen. We believe that this is representative of the likely real-world outcomes with volanesorsen under every 2 weeks dosing, regular monitoring and a PSP.

As CP is an important outcome, a number of these scenarios explore the impact of the CP calibration, excluding CP from the model, as well as using a utility for CP from the literature that represents particularly severe patients. One scenario explores the impact of continuing to treat patients who have developed CP.

As the diabetes utility in the base case represents a population with complications of diabetes, a scenario is presented with uncomplicated diabetes.

Other scenarios present the ITT analysis and one scenario presents the results for the SmPC analysis assuming that all patients are treated (i.e. the baseline population isn't reweighted).

A final scenario includes using a discount rate of 1.5% for costs and QALYs. As proposed in the NICE Methods guide, a discount of 1.5% can be applied where treatment restores people who would otherwise die or have a very severely impaired life to full or near full health. Treatment with volanesorsen impacts important long-term outcomes such as diabetes and chronic pancreatitis which severely impact quality of life. As FCS is a chronic disease,

early treatment with volanesorsen could provide impact on QoL that is sustained over the patient's lifetime.

In the PSA, parameters were varied around their standard errors (SEs) where available or assuming a SE of 10% of the mean where measures of uncertainty were unavailable (Table D17.4). 2000 simulations were run, the mean ICER being stable well before this number of runs.

12.4.3 Complete tables below as appropriate to summarise the variables used in the sensitivity analysis.

Table D17.2 Variables used in one-way scenario-based deterministic sensitivity analysis

Parameter	Mean	Lower bound	Upper bound	SE estimate
Missed doses first quarter weekly	[redacted]	[redacted]	[redacted]	Using confidence interval
Annual missed doses every 2 weeks	[redacted]	[redacted]	[redacted]	Using confidence interval
Cost nurse (GP practice)	£7.00	£5.70	£8.44	Assumption of SE of 0.1
Cost GP visit	£37.00	£30.10	£44.60	Assumption of SE of 0.1
Cost specialist visit	£128.00	£104.15	£154.28	Assumption of SE of 0.1
Cost gen hospital admission	£3,026	£2,462	£3,647	Assumption of SE of 0.1
Cost A&E	£196.60	£159.96	£236.96	Assumption of SE of 0.1
Cost specialist phone call	£70.00	£56.95	£84.37	Assumption of SE of 0.1
Cost haematologist	£227.00	£184.70	£273.60	Assumption of SE of 0.1
Cost thrombocytopenia admission	£581.00	£472.72	£700.27	Assumption of SE of 0.1
Cost chronic pancreatitis	£50,671	£41,228	£61,073	Assumption of SE of 0.1
Cost acute pancreatitis	£4,505	£3,665	£5,430	Assumption of SE of 0.1
Cost of diabetes	£3,137	£2,552	£3,781	Assumption of

				SE of 0.1
Manchester HRU				
Low risk TGs				
HRU specialist visits	2.41	1.66	3.16	Using confidence interval
HRU Gen hospital admissions	0.24	0.23	0.24	Using confidence interval
Medium risk TGs				
HRU urgent GP visits	0.07	0.00	0.13	Using confidence interval
HRU specialist visits	2.47	1.72	3.22	Using confidence interval
HRU Gen hospital admissions	0.35	0.07	0.64	Using confidence interval
HRU A&E attendances	0.49	0.12	0.86	Using confidence interval
High risk TGs				Using confidence interval
HRU urgent GP visits	0.07	0.00	0.13	Using confidence interval
HRU specialist visits	2.47	1.72	3.22	Using confidence interval
HRU Gen hospital admissions	0.35	0.07	0.64	Using confidence interval
HRU A&E attendances	0.49	0.12	0.86	Using confidence interval
CALIBER HRU				
Low risk TGs				
HRU urgent GP visits	[redacted]	[redacted]	[redacted]	Using confidence interval
HRU specialist visits	[redacted]	[redacted]	[redacted]	Using confidence interval

HRU Gen hospital admissions	[redacted]	[redacted]	[redacted]	Using confidence interval
Medium risk TGs				
HRU urgent GP visits	[redacted]	[redacted]	[redacted]	Using confidence interval
HRU specialist visits	[redacted]	[redacted]	[redacted]	Using confidence interval
HRU Gen hospital admissions	[redacted]	[redacted]	[redacted]	Using confidence interval
High risk TGs				
HRU urgent GP visits	[redacted]	[redacted]	[redacted]	Using confidence interval
HRU specialist visits	[redacted]	[redacted]	[redacted]	Using confidence interval
HRU Gen hospital admissions	[redacted]	[redacted]	[redacted]	Using confidence interval
QoL				
APPROACH EQ-5D				
U Low TG - AP naïve (volan arm)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Med TG - AP naïve (volan arm)				Using confidence interval
U High TG - AP naïve (volan arm)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Low TG- Historical AP (volan arm)				Using confidence interval
U Med TG- Historical AP (volan arm)	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG- Historical AP (volan arm)				Using confidence interval
U Low TG- Recurrent AP (volan arm)	[redacted]	[redacted]	[redacted]	Using confidence

				interval
U Med TG- Recurrent AP (volan arm)				Using confidence interval
U High TG- Recurrent AP (volan arm)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Low TG - AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Med TG - AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG - AP naïve (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Low TG- Historical AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Med TG- Historical AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG- Historical AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Low TG- Recurrent AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U Med TG- Recurrent AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG- Recurrent AP (off treatment)	[redacted]	[redacted]	[redacted]	Using confidence interval
Vignette study values				
U Low TG - AP naïve	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG - AP naïve	[redacted]	[redacted]	[redacted]	Using confidence interval
U Low TG- Historical AP	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG- Historical AP	[redacted]	[redacted]	[redacted]	Using confidence

				interval
U Low TG- Recurrent AP	[redacted]	[redacted]	[redacted]	Using confidence interval
U High TG- Recurrent AP	[redacted]	[redacted]	[redacted]	Using confidence interval
U Chronic pancreatitis - SoC	[redacted]	[redacted]	[redacted]	Using confidence interval
U Chronic pancreatitis – on volanesorsen (scenario only)	[redacted]	[redacted]	[redacted]	Using confidence interval
U of AP from literature	0.47	0.39	0.55	Using confidence interval
Duration of AP (days)	[redacted]	[redacted]	[redacted]	Using confidence interval
Utility decrements				
UD Gr 3 Thrombocytopenia	0.18	0.15	0.22	Assumption of SE of 0.1
UD Gr 4 Thrombocytopenia	0.18	0.15	0.22	Assumption of SE of 0.1
Duration Gr 1 Thrombocytopenia (days)	32.00	16.48	52.59	Using confidence interval
Duration Gr 2 Thrombocytopenia (days)	168.00	5.50	597.60	Using confidence interval
Duration Gr 3 Thrombocytopenia (days)	7.00	5.7	8.44	Assumption of SE of 0.1
Duration Gr 4 Thrombocytopenia (days)	75.00	18.18	171.32	Using confidence interval
UD Fatigue	0.12	0.09	0.14	Assumption of SE of 0.1
UD Injection site reaction	0.08	0.07	0.10	Assumption of SE of 0.1
Duration Fatigue	12.78	3.03	29.39	Using confidence interval
Duration Injection site reaction	2.85	0.07	10.51	Using confidence interval

UD Diabetes	0.23	0.18	0.27	Assumption of SE of 0.1
Temporary health states from Vignette study for calculation of Vignette AP disutility				
U of state C: Low TGs, history of AP	[redacted]	[redacted]	[redacted]	Using confidence interval
U of (C+E): Current AP event	[redacted]	[redacted]	[redacted]	Using confidence interval
U of state D: High TGs, history of AP	[redacted]	[redacted]	[redacted]	Using confidence interval
U of (D+E): Current AP event	[redacted]	[redacted]	[redacted]	Using confidence interval
Annual carer utility increase on treatment	[redacted]	[redacted]	[redacted]	Assumption of SE of 0.1
Adverse event rates				
SmPC scenario				
Annual rate of ISR - SmPC scenario	0.52	0.40	0.64	Using confidence interval
Rate gr 1 thrombocytopenia - SmPC scenario	0.28	0.18	0.39	Using confidence interval
Rate gr 2 thrombocytopenia - SmPC scenario	0.07	0.02	0.12	Using confidence interval
Prob gr 3 thrombocytopenia - SmPC scenario	1.6%	0.14%,	4.80%	Using confidence interval
Prob gr 4 thrombocytopenia - SmPC scenario	1.6%	0.28%	4.80%	Using confidence interval
ITT scenario				
% with fatigue - ITT scenario	0.12	0.04	0.25	Using confidence interval
% with ISR - ITT scenario	0.21	0.09	0.36	Using confidence interval
Annual event rate of fatigue - ITT scenario	14.24	0.74	27.74	Using confidence interval

Annual event rate of ISR - ITT scenario	19.33	14.54	24.11	Using confidence interval
Rate gr 1 thrombocytopenia - ITT scenario	0.42	0.20	0.64	Using confidence interval
Rate gr 2 thrombocytopenia - ITT scenario	0.23	0.07	0.40	Using confidence interval
Prob gr 3 thrombocytopenia - ITT scenario	2.8%	0.06%	10.49%	Using confidence interval
Prob gr 4 thrombocytopenia - ITT scenario	10.5%	2.66%	22.81%	Using confidence interval
Mortality				
RR mortality with CP	5.83	4.21	8.09	Using confidence interval
RR mortality with diabetes	1.28	1.27	1.29	Using confidence interval
Prob 1st AP is fatal	0.05	0.03	0.08	Using confidence interval
Prob 2nd AP is fatal	0.05	0.03	0.08	Using confidence interval
Prob 3rd AP is fatal	0.05	0.03	0.08	Using confidence interval
RR AP mortality with volanesorsen	0.17	0.02	1.34	Using confidence interval
Clinical outcomes				
AP rate low TG - patients with recurrent AP	0.46	0.2	1.6	The lowest per patient rate to the highest per patient rate.
AP rate med TG - patients with recurrent AP	0.46	0.2	1.6	The lowest per patient rate to the highest per patient rate.
AP rate high TG - patients with recurrent AP	0.46	0.2	1.6	The lowest per patient rate to the highest per

				patient rate.
TE of volan on AP rate med/low risk TGs	0.13	0.04	0.42	Using confidence interval
TE of volan on AP rate high risk TGs	0.13	0.04	0.42	Using confidence interval
Prob CP after 1 AP, 100 weeks	0.03	0.02	0.03	Using confidence interval
Prob CP after recurrent AP, 100 weeks	0.13	0.11	0.14	Using confidence interval

Key: HRU, healthcare resource use; U, utility; UD; utility decrement; Prob, probability; RR, relative risk; TE, treatment effect; AP, acute pancreatitis; CP, chronic pancreatitis

Table D17.3 Variables used in multi-way scenario-based sensitivity analysis

Structural assumption	**Base case**	**Other scenarios considered**
EAMS scenario	Lognormal discontinuation Treatment effect an APs Grade 4 thrombocytopenia events	No discontinuation No AP while on volanesorsen No grade 4 thrombocytopenia events
Starting population	Genetically confirmed with a history of AP	Any genetically confirmed FCS patient
Dosing schedule	285 mg weekly for three months followed by every 2 weeks maintenance dosing	APPROACH ITT analysis (note that weekly dosing is not assumed to incur additional drug costs over once every 2 weeks dosing in this scenario)
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level

Structural assumption	Base case	Other scenarios considered
		All health states have utility of 0.7 (assessment group request)
Treating chronic pancreatitis patients	Do not treat	Treat, assuming that patients have a daily HRQL benefit of 'low' vs 'high' TGs as per the vignette study
Calibration of risk of CP	60% lifetime risk of CP	42% lifetime risk of CP
Inclusion of CP as health state	Include CP	Exclude CP
Utility of CP	Assumption using low TG health state	Laramee et al. utility
Impact of volanesorsen on diabetes costs and QALYs	Volanesorsen reduces by 50%	No impact from volanesorsen
Disutility of diabetes	Diabetes with 50% complications	Uncomplicated diabetes
Carer utility gain	Include	Exclude
Discount rate	3.5% for costs and QALYs	1.5% for costs and QALYs

Table D17.4 Variable values used in probabilistic sensitivity analysis

Parameter	Base value	Distribution
Missed doses first quarter weekly	[redacted]	Gamma
Annual missed doses every 2 weeks	[redacted]	Gamma
Cost fatigue	£0.00	Fixed (no cost)
Cost ISR	£0.00	Fixed (no cost)
Cost nurse (GP practice)	£7	Gamma
Cost GP visit	£37	Gamma
Cost specialist visit	£128	Gamma
Cost TG blood test	£1.00	Fixed (very low cost)
Cost gen hospital admission	£3,026	Gamma
Cost A&E	£197	Gamma
Cost specialist phone call	£70	Gamma
Cost thrombocyte test	£0.00	Fixed (paid by Akcea)
Cost haematologist	£227	Gamma
Cost dose administration training	£0.00	Fixed (paid by Akcea)
Cost thrombocytopenia admission	£581	Gamma
Cost steroids for thrombocytopenia	£12	Fixed (very low cost)
Cost chronic pancreatitis	£50,671	Gamma
Cost acute pancreatitis	£4,505	Gamma
Cost of diabetes	£3,137	Gamma

Manchester HRU		
Low risk TGs		
HRU nurse visits (GP practice)	4.00	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	0.00	Fixed (no HRU)
HRU specialist visits	2.41	Gamma
HRU TG blood tests	4.00	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital admissions	0.24	Gamma
HRU A&E attendances	0.00	Fixed (no HRU)
Medium risk TGs		
HRU nurse visits (GP practice)	4.00	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	0.07	Gamma
HRU specialist visits	2.47	Gamma
HRU TG blood tests	4.00	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital admissions	0.35	Gamma
HRU A&E attendances	0.49	Gamma
High risk TGs		
HRU nurse visits (GP practice)	4.00	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	0.07	Gamma
HRU specialist visits	2.47	Gamma

HRU TG blood tests	4.00	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital admissions	0.35	Gamma
HRU A&E attendances	0.49	Gamma
CALIBER HRU		
Low risk TGs		
HRU nurse visits (GP practice)	[redacted]	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	[redacted]	Gamma
HRU specialist visits	[redacted]	Gamma
HRU TG blood tests	[redacted]	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital admissions	[redacted]	Gamma
HRU A&E attendances	[redacted]	Fixed (mo HRU)
Medium risk TGs		
HRU nurse visits (GP practice)	[redacted]	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	[redacted]	Gamma
HRU specialist visits	[redacted]	Gamma
HRU TG blood tests	[redacted]	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital	[redacted]	Gamma

admissions		
HRU A&E attendances	[redacted]	Fixed (no HRU)
High risk TGs		
HRU nurse visits (GP practice)	[redacted]	Fixed (unchanged with volanesorsen)
HRU urgent GP visits	[redacted]	Gamma
HRU specialist visits	[redacted]	Gamma
HRU TG blood tests	[redacted]	Fixed (unchanged with volanesorsen; Akcea would fund any additional for stopping rules)
HRU Gen hospital admissions	[redacted]	Gamma
HRU A&E attendances	[redacted]	Fixed (no HRU)
QoL		
APPROACH EQ-5D		
U Low risk TG - AP naïve (volan arm)	[redacted]	Beta
U Med risk TG - AP naïve (volan arm)	[redacted]	Beta
U High-risk TG - AP naïve (volan arm)	[redacted]	Beta
U Low risk TG- Historical AP (volan arm)	[redacted]	Beta
U Med risk TG- Historical AP (volan arm)	[redacted]	Beta
U High-risk TG- Historical AP (volan arm)	[redacted]	Beta
U Low risk TG- Recurrent AP (volan arm)	[redacted]	Beta

U Med risk TG- Recurrent AP (volan arm)	[redacted]	Beta
U High-risk TG- Recurrent AP (volan arm)	[redacted]	Beta
U Low risk TG - AP naïve (off treatment)	[redacted]	Beta
U Med risk TG - AP naïve (off treatment)	[redacted]	Beta
U High-risk TG - AP naïve (off treatment)	[redacted]	Beta
U Low risk TG- Historical AP (off treatment)	[redacted]	Beta
U Med risk TG- Historical AP (off treatment)	[redacted]	Beta
U High risk TG- Historical AP (off treatment)	[redacted]	Beta
U Low risk TG- Recurrent AP (off treatment)	[redacted]	Beta
U Med risk TG- Recurrent AP (off treatment)	[redacted]	Beta
U High risk TG- Recurrent AP (off treatment)	[redacted]	Beta
Vignette study values		
U Low risk TG - AP naïve	[redacted]	Beta
U High risk TG - AP naïve	[redacted]	Beta
U Low risk TG- Historical AP	[redacted]	Beta
U High risk TG- Historical AP	[redacted]	Beta
U Low risk TG- Recurrent	[redacted]	Beta

AP		
U High risk TG- Recurrent AP	[redacted]	Beta
U Chronic pancreatitis - SoC	[redacted]	Beta
U Chronic pancreatitis – volanesorsen (scenario only)	[redacted]	Beta
U of AP from literature	[redacted]	Beta
Duration of AP	[redacted]	Gamma
Utility decrements		
UD Gr 1 Thrombocytopenia	0.00	Fixed (no disutility)
UD Gr 2 Thrombocytopenia	0.00	Fixed (no disutility)
UD Gr 3 Thrombocytopenia	0.18	Beta
UD Gr 4 Thrombocytopenia	0.18	Beta
Duration Gr 1 Thrombocytopenia	32.00	Gamma
Duration Gr 2 Thrombocytopenia	168.00	Gamma
Duration Gr 3 Thrombocytopenia	7.00	Fixed (in one patient; rare event with little impact)
Duration Gr 4 Thrombocytopenia	75.00	Gamma
UD Fatigue	0.12	Beta
UD Injection site reaction	0.08	Beta
Duration Fatigue	12.78	Gamma

Duration Injection site reaction	2.85	Gamma
UD Diabetes	0.23	Beta
Temporary health states from Vignette study for calculation of Vignette AP disutility		
U of state C: Low TGs, history of AP	[redacted]	Beta
U of (C+E): Current AP event	[redacted]	Beta
U of state D: High TGs, history of AP	[redacted]	Beta
U of (D+E): Current AP event	[redacted]	Beta
Annual carer utility gain from treatment	0.1	Beta
Adverse event rates		
Annual rate of ISR - SmPC scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Rate gr 1 thrombocytopenia - SmPC scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Rate gr 2 thrombocytopenia - SmPC scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Prob gr 3 thrombocytopenia -	[redacted]	Beta

SmPC scenario		
Prob gr 4 thrombocytopenia - SmPC scenario	[redacted]	Beta
% with fatigue - ITT scenario	[redacted]	Beta
% with ISR - ITT scenario	[redacted]	Beta
Annual rate of fatigue - ITT scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Annual rate of ISR - ITT scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Rate gr 1 thrombocytopenia - ITT scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Rate gr 2 thrombocytopenia - ITT scenario	[redacted]	Fixed (Poisson not possible in Excel and results insensitive in OWSA)
Prob gr 3 thrombocytopenia - ITT scenario	[redacted]	Beta
Prob gr 4 thrombocytopenia - ITT scenario	[redacted]	Beta
% with fatigue - SoC	[redacted]	Fixed
% with ISR - SoC	[redacted]	Fixed
Annual rate of fatigue -	[redacted]	Fixed

SoC		
Annual rate of ISR - SoC	[redacted]	Fixed
Mortality		
RR mortality with CP	5.83	Lognormal
RR mortality with diabetes	1.28	Lognormal
Prob 1st AP is fatal	0.05	Beta
Prob 2nd AP is fatal	0.05	Beta
Prob 3rd AP is fatal	0.05	Beta
RR AP mortality with volanesorsen	0.17	Lognormal
Clinical outcomes		
AP rate low TG - patients with recurrent AP	[redacted]	Fixed. Only varied in OWSA as follows strongly left-skewed Poisson distribution
AP rate med TG - patients with recurrent AP	[redacted]	Fixed. Only varied in OWSA as follows strongly left-skewed Poisson distribution
AP rate high TG - patients with recurrent AP	[redacted]	Fixed. Only varied in OWSA as follows strongly left-skewed Poisson distribution
TE of volan on AP rate med/low risk TGs	[redacted]	Lognormal
TE of volan on AP rate high risk TGs	[redacted]	Lognormal
Prob CP after 1 AP, 100 weeks	[redacted]	Beta

Prob CP after recurrent AP, 100 weeks	[redacted]	Beta

Key: HRU, healthcare resource use; U, utility; UD; utility decrement; Prob, probability; RR, relative risk; TE, treatment effect; AP, acute pancreatitis; CP, chronic pancreatitis

The following parameters were also varied in the PSA:

- The risk of acute pancreatitis and diabetes from the AFT models were varied using a multivariate normal distribution
- The retention on treatment parametric survival curves were varied using a correlated multivariate normal distribution
- The estimated % TG lowering of individual patients in APPROACH at month 3 was varied and applied to their baseline value to obtain a probabilistic month 3 value as follows:
    - A lognormal distribution was fitted to the ln(%reduction) in TGs at month 3 vs. baseline in APPROACH and the mean and ln(standard error) summarised using STATA's dpplot function. A probabilistic month 3 TG value was obtained by varying the % reduction for each individual patient around the lognormal distribution in Excel and applying it to each patient's baseline TG value
- The predicted TGs for individual patients from the GLMM were varied using a correlated multivariate normal distribution of the model coefficients.
- The TG transition probabilities for the ITT analysis were varied using a Dirichlet distribution and the dose transition probabilities using a Beta (as discontinuation is captured using survival curves)

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

A brief rationale for parameters omitted from the PSA is provided under the "Distribution" column of Table D17.4. These largely comprise values assumed to be zero – i.e. where Akcea is funding the healthcare service, or where the impact on the ICER by the parameter is negligible.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available below.

Table D18 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£213,755

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The APPROACH trial only captured the clinically relevant outcomes of acute pancreatitis and AEs. Outcomes from the APPROACH trial are not generalisable to clinical practice due to the different posology and platelet monitoring rules which resulted in a high treatment dropout rate.

Other important long-term outcomes such as diabetes and CP can only be compared with the literature and surveys from patients on SoC. The model population is a more severe one which includes patients who have experienced AP in the past and this would naturally predict higher incidence of diabetes and chronic pancreatitis than reported in the FCS literature. As a result, the long-term prediction of number of AP events from the model base case on SoC is small (3.4 events) due to a significant proportion of these patients progressing to chronic pancreatitis (which has its own mortality risk and costs) or dying. For easier interpretation, in Table D19 the number of AP events has been calculated by setting the chronic pancreatitis probability to zero.

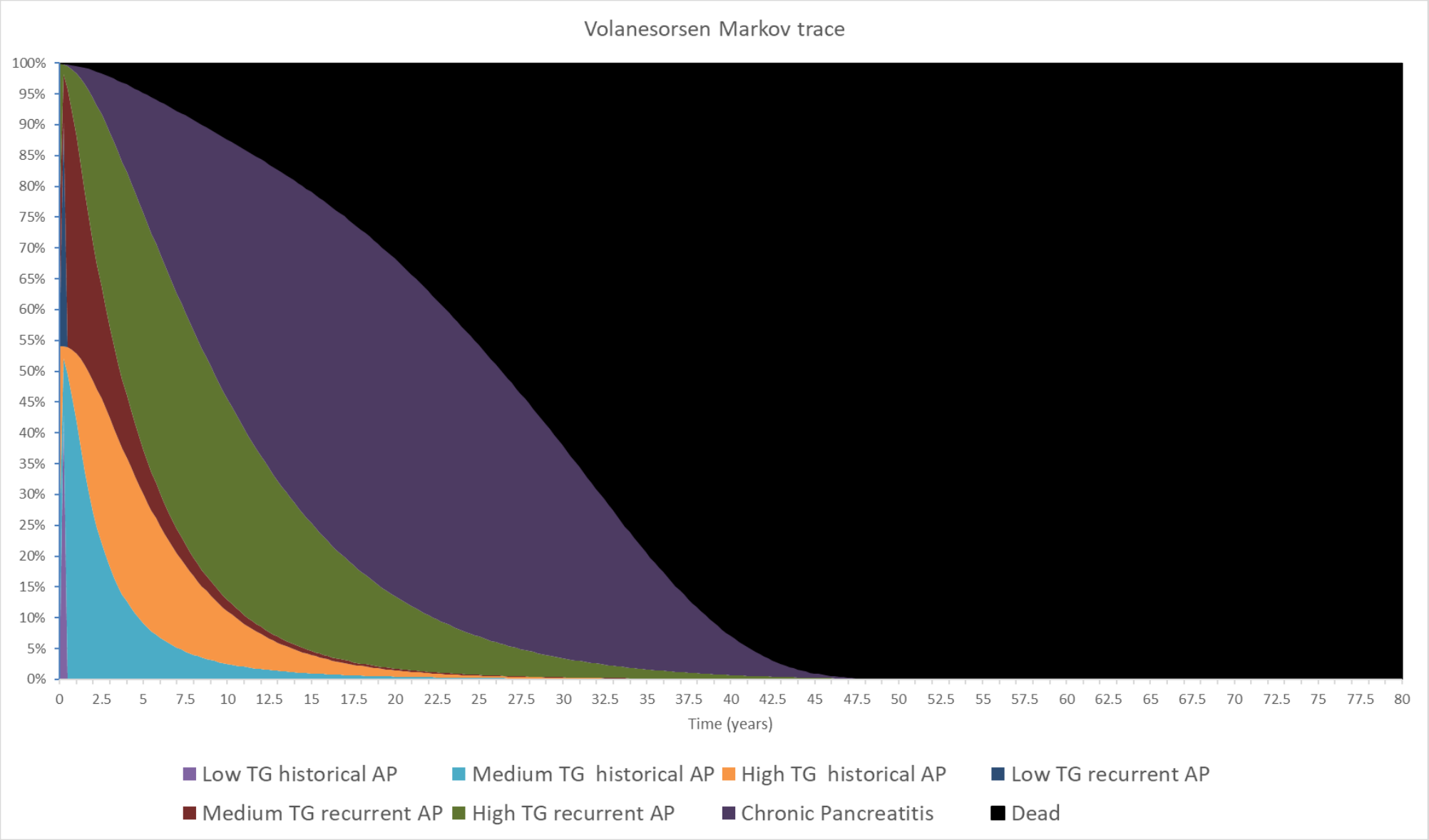
Table D19 Summary of model results compared with clinical data and/or observational data

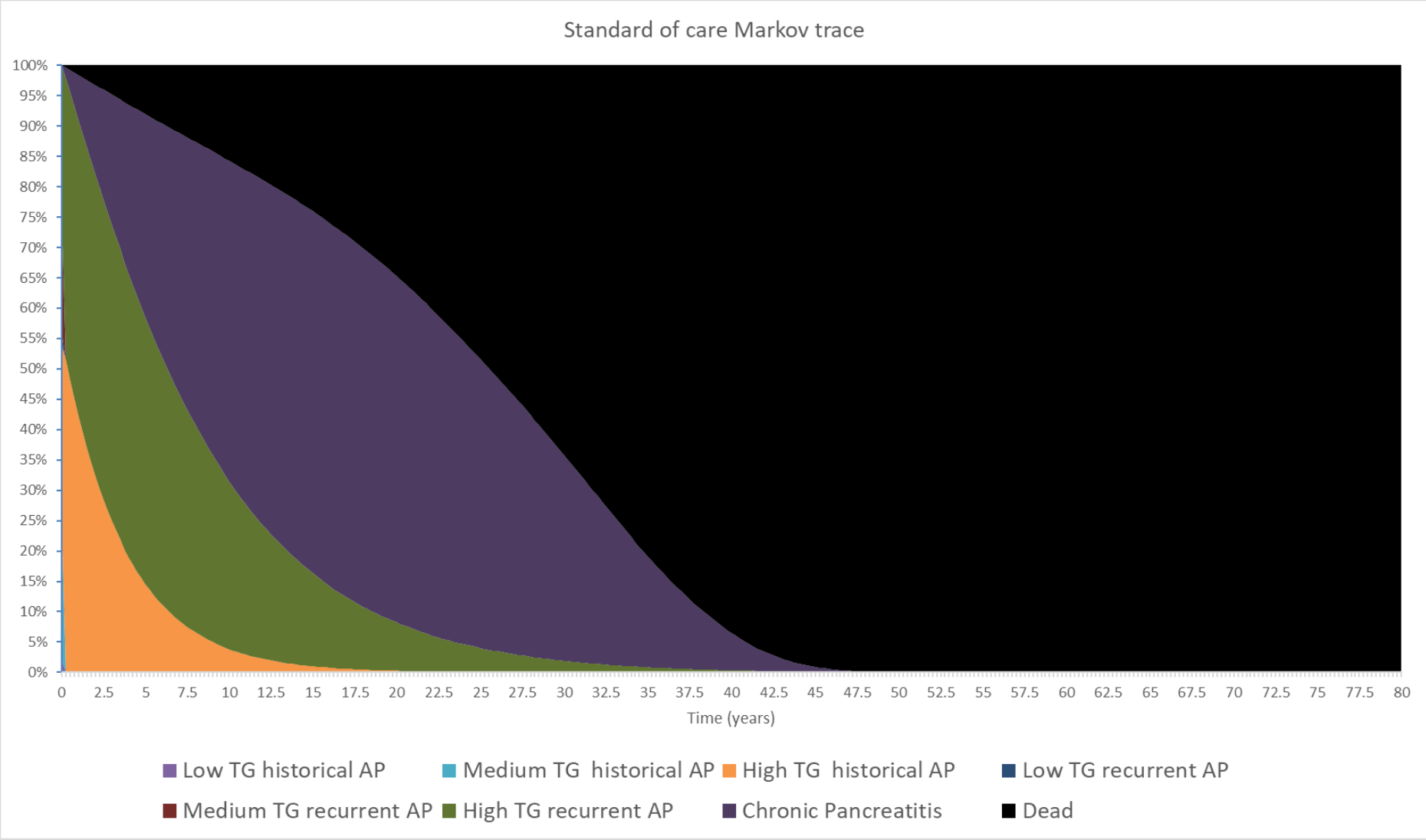
Outcome	Clinical trial result	Model result
Acute pancreatitis	Volanesorsen = [redacted] per patient year of exposure in APPROACH OLE vs [redacted] per patient year in the medical history from APPROACH OLE	SoC = [redacted] events over 59-year time horizon Volanesorsen = [redacted] events over lifetime horizon (if no treatment discontinuation is assumed other than for chronic pancreatitis)
Thrombocytopenia	[redacted] (Table 14.3.1.5.3). Only 1 'mixed dose' patient had severe thrombocytopenia (9.9.4).	thrombocytopenia events per patient are predicted over the 59-year model lifetime if no discontinuation is assumed.
Long-term outcomes		
Outcome	**Observational result**	**Model result**
Chronic pancreatitis	In FCS cross-sectional prevalence is approximately 10% (IN-FOCUS). Prevalence following recurrent AP is 36% in the literature but can be up to 60% in alcoholics (Sankaran et al., 2015),	57% prevalence of *de novo* CP after 20 years on SoC, peaking at 59.8% (this was calibrated using the clinical expert survey reported in Appendix 7).
Diabetes	In FCS cross-sectional prevalence is approximately 16% (IN-FOCUS). Prevalence in patients with high TGs and AP is up	51% prevalence of *de novo* diabetes after 20 years on SoC

	to 72% (Scherer et al., 2014).	
Mortality	In FCS AP-related mortality (including that due to longer-term complications) was 6% in a cross-sectional survey (Gaudet et al., 2016a). No all-cause mortality data is available in FCS.	35% mortality rate on SoC after 20 years on SoC.

[1]Number of AP events predicted by setting the probability of CP to zero and setting treatment discontinuation to zero.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.


Volanesorsen Markov trace
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
32.5
35
37.5
40
42.5
45
47.5
50
52.5
55
57.5
60
62.5
65
67.5
70
72.5
75
77.5
80
Time (years)
Low TG historical AP
Medium TG historical AP
High TG historical AP
Low TG recurrent AP
Medium TG recurrent AP
High TG recurrent AP
Chronic Pancreatitis
Dead


Standard of care Markov trace
100%
95%
90%
85%
80%
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
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17.5
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22.5
25
27.5
30
32.5
35
37.5
40
42.5
45
47.5
50
52.5
55
57.5
60
62.5
65
67.5
70
72.5
75
77.5
80
Time (years)
Low TG historical AP
Medium TG historical AP
High TG historical AP
Low TG recurrent AP
Medium TG recurrent AP
High TG recurrent AP
Chronic Pancreatitis
Dead

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The accrual of QALYs is based on time spent in lower-risk TG states, where day-to-day health state HRQL is higher. Staying in lower-risk TG health states also reduces AP events, which acts as a break on transition to recurrent AP and the chronic pancreatitis health state with its associated low HRQL and raised mortality risk. Staying in lower-risk TG health states reduces transition to diabetes, with is associated disutility and mortality risk.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table D20 Model outputs by clinical outcomes

This is not relevant to our model: QALYs and costs by health state are presented in Sections 12.5.6, 12.5.8 and 12.5.9.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

Table D21 Summary of undiscounted QALY gain by health state

Health state	QALY volanesorsen	QALY standard of care	Increment	Absolute increment	% absolute increment
Low risk TG-AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG-AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG-historical AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	QALY volanesorsen	QALY standard of care	Increment	Absolute increment	% absolute increment
historical AP					
High risk TG-historical AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis-disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events-disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**8.56**	**6.63**	**1.93**	**Total absolute increment**	**100%**

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator.

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care.

	Base case Total QALYs	EAMS scenario Total QALYs
Volanesorsen	[redacted]	
Standard of care	[redacted]	
Incremental	[redacted]	[redacted]

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented below.

Table D22 Summary of undiscounted costs by category of cost per patient

Item	Cost volanesorsen	Cost standard of care	Increment	Absolute increment	% absolute increment
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other health care resource costs[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic pancreatitis costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

[1]Costs in the volanesorsen arm are higher due to less patients transitioning to the chronic pancreatitis health state or dying.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented below.

Table D23 Summary of undiscounted costs by health state per patient

Health state	Cost volanesorsen	Cost standard of care	Increment	Absolute increment	% absolute increment
Low risk TG-AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG- AP Naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low risk TG-historical AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-historical AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Cost volanesorsen	Cost standard of care	Increment	Absolute increment	% absolute increment
historical AP					
Low risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Med risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk TG-recurrent AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute pancreatitis-cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events-cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided below.

Table D24 Summary of costs by adverse events per patient

Adverse event	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Grade 1	£63.11	£0.00	£63.11	£63.11	56%
Grade 2	£14.85	£0.00	£14.85	£14.85	13%
Grade 3	£3.67	£0.00	£3.67	£3.67	3%
Grade 4	£30.49	£0.00	£30.49	£30.49	27%
Total	**£112.12**	**£0.00**	**£112.12**	**Total absolute increment**	**100%**

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D17.2.

The top 15 most sensitive parameters only are presented in Table D25. All parameters that result in a difference of more than £1,000 in the ICER between the lower and upper input value are shown in Appendix 11.

Table D25 Results of deterministic one-way sensitivity analysis

Parameter	ICER with lower value	ICER with upper value	Difference
Basecase ICER	£213,755		
Annual missed doses every 2 weeks dosing	£230,991	£193,722	£37,269
AP rate high TG - patients with recurrent AP	£234,447	£198,477	£35,970
U Chronic pancreatitis - SoC	£204,237	£224,399	£20,162

Parameter	ICER with lower value	ICER with upper value	Difference
Cost chronic pancreatitis	£221,506	£205,217	£16,290
Annual carer utility from treatment	£221,279	£206,726	£14,554
AP rate med TG - patients with recurrent AP	£211,021	£224,644	£13,623
U Low TG- Historical AP	£220,501	£207,645	£12,856
TE of volan on AP rate med/low risk TGs	£210,995	£222,800	£11,805
UD Diabetes (with complications)	£219,166	£208,247	£10,918
U Low TG- recurrent AP	£219,215	£208,755	£10,460
U High TG- recurrent AP	£208,954	£218,831	£9,877
Prob recurrent AP is fatal	£215,340	£212,025	£3,315
Prob CP after recurrent AP, 100 weeks	£215,492	£212,202	£3,290
U High TG- Historical AP	£212,227	£215,320	£3,093
U of (D+E): Current AP event	£212,632	£214,965	£2,333

Key: HRU, healthcare resource use; U, utility; UD; utility decrement; Prob, probability; RR, relative risk; TE, treatment effect; AP, acute pancreatitis; CP, chronic pancreatitis

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D17.3.

Table D26 Scenario analysis results

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Base case			[redacted]	[redacted]	**£213,755**
EAMS scenario	Lognormal discontinuation Treatment effect an APs Grade 4 thrombocytopenia events	No discontinuation No AP while on volanesorsen No grade 4 thrombocytopenia events	[redacted]	[redacted]	[redacted] (£78,664 with full QALY weighting)
Starting population	Genetically confirmed with a history of AP	Any genetically confirmed FCS patient	[redacted]	[redacted]	£244,253
Dosing schedule	285 mg weekly for three months followed by every	APPROACH ITT analysis (note that	[redacted]	[redacted]	£260,216

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
	2 weeks maintenance dosing	weekly dosing is not assumed to incur additional drug costs over once every 2 weeks dosing in this scenario)			
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level	[redacted]	[redacted]	£201,999
		All health states have utility of 0.7 (assessment group request)	[redacted]	[redacted]	£267,949
Treating chronic pancreatitis patients	Do not treat	Treat, assuming that patients have a daily HRQL benefit of 'low' vs 'high' TGs as per the	[redacted]	[redacted]	£221,229

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		vignette study			
Calibration of risk of CP	60% lifetime risk of CP	42% lifetime risk of CP	[redacted]	[redacted]	£239,253
Inclusion of CP as health state	Include CP	Exclude CP	[redacted]	[redacted]	£268,250
Utility of CP	Assumption using low TG health state	Laramee et al. utility	[redacted]	[redacted]	£217,168
Impact of volanesorsen on diabetes costs and QALYs	Volanesorsen reduces by 50%	No impact from volanesorsen	[redacted]	[redacted]	£218,738
Disutility of diabetes	Diabetes with 50% complications	Uncomplicated diabetes	[redacted]	[redacted]	£236,083

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Carer utility gain	Include	Exclude	[redacted]	[redacted]	£258,623
Discount rate	3.5% for costs and QALYs	1.5% for costs and QALYs	[redacted]	[redacted]	£201,948

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12.5.13 Present results of the probabilistic sensitivity analysis described in table D17.4.

Table D27 Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£280,647
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The analysis included an analysis of probability of cost-effectiveness via a CEAC. Volanesorsen had a [redacted] probability of being cost-effective at a willingness to pay threshold of £100,000 and a [redacted] probability of being cost effective at a willingness to pay threshold of £300,000 ([redacted]).

[redacted]

[redacted]

Table D28 shows the results of the structural sensitivity analyses (see Table 17.1).

Table D28 Results of structural sensitivity analyses

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Base case			[redacted]	[redacted]	**£213,755**
Treatment discontinuation	Lognormal curve	Lognormal curve with 0.3 'hazard ratio' applied at all points	[redacted]	[redacted]	£203,466
		Loglogistic curve	[redacted]	[redacted]	£214,552
		Exponential curve	[redacted]	[redacted]	£213,991
		Weibull curve	[redacted]	[redacted]	£220,481
		No discontinuation	[redacted]	[redacted]	[redacted] (£92,242 with full QALY

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
					weighting)
Data informing SoC health states	Regressions	APPROACH SoC arm patient transitions	[redacted]	[redacted]	£213,239

12.5.14 What were the main findings of each of the sensitivity analyses?

In the base case, the model was most sensitive to the number of missed doses on every two weeks treatment (which drives volanesorsen costs), the AP rate of high TG patients with recurrent AP, the HRQL and costs of chronic pancreatitis and the AP rate of medium TG patients with recurrent AP. These results are unsurprising; AP has the highest immediate mortality risk and drives incidence of CP which is a high cost health state with low HRQL (particularly with diabetes). The higher the rate in the recurrent AP states, the higher the 'jump' in rate when a patient moves from having historical AP to recurrent AP, the higher the transition to CP and the larger the absolute benefits from volanesorsen.

Large QALY gains can be achieved through day-to-day lowering of TGs from ultra-high levels on SoC, where patients are highly symptomatic, to the lower levels on treatment where patients experience less symptoms such as abdominal pain and fatigue. The model was not very sensitive to health state costs, which are relatively low due to the infrequency of healthcare resource use, and the disutility of AP, which is a relatively infrequent event, albeit with significant mortality.

The probabilistic ICER was £280,647 compared with a deterministic ICER of £213,755. This likely relates to the very small patient numbers informing distributions, influential relative risks/treatment effects with skewed distributions and non-linearity in the model due to the interaction between multiple health states. A number of multivariate distributions were used in the PSA which may also have skewed values towards higher costs or QALYs. Given the very small patient numbers underpinning the model, probabilistic results should be interpreted with caution due to the very wide confidence intervals underpinning treatment effects.

Scenario analyses

Scenario analyses are presented in Table D26. The EAMS scenario, which Akcea believes is representative of outcomes achievable by volanesorsen in UK clinical practice, results in a lower ICER of £198,897 and [redacted] undiscounted QALYs. This QALY gain is important in the context that NICE may permit a

QALY weighting where more than 10 QALYs are achieved by an intervention. If a QALY weighting of 2.5 were permitted, the ICER would be £78,664. All survival curves were fitted to newly treated patients from the APPROACH OLE study. However, this included patients who remained on weekly dosing and stopping rules were stricter than under the SmPC. Thus far, 20 patients have initiated treatment in EAMS since July 2018 with a mean follow-up time of 7 months. Of these, only one patient has discontinued treatment, and this was for medical reasons unrelated to their FCS or treatment with volanesorsen. Therefore, it is quite possible that in practice a QALY gain far exceeding that in the base case will be achieved and that the ICER, if allocated a QALY weighting, will be well below that presented in the base case.

Including the whole FCS population results in a larger ICER due to the lower risk of AP and absolute risk of transitioning to CP and developing diabetes. The ITT scenario results in a higher ICER than the once every 2 weeks base case if weekly dosing is costed the same as biweekly and the same entry population is assumed. The ITT scenario uses a different modelling approach to the SmPC base case as it allocates patients to multiple health states conditional on dose. More patients discontinue, so drug costs are lower, and nearly half of the discontinuation occurs within the first year, which prevents any significant longer-term benefits from being realised. There is also no stopping rule, and patients who did not see a >25% reduction in effect or whose TGs remained above 22.6 mmol/L remained on treatment.

Use of the EQ-5D reduces the ICER as the QALY loss from a death is high outside the CP health states. Therefore, the absolute QALY gain from reducing mortality is greater (as observed from the larger QALY gain vs. the base case). Assuming a flat utility across all non-CP health states reduces the absolute QALY gains from reducing mortality while also removing any day-to-day utility HRQL improvement. Given the clear impact of FCS on day-to-day HRQL and evidence of improvement in HRQL on volanesorsen (see section 7.1), the company believes this to be a scenario that fails to reflect the severity of the disease and the significant positive impact from volanesorsen.

The decision whether to continue to treat patients with chronic pancreatitis has a large impact in the model (<£8k increase in the ICER), as although a large proportion of patients on SoC develop CP most of these patients will already have discontinued treatment prior to developing it, so the cost difference is small and offset by day to day gain in HRQL but not mortality.

The lower the assumed risk of transitioning to CP (via the calibration factor), the higher the ICER. This is because CP is an extremely expensive health state and has extremely low utility, not only because of FCS but because of chronic pancreatic pain and high diabetes comorbidity. As these patients are already assumed to have very low HRQL in the base case, the very low Laramée CP utility, which is only slightly higher, produces very similar results.

The ICER is relatively insensitive to the assumption that ongoing treatment with volanesorsen decreases the cost and disutility of diabetes, due to the high discontinuation rate in the base case before many patients get diabetes. On the other hand, the ICER increases quite significantly if the disutility of diabetes, which is based on 50% of patients having concomitant complications, is replaced with the disutility of uncomplicated diabetes, because QALY gains from preventing diabetes are much smaller.

Exclusion of carer utilities increased the ICER by around £45k. Discount rates of 1.5% decreased the ICER by nearly £12k, demonstrating the important impact that longer-term outcomes have in the model. The majority of patients have discontinued by 10 years, so the impact of discounting on drug costs is largely over past this timepoint, whereas patients continue to reap the benefit of having avoided progression to chronic pancreatitis well into the future.

Structural sensitivity analyses

Structural sensitivity analyses are presented in Table D28. The ICER was relatively insensitive to assumptions regarding discontinuation and choice of survival curve. However, a dramatic increase in QALYs is seen if no discontinuation is assumed (other than for stopping rules or development chronic pancreatitis), accompanied by a drop in the ICER to £202,724. Nearly [redacted] undiscounted QALYs are achievable if there is no discontinuation,

demonstrating the significant clinical benefit that patients who remain on volanesorsen can gain.

The use of patient transitions from the SoC arm of APPROACH (as per the ITT analysis) instead of the regressions was included as a validation exercise. The regressions are used to calculate mean TGs for the cohort and allocate all patients to one TG health state, whereas the SoC data from APPROACH distributes patients into multiple TG health states according to the ITT analysis of the trial. Despite these quite different approaches, use of the SoC ITT data instead of the regressions made very little difference to the ICER, demonstrating the robustness of using the regression analysis to inform health state occupancy on SoC.

12.5.15 What are the key drivers of the cost results?

The major driver of cost are the drug costs. Other than these, the major cost driver is the cost of chronic pancreatitis.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

The scope includes, if evidence allows, analysis of the subgroup of patients with diabetes (Table A1). 10 (15.2%) patients in APPROACH had type II diabetes and one patient (1.5%) had diabetes mellitus (Table C8). In the APPROACH OLE study, 12 patients (17.6%) had diabetes (Table C10). In the APPROACH study, patients on volanesorsen with a history of diabetes (n=7) saw an 80.7% reduction in their TGs (95% CI -90.9%, -70.6%) whereas patients without diabetes (n=26) saw a reduction of 69.4% (95% CI -78.5%, -60.4%) (Table 14, Akcea response to clarification questions, July 2018).

Given such small patient numbers, in particular those for which there is fully randomised data available from APPROACH, a subgroup analysis of cost effectiveness has not been carried out for the subgroup of patients with diabetes. However, the model incorporates a simple 50% reduction in the costs and disutilities of diabetes for these patients, based on the 56%

increase in insulin sensitivity observed in a randomised controlled trial of volanesorsen in diabetic patients (Digenio et al., 2016, Table D4).

We present here a subgroup analysis of a more severe group of recurrent AP patients that has experienced ≥2 adjudicated acute pancreatitis events in the past 5 years.

12.6.2 Define the characteristics of patients in the subgroup(s).

The patients in the analysis are intended to be representative of the 11 patients in the APPROACH study who had ≥2 adjudicated AP events in the past 5 years recorded in their medical history.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

This population is modelled by starting all patients in the ‘recurrent AP’ health states of the model, with the risk of AP while on SoC informed by the event rate of the 11 patients in the APPROACH trial who had ≥2 adjudicated AP events in the past 5 years recorded in their medical history. The TGs at model entry for this patient population are not captured directly from the APPROACH trial but instead are reweighted based on their AP history as carried out for the whole patient population in section 12.2.1. All risks of clinical sequelae and treatment effects on risk are as also as per the base case analysis.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Table D29.1 Subgroup analysis results scenario 1

All assumptions as per base case except for risk of AP at baseline:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£216,311
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table D29.2 Subgroup analysis results scenario 2

All assumptions as per 'EAMS scenario' except for risk of AP at baseline.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£185,394
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table D29.3 Total undiscounted QALYs scenario 1

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care when assumptions other than the population are as per the base case.

	Total QALYs
Standard of care	[redacted]
Volanesorsen	[redacted]
Incremental	[redacted]

Table D29.4 Total undiscounted QALYs scenario 2

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care when assumptions other than the population are as per the 'EAMS scenario'.

	Total QALYs
Standard of care	[redacted]
Volanesorsen	[redacted]
Incremental	[redacted]

It can be seen that volensorsen is anticipated to gain [redacted] undiscounted QALYs in a population with recurrent AP under the EAMS scenario. If a full QALY weighting of 2.5 were granted under this scenario, the ICER would reduce to £74,158.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-

reference to evidence identified in the clinical and resources sections.

A number of separate steps have been taken to validate the modelling presented in this submission.

Presentation to expert clinical advisory board

Two advisory board meetings were convened, one on November 14th, 2017 and one post-marketing authorisation on May 7th, 2019, both in Birmingham, UK. The purpose of the meeting was to review the proposed health economic model structure and key assumptions and to request clinical and economic expert input. The meetings were attended in total by 3 clinical experts (one Consultant Physician & Endocrinologist, two Consultants in Metabolic Medicine) and 2 Professors of Health Economics.

A short presentation was given on the clinical data, including results from the APPROACH and APPROACH OLE studies, as well as the available observational data from the literature. Following this, an outline of the proposed economic model structure was shared with the experts. During the presentation on the economic model structure, the experts were consulted on a range of questions including:

- Whether economic model structure accurately reflects important clinical aspects of the disease pathway.
- Whether history of acute pancreatitis is associated with increased risk of future episodes and whether experts were aware of sources of evidence to characterise this relationship.
- Whether experts expected any waning of treatment effect in the longer term that did not relate to dose pauses or discontinuations.
- What the appropriate methods would be to capture impact of dose pauses and discontinuations in the model.
- Appropriate way to incorporate diabetes within the model.

- Potential options for treatment continuation rules supplementary to those in the SmPC to be introduced in the model.

Independent model review

A review of the economic model was undertaken by an independent health economics consultant in February 2018. The scope of the review was to assess the model structure, input parameters and assumptions. The model review was carried out with reference to the NICE methods guide by an experienced health economist. Following the review, a workshop was convened to address queries regarding the model structure and assumptions and to identify model amendments and improvements.

Model QA checking

In May 2018 a model QA was undertaken by an independent health economist. A further review was carried out in July 2019 following adaptations to the model required in order to reflect the SmPC. The independent consultant conducted a full technical validation of the model, this process involved: i) checking for technical programming or calculation errors, and ii) looking for logical errors or common-sense issues related to structure, assumptions, inputs and results.

External validation

FCS is a very rare condition and consequently evidence to support validation of the economic model is limited. There are several key outcomes in the model that influence the costs and outcomes – acute pancreatitis, chronic pancreatitis and mortality. Diabetes is also captured as a comorbidity. Outcomes which were not captured in APPROACH and APPROACH OLE, such as incidence of chronic pancreatitis and diabetes, were calibrated using the literature, including several systematic reviews.

Model outputs for acute pancreatitis rates have been compared with the APPROACH OLE medical history in section 12.5.2.

12.8 Interpretation of economic evidence

The economic analysis presented in this submission demonstrates that volanesorsen would be a good use of NHS resources. The estimates presented in the OWSA are relatively narrow for such a rare disease, suggesting the model is stable, giving certainty to the results presented. The results from the SmPC and EAMS analyses demonstrate the impact discontinuation rates have on incremental QALYs and costs (and therefore ICER estimates). Both scenarios present ICER estimates suggesting volanesorsen offers value for money. This should give the NICE Committee confidence that for both these scenarios or if the reality is in between, volanesorsen would be a good use of NHS resources.

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

It is unknown whether the Lin model incorporates CP as an outcome. As AP and CP are mutually exclusive in our model, we set CP to zero to facilitate comparisons between the two models. The Lin model estimates average life expectancy of 16.45 years for patients on standard care (dietary control alone), compared with [redacted] years in our model (if starting age is set to 38 years as in Lin). Patients were expected to experience 10.16 episodes of acute pancreatitis during their lifetime in Lin, compared with [redacted] episodes in our model. The Lin model reports 3.16 life years gained and 7.7 fewer episodes of AP if TGs were reduced by 50%. These values compare with [redacted] life years gained and [redacted] fewer episodes of AP in our model if no treatment discontinuation is assumed.

It is unknown what health outcomes other than AP the Lin model included, and it is quite possible that our model includes benefits additional to AP (e.g. diabetes) that the Lin model did not capture. Our model also restricts to FCS patients with a history of AP. This may explain why our model predicts greater life years gained from treatment with volanesorsen and why the number of AP events predicted is greater. When the population in our model is broadened to

all FCS patients, the number of AP events predicted reduces to [redacted] and the number of life years gained reduces to [redacted].

A cost-effectiveness analysis of Glybera has been carried out in which a single upfront dose of Glybera was costed at € 1.1m (Han and Ni, 2015). The ICER was € 51,789/QALY, but the incremental costs and QALYs underpinning the ICER were not reported. It is difficult to make comparisons between the two models given the very different types of drug.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The cost-effectiveness analysis is relevant to all groups of patients and specialised services in England that could potentially used the technology as defined in the *final licence indication wording*. Because the scope was produced prior to receipt of European marketing authorisation, which requires patients to be genetically confirmed and at high risk of AP, there is a slight misalignment between the scope and the label.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Key strengths

- TG outcomes on volanesorsen have been obtained from a double-blind placebo-controlled trial and a large open-label study in a population that is generalisable to the UK FCS population. The APPROACH trial provides fully randomised data for the relative effect of weekly volanesorsen compared with placebo in the first 3 months of treatment, while the APPROACH OLE provides a substantial set of data informing the effect of every 2 weeks dosing.

- Data on longer-term efficacy and safety are available from the APPROACH OLE, which informed the model extrapolation beyond the

length of clinical trial. Some patients have been followed up for as long as 3 years.

- A robust GLMM model was developed to inform the treatment effect of every 2 weeks volanesorsen on fasting TGs. The model predictions have strong internal validity, largely reflecting the results of the 'mixed dose' analysis of the clinical data.

- The model is structured to capture the key clinical features of the disease and well describes the effect of volanesorsen at all baseline levels of TG, taking into account patient history of pancreatitis.

- Outcomes of acute pancreatitis, chronic pancreatitis and diabetes have been extrapolated from TG levels using statistical models derived from a large UK patient database, CALIBER.

- Both CALIBER and the Manchester study provided significant resource use information in UK patients with raised triglycerides and, in the case of the Manchester study, an English FCS patient population.

Key weaknesses

- The APPROACH trial initiated all patients on weekly dosing and the model was initially developed to reflect the conduct of the APPROACH trial. While we have made use of the best evidence available to model an every 2 weeks dosing scenario, there is uncertainty due to the lack of randomised clinical evidence

- [redacted] of patients had missing AP history (see Table C10). As this was used to calculate the counterfactual AP rate of patients on SoC, this will almost certainly underestimate the treatment effect of volanesorsen on AP.

- The memoryless feature of the model means that cumulative incidence of diabetes could not be captured; diabetes was simply captured as an increasing prevalence. The model may therefore underpredict the

benefits of volanesorsen on incidence of diabetes and the ICER overestimated.

- The memoryless feature of the model means that only exponential models could be used to derive probabilities of developing AP and diabetes. These models may not have been the best fit to the CALIBER data and may either over or under-predict event rates.

- There is a paucity of information on both the day-to-day HRQL and costs of managing chronic pancreatitis. As both of these are strong drivers of model results, there is considerable uncertainty associated with the values used.

- The analysis has not fully captured all the outcomes specified in the scope: neurological and psychological clinical data were not available nor was robust evidence regarding pancreatic necrosis, fatty liver disease and cardiovascular disease

- Patients with FCS experience splenomegaly and hepatomegaly, for which there are no specific interventions. Symptoms also overlap with the symptoms of FCS and pancreatitis. There may be an additional QALY gain from reduction of these symptoms which is not reflected in the model.

- Due to the lack of a disease-specific instrument, coupled with the potential issue of adaptation, the utility values collected during the trial likely overestimate HRQL of FCS patients.

- Patients with acute pancreatitis may experience more frequent events over time. Other than development of chronic pancreatitis, the impact of increasing severity has not been captured in the model. More frequent events would increase the costs of hospitalization over time, the disutility and mortality from FCS.

- Due to the Markovian assumption, the model cannot ‘remember’ when patients discontinued treatment with volanesorsen. Prevalence of

diabetes in patients who discontinue volanesorsen is based purely on time since model entry rather than the time since treatment discontinuation. This means that patients who have been on volanesorsen for some time then discontinue have the same risk of diabetes as patients who have never had treatment at all. This may greatly overestimate the development of diabetes in the volanesorsen arm.

- Patients with FCS take a variety of concomitant medications, including corticosteroids ([redacted] of patients in APPROACH OLE) and analgesics (including opioids) and it is unclear how many of these would be discontinued one established on treatment with volanesorsen.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Below we provide a list of activities that could enhance the economic modelling of FCS. However, it is critical that the very small patient numbers are taken into account and some pragmatism is needed in decision making as we are using economic and statistical modelling approaches designed for much larger dataset than we have available for FCS.

- A discrete event simulation model (DES) may have been more appropriate to the analyses, in order to capture the impact of incremental disease-related morbidities and patient heterogeneity. However, it is unclear to what extent this would change the results, given the lack of availability of functions linking TG levels to cost and utility. The results from our model mirror very closely the results reported in the Lin ISM.

- Further research into how high TGs affect the risk of developing diabetes and how this is modified by presence of AP would help support the epidemiology of diabetes in FCS. The AFT models of diabetes were obtained from a population with co-morbidities such as high body weight which may have confounded the results in the 10-22.6 mmol/L health states in particular. Differentiating risk of diabetes

in this health state vs. the risk in the ≥22.6 mmol/L is important in the model.

- Further studies on the resource use and cost of patients with chronic pancreatitis would provide more robust estimates of the cost of managing these patients.
- Further studies on the HRQL of patients with chronic pancreatitis would provide more robust estimates of the utility associated with HTG-induced chronic pancreatitis.
- Measurement of the HRQL of patients using an instrument developed more specifically for FCS might provide more robust estimates of utility gain from treatment with volanesorsen.
- Design and validation of an appropriate disease-specific Patient-Reported Outcome Measure would more appropriately capture FCS patients' day-to-day HRQL, and the impact on it of blood TG levels.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.

To date, [redacted] with FCS have been identified in England, of the estimated 120 patients based on prevalence estimates. Of these [redacted] have genetically confirmed FCS and another [redacted] have a phenotypic diagnosis. These phenotypically diagnosed patients will be eligible for the NHS England genetic testing program from April 2020 (see section 8.7). Assuming that all

these patients obtain a genetic diagnosis and that 80% have a history of acute pancreatitis we estimate that [redacted] patients are eligible for treatment in England.

Akcea has worked with clinicians on understanding and identifying FCS. As such we consider these estimates to represent the vast majority of eligible patients in England.

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

We anticipate that approximately [redacted] patients will have been initiated on volanesorsen by the end of year 1. This is high due to the expectation that all the EAMS patients will start treatment in year 1. Thereafter we expect patients to commence treatment at a steady rate up to [redacted] patients having been initiated by year 5, at which point we expect initiation to plateau. We estimate [redacted] patients would remain on treatment at the end of year 5, with the model projecting a small loss (i.e. 1 patient) to mortality over this timeframe.

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Costs associated with the management of FCS include those relating to routine appointments in primary care and with specialists, costs associated with the management of acute pancreatitis episodes, costs associated with the management of comorbid diabetes, and costs associated with the management of chronic pancreatitis.

13.4 Describe any estimates of resource savings associated with the use of the technology.

In Year 1, volanesorsen is estimated to save approximately £[redacted] in NHS resources, compared to standard of care management. By Year 5, cumulative NHS resource savings associated with volanesorsen are estimated at [redacted].

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

An issue for this patient population is having pancreas surgery to deal with AP prior to receiving the FCS diagnosis. While the treatment cannot prevent this, improved awareness of the disease may help prevent some of these pancreas operations due to early FCS diagnosis.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

FCS has a significant impact on work productivity, see Section 7.1. In the IN-FOCUS study (Davidson et al., 2018), only 60% of patients with FCS were employed full- or part-time. Most of those who were unemployed had been employed in the past and many attributed their unemployment to FCS. Forty percent of homemakers felt their lack of employment opportunities was due to FCS.

The symptoms of FCS can limit patients' ability to train for or perform work in their preferred career, and patients find that they may miss out on promotion because of frequent absences from work (Gelrud et al., 2017). Patients report that fatigue and an inability to concentrate limit performance at work (Gelrud et al., 2017).

The ReFOCUS study (n=22 volanesorsen-treated patients) reported that the proportion of respondents who reported no interference of FCS with work or school increased from 36% before starting volanesorsen to 64% during treatment (Arca et al 2018), a substantial improvement.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Estimated net budget impact (undiscounted) for the NHS and PSS over a 5-year period, is set out in the table below. The net cumulative budget impact in the first year of uptake is estimated at £[redacted].

The top row in the table below reports patients initiating treatment / cumulative patient numbers. The table doesn't include discontinuation or mortality, these are calculated in the economic model, therefore the table will not sum. The patient numbers are provided for clarity.

Table D30 Estimated 5-year budget impact

Year	1	2	3	4	5
Patients initiating treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative patient starts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	£1,500	£2,379	£2,739	£2,806	£2,869
Resource use savings	-£144,824	-£492,197	-£833,008	-£1,096,162	-£1,341,152
Net budget impact (in year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

The main limitations relate to uncertainties around NHS resource utilisation (as per the economic evaluation) and to uncertainties with regard to patient numbers, expected uptake and treatment discontinuation.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

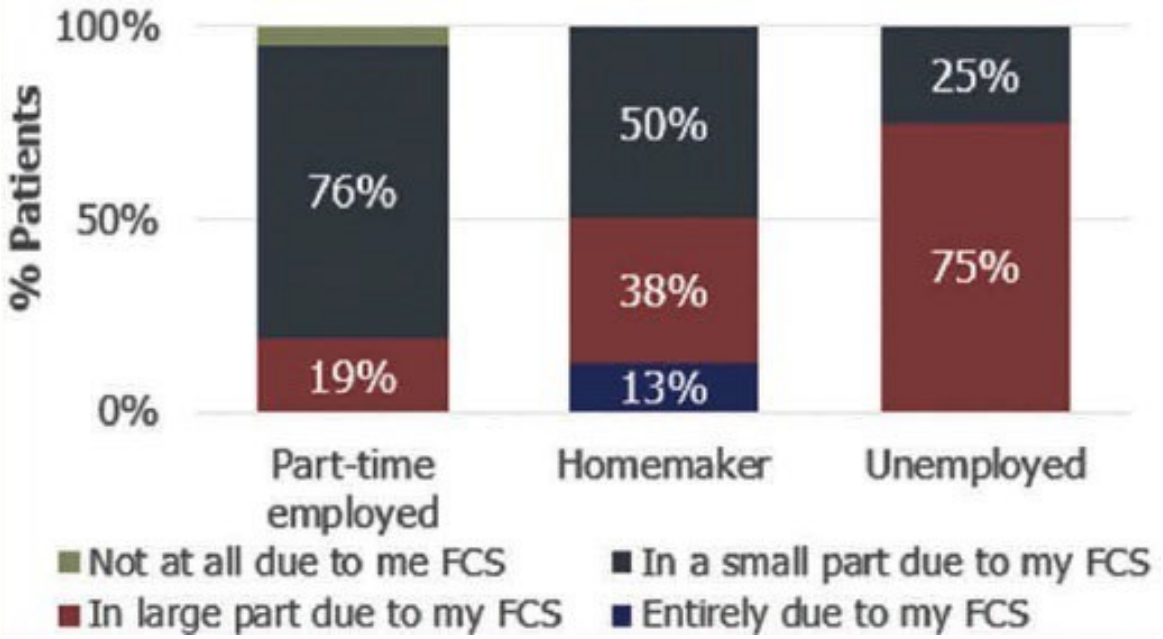
14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

Data on the wider impact of FCS, beyond the NHS are limited. Available research indicates that FCS is likely to have a substantial impact on work productivity. The In-FOCUS study supports this view (Davidson et al., 2017, Davidson et al., 2018). According to the results of this survey, among FCS patients who were unemployed or employed on a part-time basis, almost all of them (95%) reported that their employment status was a result of having FCS. Of those who reported being unemployed, 65% attributed this to FCS (Davidson et al., 2017).

FCS also has an impact on productivity in relation to time taken off from work, for those in part-time or full-time positions. Of those in the survey, 68%

patients reported taking time off. The mean number of days of work missed in the past 12 months was 30 (median = 24, range: 0–210) (Davidson et al., 2017).

Figure 38 Impact of FCS on employment status and unemployed patients



Note percentages may not add up to 100 due to rounding

Source: Davidson et al., 2017

In the literature on pancreatitis there is also evidence of an impact on work productivity. In a multi-centre study, authors observed a profound impact on the ability to work and interpersonal relationships for patients who experienced chronic pancreatitis (Gardner et al., 2010). Data from their survey of 111 patients found that 74% of patients had their work life altered by chronic pancreatitis, 60% reported that it affected their social lives, and 46% reported that it had an effect on relationships with family and friends.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

It is likely that some patients will be in receipt of welfare payments as a result of unemployment due to their disease.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Buying food suitable for FCS patients can be more expensive and requires preparation, in contrast to cheaper ‘convenience’ food. Patients are likely to incur costs associated with travel relating to the management of their condition. Additional costs for items relating to the management of their diet may also be incurred. Data relating to these elements are not currently available.

In additional to the direct annual per patient costs included in section 12.2.6, indirect costs of diabetes per patient are estimated to be £4,503 per patient per year (inflated to 2018 prices) (Hex et al., 2012). The indirect costs of managing chronic pancreatitis are estimated to be £40,183 per patient per year (inflated to 2018 prices) (Hall et al., 2014).

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

There is limited evidence on the time spent by family providing care to patients with FCS. One report (Gelrud et al., 2017), indicates that carer time may relate closely with the complications of FCS. With complications such as episodes of acute pancreatitis being under-reported by patients, carer burden may consequently be underestimated in FCS families.

Carers are reported to use annual leave to provide care for patients, during FCS complications (Gelrud et al 2017).

Data on the impact of longer-term complications arising from FCS is very limited, but a substantial proportion of patients with FCS are expected to develop chronic pancreatitis and/or diabetes in the longer term. As carer burden increases with FCS complications, it is likely that, over the life-time of FCS patients, carer time burden will be substantial, particularly for patients with diabetes or / and chronic pancreatitis.

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

Epidemiological, observational, interventional clinical research conducted in relation to the technology has significantly contributed to a much-improved understanding of the natural history of FCS, the burden of FCS on patients and their families and carers and the clinical and wider benefits the technology offers to address the high unmet need in FCS. A number of further studies are ongoing, due to commence or in planning. This includes a US study to better characterise FCS from a patient perspective (using patient-reported outcomes), a large observational study in the US to better understand the epidemiology, prevalence and natural history of FCS, an extension study of the IN-FOCUS study comparing the symptomatology and disease impact of FCS to a general population cohort, and several studies aimed at developing a FCS-specific outcome measure. Akcea is also currently undertaking a single-centre, open-label phase 2 study to evaluate the efficacy of novel compound for reduction of TG levels in patients with FCS (https://www.clinicaltrials.gov/ct2/show/study/NCT03360747?cond=FCS+Syndrome&rank=4). All these research initiatives will result in an improved understanding of the condition and possible new approaches for treatments.

14.6 Describe the anticipated impact of the technology on innovation in the UK.

From the perspective of Akcea, the adoption of volanesorsen in the NHS would allow the company to continue to invest in the UK with regards further innovative medical technologies in diseases with high unmet need. More broadly, this would be the third antisense technology product to be available in the UK, allowing this technology to be fully explored and understood facilitating the pipeline of antisense technologies across multiple companies and many disease areas. Antisense technology sits between conventional treatments and ATMPs. Access to volanesorsen will demonstrate that the UK

healthcare system can support all types of medical technology across multiple therapy areas.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

As a key part of the comprehensive risk management plan, Akcea will undertake, post-approval, the implementation of a global, multicenter observational cohort study ("registry study") of patients with FCS treated with volanesorsen. At least 100 patients will be included.

While finalisation of design is ongoing, the data captured will be sufficient to meet the requirements of the conditional marketing authorisation. Information captured in this study will include, but not be limited to:

- Determination of real world incidence rates of thrombocytopenia (and any bleeding outcomes associated)
- Determination of real world compliance with platelet monitoring requirements per the SmPC in patients receiving volanesorsen

Other measures of safety will be captured and outlined in the final design.

Further to the safety assessments, the study will aim to capture longitudinal efficacy and outcomes in patients receiving volanesorsen. These may include:

- Triglyceride levels
- Pancreatitis events
- Hospitalisations
- Quality of life assessments

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Assessments of the effectiveness of volanesorsen in routine clinical practice will be facilitated by triglyceride measurements. Triglycerides are typically measured approximately every three to six months in patients with FCS.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

The first injection administered by the patient or carer should be performed under the guidance of an appropriately qualified health care professional. Patients and/or cares should be trained in the administration of this medicinal product in accordance with the patient information leaflet.

We expect treatment with volanesorsen to be consultant-led with monitoring of bloods undertaken through the Akcea-funded Patient Support Programme, which will support the safe and effective use of the technology.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

Akcea Therapeutics has discussed and obtained feedback from clinicians and patient groups on the provision of volanesorsen treatment within current services. No additional infrastructure will be required but we would anticipate an evolution of current service, for example to ensure dietician and specialist nurse support are available in all of the treatment centres. We also expect a more formal alignment of the current treatment centres into a hub and spoke model reflective of the different services and experience in the different treatment centres.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

15.2 Describe the specifics of the MAA proposal, including:

- *The duration of the arrangement, with a rationale*

[redacted]

- *What evidence will be collected to reduce uncertainty*

[redacted]

- *How this evidence will be collected and analysed*

[redacted]

- *The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA*

[redacted]

- *Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)*

[redacted])

- *Funding arrangement, including any commercial proposals or financial risk management plans*

[redacted]

- *The roles and responsibilities of clinical and patient groups during the MAA*

[redacted]

- *What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed*

[redacted]

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

[redacted]

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched to identify the relevant clinical information:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)

The date on which the search was conducted.

The published literature searches were conducted on 19 March 2018 and were subsequently updated in June 2019. The searches of clinical trials registers were conducted on 29 March 2018 and were subsequently updated in June 2019.

The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH)

and the relationship between the search terms (for example, Boolean).

Medline

1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.
12. LMF1.tw.
13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.
14. GPIHBP1.tw.
15. dyslipid?emia.tw.
16. Hypertriglyceridemia/
17. or/1-16
18. Fibric Acids/
19. (medium adj chain adj triglycerides).tw.
20. Fatty Acids, Omega-3.tw.
21. (Nicotinic acid or Niacin).tw.
22. Statins.tw.
23. Volanesorsen.tw.
24. IONIS-APOCIIIRx.tw.
25. ISIS304801.tw.
26. Plasmapheresis.tw.
27. Alipogene tiparvovec.tw.
28. Lomitapide.tw.
29. Mipomersen.tw.
30. Pradigastat.tw.
31. IONIS-ANGPTL3Rx.tw.
32. Evinacumab.tw.
33. or/18-32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized controlled trials/
37. random allocation/
38. double blind method/
39. single blind method/
40. or/34-39
41. clinical trial.pt.
42. exp Clinical Trials as topic/
43. (clin$ adj trial$).tw.
44. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

45. placebos/
46. placebo$.tw.
47. research design/
48. or/40-47
49. exp evaluation studies/
50. prospective studies/
51. or/49-50
52. 40 or 48 or 51
53. Observational studies/
54. 52 or 53
55. case report.tw.
56. Letter.pt.
57. historical article/
58. or/55-57
59. 54 not 58
60. "animal"/
61. "human"/
62. 60 not 61
63. 17 and 33 and 59
64. 63 not 62

Embase
1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.
12. LMF1.tw.
13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.
14. GPIHBP1.tw.
15. dyslipid?emia.tw.
16. Hypertriglyceridemia/
17. or/1-16
18. Fibric Acids/
19. (medium adj chain adj triglycerides).tw.
20. Fatty Acids, Omega-3.tw.
21. (Nicotinic acid or Niacin).tw.
22. Statins.tw.
23. Volanesorsen.tw.
24. IONIS-APOCIIIRx.tw.
25. ISIS304801.tw.
26. Plasmapheresis.tw.
27. Alipogene tiparvovec.tw.

28. Lomitapide.tw.
29. Mipomersen.tw.
30. Pradigastat.tw.
31. IONIS-ANGPTL3Rx.tw.
32. Evinacumab.tw.
33. or/18-32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized controlled trials/
37. random allocation/
38. Single Blind Procedure/
39. Double Blind Procedure/
40. Crossover Procedure/
41. Placebo/
42. randomi?ed controlled trial$.tw.
43. rct.tw.
44. (random$ adj2 allocat$).tw.
45. single blind$.tw.
46. double blind$.tw.
47. ((treble or triple) adj blind$).tw.
48. placebo$.tw.
49. Prospective Study/
50. or/34-49
51. case report.tw.
52. abstract report/ or letter/
53. Editorial.pt.
54. Letter.pt.
55. Note.pt.
56. historical article/
57. or/51-57
58. 50 not 57
59. animal/
60. human/
61. 59 not 60
62. 17 and 33 and 58
63. 62 not 61
64. limit 63 to (abstracts and human and english language and (abstract report or article or article in press or conference abstract or conference paper or "conference review"))

Pubmed
Search (((chylomicronemia[MeSH Terms]) OR pancreatitis[MeSH Terms]) OR hypertriglyceridemia[MeSH Terms]) AND cost effectiveness[MeSH Terms]

Cochrane Central Register of Controlled Trials
1. "Familial chylomicronemia syndrome"
2. MeSH descriptor: [Hyperlipoproteinemia Type I] this term only
3. Lipoprotein adj Lipase adj deficien*
4. MeSH descriptor: [Hypertriglyceridemia] this term only
5. "Volanesorsen"

6. "IONIS-APOCIIIRx"
7. "ISIS 304801"
8. #1 or #2 or #3 or #4
9. #5 or #6 or #7
10.#8 and #9

Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website

The inclusion and exclusion criteria.

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome
Interventions	Volanesorsen
Outcomes	Reduction in triglyceride levels, reduction in chylomicron levels after meals, incidence of acute pancreatitis, chronic pancreatitis and/or diabetes, abdominal pain, hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions), mortality (including all-cause and pancreatitis-related mortality), reduction in apoC-III, overall and serious AEs, discontinuations (all cause, due to AEs, due to lack of efficacy), mortality.
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

The data abstraction strategy.

Data were extracted from all appropriate search results and supplemented with data obtained secondary publications as a result of manual search of bibliography primary publications. Full tect of each study was reviewed by one investigator and validated independently by a second investigator. Any discrepancies with regard to the data elements presented and extracted in an article were resolved by reaching a consensus. The study reports provided by the sponsor have also been included as primary data sources and the data was extracted for analysis from these sources. The abstratcs related to volanesorsen trials that were identified by systematic literature review were listed as related publications.

Specific outcomes from relevant studies are reported in section 9.6

17.2 Appendix 2: Search strategy for adverse events

The clinical SLR revealed no published or unpublished studies relevant to the PICO other than those within the volanesorsen programme (see Section 9.3). For this reason, a separate search for studies specifically addressing adverse events in the relevant population was not carried out.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable.

The date on which the search was conducted.

Not applicable.

The date span of the search.

Not applicable.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

The inclusion and exclusion criteria.

Not applicable.

The data abstraction strategy.

Not applicable.

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The following databases were searched to identify the relevant clinical information:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)
- PubMed

The date on which the search was conducted.

The searches of clinical trials registers were conducted on 29 March 2018 and updated in June 2019. The published literature searches in Ovid (Medline) were conducted on 27 April and in Ovid (Embase) on 3 May 2018. The search on Cochrane was conducted on 2 May 2018. The search on PubMed was carried out on 4 May 2018. Searches were updated in June 2019.

The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline via Ovid

1. (Lipoprotein adj Lipase adj deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.

7. APOC2.tw.

8. Apolipoproteins C.tw.

9. Apolipoprotein AV.tw.

10. APOA5.tw.

11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. (acute adj2 pancrea*).tw.

24. (chronic adj2 pancrea*).tw.

25. (pancrea* adj3 inflam*).ti,ab.

26. or/18,21-25

27. diabetes mellitus.mp.

28. exp diabetes mellitus/

29. exp Diabetes Mellitus, Type 2/

30. diabet*.ti,ab.

31. Diabetic Ketoacidosis.mp.

32. IDDM.tw.

33. NIDDM.tw.

34. (insulin? depend$ or insulin?depend$).tw.

35. ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.

36. ((typ$ 1 or typ$ I) adj diabet$).tw.

37. ((typ$ 2 or typ$ II) adj diabet$).tw.

38. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.

39. or/27-38

40. 17 or 26 or 39

41. Economics/
42. Socioeconomics/
43. Cost$.tw.
44. "costs and cost analysis"/
45. Cost allocation/
46. Cost-benefit analysis/
47. exp Cost effectiveness analysis/
48. ((Cost effectiveness or Cost-effectiveness) adj3 analysis).tw.
49. ((Cost utility* or Cost-utility*) adj3 analysis*).tw.
50. Cost control/
51. Economic aspect/
52. Financial management/
53. Cost savings/
54. exp Cost of illness/
55. Cost sharing/
56. "deductibles and coinsurance"/
57. Medical savings accounts/
58. exp Health care costs$/
59. Direct service costs/
60. exp Drug costs/
61. Employer health costs/
62. Hospital cost$/
63. Health care financing/
64. Health economics/
65. exp Health expenditures/
66. Capital expenditures/
67. Value of life/
68. exp economics, hospital/
69. exp economics, medical/
70. Economics, nursing/
71. Economics, pharmaceutical/
72. exp "fees and charges"/
73. exp budgets/
74. (low adj cost).mp.
75. (high adj cost).mp.

76. (health?care adj cost$).mp.

77. (fiscal or funding or financial or finance).tw.

78. exp Cost minimization analysis/

79. (cost adj estimate$).mp.

80. (cost adj variable).mp.

81. (unit adj cost$).mp.

82. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

83. or/41-82

84. letter/

85. Review/

86. Comment/

87. or/84-86

88. animal/

89. human/

90. 88 not (88 and 89)

91. (United Kingdom or UK or England or Scotland or Wales or Northern Ireland).tw.

92. NHS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

93. 40 and 83 and 87 and 91

94. 93 not 90

Embase via Ovid

1. (Lipoprotein adj Lipase deficien*).tw.

2. LPL.tw.

3. Hyperlipoprotein?emia Type I.tw.

4. (Familial adj chylomicronemia adj syndrome).mp.

5. chylomicron?emia.tw.

6. Apolipoprotein C-II.tw.

7. APOC2.tw.

8. Apolipoproteins C.tw.

9. Apolipoprotein AV.tw.

10. APOA5.tw.

11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. (acute adj2 pancrea*).tw.

24. (chronic adj2 pancrea*).tw.

25. (pancrea* adj3 inflam*).ti,ab.

26. pancreatectomy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

27. or/18,21-26

28. 17 and 27

29. diabetes mellitus.mp.

30. exp diabetes mellitus/

31. exp Diabetes Mellitus, Type 2/

32. diabet*.ti,ab.

33. Diabetic Ketoacidosis.mp.

34. IDDM.tw.

35. NIDDM.tw.

36. (insulin? depend$ or insulin?depend$).tw.

37. ((Non-insulin* or Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.

38. ((typ$ 1 or typ$ I) adj diabet$).tw.

39. ((typ$ 2 or typ$ II) adj diabet$).tw.

40. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.

41. or/29-40

42. 17 or 27 or 41

43. Economics/

44. Socioeconomics/

45. Costs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

46. "costs and cost analysis"/

47. Cost allocation/

48. Cost-benefit analysis/

49. exp Cost effectiveness analysis/

50. (Cost effectiveness or Cost-effectiveness).tw.

51. ((Cost utility* or Cost-utility*) adj3 analysis*).tw.

52. Cost control/

53. Economic aspect/

54. Financial management/

55. Cost savings/

56. exp Cost of illness/

57. Economic burden.tw.

58. Cost sharing/

59. "deductibles and coinsurance"/

60. Medical savings accounts/

61. exp Health care cost$/

62. Direct service costs/

63. Drug costs/

64. Employer health costs/

65. Hospital cost$/

66. Health care financing/

67. Health economics/

68. Health expenditures/

69. Capital expenditures/

70. Value of life/

71. exp economics, hospital/

72. exp economics, medical/

73. Economics, nursing/

74. Economics, pharmaceutical/

75. exp "fees and charges"/

76. exp budgets/

77. (low adj cost).mp.

78. (high adj cost).mp.
79. (health?care adj cost$).mp.
80. (fiscal or funding or financial or finance).tw.
81. exp Cost minimization analysis/
82. (cost adj estimate$).mp.
83. (cost adj variable).mp.
84. (unit adj cost$).mp.
85. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
86. or/43-85
87. letter/
88. Review/
89. Comment/
90. or/87-89
91. animal/
92. human/
93. 91 not (91 and 92)
94. 90 and 93
95. (UK or United Kingdom or England or Wales or Scotland or Ireland).tw.

96. 42 and 86
97. 28 and 86
98. 96 not 94
99. 97 not 94

Pubmed

Search (((chylomicronemia[MeSH Terms]) OR pancreatitis[MeSH Terms]) OR hypertriglyceridemia[MeSH Terms]) AND cost effectiveness[MeSH Terms]

Cochrane Central Register of Controlled Trials

1. "Familial chylomicronemia syndrome"
2. MeSH descriptor: [Hyperlipoproteinemia Type I] this term only
3. Lipoprotein adj Lipase adj deficien*
4. MeSH descriptor: [Hypertriglyceridemia] this term only
5. "Volanesorsen"

6. "IONIS-APOCIIIRx"
7. "ISIS 304801"
8. #1 or #2 or #3 or #4
9. #5 or #6 or #7
10.#8 and #9

Details of any additional searches (for example, searches of company databases [include a description of each database]).

Manual checking of the references lists of relevant systematic literature reviews as well as in publications identified as primary source was also carried out.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The following databases were searched to identify the relevant data on health outcomes and resource use:

- MEDLINE (via Ovid)
- Embase (via Ovid)
- Cochrane Central Register of Controlled Trials (via The Cochrane Library)

- PubMed

The date on which the search was conducted.

The searches of clinical trials registers were conducted on 29 March 2018.The published literature searches for utilities in Medline and Embase using Ovid were conducted on 1st May 2018. The search on Cochrane was conducted on 2 May 2018. The search on PubMed was carried out on 4 May 2018. Searches were updated in June 2019.

The date span of the search.

Date limit was not applied to published literature database searches and, therefore, all search results were included, from inception of the database up to the day the search was carried out.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategy used in the electronic searches for utilities associated with chylomicronaemia and pancreatitis is presented below.

Embase and Medline

1. (Lipoprotein adj Lipase deficien*).tw.
2. LPL.tw.
3. Hyperlipoprotein?emia Type I.tw.
4. (Familial adj chylomicronemia adj syndrome).mp.
5. chylomicron?emia.tw.
6. Apolipoprotein C-II.tw.
7. APOC2.tw.
8. Apolipoproteins C.tw.
9. Apolipoprotein AV.tw.
10. APOA5.tw.
11. Lipase maturing factor 1.tw.

12. LMF1.tw.

13. (glycosyl adj phosphatidylinositol adj anchored adj high adj density adj lipoprotein adj binding adj protein 1).tw.

14. GPIHBP1.tw.

15. dyslipid?emia.tw.

16. Hypertriglyceridemia/

17. or/1-16

18. exp pancreatitis/

19. exp pancreas/

20. inflammation/

21. 19 and 20

22. pancreatitis.ti,ab.

23. pancreatitis.af.

24. (acute adj2 pancrea*).tw.

25. (chronic adj2 pancrea*).tw.

26. (pancrea* adj3 inflam*).ti,ab.

27. or/18,21-26

28. 17 and 27

29. "Quality of Life"/ or Quality Adjusted Life Year/

30. quality adjusted life years/

31. (qaly or qaly$).af.

32. qaly$.tw.

33. ((quality-adjusted or quality adjusted) adj life).tw.

34. (qaly$ or qald$ or qale$ or qtime$).tw.

35. disability adjusted life.tw.

36. daly$.tw.

37. health status indicators/

38. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

39. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

40. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

41. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

42. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

43. (euroqol or euro qol or euro-quol* or euro-qol* or eq5d or eq 5d or eq-5d).tw.

44. (euroqol or euro qol or euro-quol* or euro-qol* or eq5d or eq 5d or eq-5d).af.

45. (hql or hqol or h qol or hrqol or hr qol).tw.

46. (hye or hyes).tw.

47. health$ year$ equivalent$.tw.

48. health utilit$.tw.

49. (hui or hui1 or hui2 or hui3).tw.

50. disutili$.tw.

51. rosser.tw.

52. quality of wellbeing.tw.

53. qwb.tw.

54. willingness to pay.tw.

55. standard gamble$.tw.

56. time trade off.tw.

57. time tradeoff.tw.

58. tto.tw.

59. exp models, economic/

60. *models, theoretical/

61. *models, organizational/

62. economic model$.tw.

63. markov chains/

64. markov$.tw.

65. monte carlo method/

66. monte carlo.tw.

67. exp decision theory/

68. (decision$ adj2 (tree$ or analy$ or model$)).tw.

69. or/29-68

70. letter.pt.

71. editorial.pt.

72. comment.pt.

73. or/70-72

74. animal/

75. human/
76. 74 not (74 and 75)
77. 73 and 76
78. 28 and 69
79. 78 not 77

The complete search strategy used in the electronic searches for resource use:

Please see Section 17.4.7

Details of any additional searches (for example, searches of company databases [include a description of each database]).

Supplementary searches were performed to complement the literature database searches and provide data from recent or ongoing trials. Sources for these searches included:

Registers of clinical trials: clinicaltrials.gov, clinicaltrialsregister.eu, the United States (US) Food and Drug Administration (FDA) website, European Medicines Agency (EMA) website, National Institute for Health and Care Excellence (NICE) website.

The inclusion and exclusion criteria.

Inclusion criteria	
Population	Adults with familial chylomicronaemia syndrome or pancreatitis
Interventions	Volanesorsen or usual care
Outcomes	Health-related quality of life (for patients and carers) outcomes • Symptoms such as pain and fatigue • SF-36 • EQ-5D Economic outcomes • Direct and indirect costs • Cost-effectiveness (QALYs, ICERs) • Productivity • Resource utilisation
Study design	No restriction
Language restrictions	English language
Search dates	No date limits will be applied to the searches
Exclusion criteria	
Population	Other than that described above
Interventions	Other than those described above
Outcomes	Does not report outcomes identified above
Study design	No restriction
Language restrictions	Any language other than English
Search dates	No date limits will be applied to the searches

The data abstraction strategy.

The results obtained from search strategies for economic evidence in section 17.3 (Appendix 3) and for utilities in section 17.4 (Appendix 4) were screened to identify relevant studies for resource utilisation. Data were extracted from all appropriate search results and supplemented with data obtained secondary publications as a result of manual search of bibliography of primary publications. Full text of each study was reviewed by one investigator and validated independently by a second investigator. Any discrepancies with regard to the data elements presented and extracted in an article were resolved by reaching a consensus.

Specific outcomes were captured to reflect the final NICE scope as below.

Quality of life outcomes:

- SF-36
- EQ-5D
- Pain

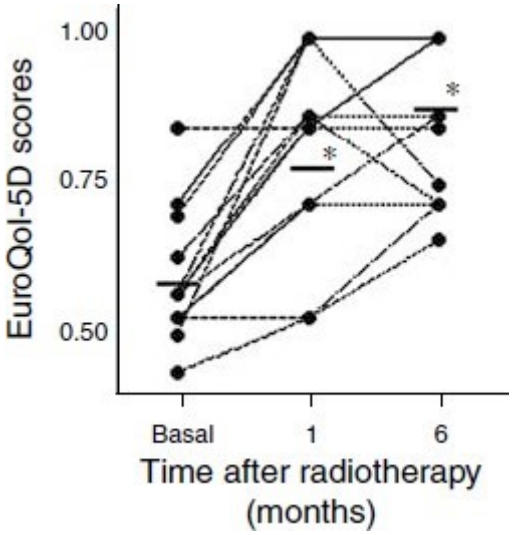
Economic outcomes:

- Direct and indirect costs
- Cost-effectiveness (QALYs, ICERs)
- Productivity
- Resource utilisation

HRQL studies found in the systematic review potentially relevant to the decision problem

Guarner et al. 2009	
Population in which health effects were measured	Patients with chronic pancreatitis who had two or more flare-ups of pancreatitis in the preceding 6 months and / or persistent pain for more than 3 months duration included in the study
Information on recruitment	The treated group comprised 4 women and 11 men with a mean age of 42 years (range: 32 – 80). The median duration of illness from diagnosis to enrolment in this study was 6 years, with a range from 6 months to 16 years. The number of flare-ups of pancreatitis after diagnosis of chronic pancreatitis ranged from 2 flare-ups to more than 15, with a median of 7.
Interventions and comparators	All 15 patients were administered a single radiation dose of 8 Gy to the pancreas.
Sample size	15 patients
Response rates	Not reported

Description of health states	Patients who had good response to radiotherapy also had significant improvement in their QoL. The mean of this group before treatment was 0.585 ± 0.103 with a highly significant difference compared with the mean at 1 month 0.809 ± 0.158 (*P* < 0.001) and at 6 months 0.866 ± 0.136 (*P* < 0.001). Difference between one and 6 months was not statistically significant.
Adverse events	No patients suffered perceptible side effects from radiotherapy apart from transient mild episodes of nausea and / or vomiting that, when present (11 out of 15 patients), appeared during the initial 12 h after treatment.
Appropriateness of health states given condition and treatment pathway.	This study is included to highlight changes in HRQL in patients with chronic pancreatitis during the treatment and follow-up of after a single dose of radiation. Data in this study are potentially relevant for longer-term health states (CP), but the patient population studies is very different to that enrolled in APPROACH
Method of elicitation	HRQL was evaluated after the administration of the EQ-5D questionnaire. The questionnaire was administered right before radiotherapy (at least 1 month after the last acute attack of pancreatitis) and at 1 and 6 months after radiotherapy.
Method of valuation	EQ-5D questionnaire has been adapted and validated to be used in Spanish. The preference value scores assigned to health states used in this study were obtained from a sample of the Spanish population.
Mapping	Not conducted
Uncertainly around values	Data are expressed as mean ± SEM.
Consistence with reference case	The data has been collected using the EQ-5D, the NICE preferred measure of HRQL and is consistent with the reference case.

Results with confidence intervals	The self-administered generic questionnaire EQ-5D was used to generate a number of discrete health states that can be assigned "preference values" ranging from 0, which represents the worst health state, to 1.  Fig. Individual preference values of the EQ-5D questionnaire beforeand after treatment (1 and 6 months) (* P < 0.001).

Laramée et al. 2013	
Population in which health effects were measured	Post-hoc analysis; long-term patient follow-up (mean of 79 months).
Information on recruitment	Trial-based cost-utility analysis, where symptomatic patients with chronic pancreatitis and a distal obstruction of the pancreatic duct but without an inflammatory mass were eligible for the study.
Interventions and comparators	Thirty-nine patients underwent randomisation toto endoscopic drainage of the pancreatic duct (19) and to surgery (20).
Sample size	39 patients enrolled
Response rates	Prospective data were collected for 31 patients (of whom 16 were endoscopically treated and 15 had undergone surgery).

Description of health states	Patient-level EQ-5D data from the trial were used to generated utility scores for both arms at baseline, 6 weeks, 3, 6, 12, 18, 24 and 79 months using the UK time trade-off tariff. The baseline utilities scores for endoscopy and surgery 0.275 (SEM=0.073, n=18) vs 0.335 (SEM=0.069, n=19); at 12 months, 0.639 (SEM=0.052, n=15) vs 0.823 (SEM=0.038, n=19) and at 24 months: 0.686 (SEM=0.062, n=13) vs 0.793 (SEM=0.052, n=17).
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway.	Study in non-FCS population, but given paucity of relevant HRQL data in CP, this study indicates the potential HRQL impact of CP.
Method of elicitation	EQ-5D questionnaire was completed by patients (EQ-5D-3L) which was used to generate utility scores.
Method of valuation	The health state preference values (utilities) for EQ-5D profiles were based on time-trade-off valuations by members of the UK general public (Dolan et al 1997).
Mapping	Not conducted
Uncertainly around values	SEM
Consistence with reference case	Given the data has been collected using the EQ-5D and valued using the UK general population preferences, it is consistent with the reference case.
Results with confidence intervals	As long-term EQ-5D data (post 24 months) were collected only at 79 months, and no difference between groups was demonstrated at 79 months (endoscopy 0.79±0.21; surgery 0.82±0.26; difference −0.03, 95% CI (−0.20 to 0.14), p=0.75)3, after 24 months, it was assumed no difference in utility score between the cohorts and applied a constant utility score of 0.79 (from the endoscopy group) to both groups.

Winter Gasparoto et al. 2015	
Population in which health effects were measured	Patients who had one single episode of acute necrotizing pancreatitis (ANP) and aged between 18 and 70 years were included in the study.
Information on recruitment	Patients admitted to hospital with acute necrotizing pancreatitis in a ten-year interval were identified. 16 patients out of the 38 survivors who were contacted to enrol in the study were included.

Interventions and comparators	No treatment intervention
Sample size	16
Response rates	Not reported
Description of health states	The average health status of all three patients across four of the five domains (mobility, self-care, usual activities and pain/ discomfort) of the EQ-5D-3L descriptive system was level 3 during acute attacks and level 1 at the time of the interview.
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	This study assessed patients' long-term QoL, after a single episode of ANP with the mean interval between the diagnosis and the study being 2.9 years (range 12 to 90 months). Although carried out in non-familial chylomicronaemia patients, the study, nevertheless, measures long term QoL outcome in patients whose symptomatology closely relates to that observed in FCS.
Method of elicitation	QoL was measured by the Medical Outcomes Study - 36-item short-form health survey (SF-36).
Method of valuation	SF-36 has been validated and culturally adapted for Portuguese speaking population in Brazil (Ciconelli et al. 1999). Results obtained were compared to Brazilian sex- and age-matched normative data (Cruz et al. 2013).
Mapping	Not conducted
Uncertainly around values	Data were reported as mean ± standard deviation, frequencies and interquartile range. QoL results were compared with normative data through interquartile range.
Consistence with reference case	Data were not recorded using EQ-5D, the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Data were reported as mean ± standard deviation, frequencies and interquartile range. Note: scoring reported here is based on the 0 to 100 total score (higher scores better). Caution when comparing with the data reported from APPROACH where a mean of 50 method was reported.

Domain	Mean	Standard deviation	95% confidence interval	Percentiles			Normative data (Median)	Status by percentiles
				25th	50th (Median)	75th		
Physical functioning	79.33	15.80	71.34-87.32	75.0	80.0	90.0	87.5	Inside
Role physical	65.00	39.87	44.83-85.17	25.0	75.0	100.0	100.0	Inside
Bodily pain	62.00	20.06	51.85-72.15	41.0	61.0	84.0	72.0	Inside
General health	65.67	21.20	54.94-76.40	57.0	65.0	85.0	72.0	Inside
Vitality	60.33	20.57	49.92-70.74	45.0	55.0	75.0	75.0	Inside
Social functioning	80.00	20.49	69.63-90.37	62.5	87.5	100.0	87.5	Inside
Role emotional	66.65	37.80	47.52-85.78	33.3	66.6	100.0	100.0	Inside
Mental health	61.60	22.92	50.00-73.20	52.0	60.0	76.0	84.0	**Out**

Neelamekam et al. 2017	
Population in which health effects were measured	Patients with a clinical diagnosis of LPLD confirmed by genetic testing were eligible for study inclusion. Patients also had to have fasting triglyceride levels above 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis
Information on recruitment	Potential participants were contacted by their regular LPLD clinician and were invited to join the study to enable 3 patient case examples to be investigated. Of four patients identified and screened, three were recruited (two from Manchester and one from London, UK) to participate in the study (patients 1, 2 and 3).
Interventions and comparators	No treatment intervention
Sample size	3
Response rates	Two of the three recruited patients completed the pre-interview diary, and all three completed the face-to-face interview, post-interview diary and follow-up telephone interview. However, patient 2, did not complete the pre-interview diary.
Description of health states	The average health status of all three patients across four of the five domains (mobility, self-care, usual activities and pain/ discomfort) of the EQ-5D-3L descriptive system was level 3 during acute attacks and level 1 at the time of the interview.
Adverse events	Not applicable

Appropriateness of health states given condition and treatment pathway.	The study was carried out in patients with a clinical diagnosis of LPLD confirmed by genetic testing. Furthermore, patients also met fasting triglyceride levels or more than 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis, thus excluding patients with secondary causes of hypertriglyceridaemia.
Method of elicitation	EQ-5D was completed by patients (EQ-5D-3L).
Method of valuation	
Mapping	Not conducted
Uncertainly around values	The mean of individual ratings for each patient was calculated for each time point (during the most severe attack compared with at the time of the interview) to obtain overall mean scores in the EQ-5D-3L and the VAS for all three patients.
Consistence with reference case	Data was collected using the EQ-5D and is consistent with the reference case
Results with confidence intervals	Results are not presented with confidence interval

Davidson et al. 2017	
Population in which health effects were measured	Patients diagnosed with FCS
Information on recruitment	Patients were recruited via recruitment flyers, word of mouth via clinicians informing patients, through patient support/advocacy groups, and social media outlets. Respondents were further screened through a series of screening questions in order to confirm their eligibility. The data from the web-based survey were collected from US respondents between 24 June 2016 and 18 November 2016
Interventions and comparators	No treatment intervention
Sample size	67 completed the screening questions and qualified for the study
Response rates	Of the 67 patients who qualified for the study, 60 completed the survey within this time frame
Description of health states	
Adverse events	Not applicable

Appropriateness of health states given condition and treatment pathway.	The study was carried out in FCS patients in USA. Furthermore, patients also met fasting triglyceride levels or more than 20 mmol/L at the time of screening and a history of acute pancreatitis or abdominal pain consistent with pancreatitis, thus excluding patients with secondary causes of hypertriglyceridaemia.
Method of elicitation	Patient-reported outcome responses were recorded using a questionnaire designed by consulting existing QOL instruments, including Short-Form 36 (SF-36) and the Pancreatitis Quality of Life Instrument (PANQOLI) as well as based on inputs from physicians treating patients with FCS, dietitians, and patients with FCS.
Method of valuation	Not conducted
Mapping	Not conducted
Uncertainly around values	
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Results are not presented with confidence interval

Gelrud et al. 2017	
Population in which health effects were measured	Patients diagnosed with FCS
Information on recruitment	Patients diagnosed with FCS were referred by lipid specialists or were self-identified and self-referred. Diagnosis of FCS was determined based on genetic analysis in five of the ten patients. The remaining five patients reported receiving a clinical diagnosis by lipid specialists.
Interventions and comparators	No treatment intervention
Sample size	10 patients
Response rates	All the 10 FCS patients participated in the advisory board discussion
Description of health states	
Adverse events	Not applicable

Appropriateness of health states given condition and treatment pathway.	The study was carried out as a face-to-face panel discussion in USA cohort. The results provide the impact on QoL in terms of clinical and psychosocial burden of having FCS. As the study was unstructured and the methodology was qualitative, it does not provide absolute utility values for the health states.
Method of elicitation	Patients were asked questions related to the clinical burden and psychosocial consequences of living with FCS. The questions were not developed from a validated instrument but based on advisory board proceedings with lipidologists who care for FCS patients. The outcome was reported as common complaints.
Method of valuation	Not conducted
Mapping	Not conducted
Uncertainly around values	The analysis was based on more descriptive assessment of the HRQL
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL; not recorded in a UK cohort and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Results are not presented with confidence interval

Arca et al. 2018	
Population in which health effects were measured	FCS patients from APPROACH OLE
Information on recruitment	All eligible patients at the time of study recruitment (N = 58) were invited to participate in the survey by the APPROACH OLE Principal Investigators, who directed potential respondents to the study website. A total of 58 eligible patients from the APPROACH OLE (41 of whom had been on volanesorsen for at least 3 months) were invited to participate. Of a final study sample of 25 respondents, 22 had been treated with volanesorsen for at least 3 months; 3 were excluded as they were treated with volanesorsen for <3 months
Interventions and comparators	Participant patients in a 52-week Phase-III clinical trial (APPROACH OLE) of volanesorsen, a second generation antisense inhibitor of APOC3, under investigation for FCS treatment, were retrospectively

	administered a survey to assess changes in their BoI/ QoL post-treatment with volanesorsen. To be considered for participation in, patients must have been enrolled and have received one or more injections of volanesorsen.
Sample size	58
Response rates	25 (3 excluded; 'Before and after' data were available for 22 respondents) responded.
Description of health states	Patients with FCS
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway.	The study was carried out in FCS patients post-treatment with volanesorsen.
Method of elicitation	Treatment-associated impacts on BoI/QoL was captured by administering web-based, research survey.
Method of valuation	Not reported
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Respondents indicated that they believed their FCS was being more effectively managed when treated with volanesorsen compared with their previous management regimen. Patients reported numerous improvements in BoI/QoL with volanesorsen treatment, including more effective overall FCS management and improvement in multiple physical symptoms; most importantly, 86% reduction in pancreatic pain. Among reductions in

	several disease-related anxieties, an 80% reduction in constant uncertainty about having an attack of pain or acute pancreatitis at any time. Multiple cognitive symptoms improved, including absence of 'Brain fog' and 77% decreased interference with work abilities, leading to an increased ability to perform professional, academic, and social obligations. Overall, the median number of symptoms experienced after initiating volanesorsen treatment decreased from 6.5 (Q1–Q3 = 2.0–13.0) prior to volanesorsen treatment to 3.5 (Q1–Q3 = 1.5–6.5) after at least 3 months of treatment (34% improvement; P < 0.05). Likewise, the number of respondents who experienced greater than 10 symptoms decreased from 41% prior to volanesorsen treatment to 14% after treatment (improvement from baseline, 66%) (Figure 2). Treatment significantly reduced the number of symptoms experienced per patient in all three domains, with decreases from baseline of 47% (2.4 vs. 4.5; P = 0.009), 47% (1.9 vs. 3.5; P = 0.007), and 46% (0.3 vs. 0.6; P = 0.030) in physical, emotional, and cognitive domains, respectively.

Davidson et al. 2018	
Population in which health effects were measured	Adult FCS patients completed the In-FOCUS web-based patient survey. Nearly all patients had triglycerides >8.4mmol/l (750mg/dL) at diagnosis and many continue to have high triglyceride levels even with management strategies
Information on recruitment	166 adult FCS patients (116 male, 50 female) from 10 countries, with majority of patients from the USA (103). The mean age was 34y (range 18-59).
Interventions and comparators	Standard of care. Over 90% of patients reported treating their FCS through dietary restriction of fat intake, with 60.0% prescribed concomitant triglyceride-lowering medication.
Sample size	166 adult FCS patients
Response rates	166 adult FCS patients completed the survey
Description of health states	Patients with FCS
Adverse events	Not reported

Appropriateness of health states given condition and treatment pathway.	The data from this study illustrates how FCS imparts a marked burden to the patient which extends beyond the recognized physical symptoms, also encompassing emotional, cognitive, economic and psychosocial consequences.
Method of elicitation	Web-based patient survey
Method of valuation	Not reported
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	The extremely restrictive dietary guidelines impacted patients' social relationships and activities. Patients reported more frequent doctor visits due to FCS and associated comorbidities including: chronic pancreatitis (11%), eating disorders (23%), diabetes (16%), and hypertension (10%). The majority of patients (64.3%) reported that FCS adversely affected their life over the past 12 months; with their stress/anxiety level (64.3%), ability to socialise (43%), ability to travel for work or leisure (48%), their mental ability (53.8%), quality of sleep (45.0%), and their feeling of self-worth (65.0%) all impacted. Over the past 12 months, 60% of patients had to take an average of 24 days off work because of FCS related problems. 44% of patients felt their disease had influenced their decision on whether to have children, or how many children to have. 72% of patients reported feeling a burden to those around them because of their FCS.

DuFour et al. 2018	
Population in which health effects were measured	FCS patients from Canadian IN-FOCUS cohort

Information on recruitment	Web-based patient survey
Interventions and comparators	No intervention
Sample size	37
Response rates	37
Description of health states	Patients with FCS
Adverse events	Not reported
Appropriateness of health states given condition and treatment pathway.	The results from this cohort study describe the challenges FCS patients face including their lengthy journey to diagnosis, management of comorbidities, and highlights the physical, emotional, cognitive and psychosocial impact on quality of life issues.
Method of elicitation	The In-FOCUS web-based patient survey was undertaken to quantify the burden of illness and quality of life from the patient's perspective
Method of valuation	Not reported
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.

Results with confidence intervals	FCS-imposed limitations on QoL were reported by 76% of patients; most reported FCS impacted their career choice and 80% indicated choosing less demanding careers due to FCS. Patients also reported significant impact on family/social relationships; 2/3 of patients reported that FCS has a significant impact on their decision on whether to have children. Patients (27%) reported constant uncertainty/emotional burden over experiencing an AP episode every month. Most common physical symptoms reported were abdominal pain (30%), pancreatic pain (27%), asthenia (22%), typically experienced 1-4X per month with moderate severity. Patients also reported experiencing cognitive symptoms such as difficulty concentrating (8%), impaired judgment (3%) and brain fog (3%). FCS-induced AP was experienced by 35% of patients, and ~14% reported developing eating disorders

Matza et al. 2018	
Population in which health effects were measured	General population participants from UK
Information on recruitment	General population participants from UK
Interventions and comparators	No intervention
Sample size	208 general population participants
Response rates	208
Description of health states	General population participants in the UK valued five health state vignettes drafted based on literature review, clinician input, and interviews with patients with FCS. Four health states described variations of FCS (high or low triglycerides, with or without history of acute pancreatitis [AP]). The fifth health state, describing an acute pancreatitis episode, was added to one of the other health states to evaluate its impact on utility
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	Among these FCS health states, symptoms typically linked to higher triglycerides and history of AP were associated with lower utility. The health state utilities estimated in this study would be useful in models examining cost-effectiveness of treatments for FCS
Method of elicitation	Time trade-off interviews

Method of valuation	Not reported
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Mean (SD) utilities were 0.80 (0.21) for low triglyceride levels without history of AP, 0.74 (0.23) for low triglycerides with history of AP, 0.60 (0.33) for high triglycerides without history of AP, and 0.46 (0.42) for high triglycerides with history of AP. The disutility (i.e., utility decrease) of AP was -0.25 when added the low triglyceride health state and -0.20 when added to the high triglyceride health state.

Priedane et al. 2018b	
Population in which health effects were measured	FCS patients from APPROACH trial
Information on recruitment	At baseline, 66 patients were recruited for this study
Interventions and comparators	No intervention. Patients completed EQ-5D-5L questionnaire at baseline of the APPROACH, a randomised, double-blind placebo-controlled 52-week multicentre clinical trial in patients with FCS. .
Sample size	66 patients
Response rates	50 out of 66 completed the EQ-5D-5L questionnaire
Description of health states	Patients with FCS
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	Appropriate as the trial was conducted in FCS patients.

Method of elicitation	Patients with FCS completed the EQ-5D-5L questionnaire which was used to generate utility scores.
Method of valuation	An index or utility score was calculated based on the EQ-5D-5L questionnaire, scaledon 0 (worst health) to 1 0 (best health), using a Crosswalk Index Value Calculator for the UK. Mean scores from EQ-5D-5L were calculated for the five dimensions of the EQ-5D-5L questionnaire, the mean VAS, and index score. Scores were stratified by presence of diabetes and history of acute pancreatitis.
Mapping	Not reported
Uncertainly around values	Patients with FCS in the APPROACH trial reported unusually high EQ VAS and index scores.The high quality of life reported by these patients on the EQ-5D-5L instrument may be due to coping mechanisms developed by patients with FCS or due to generic instruments providing insufficient coverage of symptoms related to their disorder. A disease-specific patient reported outcome questionnaire may facilitate the true assessment of impact of FCS symptoms
Consistence with reference case	Given the data has been collected using the EQ-5D and valued using the UK general population preferences, it is consistent with the reference case.
Results with confidence intervals	Baseline results only. Patients with FCS in the APPROACH trial reported unusually high EQ VAS and index scores (placebo: VAS mean 88.12, SD=8.40 index mean 0.98, SD=0.04; treatment: VAS mean 87.75, SD=10.45 index mean 0.97, SD=0.05). Patients with diabetes had a very high EQ-5D index score (0.99); while, the number of patients is too small for statistical conclusions the scores are well above published index scores for patients with diabetes

Salvatore et al. 2018	
Population in which health effects were measured	Patients with FCS and caregivers who responded on behalf of the patient with FCS
Information on recruitment	Participants were found through health-care professionals who treat patients with FCS, as well as FCS patient support groups and institutions. Potential participants were directed to the survey via a flyer, which informed them about the study. The flyer was also posted on community FCS Facebook pages by patient moderators. Patients who had previously attended patient advisory boards also received the flyer via email. The study was approved by the Institutional Review Board and ethics committees in the participating countries or institutions.
Interventions and comparators	Connection with FCS-focused support organizations
Sample size	50
Response rates	Data were collected from patients with FCS and caregivers (N = 50), who responded on behalf of the patient with FCS,

	from 2 countries (United States, Canada). Participants
Description of health states	Participants were identified as having FCS or caring for patients who have FCS if they indicated the patient had one or more of the following: familial LPLD, FCS, Fredrickson's type 1 hyperlipoproteinemia, high TG levels with a history of pancreatitis, or high TG levels with a history of severe abdominal pain that required hospitalization not due to a readily identifiable cause.
Adverse events	Not applicable
Appropriateness of health states given condition and treatment pathway.	The results from CONNECT study shows that connections to other FCS related support groups improved the QoL of patients with this rare disease.
Method of elicitation	Respondents were categorised into 3 groups (actively connected, passively connected and non-connected) self-reported their current or comparative assessments of QoL before and after connection with FCS-focused support organizations using a customised retrospective web-based survey.
Method of valuation	The impact of connectedness was assessed based on similar methodologies in other studies with questions about overall health, level of anxiety and depression, social isolation, relationship with disease state, self-worth, relationship with family and colleagues, impact on work productivity, and overall FCS symptom severity. FCS symptom severity was measured on a 7-point Likert-like scale with 1 − extremely mild, 2 − very mild, 3 − mild, 4 − moderate, 5 − slightly severe, 6 − severe, and 7 − extremely severe. QoL changes were measured before and after 'being connected' for actively and passively connected respondents while non-connected respondents were solely asked about their current QoL.
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.
Results with confidence intervals	Connected respondents showed significantly improved perceptions of overall health, disease severity, motivation to take care of health and emotional well-being ($p \leq 0.05$). Any level of connection produced noticeable benefits, but active connection in the form of regular interaction with other patients reported the greatest improvements. Additionally, respondents reported higher levels of satisfaction with their primary treating physician after being connected. The majority of patients (62%) reported joining support groups following referrals from their physicians.

Bang et al. 2019	
Population in which health effects were measured	Patients with infected necrotizing pancreatitis
Information on recruitment	168 patients with acute necrotizing pancreatitis were assessed for eligibility and 70 met criteria for randomization. Four patients were excluded post-randomization due to resolution of symptoms after percutaneous catheter placement (n=2) or protocol violation (n=2).
Interventions and comparators	Minimally Invasive Surgery vs Endoscopy Randomised (MISER) Trial in patients with necrotizing pancreatitis.
Sample size	70
Response rates	66 out of 70
Description of health states	Necrotising pancreatitis pre and post-surgery.
Adverse events	The mean number of major complications per patient was significantly higher in the surgery group (0.69 ± 1.03) compared with the endoscopy group (0.15 ± 0.44) (P =0.007).
Appropriateness of health states given condition and treatment pathway.	Potentially relevant (necrotizing pancreatitis)
Method of elicitation	SF-36. HRQL was assessed preintervention, at hospital discharge, and 3 and 6 months' post-discharge by research personnel blinded to the treatment group assignment
Method of valuation	The change in physical and mental health component scores from baseline through follow up evaluation was analysed using a repeated-measures analysis based on mixed-effects individual growth models with random intercept and slope.
Mapping	Not reported
Uncertainly around values	Not reported
Consistence with reference case	Data were not recorded using EQ-5D, which is the NICE preferred measure of HRQL and there are no published mappings in FCS. Therefore, not consistent with the reference case.

<table>
<tr>
<td>Results with confidence intervals</td>
<td>The Short Form-36 questionnaire showed significantly better physical component scores for the endoscopic treatment group at 3 months (P=0 .039).
<table>
<tr><th>Quality of life at 3-month follow-up</th><th>Endoscopy (n = 34)</th><th>Surgery (n=32)</th><th>P</th></tr>
<tr><td>MCS: β (95% CI)</td><td colspan="2">−0.22 (−9.18 to 8.87)</td><td>.962</td></tr>
<tr><td>PCS: β (95% CI)</td><td colspan="2">5.29 (0.27–10.3)</td><td>.039</td></tr>
</table>
MCS, Mental Component Score; PCS, Physical Component Score</td>
</tr>
</table>

17.5 Appendix 5: Methodology of non-RCT studies in FCS

Sections 9.1 and 9.2 provide full details of the methodology of the systematic literature review which was carried out but could not identify any studies that compared Volanesorsen with one or more other comparator in a head-to-head RCT. All the studies that were identified for which patient characteristics and treatments have been summarised in Table C3 in Section 9.2.5. However, an indirect comparison is not feasible due to the nature of the design of studies or in the case of pradigastat where the technology is not licenced in UK. For the purpose of illustrating this difficulty, all the study methodologies have been summarised in the following tables.

Study name	Gaudet D, Brisson D, Tremblay K, et al. Targeting APOC3 in the familial chylomicronemia
Objective	
Location	Chicoutimi Hospital
Design	Open-label, single arm
Duration of study	13 weeks
Patient population	3 patients
Sample size	3 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 3) and comparator(s) (n = 0)	Patients abstained from alcohol consumption for 48 hours before each study visit. After the baseline visit, patients received a 285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection. The last dose was administered on day 85, and the patients were then followed for another 91 days to monitor measures of efficacy and safety.
Baseline differences	Patient 2 had received Glybera 5 years earlier In Patients 2 and 3, measurements of LPL activity after the administration of heparin showed values that were less than 2 to 4 nmol of free fatty acids per minute per milliliter of plasma (<3% of normal levels) both before enrollment in the study
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	The patients were followed for 91 days, after the last dose has been administered on day 85, to monitor measures of efficacy and safety.
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Reduction of triglyceride levels in three patients with the familial chylomicronaemia syndrome and triglyceride levels ranging from 1406 to 2083 mg per decilitre (15.9 to 23.5 mmol per litre).
Secondary outcomes (including scoring methods and timings of assessments)	Fasting blood samples for measurement of APOC3, triglycerides, triglycerides in chylomicrons, apolipoprotein B-48, and other lipids at baseline, on day 8, and then weekly or every other week during the treatment period (until day 85) and then on days 92, 99, 127, and 176 during the safety follow-up period.

Study name	Rouis M, Dugi KA, Previato L, et al. Therapeutic Response to Medium-Chain Triglycerides and ω-3 Fatty Acids in a Patient With the Familial Chylomicronemia Syndrome
Objective	To investigate the LPL gene of a patient presenting classical features of the familial chylomicronaemia syndrome, including marked hypertriglyceridemia and recurrent episodes of pancreatitis.
Location	
Design	Case report
Duration of study	
Patient population	8-year-old black female with a history of reccurent episodes of pancreatitis requiring hospitalisation from the age of 3 with marked hypertriglyceridemia not responsive to a low-fat diet or nicotinic acid.The patient was diagnosed with LPL deficiency at 5 years old.
Sample size	1 patient
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 1) and comparator(s) (n = 17 untreated controls)	The administration (15 to 30 g/d) of an MCT oil–containing diet.
Baseline differences	NA
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	On this therapy the patient experienced no further episodes of abdominal pain or pancreatitis and the plasma lipoprotein profile remained normal for a period of 2 years
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	Analysis of lipoproteins, apolipoproteins, and plasma Lipid Analysis Quantitation of plasma HL Activity and LPL activity and mass Analysis for a circulating plasma inhibitor to rule out the presence of a potential inhibitor of the lipolytic system To determine size and abundance of LPL mRNA isolated from adipocytes as well as macrophages Sequence analysis of the LPL gene and of LPL cDNA to identify any mutations

Study name	Stroes ES, Nierman MC, Meulenberg JJ, et al. Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients.
Objective	To establish efficacy and safety of intramuscular application of this vector
Location	
Design	Open label study. LPLS447X-adeno-associated virus subtype 1(AAV1) vector was injected in the leg musculature of 8 LPL-deficient patients at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight (40 and 60 injections of 500 microliters, respectively)
Duration of study	3 months
Patient population	LPL-deficient individuals after intramuscular administration of a viral vector
Sample size	8 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 8) and comparator(s) (n =)	1(AAV1) vector was injected in the leg musculature at a dose of 1×10^{11} (n=4) or 3×10^{11} (n=4) genome copies per kilogram body weight
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	long-term follow up of triglycerides and local LPL protein and activity 31 months
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	To achieve a reduction in individual median fasting plasma TG to a level equal to or less than 10 mmol/L on top of diet, or to achieve a reduction in median fasting plasma TG equal to or more than 40% on top of diet.
Secondary outcomes (including scoring methods and timings of assessments)	Serious adverse events Median TG levels compared to baseline TG Muscle function tests and MRI-assessed fat content at the beginning versus the end of the trial.

Study name	Carpentier AC, Frisch F, Labbe SM, et al. Effect of Alipogene Tiparvovec (AAV1-LPLS447X) on Postprandial Chylomicron Metabolism in Lipoprotein

Study name	Mingozzi F, Meulenberg JJ, Hui DJ, et al. AAV-1–mediated gene transfer to skeletal muscle in humans results in dose-dependent activation of capsid-specific T cells.
Objective	
Location	Academic Medical Center, Amsterdam
Design	8 subjects were enrolled in 2 dose cohorts (4 subjects per cohort) receiving 10^{11} gc/kg and 3×10^{11} gc/kg. Vector was administered intramuscularly into multiple sites at a dose of 1.6 to 4.2×10^{11} gc/site of injection
Duration of study	
Patient population	LPL-deficient subjects with missense mutations in both LPL alleles
Sample size	
Inclusion criteria	LPL-deficient subjects with missense mutations in both LPL alleles
Exclusion criteria	
Intervention(s) (n =8) and comparator(s) (n =)	4 patients in each cohort were administered 10^{11} gc/kg and 3×10^{11} gc/kg respectively. Vector was administered intramuscularly into multiple sites at a dose of 1.6 to 4.2×10^{11} gc/site of injection
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	
Secondary outcomes (including scoring methods and timings of assessments)	

	Lipase-Deficient Patients
Objective	To determine the effect of i.m. administration of an adeno-associated viral vector (AAV1) for expression of LPL(S447X) in muscle (alipogene tiparvovec, AAV1-LPL(S447X)) on postprandial chylomicron metabolism and on nonesterified fatty acid (NEFA) and glycerol metabolism in LPLD individuals.
Location	ECOGENE 21 Clinical Research Center in Chicoutimi
Design	An open-label clinical trial (CT-AMT-011-02) Lipoprotein lipase-deficient (LPLD) subjects were administered alipogene tiparvovec at a dose of $1 \times 10^{(12)}$ genome copies per kilogram.
Duration of study	14 weeks
Patient population	LPLD subjects were diagnosed and selected based on a history of pancreatitis, fasting plasma TG greater than 10 mmol/liter, a post-heparin LPL activity 20% or less of normal, and confirmed homozygosity or compound heterozygosity for mutations in the LPL gene
Sample size	5 patients
Inclusion criteria	The LPLD subjects were diagnosed and selected based on a history of pancreatitis, fasting plasma TG greater than 10 mmol/liter, a post-heparin LPL activity 20% or less of normal, and confirmed homozygosity or compound heterozygosity for mutations in the LPL gene.
Exclusion criteria	
Intervention(s) (n = 5) and comparator(s) (n = 5)	Five overweight but otherwise healthy control subjects underwent assessment of postprandial chylomicron metabolism using similar methods except for meal fat content and tracer
Baseline differences	Two subjects had insulin-dependent diabetes mellitus (participants 1001 and 1002).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Fourteen weeks after alipogene tiparvovec administration chylomicron metabolism and plasma palmitate and glycerol appearance rates were determined
Statistical tests	Data are expressed as mean ± SD in the text and in the tables and as mean ± SEM in the figures, unless stated otherwise. Intragroup characteristics were compared by paired Student's *t* test or two-way ANOVA for repeated measures in the case of postprandial curves with pretreatment *vs.* posttreatment, postprandial time, and interaction as independent variables. A two-tailed *P*value <0.05 was considered significant.
Primary outcomes (including scoring methods and timings	Change in chylomicron metabolism in response to treatment within the LPLD group

of assessments)	Postprandial chylomicron TG levels and chylomicron 3^{H} excursion
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	Gaudet D, Méthot J, Déry S, et al. Efficacy and long term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open label trial.
Objective	To assess the long-term safety of alipogene tiparvovec and achieve a ≥40% reduction in fasting median plasma triglyceride (TG) at 3–12 weeks compared with baseline
Location	ECOGENE-21 Clinical Research Center, Chicoutimi, Quebec, Canada
Design	Open-label, dose-escalation clinical trial
Duration of study	
Patient population	14 LPLD patients with a history of pancreatitis and who participated in a prospective observational study (PREP-02)
Sample size	14 patients
Inclusion criteria	LPLD patients with a history of pancreatitis and who participated in a prospective observational study (PREP-02)
Exclusion criteria	
Intervention(s) (n = 14) and comparator(s) (n =)	Cohorts 1 (n=2) and 2 (n=4) received 3×10^{11}gc/kg, and cohort 3 (n=8) received 1×10^{12}gc/kg. Cohorts 2 and 3 also received immunosuppressants from the time of alipogene tiparvovec administration and continued for 12 weeks
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Biological activity and expression of LPL^{S447X} in the muscle was measured after 26 weeks,
Statistical tests	Because of intra-subject variability in TG levels, multiple data points were used to derive pre- and post-therapy values. The median of the six most recent measurements before the day of alipogene tiparvovec administration was used for pre-therapy values. All TG data from week 3 until and including week 12 were used for the main study post-administration TG response assessment. A linear mixed model was used to estimate the average reduction in individual TG after alipogene tiparvovec administration and whether there was a statistically significant reduction in TG calculated using median and mean values. Individual pre-therapy and post-therapy TG values until week 12, and 26, were compared using the non-parametric Wilcoxon test. A score of 0 or 1 was

	assigned to subject's TG levels to indicate success or failure (TG ≤10.00 mmol/L or > 10.00 mmol/L, respectively). Using a Chi-squared statistic, a Mixed Model Repeated Measures and Wilcoxon Signed Rank test, it was determined whether alipogene tiparvovec, or a specific dose, lowers TG significantly. All hypotheses were tested with an overall two-sided significance level of 0.05.
Primary outcomes (including scoring methods and timings of assessments)	Long-term safety profile of alipogene tiparvovec Reduction in fasting median plasma TG of at least 40%, 3–12 weeks after therapy compared to baseline
Secondary outcomes (including scoring methods and timings of assessments)	Reduction in fasting TG to ≤10.0 mmol/L within 12 weeks Biological activity and expression of $LPLS^{447X}$ in the muscle after 26 weeks Potential immune responses against $LPLS^{447X}$ and AAV1 capsid proteins Biodistribution and shedding of AAV1-LPLS447X vector DNA

Study name	Ferreira V, Twisk J, Kwikkers K, et al. Immune Responses to Intramuscular Administration of Alipogene Tiparvovec (AAV1-LPLS447X) in a Phase II Clinical Trial of Lipoprotein Lipase Deficiency Gene Therapy.
Objective	To analyse systemic and local immune responses against AAV1,for their impact on safety and the persistence of LPL transgene expression.
Location	ECOGENE-21 Clinical Research Center, Chicoutimi, Quebec, Canada
Design	An open-label, single-dose study evaluating the safety and efficacy of alipogene tiparvovec (AAV1-LPLS^{447X}),
Duration of study	14 weeks
Patient population	Five subjects with LPL deficiency (LPLD)
Sample size	5 patients
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n = 5) and comparator(s) (n =)	Five subjects with LPLD were exposed to a fixed dose of 1×10^{12} gc/kg alipogene tiparvovec administrated as a one-time series of IM injections into the lower extremities. All subjects were treated and maintained with immune suppression starting shortly before administration until 12 weeks after administration of alipogene tiparvovec
Baseline differences	None
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Subjects were monitored at predefined intervals for various clinical parameters, including routine hematology, biochemistry, and immune parameters. No hematology and routine biochemical assessments were planned after week 12, whereas immunological parameters continued to be assessed after 12 weeks. A biopsy of the injected muscle was scheduled between 14 and 52 weeks after vector administration.
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Impact of systemic and local immune responses against AAV1 on safety and the persistence of LPL transgene expression
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	Meyers CD, Tremblay K, Amer A, et al. Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome.
Objective	To assess the safety, tolerability, and effects of the DGAT1 inhibitor pradigastat on fasting and postprandial plasma TG in patients with FCS and severe hypertriglyceridemia.
Location	ECOGENE-21 clinical trial center and laboratories Chicoutimi, Canada
Design	Open-label clinical study
Duration of study	3x21 days
Patient population	Familial chylomicronaemia syndrome (FCS) patients
Sample size	Six Familial chylomicronaemia syndrome (FCS) patients
Inclusion criteria	FCS patients aged 18–75 years not on any lipid-lowering medications for ≥8 weeks prior to enrolment were eligible for the study. Patients had to meet at least two of the following criteria: fasting TG ≥890 mg/dL (>10 mmol/L); post-heparin plasma LPL activity ≤20% of normal; LPL mass >5% and/or confirmed homozygote or compound heterozygote mutations in LPL gene (null alleles) with LPL mass >5% and LPL activity ≤20%.
Exclusion criteria	Pregnant/nursing women and patients with uncontrolled diabetes or an active pancreatitis episode within 1 month of enrollment were excluded
Intervention(s) (n = 6) and comparator(s) (n =)	Patients underwent three consecutive 21 day treatment periods (pradigastat at 20, 40 & 10 mg, respectively). Treatment periods were separated by washout periods of ≥4 weeks
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Following the final 24 hour post- baseline meal tolerance test (MTT) blood sample, patients returned to their home. An end of study visit was performed at least 14 days after the final treatment period ended.
Statistical tests	A dose comparison was carried out for fasting TG data, which was analyzed using a linear mixed effect model for repeated measurements. The model included treatment, time, and treatment by time interaction as factors; baseline as a covariate; and subject as a random effect. Postprandial peak and AUC TG were analyzed for dose comparison by a linear mixed effect model, with treatment and baseline values as fixed effects and subject as a random effect; however, the

	pharmacokinetic parameters were analyzed on Day 21 using an ANOVA model with dose level as a factor, and subject as a random effect. Estimates of the treatment effect of different dose levels, together with 90% CI were obtained. Log-transformation was applied prior to the analysis and the results were back transformed and reported in the original scale. All the above analyses were repeated for secondary end points. Missing measurements for AUC were imputed by linear interpolation only if two adjacent time points had observed data and was set to missing otherwise. Missing measurements at the end of the time interval were imputed from the previous time point.
Primary outcomes (including scoring methods and timings of assessments)	Reduction in fasting triglyceride
Secondary outcomes (including scoring methods and timings of assessments)	

Study name	An Open Label, 52-week, Safety and Tolerability Extension to a Randomized, Double-blind, Placebo Controlled Study of LCQ908 in Subjects With Familial Chylomicronemia Syndrome.
Objective	To evaluate the overall long-term safety and tolerability of LCQ908 in patients with Familial Chylomicronaemia Syndrome, who either discontinued from the CLCQ908B2302/NCT01514461 study (due to tolerability issues) or completed the CLCQ908B2302/NCT01514461 study after 52 weeks. In addition, patients who had previously completed study CLCQ908A2212/NCT01146522 were eligible to participate.
Location	United States, Washington Novartis Investigative Site Seatlle, Washington, United States, 98104 Canada, Quebec Novartis Investigative Site Chicoutimi, Quebec, Canada, G7H 7P2 Novartis Investigative Site Ste-Foy, Quebec, Canada, G1V4M6 Canada Novartis Investigative Site Ouest-Montreal, Canada, H2W1R7 France Novartis Investigative Site Nantes, France, 44093 Novartis Investigative Site Paris Cedex 13, France, 75651 Germany Novartis Investigative Site Hamburg, Germany, 20246 Netherlands Novartis Investigative Site Meibergdreef 9, Netherlands, 1105 AZ South Africa Novartis Investigative Site

	Cape Town, South Africa, 7925 United Kingdom Novartis Investigative Site Manchester, United Kingdom, M13 9NT
Design	Open-label, single arm Patients abstained from alcohol consumption for 48 hours before each study visit. After the baseline visit, patients received a 285-mg dose of ISIS 304801 once weekly for 13 weeks by subcutaneous injection. The last dose was administered on day 85, and the patients were then followed for another 91 days to monitor measures of efficacy and safety.
Duration of study	52 weeks
Patient population	38 participants
Sample size	38 participants
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Subjects that either discontinue prematurely or complete the CLCQ908B2302 study after 52 weeks or FCS subjects who have previously completed study CLCQ908A2212
Exclusion criteria	1. Subjects discontinued from the CLCQ908B2302 study for serious, potentially study drug related adverse events. 2. Subjects from the CLCQ908B2302 study who have developed any other contraindication to participation (for example, renal failure) 3. History of malignancy of any organ system (other than localised basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. 4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 5. Subjects with type 1 diabetes mellitus or type 2 diabetes mellitus if HbA1C is ≥ 8.5%. 6. Treatment with fish oil preparations within 4 weeks prior to randomisation. 7. Treatment with bile acid binding resins (i.e., colesevelam, etc) within 4 weeks prior to randomisation. 8. Treatment with fibrates within 8 weeks prior to

	randomisation. Washout may occur following screening if required. 9. Glybera [alipogene tiparvovec (AAV1-LPLS447X)] gene therapy exposure within the two years prior to screening. 10. eGFR <45 ml/min/1.73m2 or history of chronic renal disease. Other protocol defined inclusion/exclusion criteria may apply.
Intervention(s) (n =) and comparator(s) (n =)	Patients initiated at 10 mg/day. After at least 8 weeks of treatment with a dose, optional up-titration to the next possible dose will be allowed. One down titration allowed from the highest dose attained.
Baseline differences	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	
Statistical tests	
Primary outcomes (including scoring methods and timings of assessments)	Number of Patients With Any Adverse Events, Serious Adverse Events and Death [Time Frame: 52 weeks]
Secondary outcomes (including scoring methods and timings of assessments)	1. Changes From Baseline in Triglyceride Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52] Blood samples were collected for a fasting lipid panel, including total triglycerides. Lipid measurements were collected after a 12 hour (overnight) fast. The maintenance of effect was assessed on triglyceride levels during continued therapy with LCQ908 for up to 52 weeks. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

2. Changes From Baseline in Cholesterol Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including cholesterol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

3. Changes From Baseline in HDL and Non HDL Cholesterol Levels up to 52 Weeks
[Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including HDL and non HDL cholesterol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

4. Changes From Baseline in Glycerol Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including glycerol level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study

CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

5. Changes From Baseline in Free Fatty Acid Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Blood samples were collected for a fasting lipid panel, including free fatty acid level. Lipid measurements were collected after a 12 hour (overnight) fast. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

6. Changes From Baseline in Apolipoprotein A1 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein A1. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) -1)*100.

7. Changes From Baseline in Apolipoprotein B-48 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein B-48. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

8. Changes From Baseline in Apolipoprotein B-100 Levels up to 52 Weeks [Time Frame: Baseline, Week 12, 24 and 52]

Fasting blood samples were collected by direct venipuncture or an indwelling cannula to evaluate the drug effect on lipoprotein biomarkers such as Apolipoprotein B-100. For patients from LCQ908 arm of study CLCQ908A2212, baseline was the assessment obtained at Week 0 of current study. For patients from study CLCQ908B2302, baseline is defined as the average of values taken Day -3 and Week 0 (randomisation) in study CLCQ908B2302. The geometric mean for the percentage (%) change is calculated from back-transforming the mean of the log transformed ratio to baseline values: (exp(mean of the log-transformed ratio to baseline values) - 1)*100.

17.6 Appendix 6: Summary of vignette study

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

17.7 Appendix 7: Clinical expert survey

17.7.1 Questionnaire

CLINICAL EXPERT QUESTIONS

1) Description of Chronic Pancreatitis presentation in FCS: symptomatology and management.

For the health economic evaluation of Volanesorsen by NICE, Akcea need to assess the progression of patients with FCS over the course of an individual's lifetime. A proportion of patients with FCS will experience repeat episodes of acute pancreatitis, and some will go on to develop chronic pancreatitis (CP).

There is a lack of evidence in the literature with regard to the management and use of healthcare resources associated with these conditions. As this has significant health economic relevance, Akcea need to provide NICE with detailed insights in the absence of clear evidence.

With this in mind, please could you answer the following questions:

a) What symptoms, if any, are typical of patients with high triglyceride (HTG) related CP?

Notes:

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b) What healthcare resources are required to manage these symptoms (circle) (drugs, outpatient appointments, tests and investigations, A&E attendances, hospital admissions including surgical intervention/s and/or ICU)?

Notes:

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c) In your experience, what proportion of these patients require hospital admission, surgical intervention, ICU admission/ nursing care at home/ palliative care?

Notes ----------

2) Health related quality of life for FCS patients with Chronic Pancreatitis.

The overall health status (QoL) measure, known in health economics as the 'utility', places overall health status on a scale from 0 (dead) to 1 (perfect health).

Akcea has commissioned independent research to estimate the utilities for patients according to different combinations of disease history – including both triglyceride level and history of acute pancreatitis (see table below). For example, a patient with high triglycerides and a history of acute pancreatitis is estimated to have a utility of [redacted].

Table 1 Utility values by health state

Health State	Utility estimate
Low triglycerides, no history of acute pancreatitis	[redacted]
High triglycerides, no history of acute pancreatitis	[redacted]
Low triglycerides, history of acute pancreatitis	[redacted]
High triglycerides, history of acute pancreatitis	[redacted]

In the model, we also require an estimate for the utility associated with CP. Unfortunately, there is very little evidence in the literature about utilities for CP.

The closest approximation can be found in a paper which reported EQ5D utilities from a cohort of CP patients awaiting surgery, and at follow up.[2] However, the majority of patients in this study had an alcohol- related cause of CP which is unlikely to be comparable to an FCS population with CP. Utilities for this alcohol- related CP group at baseline were 0.335 or 0.275 (endoscopic drainage and surgery group) respectively.

Given that the FCS population with CP may be different from a population with alcohol- related CP, is the figure [redacted] described above [for acute pancreatitis, high triglycerides] appropriate enough for the group of patients we are considering ie FCS patients with CP? Put another way, is it reasonable to assume that the utility associated with CP is at best equivalent to that for "High triglycerides, history of acute pancreatitis"? (as set out in Table 1).

Q Do you agree with this reasoning? Yes/ No

If no, please explain?

Can you also help our understanding by answering the following questions:

a) Could you give us an impression of the impact of CP on a patient in terms of the following:

	High	Med	Low
Mobility			
Usual activities			
Pain			
Anxiety/ depression			

[2] Laramée P, Wonderling D, Cahen DL, et al Trial-based cost-effectiveness analysis comparing surgical and endoscopic drainage in patients with obstructive chronic pancreatitis BMJ Open 2013;3:e003676. doi: 10.1136/bmjopen-2013-003676

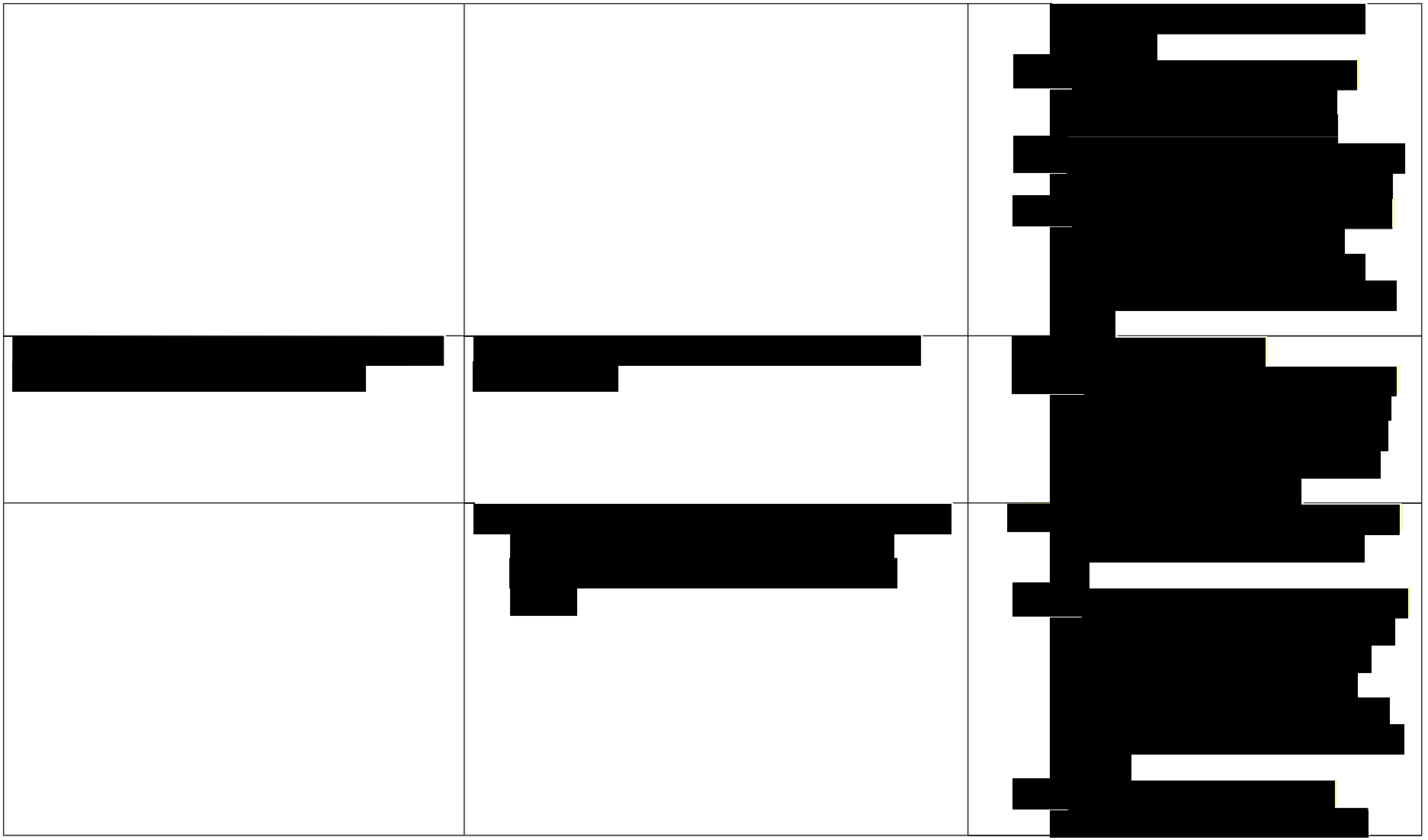
Sleep			
Fatigue			

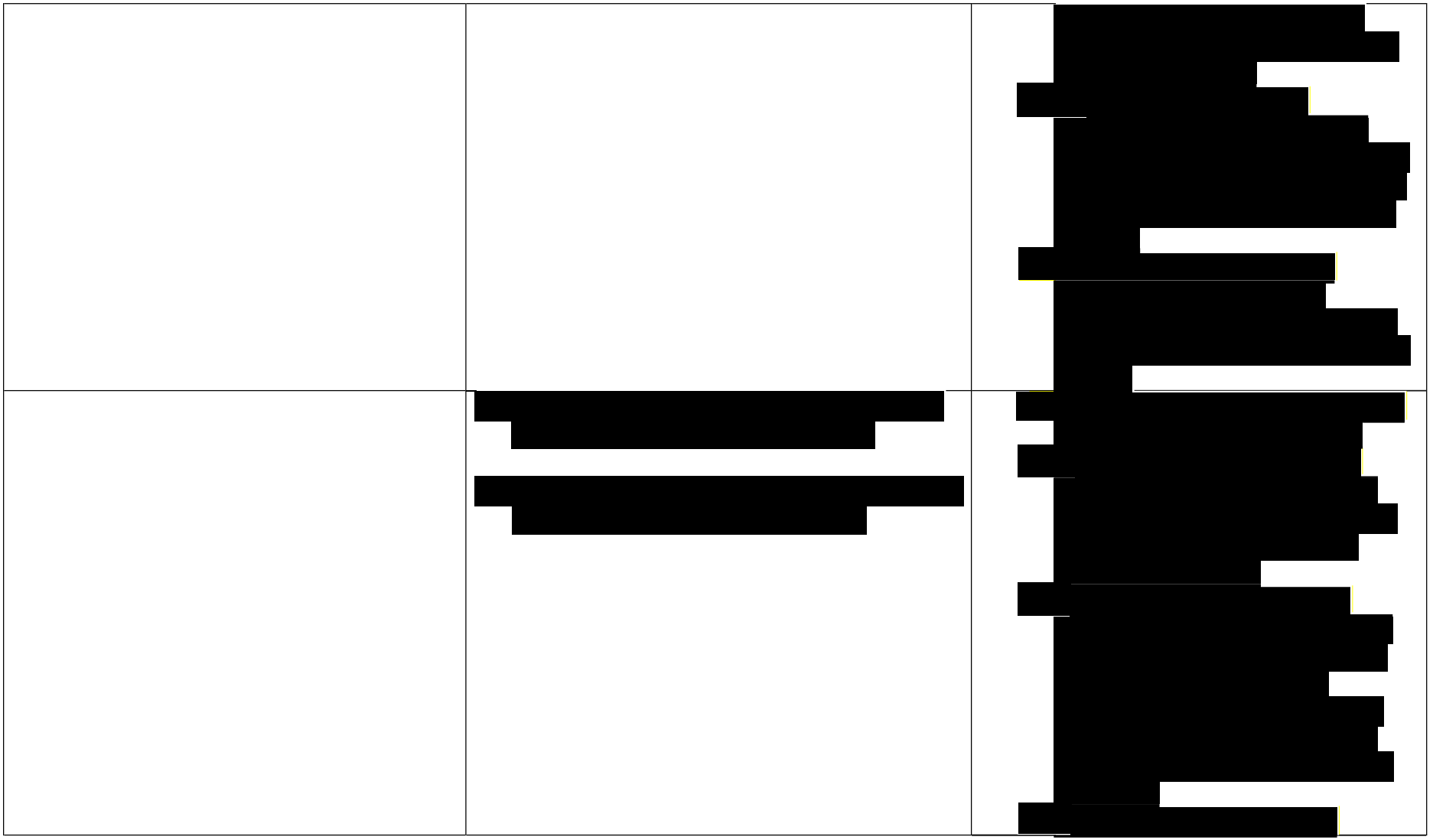
b) Could you please comment on the impact of CP on carers and families? High/ Med/ Low

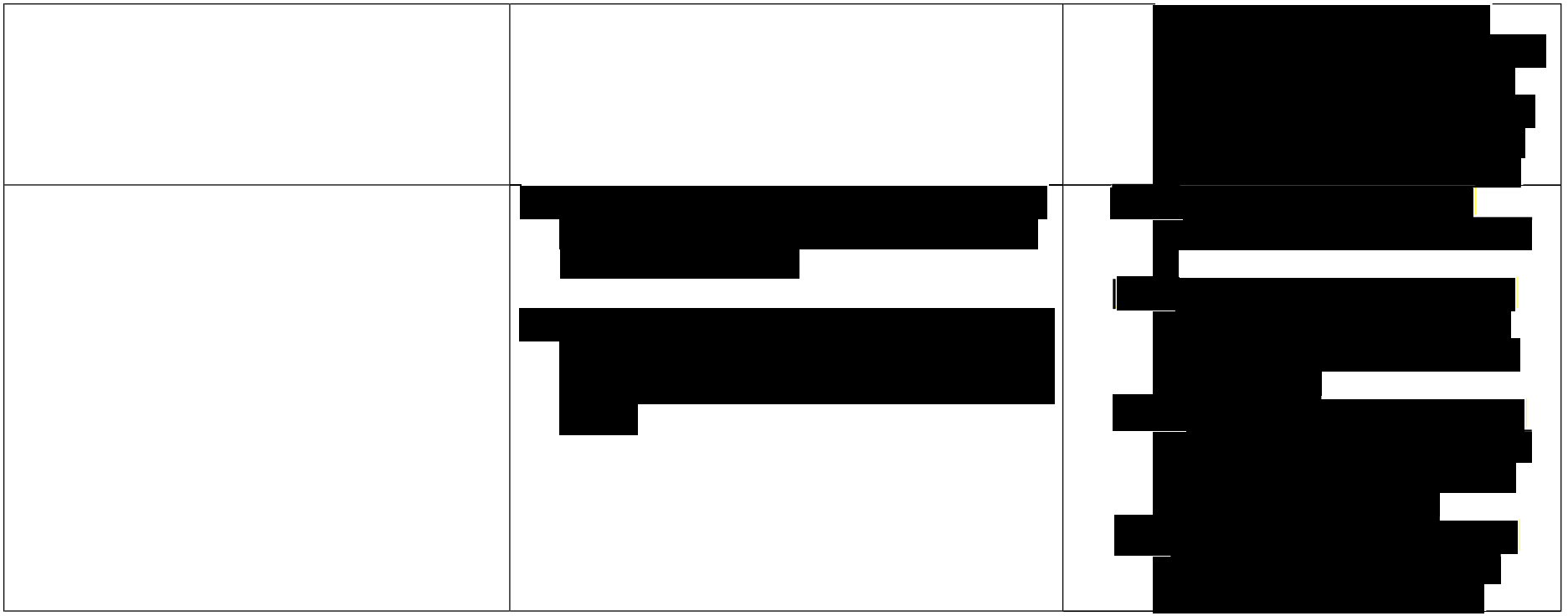
Are there any specific patients for whom this carer burden may be particularly significant?

c) Finally, could you give us an idea of the risk of an untreated patient with FCS developing CP in the course of their lifetime? What is the proportion of FCS patients that will ultimately progress to CP at some stage during their life time? Suggest a percentage
eg 25%, 50%, 75%, other % [INSERT]

[redacted]







17.8 Appendix 8: GLMM model

Post-hoc regression analysis informing response to every 2 weeks volanesorsen

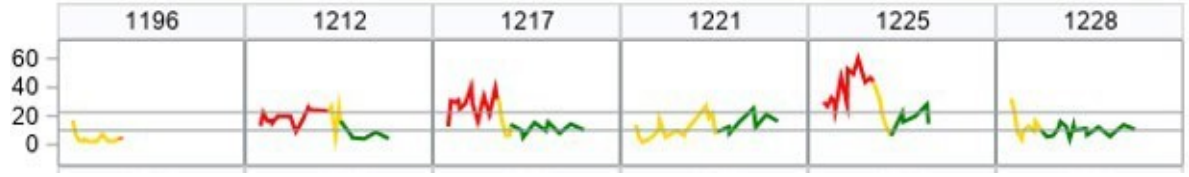
Neither the posology in APPROACH nor that in APPROACH OLE are generalisable to the posology in the SmPC, which recommends 3 months of weekly dosing followed by every 2 weeks dosing. APPROACH OLE permits down-titration to every 2

weeks dosing due to AEs (namely low platelet levels), but only 14 patients conformed closely to the SmPC posology (initiated treatment on weekly and then reduced every 2 weeks within 3 months for platelet count <140,000/mm3 or at 3 months ±2 weeks).

To overcome this issue of limited patient data, regression analysis was applied to all TG patient observations collected within APPROACH and APPROACH OLE to understand the incremental impacts of differing dosage regimens allowing for patient's underlying TG levels. In conducting this, patient timelines were constructed which not only recognised current dosage levels and time on dosage, but also measured time since previous dosage regimens. This permitted an analysis which could incorporate kick-in and wash-out periods. In total, the dataset comprised of 1,508 unique TG observations collected in 90 patients up to the February 2019 cut-off.

Figure 39 shows the TG observations over time for a selection of 6 patients from the trial as well as the thresholds for TG classifications.

Figure 39 TG readings (mmol/L) from patients in APPROACH/APPROACH/OLE



Key: red lines denote untreated/placebo, yellow every week dosing and green every 2 weeks dosing.

Although the economic model is driven by TG categories given different treatment regimens, we adopted an approach of modelling TG levels directly and then converting the mean predictions into categories.

Due to the non-zero and skewed nature of the data, linear regression models which assume a Normal distribution of error terms were considered inappropriate. Further inspection of the data revealed that a Generalised Linear Model approach with a gamma distribution and log link function captured the appropriate features of the data including the relationship between the expectation and standard deviation around the deviation (i.e. not constant and increasing proportionately as the expectation increases).

A further consideration was the clear levels of heterogeneity between patients with very different starting levels of TG which often remain even after treatment. In order to accommodate time-invariant differences between patients, a Random Effects specification was adopted for the regression model.

As with a standard GLM the mixed model GLMM has the three standard parts: a distributional assumption; a systematic component and a link function.

Following the notation outlined in Fitzmaurice, Laird and Ware (2011), the systematic component is given by η_{ij} for patient i at observation j in the GLMM is given by:

$$\eta_{ij} = X'_{ij}\beta + Z'_{ij}b_i$$

Where X'_{ij} is a matrix containing patient-observation specific values of the explanatory variables and β is a vector of parameters that converts those explanatory variables into a systematic impact on the dependent variable, Y_{ij}. This element is the 'fixed' effect component of the mixed model.

$Z'_{ij}b_i$ captures the subject specific deviation from the mean and represents the 'random' effect component of the regression model. b_i are assumed to vary independently between subjects with $b_i \sim N(0, G)$.

Given this linear formulation which incorporates both the impact of explanatory variables, the dosage regime dummy variables and the impact of subject heterogeneity, the random effects, the expected outcome for any given individual i is given by:

$$E(Y_{ij}|b_i) = g^{-1}(\eta_{ij})$$

Where g^{-1} is the inverse of a specified link function $g(.)$

In addition the variance of the outcome variable, Y_{ij} is given by:

$$Var(Y_{ij}|b_i) = v\{E(Y_{ij}|b_i)\}\phi$$

Where $v(.)$ is a known variance function which systematically relates the variation of Y_{ij} to the expectation of Y_{ij} and is determined by the choice of distribution for the GLMM and ϕ is a dispersion parameter to be estimated within the model.

Based on the nature of the data – skewed, heteroscedastic and non-zero we have opted for a **Gamma distribution** combined with a **log link function**, which therefore allows to replace $g(.)$ by chosen link function and $v(.)$ by choice of distribution such that:

$$E(Y_{ij}|b_i) = \exp(\eta_{ij})$$

$$Var(Y_{ij}|b_i) = E(Y_{ij}|b_i)^2\phi$$

There are several advantages of fitting a GLMM directly to patient TG values in order to predict the effect of every 2 weeks volanesorsen:

- The model captures the individual heterogeneity of patient responses to volanesorsen on the natural measurement scale, avoiding the need for smearing
- The model accounts for any change in effect over time (e.g. relaxation of diet or effect of dose pauses)
- The predictions reflect the impact of volanesorsen on not only the estimated mean TG value for each patient, but also the impact on the variance in individual TG measurements (and the potential for spiking into ultra-high TG values with a heightened risk of AP).

The design matrix, X'_{ij}, features the parameters of interest, whose effect we wish to estimate. To accommodate periods of kick-in of new treatments and wash-out of old treatments, dummy variables for 9 different dosage regimes were constructed rather than

just 3 regimes (no treatment; every two weeks and every week). These reflected not only current treatment but also the extent to how long they had been on that treatment and how long they had off another. These treatment dummies are:

1. No treatment (NT)
2. No treatment wash-out from every two weeks (WO_10)
3. No treatment wash-out from every week (WO_20)
4. Every two weeks kick-in from no treatment (KI_01)
5. Every two weeks (ETW)
6. Every two weeks wash-out from every week (WO_21)
7. Every week kick-in from no treatment (KI_02)
8. Every week kick-in from every two weeks (KI_12)
9. Every week (EW)

The text in brackets represents the short-hand names used in SAS 9.4. Every observation was uniquely allocated to one and only one of these distinct and exhaustive dosage categories. For example, an observation from a patient who was on an every two week dose but had just recently switched from an every week dose would be assigned a 1 for dummy variable 6 (Every two weeks

wash-out from every week) and a 0 for all other dummies. At some point in time and assuming the patient remains on every two weeks, further observations would be assigned to category 5 (Every two weeks.)

Accounting for time on dose and previous dose was considered an essential component of the model given the long half-life of volanesorsen and the time to steady state TG levels after any dosing change. However, defining what the durations should be for kick-in and wash-out periods is challenging in the absence of a clear clinical consensus and/or robust empirical data.

Our approach was to allow the data to guide the choice of these periods by applying the principal of maximum likelihood to guide the selection of durations. We did this by sampling independent random values of kick-in and wash-out durations for each of the relevant dummy variables (2,3,4,6,7 and 8) form a U(0,365) distribution 10,000 times. For each simulation of durations we constructed an analysis dataset using the sampled definitions of durations and estimated the model using the outlined GLMM. In each case we recorded the log-likelihood.

Inspection of the log-likelihoods indicated strong empirical support for a 30-day definition for a kick in period from no treatment to every two weeks. Fixing this parameter at 30 days and re-running the simulation again in a step-wise manner the regression models suggested a wash-out period of 35 days from every two weeks to no treatment and a wash-period of 95 days from every week to no treatment. This process did not produce strong empirical support for narrowing down the values of the other parameters and so these values were chosen on a rather arbitrary basis. A kick-in period of 95 days was assumed for going from no treatment to every week on the basis of it being the opposite of the wash-out period which is indicated in every two weeks. The values for kick-in and wash-out between every week and every two weeks was selected at the midpoint between 95 and 35 days.

A summary of the categorical linear predictors and their respective kick-in and wash-out times is shown below.

Categorical dose predictors in GLMM

Abbreviated predictor	Definition	Length of Kick-in/Washout (days)
NT	No treatment	
WO_10	No treatment Wash-Out from every two weeks	35
WO_20	No treatment Wash-Out from every week	95
KI_01	Every two weeks Kick-In from no Treatment	30
ETW	Every two weeks	
WO_21	Every two weeks Wash-Out from every week	65
KI_02	Every week Kick-In from no treatment	95
KI_12	Every week Kick-In from every two weeks	65
EW	Every week	

Results

The GLMM model outlined with a gamma distribution and log link function with a design matrix consisting of 9 dummy variables (the no treatment dummy is excluded for identification) and a random effect specification with results clustered within patients yields the following results:

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	3.115	0.072	43.53	<.0001
No treatment	0.000	.	.	.
No treatment Wash-Out from every two weeks	-0.700	0.120	-5.84	<.0001
No treatment Wash_Out from every week	-0.899	0.088	-10.27	<.0001
Every two weeks Kick-In from no Treatment	-0.481	0.181	-2.66	0.008
Every two weeks	-0.705	0.050	-13.98	<.0001
Every two week Wash-Out from every week	-0.897	0.073	-12.28	<.0001
Every week Kick-In from no treatment	-0.667	0.061	-10.99	<.0001
Every week Kick-In from every two weeks	-0.799	0.263	-3.04	0.0024

Every week	-1.166	0.037	-31.25	<.0001
G (RE variance)	0.4011	0.063		
β Squared	0.2423	0.009		

Although not in the original metric the results have an intuitive appeal. Negative values indicated lower TG values and all dosage dummies relative to the omitted category '*no treatment*' have a negative and statistically significant coefficient which indicates a lower expected TG value.

In addition, although being in a '*wash-out period from every two weeks*' has an impact relative to '*no treatment*', it is smaller than being in the '*wash-out period from every week*'. Similarly, whilst '*every two weeks*' has a bigger impact than '*no treatment wash-out from two weeks*', and a bigger impact than a '*kick-in every two weeks from no treatment*', it has a lower impact than if it were in the '*wash-out period from every week'*. And finally, '*every week*' has the biggest impact of all and exceeds the '*kick-in period from every two-weeks'* which in turn exceeds that of the '*kick-in period from no treatment*'.

The model also estimates a variance of the random effects of the underlying population and is shown by the parameter G. This is significantly different from zero and indicates that there is significant heterogeneity within in the population. Empirical Bayesian Estimates of the underlying individual specific intercept terms (random effects) were also estimated and range from -1.84 to 1.02 where the average individual has a RE equal to 0.

The final parameter estimated is $\beta\beta$ squared which identifies the square of the scale parameter in a gamma distribution.

Goodness of fit measures indicated a RMSE of just 7.8 and an average absolute error term of 5.3. Nine of the ten largest residuals occurred in no treatment where a very high TG value was observed, quite a bit higher than the predicted values which were already at the high scale. This is to be expected an again is indicative of a gamma distribution where the variance is a feature of the expectation squared – we would therefore most likely expect to see outliers where the prediction is higher.

Combing the parameter values with a patient RE and taking the exponent of this value yields the expected TG value. Below we show the expected TG values for all possible treatment regimens for: the patient with the lowest RE i.e. the patient who will systematically have the lowest TG scores (dubbed 'best' patient), the average patient (i.e. RE = 0) and the 'worst' patient, the patient with the highest RE and has the highest expected TG score conditional on treatment.

Expected TG score	Best Patient (RE = -1.84)	Average Patient (RE = 0)	Worst Patient (RE = 1.02)
No treatment	3.59	22.54	62.76
No treatment Wash-Out from every two weeks	1.78	11.20	31.18
No treatment Wash_Out from every week	1.46	9.17	25.54

Every two weeks Kick-In from no Treatment	2.22	13.93	38.80
Every two weeks	1.77	11.13	31.00
Every two week Wash-Out from every week	1.46	9.19	25.60
Every week Kick-In from no treatment	1.84	11.57	32.22
Every week Kick-In from every two weeks	1.62	10.14	28.24
Every week	1.12	7.03	19.56

In addition to the RMSE and absolute error measures of the goodness of fit, the estimated % reduction in TGs from baseline by dose is shown below. The predictions are in line with the trends observed in Figure 20 and Figure 24 as well as the results reported in Table C17.

Percentage reduction in TGs from baseline predicted by the GLMM

	NT	**ETW**	**EW**	**Relative % lowering ETW vs. EW**
>= 70kg	-15.0%	43.2%	64.2%	0.67
< 70kg	-10.8%	45.0%	65.5%	0.69

A further validation exercise was carried out by comparing the predicted TG value on every 2 weeks (ETW) dosing for APPROACH volanesorsen arm patients with their actual baseline and month 3 TG values (the latter reflecting response to weekly dosing). Any patient whose baseline TG value was below the predicted ETW dosing value or whose month 3 TG value was above the predicted ETW value was further investigated. Only 2 out of 33 patients failed this simple test:

- One patient had a predicted value on ETW that was less than the actual month 3 value of 25 mmol. This patient was the *only* patient not to have achieved TG levels below 22.6 mmol by month 3 in the volanesorsen arm, the GLMM prediction apparently being skewed by several TG readings below 10 in the weeks preceding the month 3 endpoint measurements. The predicted value on ETW dosing for this patient was adjusted in the model such that it was 67% of the effect of the month 3 percentage reduction from baseline (the relative effect of ETW vs weekly dosing, see previous table).

- One patient had a predicted value on ETW that was above the patient's baseline value. This patient was the only patient not to have achieved a % reduction of >25% in APPROACH and had subsequent TG readings while on treatment that were above 22.6 mmol. The patient was identified in the CSR as an extreme outlier in terms of response throughout the APPROACH trial.

Notably, based on their actual APPROACH month 3 values, both of these patients failed the stopping rule according to the SmPC and therefore their predictions on ETW dosing become redundant in the model. The set of APPROACH patient predictions for untreated, weekly and every 2 weeks dosing are presented in the *'GLMM TG model'* sheet and below.

GLMM model predictions by APPROACH patient

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

subjid	Arm	Base TG	Month 3 TG	Weight category	Random Effect	Exp_NT	Exp_ETW	Exp_EW
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: subjid, subject id, PBO, placebo, ;VOLAN, volanesorsen; TG, triglyceride; Exp, expected; NT, not treated; ETW, every two weeks; EW, every week

Strengths and Weaknesses of GLMM model

The GLMM model was developed to inform the treatment effect of every 2 weeks volanesorsen on fasting TGs. Model predictions have strong internal validity, largely reflecting the results of the 'mixed dose' analysis of the clinical data. The predictions of treatment effect on every 2 weeks dosing from the GLMM were informed by patients who reduced dosing frequency during the APPROACH or APPROACH OLE trials. As these patients reduced dose for tolerability/safety reasons rather than at random, there may be systematic differences between the characteristics of these patients and the full randomised population. There is little evidence, however, to suggest that this is the case. The most likely characteristic that could lead to dose reduction is body weight (see section 8.7), yet little difference in effect size was predicted for patients weighing more than vs. less than 70kg.

17.1 Appendix 9: Modelling of efficacy data from APPROACH

Modelling of APPROACH ITT

In the ITT modelling, patients can move both between dose categories and between TG categories conditional on the dose received in the quarter of the TG reading (TGs were measured near the end of the quarter in APPROACH).

Derivation of dose transition matrices

To capture dose changes, patients in APPROACH were categorised into one of three mutually exclusive dose categories in each quarter, as described in the table below. Dose pauses were not categorised into a separate dosing category and were instead applied as a dose intensity reduction to drug costs in full and reduced dose health states. As no sensitivity analysis is carried out for the APPROACH ITT scenario the dose intensity on weekly dosing is [redacted]%, which was the intensity on weekly treatment after accounting for dose pauses.

3x3 patient transition matrices were then extracted to capture movement between doses over each quarter, with movements in quarters 2-4 being grouped to create transition probabilities that could be used in a post year-1 extrapolation of the ITT data.

Derivation of dose categories in ITT analysis

Dose category	Coding algorithm
Full dose	Assumed on full dose if patient was classed as being on weekly dosing and had at least 7 doses in that cycle.
Reduced dose	Assumed on reduced dose if patient was classed as being on once every weeks dosing or had 6 or more pauses in that cycle. (The majority of patients who reduced dose did so in the first half of the cycle).

Discontinued	Assumed to have discontinued if discontinued in the first half of that cycle. If drug was discontinued in the second half of the cycle, the discontinuation was counted as taking place in the next cycle, as the effect of discontinuation on TGs was unlikely to manifest until then.
Dose pause (full dose)	Applied as a dose intensity % to drug costs in cycles where patient was on weekly dose, calculated using the mean number and duration of pauses for patients in APPROACH.

Derivation of TG transition matrices

The trial baseline, Month 3, Month 6 and Month 12 endpoints informed the respective TG levels used in the model. Where there was missing data (none for Month 3, 4/33 at Month 6, 6/33 at Month 12), these clinical endpoints were imputed via bootstrap imputation and multiple imputation assuming Missing at Random. In the multiple imputation analysis fasting TG values were imputed using a model that contained the following variables: baseline fasting TG and fasting TG values at post-baseline visits, the two randomisation stratification factors, with analysis stratified by treatment. Following a request by the FDA, a bootstrap analysis was carried out which considered the effect of discontinuation, as described below:

- For volanesorsen patients who terminated before Month 6, missing Month 6 TG results were imputed from volanesorsen patients who terminated before Month 6 but with Month 6 TG measured.
- For volanesorsen patients who terminated early with Month 12 TG result missing, missing data were imputed from volanesorsen patients who terminated early but with Month 12 TG measured.

- Missing data for placebo patients at Month 6 or Month 12 was imputed using bootstrap method from placebo patients with TG results at Month 6 or Month 12.

- The bootstrap imputation was repeated 5000 times. The estimates from 5000 fitted models for each of the 5000 imputed datasets were combined to provide an overall estimate with corresponding confidence intervals and p-value.

As there was no formal Month 9 endpoint in APPROACH, TG levels collected between the end of Month 6 and start of Month 10 were used where available and missing values for Month 9 imputed using the average of the Month 6 and Month 12 endpoints for that patient (including imputed endpoints).

A summary of the clinical data used to derive the transition probabilities between TG states in the ITT analysis is provided below:

Derivation of fasting TG levels in ITT analysis

Fasting TG measurement in model	**Clinical data informing TG measurement**
Baseline fasting TGs	Baseline TG levels were obtained in the final two weeks of the 8-week screening period.
Month 3 fasting TGs	Average of the Week 12 and Week 13 assessments.
Month 6 fasting TGsx	Average of Week 25 and Week 26 fasting assessments.
Month 9 fasting TGs	No formal endpoint value was available for this time point. Therefore, TGs were estimated as follows: • Use Week 38 TG value. If this is missing: • Use Week 32 value. If this is missing:

	• Use the average of the Month 6 and Month 12 endpoints.
Month 12 fasting TGs	Average of the Week 50, Week 51 and Week 52 fasting assessments.

After extraction of the TG values per quarter, TGs values for each patient were categorised into one of the three TG risk categories, with TGs<10 mmol placed in the 'low risk', 10≤TG<22.7 mmol 'medium risk' and ≥22.7 mmol 'high risk' categories respectively. 3x3 transition matrices were then created to capture the movements of patients between each TG category, conditional on volanesorsen dose by quarter using the following algorithms:

- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if on full dose in quarter (T+1)
- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if on reduced dose in quarter (T+1)
- TG category$_{(\text{Quarter T})}$ -> TG category$_{(\text{Quarter T+1})}$ if discontinued in quarter (T+1)
- Dosing category$_{(\text{Quarter T})}$->Dosing category$_{(\text{Quarter T+!})}$

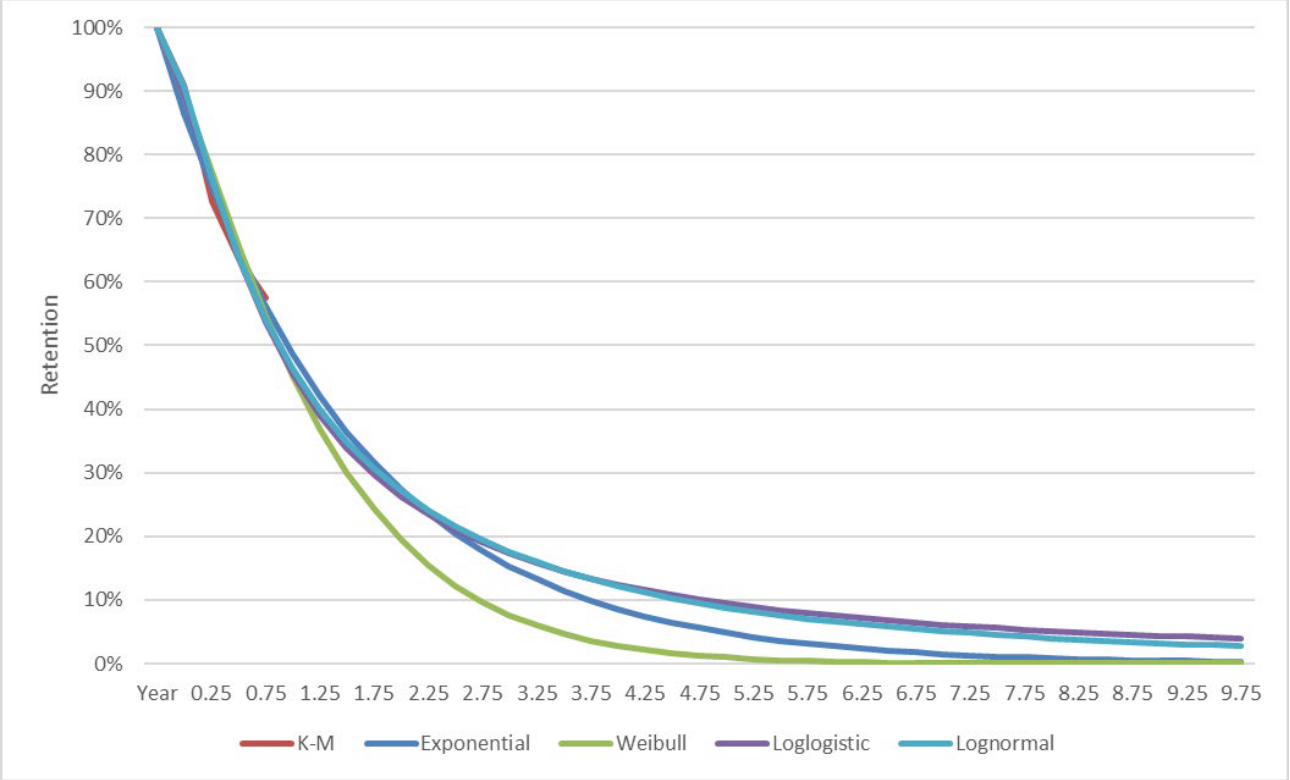
The patient transitions for Months 4 to 12 (Quarters 2 to 4) were summed to derive a constant transition matrix for Months 4 to 12. This allowed the extrapolation of transitions beyond 1 year in the ITT analysis to be based on the average over the last 9 months rather than simply the last observation carried forward.

For the SoC arm, the same process was repeated to obtain patient TG transitions, except that the constant transition matrix was based on transitions from month 0 to 12. Patients who discontinued volanesorsen in the ITT analysis were allocated the transition matrix for standard of care, to avoid any hangover in treatment effect from being extrapolated over the longer term.

Retention on treatment

Parametric survival functions were fitted to the ITT data using the same methods as the base case. They are not fully reported here give the high discontinuation rate in APPROACH and the lack of generalisability to the licence. The exponential, Weibull, lognormal and loglogistic were selected for inclusion in the model based on goodness of fit statistics and visual fit (Figure 40). Together, these different curve types also largely captured the range in longer-term retention observed across the range of survival curves. Lognormal was selected for the base case but produced results very similar to the loglogistic.

Figure 40 Parametric survival functions of retention in ITT analysis

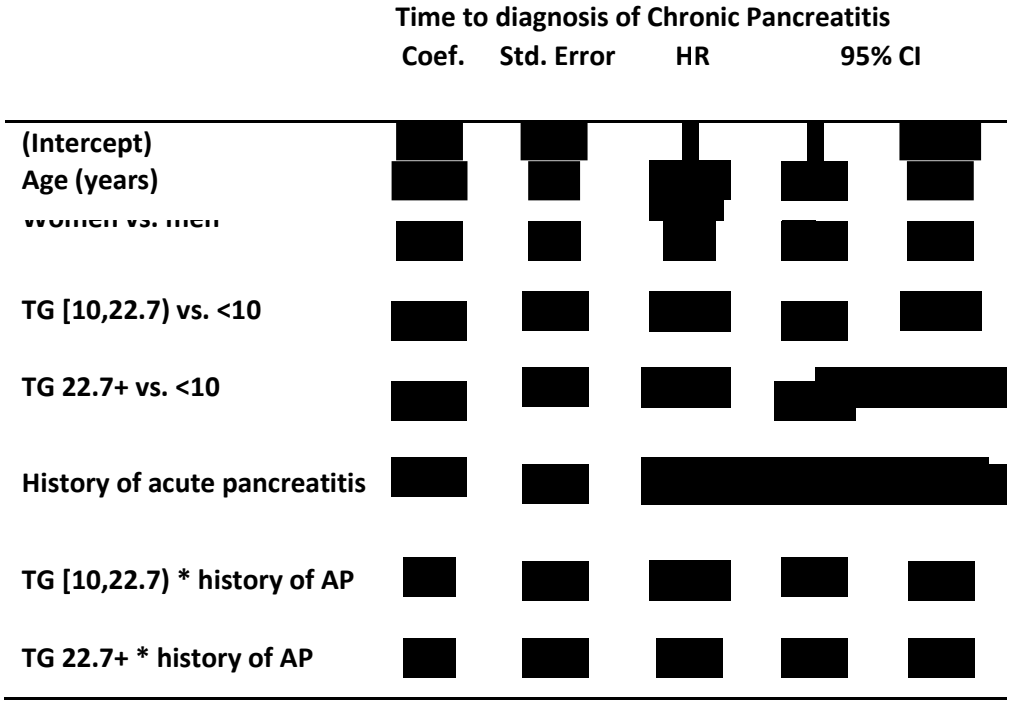


17.2 Appendix 10: AFT model outputs

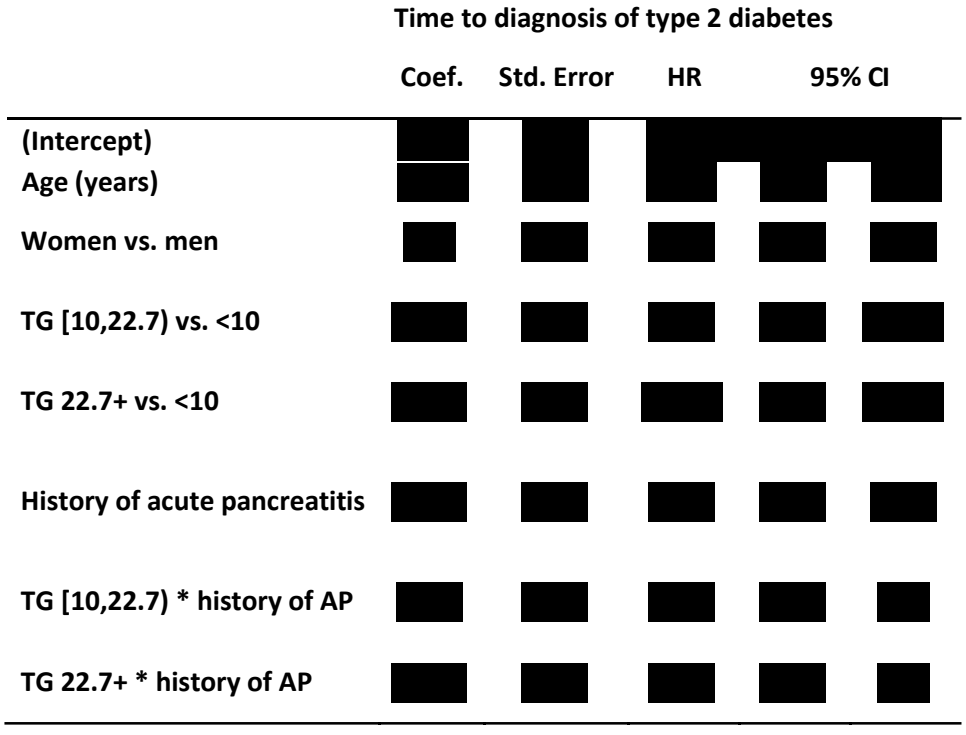
Time to first/next Acute Pancreatitis event

	Time to first Acute Pancreatitis event			
	Coef.	Std. Error	HR	95% CI
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Women vs. men	[redacted]	[redacted]	[redacted]	[redacted]
TG [10,22.7) vs. <10	[redacted]	[redacted]	[redacted]	[redacted]
TG 22.7+ vs. <10	[redacted]	[redacted]	[redacted]	[redacted]
History of acute pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
TG [10,22.7) * history of AP	[redacted]	[redacted]	[redacted]	[redacted]
TG 22.7+ * history of AP	[redacted]	[redacted]	[redacted]	[redacted]

Time to diagnosis of Chronic Pancreatitis



Time to diagnosis of type 2 diabetes



17.1 Appendix 11: OWSA extended results

Only parameters where the difference between the lower input and the upper input results in a >£1,000 difference in the ICER are shown.

Parameter	Low	High	Diff
Basecase ICER	£213,755		
Annual missed doses every 2 weeks dosing	£230,991	£193,722	£37,269
AP rate high TG - patients with recurrent AP	£234,447	£198,477	£35,970
U Chronic pancreatitis - SoC	£204,237	£224,399	£20,162
Cost chronic pancreatitis	£221,506.18	£205,216.53	£16,289.65
Annual carer utility from treatment	£221,279	£206,726	£14,554
AP rate med TG - patients with recurrent AP	£211,021	£224,644	£13,623
U Low TG- Historical AP	£220,501	£207,645	£12,856
TE of volan on AP rate med/low risk TGs	£210,995	£222,800	£11,805
UD Diabetes (with complications)	£219,166	£208,247	£10,918
U Low TG- recurrent AP	£219,215	£208,755	£10,460
U High TG- recurrent AP	£208,954	£218,831	£9,877
Prob recurrent AP is fatal	£215,340	£212,025	£3,315
Prob CP after recurrent AP, 100 weeks	£215,492	£212,202	£3,290
U High TG- Historical AP	£212,227	£215,320	£3,093

Parameter	Low	High	Diff
U of (D+E): Current AP event	£212,632	£214,965	£2,333
U of (C+E): Current AP event	£212,721.34	£214,811.21	£2,089.87
U of state D: High TGs, history of AP	£214,797	£212,732	£2,065
U of state C: Low TGs, history of AP	£214,581	£212,983	£1,598
Missed doses first quarter weekly dosing	£214,346	£212,837	£1,508
HRU Gen hospital admissions	£212,403	£213,755	£1,352
AP rate low TG - patients with recurrent AP	£213,547	£214,664	£1,118
RR AP mortality with volanesorsen	£213,634	£214,721	£1,088

Key: HRU, healthcare resource use; U, utility; UD; utility decrement; Prob, probability; RR, relative risk; TE, treatment effect; AP, acute pancreatitis; CP, chronic pancreatitis

18 Related procedures for evidence submission

Cost- effectiveness models

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the Evidence Review Group, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the Evidence Review Group with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should

be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised

Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under [redacted] and information submitted under [redacted].

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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Highly Specialised Technology Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Dear Claire,

The Evidence Review Group, School of Health & Related Research Sheffield and the technical team at NICE have looked at the submission received on 30 August 2019 from Akcea Therapeutics. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions **by 5:00pm, Monday 30 September 2019**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under '[redacted]' in turquoise, and all information submitted under '[redacted]' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for confidential information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Yelan Guo, Technical Adviser (yelan.guo@nice.org.uk). Any procedural questions should be addressed Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely

Janet Robertson
Associate Director
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Please note that company submission (CS) page numbers may be incorrect by +/-1 or 2 pages. The document seems to generate different page numbers on different PCs.

Section A: Clarification on effectiveness data

Literature searching

A1. Appendices 1, 3 and 4 of the CS each begin with text which appears to have been pasted directly from the NICE Guide to the methods of technology appraisal, setting out the minimum requirements of databases to be searched. In each case, this is immediately followed by the company's account of its own searches that do not appear to have included all of the specified sources. Please provide evidence of the searches, if conducted, of (a) Medline In-Process (b) EconLit (c) NHS EED.

A2. The inclusion criteria for the review of clinical evidence (CS Appendix 1 P325) state that no restrictions have been applied to study design. However, the Medline and EMBASE searches for this review both appear to have applied a search filter (source uncited) restricting results to RCTs. Please explain this apparent contradiction.

A3. The PubMed searches for each review rely exclusively on MeSH indexing terms. Please explain why no free-text terms were used in these searches and comment on the implications for the retrieval of in-process and 'online ahead of print' records in PubMed which would not yet have been indexed.

A4. Please clarify why an English language limit was applied to the EMBASE search for clinical evidence (CS, Appendix 17.1, P324 line 64) but not the Medline search.

A5. Please acknowledge the sources of the search filters used to identify eligible study types in each of the reviews, providing citations to published validation studies where available.

General and background

A6. Please clarify what definition of high risk patients is preferred by Akcea, in interpreting the license and throughout the submission? Please clarify if a definition of prior AP history OR high TG levels (>20mmol/L or >22.7mmoml/L) at baseline was considered? Please clarify how English clinicians are likely to interpret this criteria, and any supporting evidence?

A7. P21 - Please clarify how the initiation of a genetic testing service in the UK may change the estimate of the number of FCS patients in the UK? For example, will more patients with multifactorial chylomicronaemia syndrome be found to have FCS?

A8. Please clarify whether clinicians will have to spend additional (to normal clinical practice) time considering monitoring data collected by Akcea for each patient?

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A9. P153. Please clarify how patients will be supported in clinical practice to maintain their diets?

Clinical effectiveness data

A10. **Priority Question:** Analysis of bi-weekly dosing schedule (p130 and p391). For the following analyses, please use the later data cut point of February 2019, or any subsequent data cut point, for patients who have conformed with the licensed dosing schedule, drawing patients from all three trials? If this analysis is not possible, please respond to following items, a-f, using the analysis of 14 patients provided in the submission.

a. Please clarify what the efficacy data (as per Table C19 and for pancreatitis events alone) are for these patients. Please clarify what Figure 24 of the CS would look like for these patients?

b. Please clarify if the baseline characteristics of these patients differ from the whole trial populations? Please clarify the impact of any imbalances on results.

c. Please clarify why each patient in the analysis of bi-weekly dosing had a dose reduction, and if this was for an adverse event, please specify the adverse event? Please clarify if inclusion of only patients with adverse events in the n=14 analysis reported in the submission will affect the generalisability of the findings?

d. Please clarify how many of these patients could be considered at "high risk of pancreatitis" in accordance with the license? Please provide this assuming a definition of a) prior pancreatitis, b) recurrent admissions for pancreatitis c) prior pancreatitis OR high TG levels, d) prior pancreatitis AND high TG levels, e) recurrent admission for pancreatitis OR high TG levels and f) recurrent admission for pancreatitis AND high TG levels.

e. Please clarify what the adverse event rates are for patients whilst on bi-weekly dosing? Especially thrombocytopenia and injection site reactions. Please clarify if these rates are different according to time since reducing dose?

f. Please clarify what the discontinuation rates are for patients whilst on bi-weekly dosing? Please clarify what Figure 12 would look like for patients on bi-weekly dosing? Please provide reasons for discontinuation.

A11. Text on P19 states "*Twenty-five patients have been identified as eligible, of whom 20 were on treatment as of 31 July 2019. EAMS uses a similar platelet monitoring and dose adjustment schedule as that in the SmPC. No EAMS patient has had a platelet level < 50 x 109/L with the monitoring and dosing programme in place. TG and other available data are currently being collected for the EAMS cohort. With the NICE Committee's permission Akcea will provide this information in advance of the November Committee Meeting. Anecdotal feedback from EAMS supports that value of this product to patients with clinicians reporting patients getting and keeping jobs,*

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going on holiday and forming partnerships, all for the first-time as adults, since starting treatment."

a. Please clarify from what wider population the 25 patients were identified? What criteria were used to judge eligibility? Why are 5 patients not on treatment?

b. How does the treatment schedule and monitoring/dose adjustment differ from the license? Did all patients meet the licensed indication of being at high risk of pancreatitis? How many patients would have passed the stopping rule?

c. How long have patients been on treatment?

d. Text in Table A2 suggests no EAMS patients uptitrated. However, text on p157 (and elsewhere) suggests one EAMS patient uptitrated. Please clarify which is correct? Please clarify why they were uptitrated?

A12. Table C6 states follow-up was for 13 weeks, but Figure 9 states post-treatment evaluation was for weeks 53-56. Please clarify how these are defined and why follow-up and post-treatment evaluation have different values? Were patients who entered the open-label extension followed up for 13 weeks? What analyses does the 13 week follow-up contribute to?

A13. The inclusion criteria state that patients had to have fasting TG ≥750 mg/dL (8.4 mmol/L) at screening (p72 of CS). A secondary outcome is treatment response rate, but this only included patients with baseline TG >750 mg/dL. This appears to imply that patients with an exact TG level of 750 mg/dL at baseline were excluded, since patients with TG <750 mg/dL were excluded from the trial. Is this correct? How many patients were excluded from this analysis due to this criteria?

A14. P86, Figure 11.

a. Please clarify the data in the box that starts "lost to follow-up" - could patients be listed both in "lost to follow-up" and in "discontinued"? Please further clarify which of these patients entered APPROACH OLE? Table C11 states 14 patients did, but we cannot see how this tallies with the numbers given in Figure 11, as patients had to have successfully completed APPROACH to enter the OLE (Table C7).

b. Clarify whether the patient who was allocated to placebo but did not receive placebo received volanesorsen? Were the results adjusted for this discrepancy?

A15. Please clarify how many patients had genetic confirmation across all three trials? Please clarify if there is any evidence that type of genetic mutation impacts on prognosis or would alter the relative efficacy of volanesorsen?

A16. P90-91, Figures 12&13 - Please could you include data for APPROACH volanesorsen patients who enter APPROACH OLE, continuing the APPROACH plot from month 12 onwards.

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A17. We note that there is some evidence [redacted], thought this may be due to other factors (e.g. dose reductions). Please could you explain and provide supporting evidence to clarify why:

a. [redacted].

A18. On p112 it [redacted] Please clarify what the results of this sub-group analysis were?

A19. On P132 it says "*A post-hoc analysis showed that patients with a history of pancreatitis attacks achieved similar reductions in TG levels…*". Please clarify what the results of this sub-group analysis were?

Statistical analyses

A20. **Priority Question:** CS p168 stated that the baseline distribution of patients in the SmPC analysis is based on the subgroup of patients in APPROACH who had a history of AP and all the patient TG data were used and were reweighted at model entry. Please justify the use of reweighting, and clarify how the reweighting was conducted.

A21. Please clarify how many patients from APPROACH OLE were included in the calculation of the medical history AP rate and how they were selected, and how the patient-years were counted when calculating the rate. Please also clarify how the AP rate for these patients while on volanesorsen in APPROACH was calculated as CSR Table 14.3.2. adhoc2 is missing from submission.

A22. Clarify whether an estimate of efficacy based on a self-control could be confounded by factors such as regression to the mean or due to the effects of enrolment in a study effect.

A23. Please clarify whether Appendix 9 is only relevant to the APPROACH ITT scenario in the economic modelling?

A24. Please clarify what software was used to perform the analyses in the CALIBER study. Please also clarify what was the estimate for the baseline hazard in the exponential model for acute pancreatitis (Akcea 2018a (CALIBER) Table 26) and the relationship between the baseline hazard and the intercept listed in Table 26.

A25. Generalised linear mixed model (GLMM) analysis

a. Please clarify what software was used to perform the GLMM analysis.

b. Please also clarify what was the response variable used in the GLMM.

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c. Please provide evidence indicating support for the estimated length of kick-in/washout days.

d. Please comment on the impact on the regression analysis results of choosing a different kick-in/washout days.

e. Please provide the interpretation of the estimated intercept and parameter "No treatment Wash-Out from every two weeks".

f. Please clarify how the predictions of TG levels for APPROACH patients was calculated using subjid 1004 and 1038 as examples.

The vignette

A26. It appears that "historical" and "recurrent" acute pancreatitis, which are the categories used in the model, were not defined separately in the vignette. Please clarify why "historical" should be considered as more like "recurrent" than like "naïve"? Table C29, p147

A27. Please clarify whether the vignettes were validated by FCS patients before use in the study?

A28. Clarify if a manuscript based on the vignette has been submitted for publication If so, please provide reviewer's comments.

<u>Section B: Clarification on cost-effectiveness data</u>

B1. **Priority Question:** Provide a revised base case analysis and relevant sensitivity and scenario analyses having amended the model based on your responses to the clarification questions.

B2. **Priority Question:** Provide an ICER for the historic AP subgroup and the recurrent AP subgroup.

B3. **Priority Question:** Clarify why the utilities are not age-adjusted? Provide results incorporating age-adjustment.

B4. **Priority Question:** The probability of AP per cycle for historical patients has been calculated from CALIBER data. Provide a sensitivity analyses using the rates derived from the medical history of patients in CS6 and CS7. If possible, explore whether the ICER is sensitive to assumptions in the relative frequency of APs between the TG levels being mindful to ensure the average TP rate across all groups is maintained.

B5. **Priority Question:** Please provide results of the economic analyses for scenarios [redacted]

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B6. **Priority Question:** Clarify why the costs for volanesorsan are half cycle corrected so that, after the first cycle, 3 vials are assumed to be provided to patients who discontinue / die. The ERG believes that the appropriate value would be 3.5 vials given the timing of the vials (assuming one vial prescribed at a time) or 4.0 (assuming two vials prescribed simultaneously). It might be easier to adjust the model to add on this addition (part) vial at death or discontinuation. Clarify how often vials would be dispensed.

B7. **Priority Question:** Apparent error in the model. In 'outcomes data' cells i12:i16 should reference row 'm' not row 'k'. This is a likely source of the higher ICER in PSA

B8. **Priority Question:** Clarify whether the relative risk of mortality between the high and low TG groups in the Wang et al paper is likely to be confounded due to the imbalance in characteristics such as organ failure and systemic complications. Provide an analysis where the relative risk of mortality is set to 1.

B9. **Priority Question:** Please add in a function to allow a user-defined discontinuation rate. Currently the model only allows the fit to the study data which the company contend is not appropriate, and no discontinuation, which may also be viewed as inappropriate.

B10. **Priority Question:** Clarify why it is assumed that people cannot die from a grade 4 thrombocytopenia. Provide an analysis allowing death from thrombocytopenia.

B11. **Priority Question:** Clarify why the value of £50,671 per year for patients with CP, taken from Hall *et al.*, was considered preferable to the direct costs of £9,465 reported in Dennison *et al*. Provide a sensitivity analysis using the costs of Dennison inflated to 2018 prices.

B12. Clarify whether there are any known associations between changes in TG levels and changes in the rate of adverse events rather than associations between absolute values. Relationships between changes are likely to be preferable to associations based on absolute values as confounders may stop the relationship between absolute values from being realised when TG levels are changed.

B13. Linked to Clinical effectiveness question A17. Clarify the impact on the ICER and the QALYs gained if it is assumed treatment stops working at 10 years and all patients discontinue at this point.

B14. Clarify why, given that at study entry 46% of people on standard of care (SoC) are in low or medium TG level states, that all patients on SoC are assumed in the base case to reside in the high TG state. Explore the impact on the ICER of assuming that patients who receive SOC are distributed across the states in these proportions, potentially altering the distributions for volanesorsen so that SoC does not have a greater proportion of people in the low TG state.

B15. Clarify what systems are in place in clinical practice to ensure that missed doses are not associated with costs.

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B16. Please provide additional information such as the distributions (and parameter values) for tables where these are not given such as D17.4

B17. P258-259 states that "*Poisson not possible in Excel*". Clarify why a Poisson distribution is not possible in Excel with reference to the Excel function 'Poisson.dist'

B18. Please provide the same plots as in Section 12.5.3 for the EAMS scenario

B19. Please provide the missing values in the table in Section 12.5.7

B20. The proportions of patients in each TG level category are likely to be biased using the probabilistic mode, as in the 'Start and Stop Populations' sheet the sum of K32:K64 is greater than the sum of O32:O64 in the vast majority (99%) of simulations. Please provide an amended model where the deterministic values for the 3 month period can be combined with the probabilistic model. If uncertainty was to be explored the ERG believes that bootstrapping the patient data is anticipated to provide a less biased dataset.

B21. Confirm whether the age of the patients do not change over the model and thus in the historical AP group, based on the formulae in 'Outcomes data' the AP rate will under-predicted as patients age. Clarify what impact this may have on the ICER.

B22. Clarify why the probability of CP is taken from the 100 week time point (p190 of CS) in Yadav 2012 when the data appears to be for 100 months (Figure 3 in Yadav 2012; Figure 34 of CS). Clarify why 60% of patients with CP was taken as the target when the consensus of the clinicians suggested this value was lower. Provide sensitivity analyses using a target of 30%.

B23. Please add the costs of SoC within the model. Whilst these are equal in both arms there is a mortality difference assumed meaning that patients receiving volanesorsen would receive SoC for longer.

B24. There is an apparent error in the model in the Transition probabilities sheet, cell D284. We believe the formula should read "Pr_low_recAP_CP" rather than "OFFSET(Pr_low_recAP_CP,0,1)". Please amend the model.

B25. Assuming 26 bi-weekly periods within a year will underestimate the cost of volanesorsen. We believe that using 26.09 would be more accurate. Please amend the model.

B26. On p130, it is stated "*Because of small patient numbers, using the above data in the economic model resulted in unstable ICER estimates."* Please clarify whether 36 or 14 patients entered the model, and please clarify in what way the ICER was "unstable" and provide the modelling analysis.

Section C: Textual clarifications and additional points

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C1. Figure 20 appears to have an unusual time scale. [redacted] Please clarify what the figure looks like using a consistent linear scale?

C2. On p85, it states "*these analyses were post-hoc*". Please clarify which analyses?

C3. On page 106, under the heading "*secondary endpoints: Pain*" please clarify which analyses were pre-planned, which pre-planned exploratory analyses, and which were not pre-planned? What is the difference between a pre-planned exploratory analysis and a pre-planned analysis?

C4. Confirm whether the text in the third bullet point of page 13 is correct or not. We believe the model only evaluates what is termed the more restrictive stopping rule.

C5. Clarify whether the domain scores in Table C27 are correct

C6. Clarify the apparent mismatch in carer utility in Table C29 between 0.02 and 0.1

C7. Clarify whether on P181 it should be 'all patients in APPROACH with a history of AP' rather than 'all patients in APPROACH'

C8. Should the weighting value on P286 be CIC?

C9. P168: "*Although discontinuation due to platelet issues on weekly dosing was more likely in patients with lower body weight, this effect is greatly reduced on every 2 weeks dosing (see section 9.9.4) and patients may discontinue for a variety of other reasons*." and P409: "*The most likely characteristic that could lead to dose reduction is body weight (see section 8.7), yet little difference in effect size was predicted for patients weighing more than vs. less than 70kg*." Sections 9.9.4 and 8.7 do not contain any text relating to low body weight. Body weight does not appear to have entered the model. Please clarify the relevance of these statements, and if appropriate, which sections should have been referenced?

C10. P187: "*For patients to change to a worse health state, mean TG values would need to increase to above 22.6 mmol, which is not supported by the available clinical data (Table C17), which suggests a sustained % reduction from baseline of above 40% over the longer term*" Table C17 reports pancreatitis event rates in APPROACH. Please clarify which table should be referenced.

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30 Sept 2019

Dear Janet,

Re: Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for sharing the questions from the ERG regarding the above assessment and for the TC allowing us to clarify a number of points.

Please find below the responses to the original clarification questions and responses to the additional queries that arose during the TC.

The response contains both Commercial and Academic in Confidence information (marked up). As we are using the most up to date data cut we have a large volume of AIC data. Publication dates for the OLE data are not yet confirmed. We have uploaded a revised economic model, new references and an Appendix E for the response to the clarification questions onto NICEdocs.

If you have any further questions please don't hesitate to contact us.

Best wishes

[redacted]

Claire Grant

Director Market Access and Policy

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Please note that company submission (CS) page numbers may be incorrect by +/-1 or 2 pages. The document seems to generate different page numbers on different PCs.

Section A: Clarification on effectiveness data

Literature searching

A1. Appendices 1, 3 and 4 of the CS each begin with text which appears to have been pasted directly from the NICE Guide to the methods of technology appraisal, setting out the minimum requirements of databases to be searched. In each case, this is immediately followed by the company's account of its own searches that do not appear to have included all of the specified sources. Please provide evidence of the searches, if conducted, of (a) Medline In-Process (b) EconLit (c) NHS EED.

Company response: Akcea's systematic literature review of the clinical evidence was conducted in MEDLINE, including Medline in Process, (via Ovid) Embase (via Ovid) and Cochrane Central Register of Controlled Trials (via The Cochrane Library).

The SLRs for economic evidence and resource utilisation searched MEDLINE, including Medline in Process (via Ovid), Embase (via Ovid), Cochrane Central Register of Controlled Trials (via The Cochrane Library) and PubMed. NHS EED and EconLit were not searched. We recognise this is a limitation in our submission and have conducted a rudimentary check in these databases using FCS-related keywords. A total of 10 hits were retrieved using EconLit, none of which were relevant. The search in NHS EED returned no hits.

A2. The inclusion criteria for the review of clinical evidence (CS Appendix 1 P325) state that no restrictions have been applied to study design. However, the Medline and EMBASE searches for this review both appear to have applied a search filter (source uncited) restricting results to RCTs. Please explain this apparent contradiction.

Company response: Search filters restricting to RCTs were originally included in our search strategy. As this did not return any relevant studies, we subsequently broadened the search by changing the AND operator for the RCT filter to an OR (see line 52 of the search strategy and lines 40, 48 and 51 feeding into it). The RCT search terms themselves were kept within the strategy for reference and to facilitate further adaptation should the search be rerun at a later date. Therefore, the search strategy does not restrict to RCTs.

A3. The PubMed searches for each review rely exclusively on MeSH indexing terms. Please explain why no free-text terms were used in these searches and comment on the implications for the retrieval of in-process and 'online ahead of print' records in PubMed which would not yet have been indexed.

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Company response: The PubMed search was an additional search, included to ensure that all the relevant subject literature had been captured (as Medline via Ovid and PubMed have slightly different syntaxes). Only MeSH terms were used in this search. This additional search did not return any further papers to those found using Ovid. Free text search terms were used in the main search of MEDLINE (via Ovid) (see lines 1-32 of the MEDLINE search strategy). The Medline searches included In Process citations.

A4. Please clarify why an English language limit was applied to the EMBASE search for clinical evidence (CS, Appendix 17.1, P324 line 64) but not the Medline search.

Company response: The English language limit was applied purely to minimise the quantity of non-English language publications during the EMBASE database search, anticipating that EMBASE would return a substantial number more hits than Medline, as is typical in these database searches.

A5. Please acknowledge the sources of the search filters used to identify eligible study types in each of the reviews, providing citations to published validation studies where available.

Company response: A database search strategy was developed using a combination of Medical Subject Headings, key disease terms, subject specific (clinical effectiveness and cost effectiveness) search filters identified from other HST applications, along with search filters developed by the Scottish Intercollegiate Guidelines Network for searching OVID databases MEDLINE and EMBASE (SIGN, 2019).

General and background

A6. Please clarify what definition of high risk patients is preferred by Akcea, in interpreting the license and throughout the submission? Please clarify if a definition of prior AP history OR high TG levels (>20mmol/L or >22.7mmoml/L) at baseline was considered? Please clarify how English clinicians are likely to interpret this criteria, and any supporting evidence.

Company response: Akcea recognises that the label indication wording 'high risk of pancreatitis' is open to interpretation. In its evidence submission, Akcea UK has taken the view that patients most likely to be treated with volanesorsen in routine clinical practice in the UK are those with a history of acute pancreatitis. In the base case this is any documented history of acute pancreatitis. We also test more restrictive definitions: one AP in the last five years and two APs in the last five years. It is also possible to consider the eligible population by TG level.

We validated the definition of high risk patients with UK EAMS clinicians in early Sept 2019 and they agreed to the definition below. It should be noted this was in open discussion as opposed to, for example, a Delphi panel/consensus statement approach:

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High risk for pancreatitis

The advisors considered that the following factors would confer a high risk of pancreatitis in patients with FCS:

- *A prior episode of acute pancreatitis caused exclusively by raised TG levels, or known chronic pancreatitis*
- *Persistent TG levels >10 mmol/L*

The advisors noted however, that it is possible for patients to experience pancreatitis with TG levels below 10 mmol/L, and that relative risk and absolute risk of pancreatitis are different terms. Generally, it was accepted that risk of pancreatitis increases with subsequent increases in TG levels. (AKCEA 2019c)

A7. P21 - Please clarify how the initiation of a genetic testing service in the UK may change the estimate of the number of FCS patients in the UK? For example, will more patients with multifactorial chylomicronaemia syndrome be found to have FCS?

Company response: From April 2020 Genomics England are scheduled to provide genetic testing of suspected FCS patients in England, as part of the wider restructuring of genetic testing across multiple diseases. Importantly, genetic testing for FCS has been available to clinicians in the UK for a number of years via the University of Aberdeen, and more recently via the South West Genomic Laboratory, Bristol. The cost of genetic tests has been borne by the NHS in Scottish for patients in Scotland and by the host NHS Trust for patients from England, Wales or Northern Ireland.

Given that there is already an established genetic testing programme for FCS, we do not anticipate the change in April 2020 to have a notable impact on FCS / multifactorial chylomicronaemia syndrome (MCS) patient numbers.

FCS and MCS are distinct patient populations. FCS can be accurately identified, and differentiated from MCS, by a clinical scoring system that has been demonstrated to exhibit strong sensitivity and specificity with genetically confirmed FCS (Moulin P, 2018). Wider availability of genetic testing in the UK is expected to increase the number of genetically confirmed FCS patients within the population of those currently clinically diagnosed, not to increase the overall FCS patient population.

Anecdotally, increased genetic testing of clinically diagnosed FCS patients is identifying a small number of patients who don't have any of the five main mutations, in effect reducing the number of volanesorsen-eligible FCS patients. Though, to reiterate, we don't expect a notable increase in the total number of either MCS or FCS patients due to the Genomics England genetic testing programme.

A8. Please clarify whether clinicians will have to spend additional (to normal clinical practice) time considering monitoring data collected by Akcea for each patient?

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Company response: Volanesorsen treatment requires monitoring of platelet levels as guided by the SmPC. Akcea Therapeutics will be providing a nurse-led patient support programme (PSP) following commercial availability of the medicine, through Ashfield. Amongst other activities, the Ashfield nurse will be responsible for collecting blood from each patient and coordinating measurement of platelet levels via an approved third-party provider (Spire Healthcare) and relaying the results to the prescribing physician. Responsibility for making any adjustment to prescribing based on the results of the blood test lies with the lead NHS clinician. As such, some time to review the results and any resultant dose adjustment will be required. However, we do not expect this to differ significantly from that associated with the routine management of such patients.

A9. P153. Please clarify how patients will be supported in clinical practice to maintain their diets?

Company response: Akcea has a selection of materials that will support patients in managing a low fat diet: nutritional toolkit, dietary tips & dietary recipe advice. These have all been developed in conjunction with the Patient Advocacy Group LPLD Alliance/Action FCS. There is also information for health care professionals on the benefits and importance of maintaining a low fat diet for patients with FCS.

We are actively working with specialist dieticians and expert chemical pathologists and lipidologists to identify other ways in which dietary support for patients with FCS can be provided.

Clinical effectiveness data

A10. **Priority Question:** Analysis of bi-weekly dosing schedule (p130 and p391). For the following analyses, please use the later data cut point of February 2019, or any subsequent data cut point, for patients who have conformed with the licensed dosing schedule, drawing patients from all three trials? If this analysis is not possible, please respond to following items, a-f, using the analysis of 14 patients provided in the submission.

Company response: The latest data available are from the Feb 2019 data cut. We expect the next data cut to be available before the end of 2019 however, an exact date has yet to be confirmed. Scrutinising the data across all three trials reveals only 14 (treatment-naïve) patients from CS7 confirmed with the final label dosing regimen. An analysis of these 14 patients had not been carried out for the submission. Instead, Akcea used a GLMM model to populate the data. Analysis relating to the 14 patients, presented below, is a newly conducted analysis for these clarification questions.

a. Please clarify what the efficacy data (as per Table C19 and for pancreatitis events alone) are for these patients. Please clarify what Figure 24 of the CS would look like for these patients?

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Company response: The efficacy data for the 14 patients who conformed with the licensed dosing schedule are provided below. All these patients were treatment-naïve patients at enrollment in APPROACH OLE. [redacted].

As with any study population of this small size, caution in interpretation of the results is needed.

Table 1 Outcomes from APPROACH OLE in 14 Patients who Conformed with SmPC Dosing Schedule

[redacted]

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Figure 24 of the Akcea evidence submission provided a trace of TG levels over time following dose frequency reduction. We have provided the data for the full time on treatment, not just from the point of frequency reduction (which occurred at around 3 months +/- 2 weeks) for these 14 patients who conformed to the SmPC posology. See plot from start of active treatment in figure below.

Figure 1 Change in TG levels over time in APPROACH OLE in 14 Patients who Conformed with SmPC Dosing Schedule

[redacted]

b. Please clarify if the baseline characteristics of these patients differ from the whole trial populations? Please clarify the impact of any imbalances on results

Company response: As shown in the table below, the baseline characteristics of the 14 patients who have conformed with the licensed dosing schedule are similar to those of the whole trial population. [redacted]

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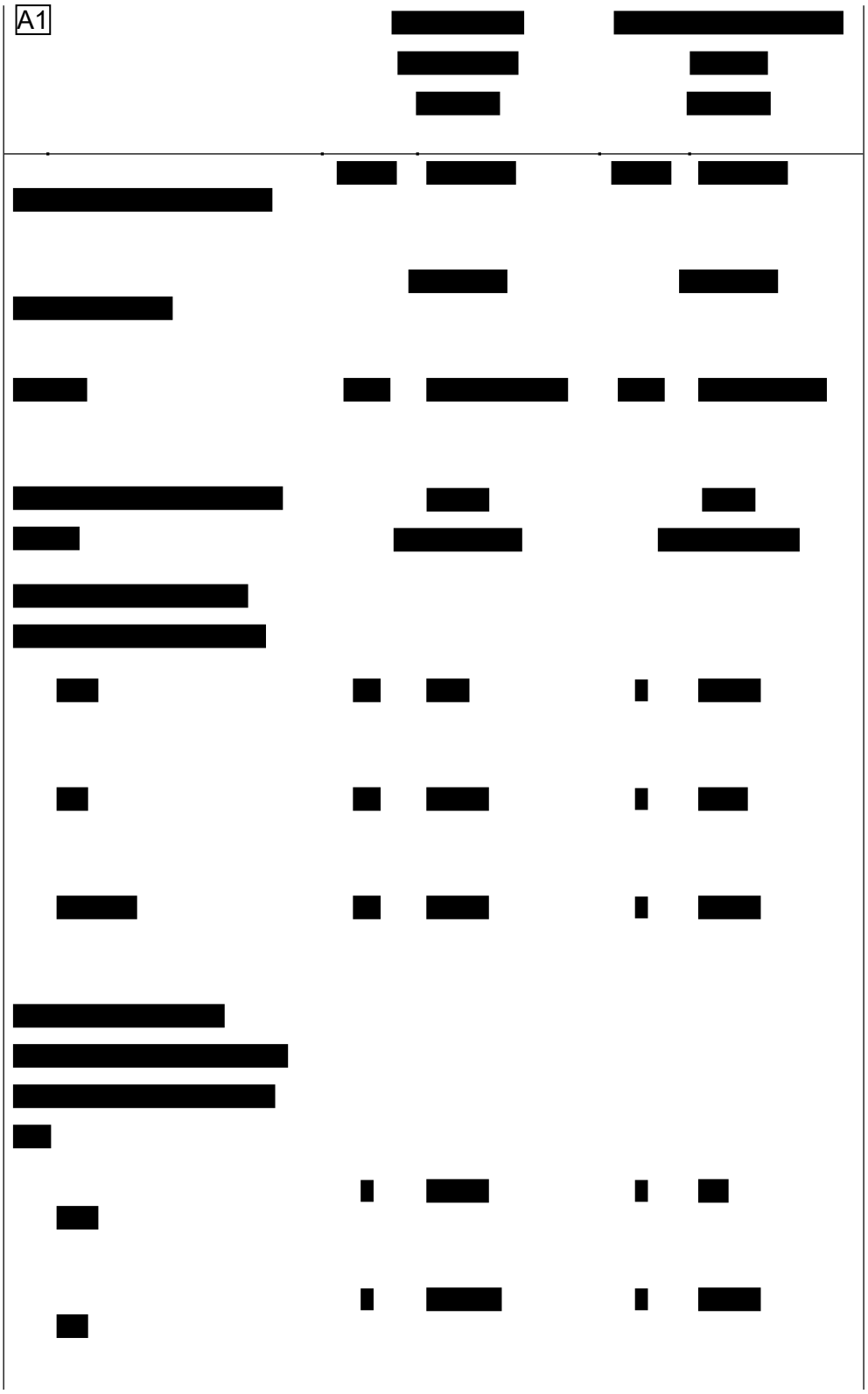
Table 2 Baseline characteristics from APPROACH OLE in 14 Patients who conformed with SmPC Dosing Schedule and overall population



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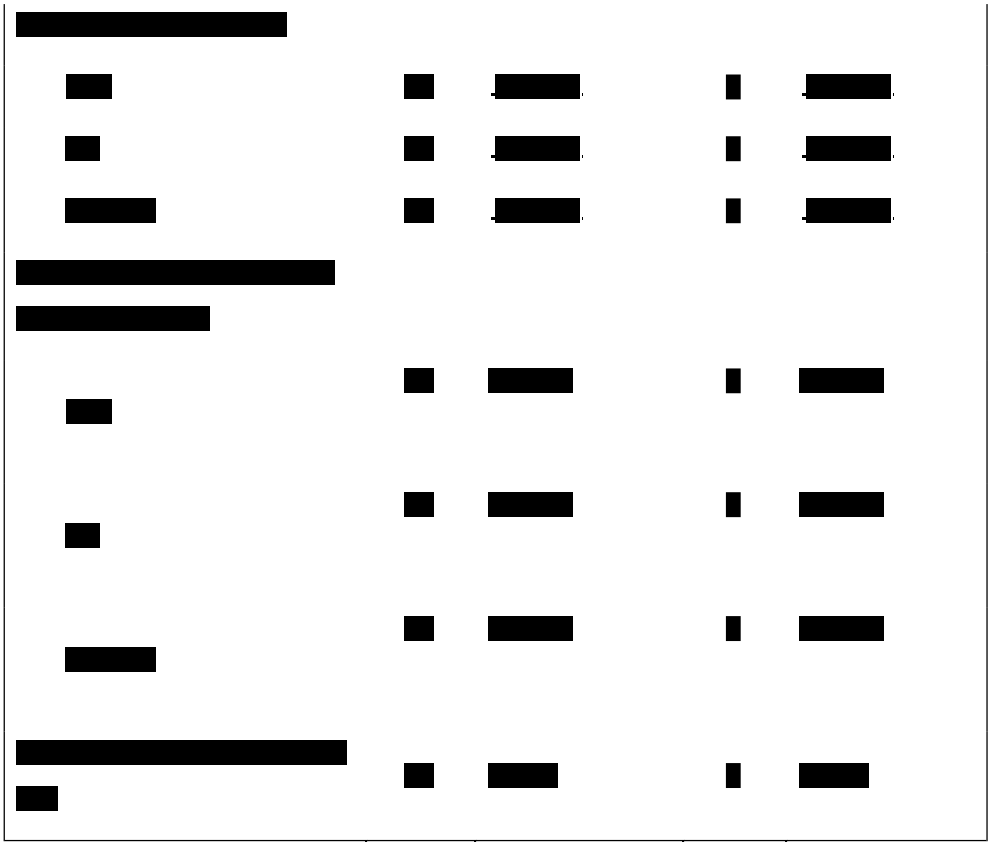

*Treatment-naïve group baseline only
Source: Table 14.1.1.1, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

c. Please clarify why each patient in the analysis of bi-weekly dosing had a dose reduction, and if this was for an adverse event, please specify the adverse event? Please clarify if inclusion of only patients with adverse events in the n=14 analysis reported in the submission will affect the generalisability of the findings?

Company response:

d. Please clarify how many of these patients could be considered at "high risk of pancreatitis" in accordance with the license? Please provide this assuming a definition of a) prior pancreatitis, b) recurrent admissions for pancreatitis c) prior pancreatitis OR high TG

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levels, d) prior pancreatitis AND high TG levels, e) recurrent admission for pancreatitis OR high TG levels and f) recurrent admission for pancreatitis AND high TG levels.

Company response: Please note that the following is based on all 14 patients, of which 4 had missing data for history of acute pancreatitis. The number (%) of patients considered at "high risk of pancreatitis" for each of the provided definitions is as follows:

[redacted]

e. Please clarify what the adverse event rates are for patients whilst on bi-weekly dosing? Especially thrombocytopenia and injection site reactions. Please clarify if these rates are different according to time since reducing dose?

Company response: [redacted]

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[redacted]

f. Please clarify what the discontinuation rates are for patients whilst on bi-weekly dosing? Please clarify what Figure 12 would look like for patients on bi-weekly dosing? Please provide reasons for discontinuation.

Company response: Of the 14 patients who conformed with the licensed dosing schedule[redacted]

For the overall 36 patients who were treated with every 2 weeks dose of volanesorsen for more than 3 months, the reasons for discontinuation in 14 patients were adverse events (10 patients), voluntary withdrawal (3 patients), and physician decision (1 patient). The Kaplan-Meier plot for these 36 patients ('Mixed Dose' group) vs. the remaining 45 patients ('High Dose' group) is provided.

Figure 2 Kaplan-Meier Plot for Patients Discontinuation Through Month 24 by Dose Group - Subjects from CS6 and CS7 who received Volanesorsen (N=81)

[redacted]

A12. Text on P19 states "*Twenty-five patients have been identified as eligible, of whom 20 were on treatment as of 31 July 2019. EAMS uses a similar platelet monitoring and dose adjustment schedule as that in the SmPC. No EAMS patient has had a platelet level < 50 x 109/L with the monitoring and dosing programme in place. TG and other available data are currently being collected for the EAMS cohort. With the NICE Committee's permission Akcea will provide this information in advance of the November Committee*

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Meeting. Anecdotal feedback from EAMS supports that value of this product to patients with clinicians reporting patients getting and keeping jobs, going on holiday and forming partnerships, all for the first-time as adults, since starting treatment."

a. Please clarify from what wider population the 25 patients were identified? What criteria were used to judge eligibility? Why are 5 patients not on treatment?

   The eligibility criteria patients had to meet in order to receive treatment within the volanesorsen EAMS was, an adult patient with a diagnosis of FCS. Therefore, the pool of patients from which the 25 EAMS patients were identified was those with a clinical or a genetic diagnosis of FCS and aged ≥18 years. However, clinicians actually only considered patients for the scheme if they had genetically confirmed disease and a poor current symptomology or clinical history (recurrent abdominal pain and acute pancreatitis), despite dietary intervention and currently available medication. The patient also had to be willing to follow the platelet monitoring schedule in the treatment protocol. Five patients are registered for the volanesorsen EAMS in NHS England BlueTeq portal and are expected to commence treatment in the coming weeks, pending the results of genetic testing and other clinical considerations (4 patients), and completion of follow up in the open label extension clinical trial (1 patient).

b. How does the treatment schedule and monitoring/dose adjustment differ from the license? Did all patients meet the licensed indication of being at high risk of pancreatitis? How many patients would have passed the stopping rule?

   Treatment and Monitoring schedule: The treatment and monitoring schedules differ between the volanesorsen EAMS and the SmPC as outlined in the tables below. The main difference being the volanesorsen EAMS employed a lower start dose (300mg volanesorsen sodium *every 2 weeks*) compared to that within the subsequent SmPC (285mg volanesorsen {equivalent to 300mg volanesorsen sodium} *every week*. Thereafter moving to every 2 week dosing. Both protocols allow for dose adjustment between weekly and every 2 week dosing based on efficacy and platelet levels.:

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Volanesorsen EAMS:

Table 1. Volanesorsen ; Platelet (PLT) Monitoring and Treatment Recommendations

PLT Level (count x 10^9/L)	Dose schedule			PLT Monitoring
	Body Weight < 70 kg	Body Weight ≥ 70 kg		
Normal (≥140)	Every 2 weeks	Every 2 weeks	Weekly+	Every 2 weeks
100-140	Every 2 weeks	Every 2 weeks	Weekly+	Weekly until stable
75-100	Pause, resume every 2 weeks when ≥100 x 10^9/L		Every 2 weeks+	Weekly
50-75	Pause, resume every 2 weeks when ≥100 x 10^9/L			Twice per week until stable
<50	Discontinue volanesorsen**			Every other day until stable*

+For patients up-titrated to a dose of 300 mg once weekly
**Daily if PLT <25 x 10^9/L/mm^3; if platelet count <25 x 10^9/L steroid therapy should be considered
**For any patient dose paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment should be carefully considered. For discontinued patients, a haematologist should be consulted prior to resuming treatment

Waylivra (volanesorsen) SmPC:

Table 1. Waylivra monitoring and treatment recommendations

Platelet Count (x10^9/L)	Dose (285 mg prefilled syringe)	Monitoring Frequency
Normal (≥140)	Starting dose: Weekly After 3 months: Every 2 weeks	Every 2 weeks
100 to 139	Every 2 weeks	Weekly
75 to 99	Pause treatment for ≥4 weeks and resume treatment after platelet levels ≥ 100 x 10^9/L	Weekly
50 to 74[a]	Pause treatment for ≥4 weeks and resume treatment after platelet levels ≥ 100 x 10^9/L	Every 2-3 days
Less than 50[a, b]	Discontinue treatment Glucocorticoids recommended	Daily

[a] See section 4.4 for recommendations regarding use of antiplatelet agents/NSAIDs/anticoagulants
[b] Consultation of a haematologist is needed to reconsider the benefit/risk for possible further treatment with volanesorsen.

Patient population: As outlined above, all patients receiving treatment within the volanesorsen EAMS had genetically confirmed disease and had previously experienced acute pancreatitis and/or were experiencing poor symptomology (i.e.

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deemed to be a high risk of acute pancreatitis) despite adherence to low fat diet and currently available lipid lowering medication. Therefore, all patients should be considered to fall within the therapeutic indication within the current SmPC. One patient on the EAMS was initiated prior to genetic confirmation, however this has now been confirmed.

Stopping rule: The triglyceride-lowering efficacy of volanesorsen administered by the EAMS dosing scheduled is currently being captured (this is not routinely available within the scheme), so it is not possible to comment at this time how many patients would have passed the stopping rule. This information should be available by the November committee meeting, although it should be noted that the stopping rule within the SmPC related to treatment at a dose 2-fold higher than that employed within the volanesorsen EAMS.

c. How long have patients been on treatment?

As of September 30th 2019 the length of treatment with volanesorsen within the EAMS ranges from 15m to 1m. However, since some patients have transitioned into the volanesorsen EAMS from a 2 year open label extension study, and some from the 1 year RCT which preceded that, a handful of patients are approaching 4 years on treatment.

d. Text in Table A2 suggests no EAMS patients uptitrated. However, text on p157 (and elsewhere) suggests one EAMS patient uptitrated. Please clarify which is correct? Please clarify why they were uptitrated?

As of September 20th 2019, one patient within the volanesorsen EAMS has been up titrated from 300mg volanesorsen sodium every 2 weeks, to 300mg every week. This took place after 40 weeks of treatment to increase the triglyceride lowering efficacy. We were alerted to this by the treating physician within the week of the NICE HST submission, hence the error in Table A2 which was not updated to reflect this.

A13. Table C6 states follow-up was for 13 weeks, but Figure 9 states post-treatment evaluation was for weeks 53-56. Please clarify how these are defined and why follow-up and post-treatment evaluation have different values? Were patients who entered the open-label extension followed up for 13 weeks? What analyses does the 13 week follow-up contribute to?

Company response: There is a typo in Figure 9: the post-treatment evaluation period should be weeks 53-65. Patients who entered the OLE were not followed up in the APPROACH post-treatment period unless there was a delay in entering the OLE. The assessments are outlined in Schedule of the APPROACH protocol, see Appendix at the end of this document. The 13-week follow-up contributes mostly to safety assessments, which also occur if the patient moves over to the OLE. Additional

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assessments in the follow-up (that are also done in the OLE) include: lipids (this includes triglycerides), HbA1c, symptom diary (i.e. abdominal pain) and Quality of Life Assessments.

A14. The inclusion criteria state that patients had to have fasting TG ≥750 mg/dL (8.4 mmol/L) at screening (p72 of CS). A secondary outcome is treatment response rate, but this only included patients with baseline TG >750 mg/dL. This appears to imply that patients with an exact TG level of 750 mg/dL at baseline were excluded, since patients with TG <750 mg/dL were excluded from the trial. Is this correct? How many patients were excluded from this analysis due to this criteria?

Company response: The TG ≥750 mg/dL criteria was only required at Screening and not at Baseline. This was because TG values have a lot of variability and so if a patient was confirmed to have FCS by genetics or the enzymatic test for LPL activity (predominantly a US diagnostic tool) during the screening period they could enter the treatment phase of the trial even if their TG values were lower than 750 mg/dL at baseline. The analysis of treatment response rate compared to TG levels at 3, 6 and 12 months with TG level at baseline it was *only* assessed in patients that had TG ≥750 mg/dL at baseline. This meant three volanesorsen patients and two placebo patients were excluded from this analysis. (The three volanesorsen patients who had TG<750 mg/dL at baseline had TG <750 mg/dL on treatment).

A15. P86, Figure 11.

a. Please clarify the data in the box that starts “lost to follow-up” - could patients be listed both in “lost to follow-up” and in “discontinued”? Please further clarify which of these patients entered APPROACH OLE? Table C11 states 14 patients did, but we cannot see how this tallies with the numbers given in Figure 11, as patients had to have successfully completed APPROACH to enter the OLE (Table C7).

Company response: No, patients could not be listed in both “lost to follow-up” and in “discontinued”. ‘Discontinued’ are patients who did not complete the treatment period. ‘Lost to follow-up’ are patients who completed treatment and entered, but did not complete, the post-treatment period (the Figure 11 footnote is incorrect).

Patients who entered the OLE while they were in the post-treatment period are listed in Figure 11 (six volanesorsen and 15 placebo). An additional eight volanesorsen patients and 15 placebo patients immediately entered the OLE after completing the treatment period and did not enter the APPROACH post-treatment period. Patients only needed to successfully complete the APPROACH treatment period to be eligible for OLE.

b. Clarify whether the patient who was allocated to placebo but did not receive placebo received volanesorsen? Were the results adjusted for this discrepancy?

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Company response: The patient allocated to placebo did not receive any Study Drug, placebo or volanesorsen. Yes, the results were adjusted for this.

A16. Please clarify how many patients had genetic confirmation across all three trials? Please clarify if there is any evidence that type of genetic mutation impacts on prognosis or would alter the relative efficacy of volanesorsen?

Company response: Of the 92 patients with FCS across all three trials, including 3 patients who were randomized to the placebo group in APPROACH and did not roll over to APPROACH OLE, 82 patients had genetic confirmation based on disease history or on-study evaluation.

In APPROACH, patients with mutations in the lipoprotein lipase (LPL) gene had a higher incoming triglyceride level compared to patients with mutations in non-LPL genes (GPIHBP1, LMF1, APOA5 and APOC2) or those without genetic confirmation. However, there were no major differences in relative reduction from baseline in triglycerides among patients with LPL mutation, non-LPL mutation, and no mutation. To our knowledge, and based on the data in the trial, there is no evidence or data relating genetic mutation to other aspects of FCS: rates of pancreatitis events or predisposition to diabetes for example.

A17. P90-91, Figures 12&13 - Please could you include data for APPROACH volanesorsen patients who enter APPROACH OLE, continuing the APPROACH plot from month 12 onwards.

Company response: The APPROACH OLE data for APPROACH volanesorsen patients who entered APPROACH OLE have been included in updated Figures 12 and 13 as requested.

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Updated Figure 12: Treatment persistence with volanesorsen up to Week 104: APPROACH OLE (FAS)

Updated Figure 13: Treatment persistence with volanesorsen up to Week 104: APPROACH OLE (patients with history of acute pancreatitis)

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[redacted]

Source: Figure 14.3.10.adhoc4.1, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file

A18. We note that there is some evidence [redacted] thought this may be due to other factors (e.g. dose reductions). Please could you explain and provide supporting evidence to clarify why:

- [redacted]
- [redacted]
- [redacted]

Company response: The apparent waning over time is almost entirely due to dose reductions and pauses. The naïve patients started APPROACH OLE at 300 mg/week and then dose reduced/paused over time in the study. The 3 COMPASS volanesorsen patients either entered the OLE on full dose or had not dose reduced for very long prior to entering the OLE and hence appear similar to the naïve patients. Many of the APPROACH volanesorsen patients were already stable on a reduced dose or did not need to dose reduce during, or prior to entering, the APPROACH OLE.

A19. On p112 it says "*results were similar in patients with a history of acute pancreatitis...*". Please clarify what the results of this sub-group analysis were?

Company response: This statement above refers to the analysis of reduction in fasting triglycerides. The results for the subgroup of patients with a documented history of acute pancreatitis are summarised in the table below.

Table 3 Results for the subgroup of patients with a documented history of acute pancreatitis

[redacted]		
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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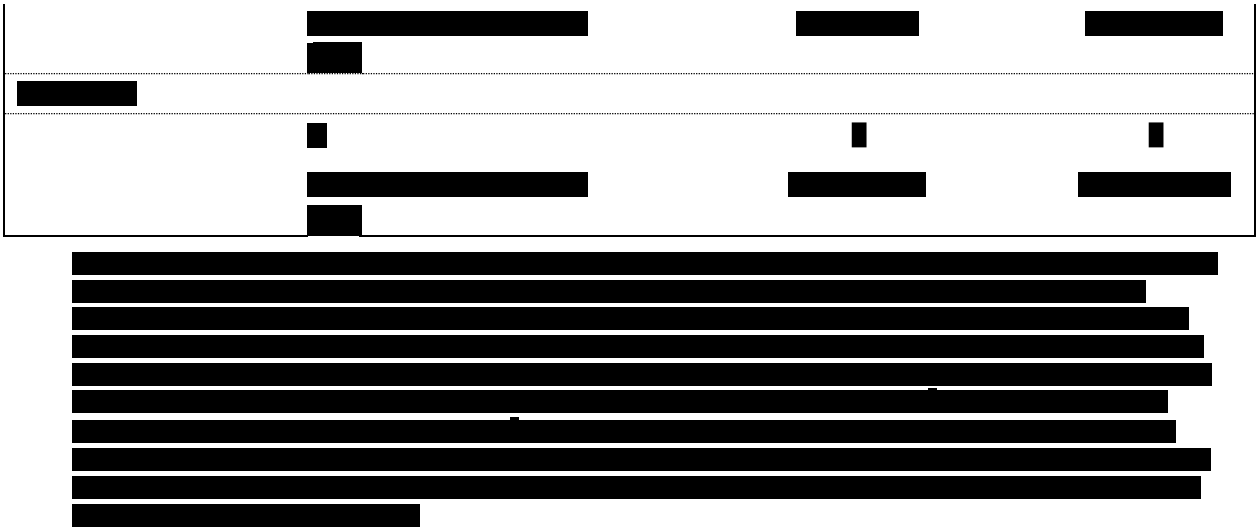

A20. On P132 it says "*A post-hoc analysis showed that patients with a history of pancreatitis attacks achieved similar reductions in TG levels…*". Please clarify what the results of this sub-group analysis were?

Please see the response to A18.

Statistical analyses

A21. **Priority Question:** CS p168 stated that the baseline distribution of patients in the SmPC analysis is based on the subgroup of patients in APPROACH who had a history of AP and all the patient TG data were used and were reweighted at model entry. Please justify the use of reweighting,and clarify how the reweighting was conducted.

Company response: By re-weighting the following was meant: The proportion of patients entering the model in each TG health state was driven by the APPROACH baseline characteristics. The base case model considers only patients with a history of AP. In APPROACH this was a binary measure defined as "a documented diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made." Comparing the baseline TG levels of all patients in APPROACH with only those who had a history of AP suggests those with a history of AP are skewed towards higher TG levels.

Balancing the need to include as much trial data as possible with the need to accurately represent the base case population, we adjusted the proportion of patients entering each TG health state at the start of the model. The same approach is used after the stopping rule to ensure that the redistribution is maintained. To illustrate, the proportions of patients in each TG category at baseline for the full APPROACH population vs. those with a history of AP is shown below:

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Population	< 10 mmol	10-22.6 mmol	≥22.6 mmol
All APPROACH patients	9.1%	40.9%	50.0%
Patients with a history of AP	4.0%	42.0%	54.0%
Patients starting TG health state in the economic model	4.0%	42.0%	54.0%

A22. Please clarify how many patients from APPROACH OLE were included in the calculation of the medical history AP rate and how they were selected, and how the patient-years were counted when calculating the rate. Please also clarify how the AP rate for these patients while on volanesorsen in APPROACH was calculated as CSR Table 14.3.2. adhoc2 is missing from submission.

Company response: In the medical history calculation all 68 patients enrolled in OLE were included, amounting to 340 patient-years (assuming 5 years of medical history per patient). Of these, 30 patients had experienced a total of 77 events within 5 years of enrolment. 77/340 gives a rate of 0.23 event per patient-year. Of the 68 patients enrolled in OLE, 24 patients had missing data for documented history of AP, so the medical history rate may be an underestimate.

As of February 28th, 2019, three of the 68 enrolled patients had experienced an AP event while on treatment. The total exposure time of the 68 patients was 101.13 patient-years (including index study exposure). 3/101.13 gives a rate of 0.0297 i.e. 2.97% per patient year.

A23. Clarify whether an estimate of efficacy based on a self-control could be confounded by factors such as regression to the mean or due to the effects of enrolment in a study effect.

Company response: It is possible that factors such as regression to the mean or effects of enrolment in the study would confound the results: being in the study means better adherence to diet or people seek to enrol in the study because of recently having a pancreatitis event. However, given the available data, we felt comparison of on-treatment rates with an off-treatment historical control was the most suitable method to inform treatment effect on AP with the data available to us.

A24. Please clarify whether Appendix 9 is only relevant to the APPROACH ITT scenario in the economic modelling?

Company response: Yes, this is correct.

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A25. Please clarify what software was used to perform the analyses in the CALIBER study. Please also clarify what was the estimate for the baseline hazard in the exponential model for acute pancreatitis (Akcea 2018a (CALIBER) Table 26) and the relationship between the baseline hazard and the intercept listed in Table 26.

Company response: All analyses performed within the CALIBER study were undertaken using R Analytics software. The coefficients represent those of an accelerated failure time (AFT) model. The linear predictors in the CALIBER tables therefore represent the log of the linear predictors of the time to failure (i.e. time to event of interest). The time to failure is simply the inverse of the hazard rate λ.

For the time to AP example the 'baseline failure time' (inverse of hazard rate) would be represented by a male in the <10 mmol TG category with no history of pancreatitis i.e. 8.306 (intercept) – 0.12*age. The other predictors are added to this. These included TG categories (represented by categorical covariates vs. the <10 mmol reference) and history of AP (a categorical covariate vs. the AP naïve reference). There are also interaction terms between TG category and AP history (a categorical covariate vs. <10 mmol reference and AP naïve reference). Although sex is a categorical variable (with males as reference), the coefficient has been multiplied by the % female to obtain the linear predictor for "mean" sex in the model as is often convention within economic models. It is important to bear in mind that as Akcea did not have access to the CALIBER datasets, it had limited control in specifying the models.

As a result of exploring this for the ERG, we realised that the treatment effect on AP was applied incorrectly; rather than applying it to the sum of the covariates on the log scale it should be applied to the failure time on the natural scale. This has now been corrected in cells F11:G16 of the *Outcomes data* sheet.

A26. Generalised linear mixed model (GLMM) analysis

a. Please clarify what software was used to perform the GLMM analysis.

Company response: This was performed in SAS 9.4.

b. Please also clarify what was the response variable used in the GLMM

Company response: The response variable was fasting TG in mmol/L.

c. Please provide evidence indicating support for the estimated length of kick-in/washout days

Company response: It is estimated to take approximately 3 months to reach near maximum triglyceride lowering given the volanesorsen half life of 1 month. Similarly, it is estimated to take 3 months to wash out approximately 90% of volanesorsen.

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d. Please comment on the impact on the regression analysis results of choosing a different kick-in/washout days.

Company response: An exploratory analysis was carried out whereby the kick-in and washout days were set to zero and compared with the results when the kick-in and washout days in the base case were doubled. This made little difference to the point estimates of the coefficients.

	no kick in or wash out effect		base case		base case durations *2	
	Estimate	Std Error	Estimate	Std Error	Estimate	Std Error
Intercept	3.025	0.071	3.115	0.072	3.116	0.071
Every two weeks	-0.680	0.047	-0.705	0.050	-0.705	0.057
Every week	-0.968	0.036	-1.166	0.037	-1.187	0.041
No treatment	0	.	0	.	0	.

e. Please provide the interpretation of the estimated intercept and parameter “No treatment Wash-Out from every two weeks”.

Company response: The model takes the form:

Predicted TG value (mmol) = $\exp(RE + \beta_0 + \beta_{\text{dose category}} + \varepsilon)$

where β_0 represents the fixed intercept common to all patients, RE represents the random intercept unique to individual patients and ε represents the random error term.

Parameter “No treatment washout from every two weeks” is a categorical predictor that is multiplied by 1 to predict TG levels for a patient that has discontinued every two weeks treatment but is within the washout period and still subject to some residual treatment effect.

f. Please clarify how the predictions of TG levels for APPROACH patients was calculated using subjid 1004 and 1038 as examples.

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Company response: Examples of how the TGs are predicted are provided in cells AL6:AM115 of the *GLMM TG model* sheet (these are the probabilistic values predicted directly from the probabilistic model coefficients presented in R5:R14).

For 1004 and 1038, some worked examples of the linear predictors and the predicted TG value are provided below:

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Table 4 Worked examples of linear predictors and predicted TG values

Subjid	Prediction for	RE	Intercept	No treatment	ETW treatment	EW treatment	Sum of covariates on log scale	Predicted TG
1004	No treatment	0.49	3.115	0			3.60	exp(3.60) = 36.69
	Every 2 weeks	0.49	3.115		-0.705		2.90	exp(2.90) = 18.13
	Weekly	0.49	3.115			-1.166	2.44	exp(2.44) = 11.44
1038	No treatment	-1.47	3.115	0			1.64	exp(1.64) = 5.17
	Every 2 weeks	-1.47	3.115		-0.705		0.94	exp(0.94) = 2.55
	Weekly	-1.47	3.115			-1.166	0.48	exp(0.48) = 1.61

The vignette

A27. It appears that “historical” and “recurrent” acute pancreatitis, which are the categories used in the model, were not defined separately in the vignette. Please clarify why “historical” should be considered as more like “recurrent” than like “naïve”? Table C29, p147

Company response: We interpreted the vignettes at face value, whereby the vignettes for someone “who had experienced acute pancreatitis” would be allocated to *any* patient with a history of AP. We acknowledge, that the description that “the patient was still experiencing lingering effects” may not be applicable to all patients who had experienced an AP event in the past. We have therefore changed the utility for the ‘historical’ AP states to one calculated as a weighted average of the ‘AP naïve’ utility values and the ‘recurrent AP’ utility values. We have set the proportion contributed by each of these to be 50% in the revised analyses. This proportion can be modified by the ERG as required.

A28. Please clarify whether the vignettes were validated by FCS patients before use in the study?

Company response: A brief description of the role of patients in the creation and validation of the vignettes is provided. We have italicised the patient validation in the study:

[redacted]

A29. Clarify if a manuscript based on the vignette has been submitted for publication If so, please provide reviewer’s comments.

Company response: The document has been submitted for publication. We do not yet have reviewer's comments.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Provide a revised base case analysis and relevant sensitivity and scenario analyses having amended the model based on your responses to the clarification questions.

Company response: These are provided at the end of this document, labelled as per the original submission (ie, same table and figure numbers as in the main dossier). Note the difference in the base case ICER is £2,810 with these amendments.

B2. **Priority Question:** Provide an ICER for the historic AP subgroup and the recurrent AP subgroup.

Company response: The model is currently only structured to provide an ICER for any patient with a history of AP (including a proportion with recurrent AP) or the subgroup with recurrent AP only. It is not currently possible to estimate the ICER for patients with historical AP but not recurrent AP. We can, however, provide a simple calculation, assuming that the 'history of AP' ICER represents the weighted average of the ICER of the two subgroups as follows:

- Proportion of the 'history of AP' population that have 'recurrent AP' is 46% (the sum of cells R8:T8 in the 'Start and stop populations' sheet).
- ICER of the 'history of AP' population = £216,565
- ICER of the 'recurrent AP' population (≥1 event in the past 5 years) = £225,488
- Estimated ICER of the 'historical AP' population = (£216,565 – 48%*£225,488)/54% = £200,613.

The better ICER from the 'historical AP' patients demonstrates the benefit of giving volanesorsen before the 'damage is done' i.e. before they have had enough AP events to make the risk of CP and mortality much higher, even when TG levels are reduced.

B3. **Priority Question:** Clarify why the utilities are not age-adjusted? Provide results incorporating age-adjustment.

Company response: An age adjustment of the utilities has now been included in the model as requested, using the -0.00029 annual decrement reported in Sullivan et al., 2011. This is included within the updated analyses.

B4. **Priority Question:** The probability of AP per cycle for historical patients has been calculated from CALIBER data. Provide a sensitivity analyses using the rates derived from the medical history of patients in CS6 and CS7. If possible, explore whether the ICER is sensitive to assumptions in the relative frequency of APs between the TG levels being mindful to ensure the average TP rate across all groups is maintained.

Company response: To clarify, we used the APPROACH definition of history of acute pancreatitis, which was defined as "a documented diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made." In APPROACH, a patient could have a history of acute pancreatitis, but the AP may not necessarily have occurred in the past 5 years.

For those patients in APPROACH who had experienced an AP event in the past 5 years, the assumption was made that these were recurrent events and not their first, see Table D4 of the submission. The AP rate of these APPROACH patients was therefore allocated to the 'recurrent AP' health states. The AP rate of patients in APPROACH who had experienced an AP historically, but not in the past 5 years, can therefore be considered relevant to the 'historical AP' health states. Clearly no rate can be calculated for these patients, as we have no record of when the event occurred or whether there were multiple events. All we can state is that their AP does not appear to be recurrent, but that they nevertheless remain at risk of further AP. We used the CALIBER data to inform the 'historical AP' states as this was the only available source. We recognise that CALIBER is a database of non-FCS patients, but we believe that, if anything, CALIBER underestimates the incidence of AP in FCS as these non-FCS patients would not have the sustained high triglycerides over an extended timeframe as experienced by FCS patients. In a study by Gaudet et al. (2016a), there were 67 AP hospitalisations in 251 FCS patients vs. only 14 AP hospitalisations in 1,981 patients with multifactorial chylomicronemia. In support of the CALIBER predictions, the model predictions of number of AP events experienced over the remaining patient lifetime are in line with the literature.

We have been unable to find a way of adjusting the relative AP rate between the three groups while maintaining the overall rate identical, therefore this has not been carried out.

B5. **Priority Question:** Please provide results of the economic analyses for scenarios [redacted]

Company response: [redacted]. The mechanism by which we will address this is not yet finalised. [redacted] This [redacted] drug costs and an increase in the ICER of approximately £45,000 compared with the base case. The base case assumes a mechanism by which there is not a higher cost for the initiation phase. This (higher cost for the initiation phase) is included in the scenario analyses reported in the revised Table D26, labelled ERG Qu B5.

B6. **Priority Question:** Clarify why the costs for volanesorsan are half cycle corrected so that, after the first cycle, 3 vials are assumed to be provided to patients who discontinue / die. The ERG believes that the appropriate value would be 3.5 vials given the timing of the vials (assuming one vial prescribed at a time) or 4.0 (assuming two vials prescribed simultaneously). It might be easier to adjust the model to add on this addition (part) vial at death or discontinuation. Clarify how often vials would be dispensed

Company response: The first company base case (June 2018) did not include a half cycle correction. The half-cycle correction was incorporated into the model in response to an ERG request in the previous clarification questions and made very little difference to the model results.

To clarify, only patients are half-cycle corrected in the model and not the costs themselves. The costs from the first two cycles (3 months of full dose, plus the 3 months post-stopping rule/dose adjustment) are *not* calculated from half-cycle corrected patients, as this includes the decision tree for the stopping rule. The costs from the third cycle onwards are calculated using half-cycle corrected patients (the average of those from cycle 3 and cycle 4). Notwithstanding this, the model is based on the mean of a cohort and not a single patient. Given that patients can potentially discontinue at any point during a cycle, it is reasonable to have cost calculations based on half syringes.

The volanesorsen pre-filled syringes will be supplied via a homecare company. It is the current expectation that clinicians will write 6 monthly prescriptions but that the homecare company will only delivery one month of syringes at a time. This is to minimise the risk of waste or a patient injecting when they should be dose pausing.

B7. **Priority Question:** Apparent error in the model. In 'outcomes data' cells i12:i16 should reference row 'm' not row 'k'. This is a likely source of the higher ICER in PSA

Company response: We thank the ERG for finding this error, which we have now corrected it. It does indeed reduce the PSA ICER substantially and shows much greater consistency with the deterministic ICER. PSA ICER = £220,056; DSA ICER = £217,350. The updated probabilistic base case ICER is reported below in the updated table D27 and figure 37 reports the revised CEAC.

B8. **Priority Question:** Clarify whether the relative risk of mortality between the high and low TG groups in the Wang et al paper is likely to be confounded due to the imbalance in characteristics such as organ failure and systemic complications. Provide an analysis where the relative risk of mortality is set to 1.

Company response: Organ failure and systemic complications would only be confounders if these were present in the patients at baseline, prior to the AP event. Wang et al (2016) evaluated how many of the APs were accompanied by serious complications, including organ failure. Elevated serum TGs are known to be correlated with persistent

organ failure in AP (Nawaz et al., 2015), which is itself associated with adverse outcomes including mortality. The higher mortality rate in high TG patients in Wang is to be expected and is likely to have been a consequence of greater rates of organ failure due to high serum TGs. It is therefore reasonable to assume that a treatment that dramatically lowers serum TGs would result in a lower mortality rate from AP. Reduced severity of AP is supported by the longer-term follow up data of patients who received Glybera (Gaudet et al., 2016b).

Setting the relative risk to 1 increases the ICER very marginally. The results of this are reported in Table D26.

B9. **Priority Question:** Please add in a function to allow a user-defined discontinuation rate. Currently the model only allows the fit to the study data which the company contend is not appropriate, and no discontinuation, which may also be viewed as inappropriate.

Company response: As described in section 12.4.1 of the submission, one of our structural sensitivity analyses included 'lifting' the base case lognormal curve by a hazard ratio of 0.3. This hazard ratio is a user-defined value that can be entered in the Controls sheet in cell D30 and can be applied to any of the survival curves selected in the model. The ERG can explore a constant discontinuation rate by selecting the exponential curve option in the Controls sheet and applying a hazard ratio in cell D30. To assist the ERG, the estimated annual discontinuation rate is displayed in Controls cell G30 (assuming a constant annual rate) and the 10-year cumulative retention is displayed in cell I30.

B10. **Priority Question:** Clarify why it is assumed that people cannot die from a grade 4 thrombocytopenia. Provide an analysis allowing death from thrombocytopenia.

Company response: In the trials, thrombocytopenia was graded as mild, moderate or severe. We converted this to grades for the purpose of finding utility and cost values to populate the economic model. Severe thrombocytopenia was rare in patients on every 2 weeks dosing; only 1 patient had severe thrombocytopenia while on every 2 weeks dosing. There were no fatalities due to thrombocytopenia in APPROACH, APPROACH OLE or COMPASS. While there is an inherent mortality risk with severe/grade 4 thrombocytopenia, mortality rates from severe thrombocytopenia in the literature cannot be generalised to thrombocytopenia from volanesorsen as they are also associated with the underlying condition leading to the thrombocytopenia (e.g. heparin-induced, idiopathic thrombocytopenia purpura, chemotherapy-induced, Gauer et al., 2012). In the absence of any mortality data for volanesorsen induced grade 4 thrombocytopenia and given the very 'protective' monitoring regimen now in place, we used the simple assumption in the model of no risk of volanesorsen-associated grade 4 thrombocytopenia mortality. We recognise this simplifying assumption is imperfect however, it should have minimal impact on estimates results due to the low likelihood of mortality and the consequent impact on the QALY gain.

B11. **Priority Question:** Clarify why the value of £50,671 per year for patients with CP, taken from Hall *et al.*, was considered preferable to the direct costs of £9,465 reported in Dennison *et al*. Provide a sensitivity analysis using the costs of Dennison inflated to 2018 prices.

Company response: The £50,671 cost from Hall is an all-inclusive health state cost. The £9,465 costs from Dennison included only the costs of interventional procedures including surgery, hospital admissions and analgesic costs (see figure 4 of Dennison et al.). Community costs, follow-up costs and costs of diabetes were assumed to be equal both before and after surgery, so were excluded from the analysis in Dennison. Hall et al. includes all direct healthcare costs relevant to the management of chronic pancreatitis.

Reducing the cost of the chronic pancreatitis health state to £9,465, an underestimate of the associated management costs, increases the ICER to £250,703.

B12. Clarify whether there are any known associations between changes in TG levels and changes in the rate of adverse events rather than associations between absolute values. Relationships between changes are likely to be preferable to associations based on absolute values as confounders may stop the relationship between absolute values from being realised when TG levels are changed.

Company response: We are unaware of any confounders that may impact the effect of absolute TG level on rate of AP, other than AP history. We have attempted to account for this in the model by (1) incorporating a covariate for history of pancreatitis in the CALIBER predictions, and (2) assuming that once a patient has recurrent acute pancreatitis, their ongoing risk on SoC does not differ by TG level but that volanesorsen has a treatment effect on their risk. There may be other confounders, but we are unaware of any data in the literature that could be incorporated into the model to test this.

B13. Linked to Clinical effectiveness question A17. Clarify the impact on the ICER and the QALYs gained if it is assumed treatment stops working at 10 years and all patients discontinue at this point.

Company response: In the current base case, only 4% of patients are assumed to be on treatment after 10 years. The ICER when all patients discontinue after this point is included in the updated structural analyses table D28: ICER estimate of £217,385.

B14. Clarify why, given that at study entry 46% of people on standard of care (SoC) are in low or medium TG level states, that all patients on SoC are assumed in the base case to reside in the high TG state. Explore the impact on the ICER of assuming that patients who receive SOC are distributed across the states in these proportions, potentially altering the distributions for volanesorsen so that SoC does not have a greater proportion of people in the low TG state.

Company response: As explained on page 185 (section 12.2.1) of the submission, we took the approach of the York psoriasis model, which is driven by change in mean values. Given the very small patient numbers, uncertainty associated with an ultra-orphan disease, and the lack of treatment resistance/loss of response, we felt that using means was a reasonable approach. The patients are distributed across health states at baseline to allow compatibility of the baseline patient distribution with the ITT analysis, which uses transition probabilities and therefore distributions across health states. It is also more transparent given that individual patient data is used to drive the stopping rule. After the first two cycles, a mean for the cohort is calculated and therefore patients are allocated to a single health state.

We have now included a scenario whereby patients are distributed across TG health states throughout the time horizon, using the predicted TG values from the GLMM for patients on volanesorsen and the actual health state distributions from the placebo arm for SoC (as calculated for the ITT analysis in Appendix 9). This has been added as an additional option in the Controls cell D27 "SmPC dosing – distributions". The option "CS6 transitions" should be selected in cell D35 (source of transitions for SoC, the alternative being use of the GLMM predictions for SoC).

The ICER assuming that patients are distributed across health states is provided in table D28.

B15. Clarify what systems are in place in clinical practice to ensure that missed doses are not associated with costs.

Company response: Volanesorsen is expected to be delivered to patients' homes by a Homecare company. The Homecare company will only deliver one month's worth of syringes at a time. There will also be a Patient Support Programme with a dedicated nurse assigned to each patient to take bloods and ensure that any blood results are flagged with the lead clinician. The nurse can also check on syringe stock in the patient's home or in discussion with the patient. Should the nurse identify syringes that have not been used in line with expected dosing regimen this is reported to the lead clinician.

The shelf life associated with this product is 'forgiving', see below extract from the relevant part of the SmPC (AKCEA 2019b). The shelf life alongside the controlled release of syringes to the patient should minimise the risk of waste.

6.3 Shelf life
3 years

This medicinal product can be removed from refrigeration and stored, in the original carton, at room temperature (below 30 °C) for up to 6 weeks. In this 6-week period, it can be kept as needed between refrigerated and room temperature (up to 30 °C). This medicinal product must be discarded immediately if not used within the 6 weeks after the first time it is removed from refrigerated storage.

B16. Please provide additional information such as the distributions (and parameter values) for tables where these are not given such as D17.4

Company response: We apologise for the missing parameters and believe that these all relate to the EQ-5D values from the APPROACH trial. In summary, all patients on treatment in the model were allocated the 6-month EQ-5D value of patients in the volanesorsen arm of APPROACH and all patients off treatment were allocated the 6-month EQ-5D value of patients in the SoC arm of APPROACH. Note that stratifying the EQ-5D further (e.g. by AP history or by TG level) lacked face validity, i.e. patients with higher TGs having better HRQoL.

These two values, which are the only values used in the EQ-5D scenario, are summarised below:

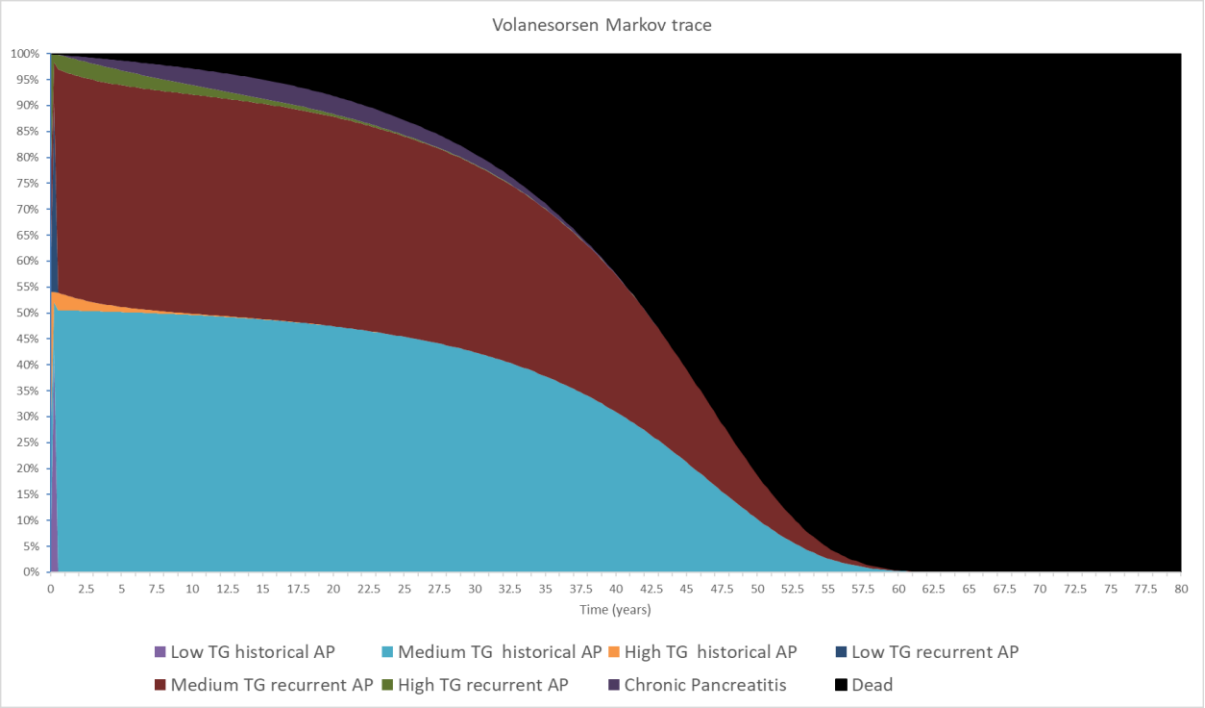
Parameter	Mean	95% confidence interval	Distribution in PSA	Source
Any patient in volanesorsen arm	[redacted]	[redacted]	[redacted]	Month 6 values, Table 14.2.3.3.2, APPROACH CSR
Any patient in SoC arm	[redacted]	[redacted]	[redacted]	Month 6 values, Table 14.2.3.3.2, APPROACH CSR

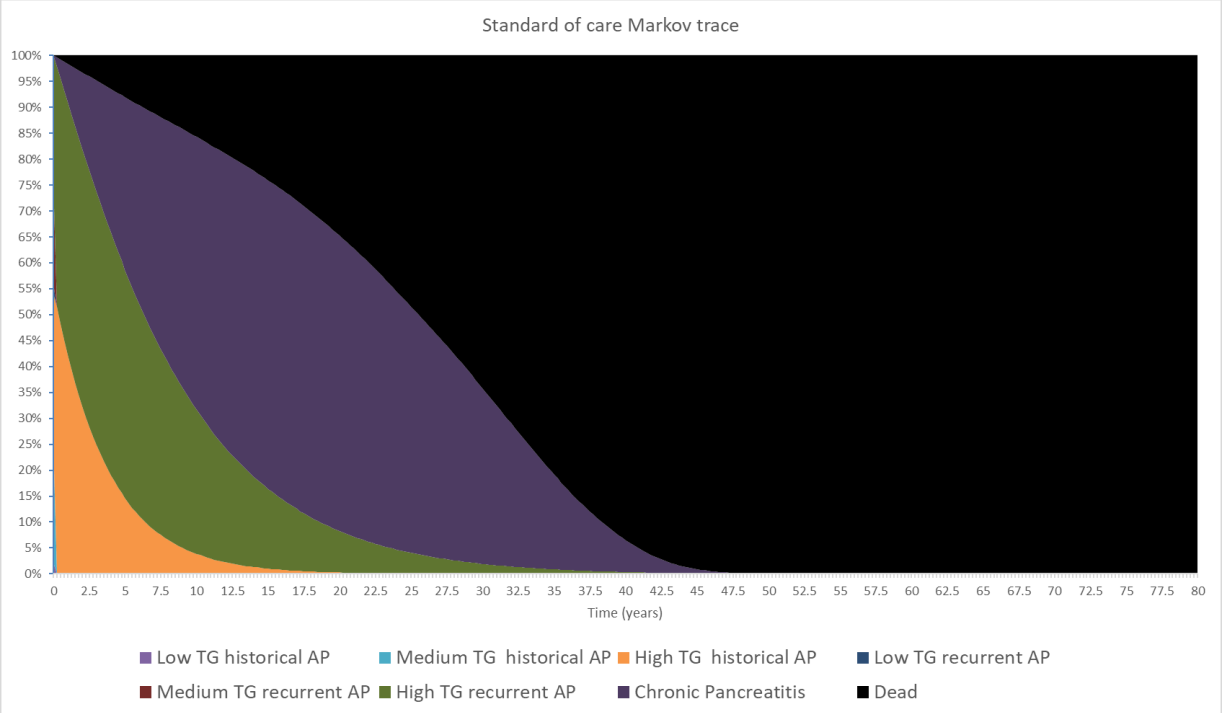
B17. P258-259 states that "*Poisson not possible in Excel*". Clarify why a Poisson distribution is not possible in Excel with reference to the Excel function 'Poisson.dist'

Company response: The Excel function POISSON.DIST takes the form POISSON.DIST(x, lambda, cumulative) and returns the probability (cumulative or mass) of a rate x given the mean rate lambda. As per other functions used in PSA such as NORMINV, BETAINV, GAMMAINV and LOGINV, the inverse of this function is required to predict the value x given a probability. Such a function does not exist in Excel for the Poisson distribution.

B18. Please provide the same plots as in Section 12.5.3 for the EAMS scenario

Company response: Please find these plots below.





B19. Please provide the missing values in the table in Section 12.5.7

Company response: The missing values from the table in the dossier submitted on the 30th Aug have been updated here. These are the results from the model submitted on the 30th Aug 2019.

	Base case Total QALYs	EAMS scenario Total QALYs
Volanesorsen	[redacted]	[redacted]
Standard of care	[redacted]	[redacted]
Incremental	[redacted]	[redacted]

In line with requested amends in this section, this table has been updated (section 12.5.7 at the end of this document).

B20. The proportions of patients in each TG level category are likely to be biased using the probabilistic mode, as in the 'Start and Stop Populations' sheet the sum of K32:K64 is greater than the sum of O32:O64 in the vast majority (99%) of simulations. Please provide an amended model where the deterministic values for the 3 month period can be combined with the probabilistic model. If uncertainty was to be explored the ERG believes that bootstrapping the patient data is anticipated to provide a less biased dataset

Company response: This amend has been included in the model submitted with the clarification responses.

B21. Confirm whether the age of the patients do not change over the model and thus in the historical AP group, based on the formulae in 'Outcomes data' the AP rate will under-predicted as patients age. Clarify what impact this may have on the ICER.

Company response: The ERG is correct, age does not change with respect to the CALIBER predictions of acute pancreatitis and diabetes. Implementing this at each model cycle for each health state would have been computationally burdensome. The predicted cycle probability of acute pancreatitis in the low, medium and high TG historical health states on SoC at the model starting age of 41 is 0.877%, 2.130% and 5.204%, respectively. At age 85, these predictions would be 1.482%, 3.585% and 8.663%, respectively. The model therefore under predicts AP rate on SoC, may slightly under predict AP costs, disutility and mortality and therefore may under predict the benefit of volanesorsen. However, these differences are likely to be small given the small absolute differences in AP rate between age 41 and 85, which would increase gradually over time. For example, replacing the age in the predictive equations of AP with 85 reduces the ICER by less than

£2,500. Therefore, a gradual change might be anticipated to have an even smaller impact. It should be noted as well that age was not a significant predictor in the model of incidence of AP. As we did not have access to the CALIBER data, we were unable to test statistical fit with vs. without the covariate for age.

B22. Clarify why the probability of CP is taken from the 100 week time point (p190 of CS) in Yadav 2012 when the data appears to be for 100 months (Figure 3 in Yadav 2012; Figure 34 of CS). Clarify why 60% of patients with CP was taken as the target when the consensus of the clinicians suggested this value was lower. Provide sensitivity analyses using a target of 30%

Company response: This was an error: the time point does indeed represent months. We have updated the model accordingly and recalibrated the probability to obtain a target of 60%. The value of 60% was used based on clarification with two clinicians about expected lifetime rate of CP in the 'high risk' patient population. Note, while there is not a date stamp on Appendix 17 in the submission, it was conducted prior to the final label wording. As the relative difference in probability of CP between AP naïve and recurrent AP patients remains the same, and the absolute probability of CP is driven mainly by the calibration, the impact on the results is small. This change is incorporated in the updated results. A sensitivity analysis assuming the peak prevalence of CP is 30% has been included in table D26.

B23. Please add the costs of SoC within the model. Whilst these are equal in both arms there is a mortality difference assumed meaning that patients receiving volanesorsen would receive SoC for longer.

Company response: As noted in the submission there is no approved SoC treatment for FCS and no clear guidelines on SoC medication. An analysis was carried out based on the most frequent concomitant medications taken at baseline in APPROACH OLE (see table C10 of the submission), using cost comparison charts compiled by Newcastle CCG (2019). This analysis is attached in the file *FCS SoC Treatment costs.xlsx* and amount to approximately £372/year (Akcea, 2019d). This cost has been added to all health states in the model in the updated analyses.

B24. There is an apparent error in the model in the Transition probabilities sheet, cell D284. We believe the formula should read "Pr_low_recAP_CP" rather than "OFFSET(Pr_low_recAP_CP,0,1)". Please amend the model

Company response: Thank you for pointing out this error. It only affects the ITT analysis and we have updated the result in the updated scenario analysis table D26.

B25. Assuming 26 bi-weekly periods within a year will underestimate the cost of volanesorsen. We believe that using 26.09 would be more accurate. Please amend the model.

Company response: This has been changed as requested.

B26. On p130, it is stated "*Because of small patient numbers, using the above data in the economic model resulted in unstable ICER estimates."* Please clarify whether 36 or 14 patients entered the model, and please clarify in what way the ICER was "unstable" and provide the modelling analysis.

Company response: Apologies for clumsy wording here. It should have read, *With such small patient numbers using the observed data (n=14) would likely have resulted in highly unstable ICER estimates.*

No analyses had been performed on the 14 patients at time of dossier submission due to concerns about the interpretation and stability of ICER estimates resulting from such small patient numbers. In addition the results are likely to be biased as these are all patients that dose reduced early in the trial due to platelet issues. In the model the data from all 66 patients recruited to APPROACH were included. The GLMM was informed by 90 patients who were recruited in APPROACH and/or APPROACH OLE.

Additional request 1. Following the clarification TC with the ERG, NICE and the company some further scenarios were requested with respect to the licensed population of 'at high risk for acute pancreatitis'.

Company response: In addition to the base case, we explore definitions in line with question A10d and a further scenario for only patients with TGs >22.6 mmol (note that a scenario for patients with ≥2 AP events in the past 5 years has already been explored in the subgroup analysis in section 12.6 of the submission, updated here). The results of these are in the updated scenario analysis table D26.

Additional request 2. Following the ERG clarification call, the ERG listed some minor changes to the model, including:

a. Amending 365 to 365.25 in the utilities inputs

This has been updated and is used in the revised base case reported in table D26 below.

b. Setting PSA values for Grade 3 and Grade 4 equal and the PSA values for the first, second and recurrent AP being fatal equal

This has been updated and is used in the revised base case reported in table D26 below.

c. Including parameters with confidence intervals in the PSA. Please note that the missing parameters were rates.

As explained in the response to question B17 these should be modelled using a Poisson, the inverse function for which does not exist in Excel. Instead we have used left-truncated normal distributions.

Additional request 3. Following the ERG clarification call, the ERG requested clarification with respect to how the vignette utilities were applied.

Company response: It was the intention to allocate all patients on volanesorsen the low TG vignette utility and all patients on SoC the high TG vignette utility. The rationale for this approach was explained in section 10.1.9 of the submission "Based on the substantial reduction in TGs observed in patients receiving volanesorsen (from a mean of 26.2 mmol/L to a predicted mean of 12.1 mmol/L on every 2 weeks), accompanied by the improvement in quality of life reported in the ReFOCUS study, patients on treatment in the cost effectiveness analysis are assumed to have the utility of the 'low TG' health states from the EVA-22200 vignette study and those off treatment have the utility of the 'high TG' health states. Due to the stopping rules, no patients on volanesorsen are anticipated to have 'high TGs'." No specific TG values representing 'high' vs 'low' were defined for the vignette study, and as the ERG has itself alluded to in question B12, the change in TG levels experienced by patients on volanesorsen may be more important than the absolute TG values with respect to HRQoL.

In table D8, we simply present the low and high TG vignette values, there is no 'medium TG' vignette value in the submission. There are parameters for 'medium TG' on the EQ-5D, but these are simply a legacy from prior analyses (as explained in B16, further stratification produced nonsensical values). The EQ-5D values in the model also differ by arm and not by TG category.

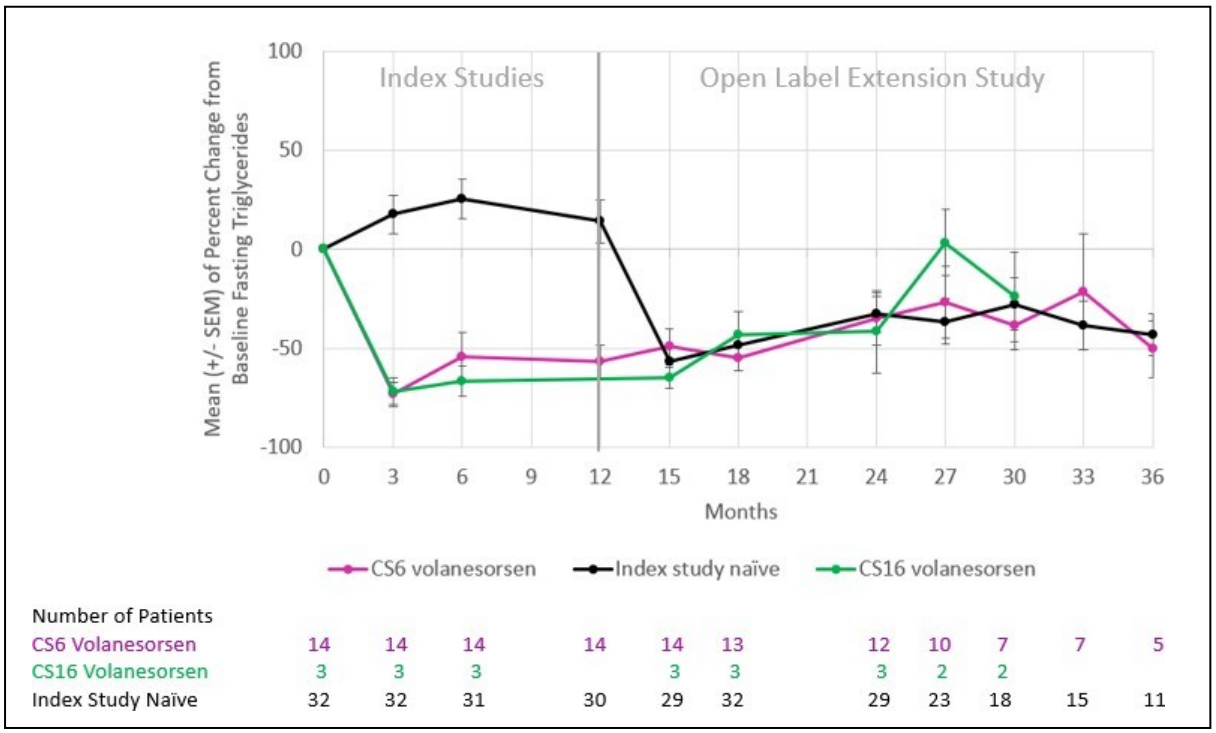
The 'tiered utility by TG' column identified by the ERG is not used in the model. This is a legacy from the previous version of the model submitted to NICE. Akcea does not feel this analysis to be relevant as the categorisation penalises patients who have achieved a significant reduction in TGs (as required by the stopping rule), have achieved improvement in HRQoL but have not changed health state. However, should the ERG wish to explore this option, it has now been included under the choice of utility inputs drop-down in the Controls sheet D29.

Section C: Textual clarifications and additional points

C1. Figure 20 appears to have an unusual time scale. For example, the first four time points are a month apart, but weeks 12 and 13 appear at the same distance apart as these months; weeks 52 and 64 are also the same distance as the months. Please clarify what the figure looks like using a consistent linear scale?

Company response: Figure 20 was revised using a consistent linear scale and data from Table 14.2.1.1.2.

Revised Figure 20



C2. On p85, it states "*these analyses were post-hoc*". Please clarify which analyses?

Company response: This refers to the mixed-dose regimen analyses (June 2018 data cut-off) that are reported briefly in section 9.9.4.

C3. On page 106, under the heading "*secondary endpoints: Pain*" please clarify which analyses were pre-planned, which pre-planned exploratory analyses, and which were not pre-planned? What is the difference between a pre-planned exploratory analysis and a pre-planned analysis?

Company response: Pain analyses were classified according to the statistical analysis plan (SAP) as described in the table below. 'Pre-planned' refers to secondary endpoint analyses included within the SAP and 'Pre-planned exploratory' refers to tertiary or exploratory analyses included within the SAP. Unplanned analyses were not included within the SAP.

Analysis type	Summarized according to SAP 304801-CS6 V2 (03Feb17)	Results on page 106 'Secondary Endpoints: Pain'
Pre-planned secondary analysis	The maximum intensity of abdominal pain related to disease will be collected on the FCS symptom questionnaire and reported by patients weekly on Bracket electronic patient reported outcomes (ePRO). The average of maximum intensity of patient reported abdominal pain score during the treatment period will be compared between the volanesorsen group and placebo groups using a two-sample t-test.	First paragraph
Pre-planned exploratory analysis	Two (2) exploratory analyses will be performed in the subset of FAS patients who reported any abdominal pain score > 0) during the screening period and Week 1. The first exploratory analysis will be performed to compare the change from Baseline in the average of maximum intensity of patient reported abdominal pain between the volanesorsen group and placebo groups in this subset of patients using an ANCOVA model with two stratification factors and baseline maximum intensity of abdominal pain as covariates. The second exploratory analysis will be performed to compare the change from Baseline in the worst weekly patient reported maximum intensity abdominal pain score during the treatment period using an ANCOVA model with two stratification factors and baseline of worst maximum intensity as covariates in this subset. A summary of abdominal pain by the following categories will also be provided: no pain, pain score: 0), mild (pain score: 1-3), moderate pain score: 4-6), or severe (pain score: 7-10).	Second paragraph
Unplanned analysis	Not described in SAP	Last paragraph with 3 bullets

C4. Confirm whether the text in the third bullet point of page 13 is correct or not. We believe the model only evaluates what is termed the more restrictive stopping rule

Company response: This is an error. The more restrictive stopping rule is used as the model base case. We are aware that there are different interpretations of the stopping rule and so testing the model with the less restrictive approach reduces the ICER by £376.

C5.Clarify whether the domain scores in Table C27 are correct

Company response: Company response: The domain scores in Table C27 were rounded to an integer and, in 4 cases, were incorrectly transcribed. Output Tables 14.2.8.2.1 and 14.2.8.2.2 were used to revise Table C27, including two significant digits for each domain mean and standard deviation, as displayed below. Changes are shown in blue font.

Revised Table C27 EQ-5D-5L scores (FAS): APPROACH OLE

	Mean (SD) score							
	Baseline*		Week 13		Week 26		Week 52	
Dimensions	APPROACH-volanesorsen (n = 12)	Treatment-naïve (n = 33)	APPROACH-volanesorsen (n = 10)	Treatment-naïve (n = 36)	APPROACH-volanesorsen (n = 9)	Treatment-naïve (n = 38)	APPROACH-volanesorsen (n = 8)	Treatment-naïve (n = 26)
Overall health status VAS	[redacted]							
Index score	[redacted]							
Mobility	[redacted]							
Self-care	[redacted]							
Usual activities	[redacted]							
Pain/discomfort	[redacted]							
Anxiety/ depression	[redacted]							

*Baseline is defined as the last non-missing measurement on Week 1 of the double-blind study for the APPROACH-volanesorsen group and the last non-missing measurement on Week 1 of the OLE study baseline for the treatment-naïve group. Overall health status VAS scored on a 100 mm scale, where 0 = worst health imaginable and 100 =

best health imaginable. Individual domains scored on a scale of 1 to 5, where 1 = no problems and 5 = extreme problems. VAS, visual analogue scale. Source: Table 14.2.8.2.1, Table 14.2.8.2.2, APPROACH OLE interim analysis (data cut off 28 Feb 2019), Akcea data on file.

C6. Clarify the apparent mismatch in carer utility in Table C29 between 0.02 and 0.1

Company response: We apologise for this typo, the value in the model is 0.1.

C7. Clarify whether on P181 it should be 'all patients in APPROACH with a history of AP' rather than 'all patients in APPROACH'

Company response: The correct description is 'all patients in APPROACH'. As history of acute pancreatitis is not a known effect modifier of volanesorsen, the TG data of all patients in APPROACH was used in the analysis. AP history was only used as a means of redistributing the proportions of patients that entered the model in the different AP history and TG health states (see response to A20).

C8. Should the weighting value on P286 be CIC?

Company response: Thank you for spotting this, it should be CIC.

C9. P168: "*Although discontinuation due to platelet issues on weekly dosing was more likely in patients with lower body weight, this effect is greatly reduced on every 2 weeks dosing (see section 9.9.4) and patients may discontinue for a variety of other reasons*." and P409: "*The most likely characteristic that could lead to dose reduction is body weight (see section 8.7), yet little difference in effect size was predicted for patients weighing more than vs. less than 70kg*." Sections 9.9.4 and 8.7 do not contain any text relating to low body weight. Body weight does not appear to have entered the model. Please clarify the relevance of these statements, and if appropriate, which sections should have been referenced?

Company response: We apologise for the confusion regarding the reference to body weight, which was based on sections in the previous NICE submission. The statements refer to the wording in section 4.4 of the SmPC "Patients with lower body weight (less than 70 kg) may be more prone to thrombocytopenia during treatment with this medicinal product." By inference, patients with lower body weight therefore might be more likely to discontinue volanesorsen as a result of platelet issues, which would mean that discontinuation would not be at random. This potential weight effect becomes less important on every 2 weeks dosing and is diluted by discontinuation for non-platelet issues.

This can be further extended to the narrative on page 409; if lighter patients are more likely to experience platelet issues then they are also more likely to have had dose reductions in APPROACH and APPROACH OLE. The 13 patients who had dose reductions weighed on average 59kg vs. the full CS7 population average of 65kg. If body weight were also a treatment effect modifier of once every 2 weeks volanesorsen, then the results of the

efficacy analysis of once every 2 weeks dosing might be considered biased. On page 409 we point out that no such difference was observed in the GLMM predictions, which adjust for patient heterogeneity via the random effects element, therefore the GLMM predictions are likely to be representative of the treatment effect of every 2 weeks dosing within the licensed population.

C10. P187: "*For patients to change to a worse health state, mean TG values would need to increase to above 22.6 mmol, which is not supported by the available clinical data (Table C17), which suggests a sustained % reduction from baseline of above 40% over the longer term*" Table C17 reports pancreatitis event rates in APPROACH. Please clarify which table should be referenced.

Company response: Apologies, we intended to refer to the % reduction from baseline data in table C19.

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Revised base case results

Table D18 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£216,565
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Section 12.5.7

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care.

	Base case Total QALYs	EAMS scenario Total QALYs
Volanesorsen	[redacted]	[redacted]
Standard of care	[redacted]	[redacted]
Incremental	[redacted]	[redacted]

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Table D25 Results of deterministic one-way sensitivity analysis

Parameter	ICER with lower value	ICER with upper value	Difference
Basecase ICER	£216,565		
Annual missed doses every 2 weeks dosing	£233,845	£196,481	£37,364
AP rate high TG - patients with recurrent AP	£236,987	£201,221	£35,766
TE of volan on AP rate med/low risk TGs	£211,532	£233,145	£21,613
U Chronic pancreatitis - SoC	£207,281	£226,911	£19,630
U Low TG- recurrent AP	£225,766	£208,397	£17,369
Cost chronic pancreatitis	£224,017	£208,358	£15,659
Annual carer utility from treatment	£224,185	£209,447	£14,739
AP rate med TG - patients with recurrent AP	£213,702	£228,042	£14,340
U High TG- recurrent AP	£210,759	£222,760	£12,002
UD Diabetes (with complications)	£221,874	£211,153	£10,721
U Low TG - AP naïve	£219,492	£213,856	£5,636

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Parameter	ICER with lower value	ICER with upper value	Difference
Prob CP after recurrent AP, 100 weeks	£218,306	£215,008	£3,298
Prob recurrent AP is fatal	£218,042	£214,940	£3,102
UD age	£212,380	£215,412	£3,031
U of (D+E): Current AP event	£215,472	£217,743	£2,270

Key: HRU, healthcare resource use; U, utility; UD; utility decrement; Prob, probability; RR, relative risk; TE, treatment effect; AP, acute pancreatitis; CP, chronic pancreatitis

Table D26 Scenario analysis results

Scenario assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Base case			[redacted]	[redacted]	**£216,565**
EAMS scenario	Lognormal discontinuation Treatment effect an APs Grade 4 thrombocytopenia events	No discontinuation No AP while on volanesorsen No grade 4 thrombocytopenia events	[redacted]	[redacted]	[redacted] (£79,575 with full QALY weighting given)

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Scenario assumption	**Base case**	**Other scenarios considered**	**Incremental costs under scenario**	**Incremental QALYs under scenario**	**ICER under scenario**
Starting population	Genetically confirmed with a history of AP	Any genetically confirmed FCS patient	[redacted]	[redacted]	£247,652
Dosing schedule	285 mg weekly for three months followed by every 2 weeks maintenance dosing	APPROACH ITT analysis (note that weekly dosing is not assumed to incur additional drug costs over once every 2 weeks dosing in this scenario)	[redacted]	[redacted]	£260,587
Choice of HRQL inputs	Vignette study	Trial EQ-5D, analysed by arm and by TG-level	[redacted]	[redacted]	£210,840
		All health states have utility of 0.7 (assessment group request)	[redacted]	[redacted]	£279,539

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Scenario assumption	**Base case**	**Other scenarios considered**	**Incremental costs under scenario**	**Incremental QALYs under scenario**	**ICER under scenario**
Treating chronic pancreatitis patients	Do not treat	Treat, assuming that patients have a daily HRQL benefit of 'low' vs 'high' TGs as per the vignette study	[redacted]	[redacted]	£224,072
Calibration of risk of CP	60% lifetime risk of CP	42% lifetime risk of CP	[redacted]	[redacted]	£241,099
		30% lifetime risk of CP (ERG Qu B22)	[redacted]	[redacted]	£248,104
Inclusion of CP as health state	Include CP	Exclude CP	[redacted]	[redacted]	£269,167
Utility of CP	Assumption using low TG health state	Laramee et al. utility	[redacted]	[redacted]	£219,851

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Scenario assumption	**Base case**	**Other scenarios considered**	**Incremental costs under scenario**	**Incremental QALYs under scenario**	**ICER under scenario**
Impact of volanesorsen on diabetes costs and QALYs	Volanesorsen reduces by 50%	No impact from volanesorsen	[redacted]	[redacted]	£221,599
Disutility of diabetes	Diabetes with 50% complications	Uncomplicated diabetes	[redacted]	[redacted]	£238,420
Carer utility gain	Include	Exclude	[redacted]	[redacted]	£261,999
Discount rate	3.5% for costs and QALYs	1.5% for costs and QALYs	[redacted]	[redacted]	£205,016
Population (post ERG clarification call question B27)	Patients with a history of AP	Patients with recurrent admissions for AP (1+ AP in last 5 yrs for all TG levels)*	[redacted]	[redacted]	£225,488

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Scenario assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		Prior pancreatitis OR high TG levels (History of AP if baseline TGs <22.6; any AP history if baseline TGs >22.6)	[redacted]	[redacted]	£229,548
		Prior pancreatitis AND high TG levels (History of AP if baseline TGs >22.6, lower baseline TG categories don't start)	[redacted]	[redacted]	£215,248
		Recurrent admission for AP OR high TG levels (1+ AP in last 5 yrs for TGs <22.6, any AP history for TG>22.6)	[redacted]	[redacted]	£234,921

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Scenario assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		Recurrent admission for AP AND high TG levels (1+ AP in last 5 yrs for TGs <22.6, lower baseline TG categories don't start)	[redacted]	[redacted]	£225,553
		Any patient with high TGs (any AP history if baseline TGs >22.6)	[redacted]	[redacted]	£237,992
Cost of CP	£50,671	£9,465 (ERG Qu B11)	[redacted]	[redacted]	£249,079
Cost of first 3 months volanesorsen	Same as every 2 weeks dosing	Cost doubled (ERG Qu B5).	[redacted]	[redacted]	£244,522
RR of mortality from AP	Relative risk of 0.17 applied	No reduction in mortality (ERG Qu B8)	[redacted]	[redacted]	£217,350

.* for the population scenarios, the wording in brackets refers to the settings selected in the Controls sheet D16:D18.

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Table D27 Probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]	-	-	-	
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£220,056
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The analysis included an analysis of probability of cost-effectiveness via a CEAC. Volanesorsen had a [redacted] probability of being cost-effective at a willingness to pay threshold of £100,000 and a [redacted] probability of being cost effective at a willingness to pay threshold of £300,000 (

[redacted]

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Figure 37 Cost-effectiveness acceptability curve for volanesorsen

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Table D28 Results of structural sensitivity analyses

Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
Base case			[redacted]	[redacted]	**£216,565**
Treatment discontinuation	Lognormal curve	Lognormal curve with 0.3 'hazard ratio' applied at all points	[redacted]	[redacted]	£206,557
		Loglogistic curve	[redacted]	[redacted]	£217,383
		Exponential curve	[redacted]	[redacted]	£216,757
		Weibull curve	[redacted]	[redacted]	£223,154
		No discontinuation	[redacted]	[redacted]	[redacted] (£100,332 with full QALY weighting)

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Structural assumption	Base case	Other scenarios considered	Incremental costs under scenario	Incremental QALYs under scenario	ICER under scenario
		Lognormal curve with all patients discontinued after 10 years (ERG Qu B13)	[redacted]	[redacted]	£217,385
Data informing SoC health states	Regressions	APPROACH SoC arm patient transitions	[redacted]	[redacted]	£217,125
TG health state allocation	Based on mean TG value (all patients in one TG health state)	Distributed across TG health states (ERG Qu B14)	[redacted]	[redacted]	£214,481

Table D29.1 Subgroup analysis results scenario 1

All assumptions as per base case except for risk of AP at baseline:

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Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£219,004
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table D29.2 Subgroup analysis results scenario 2

All assumptions as per 'EAMS scenario' except for risk of AP at baseline.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Standard of care	[redacted]	[redacted]	[redacted]				
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£189,506
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table D29.3 Total undiscounted QALYs scenario 1

Volanesorsen gains 1.73 undiscounted QALYs vs. standard of care when assumptions other than the population are as per the base case.

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	Total QALYs
Standard of care	[redacted]
Volanesorsen	[redacted]
Incremental	[redacted]

Table D29.4 Total undiscounted QALYs scenario 2

Volanesorsen gains [redacted] undiscounted QALYs vs. standard of care when assumptions other than the population are as per the 'EAMS scenario'.

	Total QALYs
Standard of care	[redacted]
Volanesorsen	[redacted]
Incremental	[redacted]

It can be seen that volanesorsen is anticipated to gain [redacted] undiscounted QALYs in a population with recurrent AP under the EAMS scenario. If a full QALY weighting of 2.5 were granted under this scenario, the ICER would reduce to £75,802.

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Appendix: Schedule of the APPROACH protocol

Appendix A Schedule of Procedures

Study Period	Screen/ Run In[a]	Baseline Visit	Treatment Period																						Post Treatment Follow-up		
								Primary Endpoint						Month 6								Month 12					
Study Week	-8 to -2	-2 to -1	Wk 1	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 13	Wk 15 & 17	Wk 19	Wk 21 & 23	Wk 25	Wk 26	Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Wk 50	Wk 52 or Early Term	Wk 54 & 56	Wk 58	Wk 65
Study Day	-56 to -15	-14 to -7	1	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent	X																									
Outpatient Visit	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X
Inclusion/Exclusion Criteria	X	X																								
Medical History[b]	X																									
Vital Signs (+ body weight)	X[c]	X	X	X		X			X		X			X		X		X		X			X		X	X
Physical Examination	X		X						X					X				X					X			X
12- lead ECG (triplicate)	X								X					X				X					X			X
Echocardiogram	----------X----------													X[m]									X[m]			X
Urinalysis[d]	X[n]	X	X[n]	X		X			X[n]		X			X[n]				X[n]					X[n]		X	X[n]
Fundus Photography	----------X----------																						X[m]			
MRI liver and spleen	----------X----------																						X[m]			
Genetic testing for FCS diagnosis (if not available in medical history)[e]	----------X----------																									
Postheparin Lipoprotein Lipase (mass/activity)[f]	----------X----------								-----X----																	
Postprandial Assessments[f]	----------X----------								-----X----																	
Blood Draw (Fasting)[d] Chemistry Panel	X	X	X	X		X			X		X			X		X		X		X			X		X	X
CBC with Differential[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Lipid Panel	X	X	X	X		X		X	X		X		X	X		X		X		X		X	X	X	X
Coagulation (aPTT, PT, INR)	X					X			X					X				X				X			
Hepatitis B, C, HIV	X																									
HbA1c	X		X						X					X				X					X			X
hsCRP			X						X					X									X			X
Sedimentation Rate			X						X					X									X			X
Complement (C5a, Bb)			X						X					X									X			X
Troponin I[h]	X		X						X					X									X			X
Plasma PK - ISIS 304801			X	X		X			X		X			X		X		X		X			X		X	X
ISIS 304801 Antibodies			X	X		X			X					X				X					X			X
FSH (women only, if applicable)	X																									
Serum Pregnancy Test[i]	X	X		X		X			X		X			X		X		X		X			X		X	X
Archived Serum & Plasma Samples[j]			X						X					X									X			X
Archived blood sample for potential gene sequencing related to hypertriglyceridemia[e]	----------X----------																									
Weekly Study Drug: SC Injection			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X						X					X									X			X
Diet/Alcohol Counseling[k]	X	X	X	X		X			X		X			X		X		X		X			X			X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

a Screening procedures performed and the patient starts the diet, lifestyle and medication stabilization period and symptom diary. Up to 4 visits may be required during the diet stabilization period in order to schedule and collect post heparin lipoprotein lipase, MRI, echocardiogram, and postprandial assessments

b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

c Height only required at Screening

d Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

e To be collected prior to first dose; genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

Appendix A Schedule of Procedures *Continued*

f Baseline assessment should be completed at least 48 hrs prior to the first dose; on-treatment assessment can be done between Week 13 and Week 19 visits, inclusive. Post heparin lipoprotein lipase sampling and postprandial assessments may not be conducted on the same day. If either of these procedures is conducted at the Week 13 or Week 19 visit, Study Drug administration and laboratory sampling should be completed prior to beginning the procedure

g Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

h All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

i Females of childbearing potential only

j Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of ISIS 304801

k To reinforce compliance to the diet and alcohol restrictions

l Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

m There is a window of +/- 7 days for MRI, echocardiograms and fundus photography during the treatment period in order to facilitate scheduling

n Expanded urinalysis (see Appendix B)

As discussed on the clarification call between the company, NICE and the ERG, The ERG are writing to detail minor limitations identified within the model since the submission of the clarification questions. It is anticipated that these will have very limited impact on the ICER but can then be dismissed.

During the partial check of the model to date, I believe I have identified a potential error within the model that will also be detailed. If this is not an error please provide the rationale for the use of the current data. The model has not been fully scrutinised but I am aware that you need time to produce results for the clarification response.

Finally, as discussed on the call, it is possible that the committee may want to see additional subgroup analyses, for example, only patients with a high TG level being treated, or only those patients with 2 or more APs within the last year. The ERG will run these should the company not have time to do this themselves.

Minor Limitations

On the HRQoL inputs sheet there are multiple occasions where it has been assumed that there are 365 days in a year – please amend to 365.25

Currently it is possible that the utility decrement for a Grade 3 thrombocytopenia could be higher than for a Grade 4 thrombocytopenia in the PSA. As these are assumed to be the same mean and distribution it would be logical to set these to the same value in the PSA. Similarly, the probably of the first, second and recurrent AP being fatal should be set to the same sampled value.

Within the parameters sheet there are a number of variables that are being used, with specified upper and lower bounds, but where the value is assumed to be fixed. Please incorporate these variables into the PSA, keeping linked values consistent where appropriate (for example the AP rates at low, medium and high TG levels)

Potential Error

Table D8 provides the utility values assumed in the base case in the Health state utilities section. These numbers appear to be consistent with the 'Tiered utility by TG' column in the 'Model HRQoL' sheet, with an assumption that medium TG levels would take a value equal to the average of the Low TG and High TG levels. However, in the submitted model the base case uses the 'By arm vignette utility' which is not concordant with the data from the vignette. For example, Table D8 states that the High TG recurrent AP state has a utility of [redacted], with this value being [redacted] in the by arm vignette utility for volanesorsen, but [redacted] in the 'Tiered utility by TG column. As the vignette appears to estimate the utility in a particular health state rather than an effect generated by volanesorsen it would also appear correct to set the same health state values for both volanesorsen and SoC, with the benefit associated with volanesorsen generated by improved health states. The 'Tiered utility by TG' approach does this, whereas the 'By arm vignette utility' does not. Please confirm whether this approach was intended.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your views on the condition, the technology and the way it should be used in the NHS.

Patients, carers and patient organisations can provide a unique perspective on the condition and the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

About you

Your name: [redacted]

Name of your organisation: LPLD Alliance

Brief de*scrip*tion of the organisation:
(*For example: who funds the organisation? How many members does the organisation have? What proportion of the total English patient population does this represent?)*

LPLD Alliance is a charity registered in March 2016. The aims of the charity are to raise awareness and educate about LPLD and related conditions (FCS). to support patients with FCS to lead a full, active and integrated life and to advocate for excellent care and access to new medicines. It has a board of six trustees, four of whom have FCS. The charity has been funded by a start-up and education grants from Akcea Therapeutics, an unrestricted grant from Chiesi Pharmaceutici, consultancy payments from Akcea Therapeutics and HEART UK, and from donations. All trustees are volunteers and all the work that they do for the charity is unpaid. One trustee was paid by the charity to make films for the purposes of patient advocacy.

The evidence given in this submission was approved by trustees of the charity and has been gathered through a mixture of written submissions and telephone interviews based around the set of questions in this template. At the time of writing 20 patients and eight caregivers had responded. Of the patients who responded 18 live in England and Wales, ten have taken Waylivra/Volanesorsen, and all their answers are reflected in this submission. Other evidence used has been taken from discussions at patient meetings, through the Facebook support group (which has 72 members), and a webinar.

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology? **X**

- a carer of a patient with the condition for which NICE is considering this technology?

- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) **X Founder and chair of trustees**

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: ***NONE***

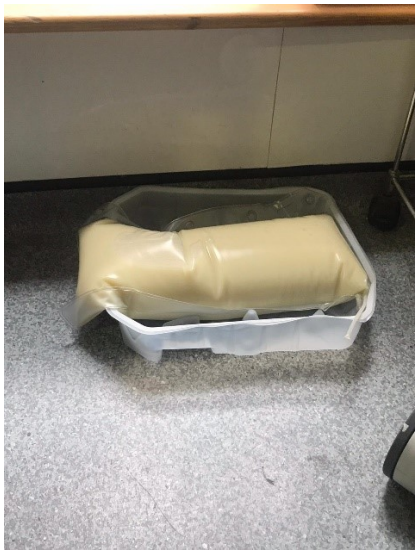
How does the condition impact on patients, their families or carers?

1(i). Please describe whether patients experience difficulties or delays in receiving:
- a diagnosis
- appropriate treatment
- helpful information about the condition

and the impact these difficulties have on patients and their families or carers.

Overview

FCS is a condition caused by a problem with the enzyme lipoprotein lipase. People with FCS are unable to properly digest fats which then travel around the bloodstream giving their blood the creamy-white appearance typical of the condition. Patients have very raised triglyceride levels which put them at risk of pain and pancreatitis, and of other symptoms such as hepatosplenomegaly, steatorrhea and xanthoma which can be unsightly and painful. Patients also experience fatigue and neurocognitive difficulties such as poor memory and confusion, described as 'brain fog'.



Images above are of fat extracted from a patient's blood through the process of plasmapheresis to manage her pregnancy. The patient's triglyceride levels were 'only' 23mmol/L.

Five genes have so far been identified as the cause of FCS and as there are mutations on different parts of the genes the clinical manifestation of the condition can vary widely. Patients are believed to be at risk of pancreatitis if their triglycerides are above 10mmol/L.

There is no treatment currently approved to help manage the condition and current recommendations are that patients limit their total fat intake to less than 20g per day, eat no simple sugars and drink no alcohol. Many patients aim to eat around 10g fat to try and manage their symptoms. To put this in context, 10g of fat is equivalent to two teaspoons of oil or two and a half digestive biscuits. One medium avocado is about 26g fat. Patients are advised to exercise and refrain from smoking.

Delays in diagnosis, appropriate treatment and information about the condition

Diagnosis can occur at various stages of life. We are in touch with patients diagnosed at birth through to late middle age. There tends to be a long delay receiving the correct diagnosis of FCS and patients can be diagnosed with and treated for conditions they don't actually have. The delay in receiving the correct diagnosis leads to a delay in receiving correct FCS management advice which means prolonged unnecessary suffering and increases the risk of long-term pancreatic damage and problems with mental health.

One patient reports experiencing lots of stomach pain and had her gallbladder removed to alleviate it. Her FCS has only been diagnosed since this operation after the pain continued and when her bloods were checked in line with recommendation for a new medication she was to be prescribed

> 'I was only diagnosed in November, I am 38 and have already been through gallbladder removal which has caused me to have severe bile acid malabsorption, but I probably didn't need to have my gallbladder removed.'

Other patients have had their gallbladder removed in an effort to help reduce pain although it seems that in no cases has this been effective for symptoms caused by FCS

> 'I had my gall bladder removed on recommendation of my consultant who thought it might reduce the number of episodes of pancreatitis.'

> 'They took my gall bladder out…. No difference. They did think it might be what was giving me stomach pains. It wasn't.'

Some are diagnosed after their sibling had experienced difficulties and were given a diagnosis having had less pronounced symptoms which had been misinterpreted

> 'I was diagnosed with FCS at the age of 11. This is because my mother realised I had similar symptoms to my younger sister, although not as pronounced.'

The quality of information given to patients varies depending on how long ago they were diagnosed and at what age. For those diagnosed as young children there was often good information and dietitian support

> 'My mum felt she was given good information when we were small, we were under a good consultant and had access to a dietitian and had recipes with MCT oil.'

This was not always the case however

> 'Even some of the professionals we have come across, during his visits to the hospital have not been able to provide any good dietary advice other than keep it low fat. When I asked for recipes from dietitian none were provided. We were given MCT Oil to cook with, but advised to cook on high heat, which made the oil burn and food taste bad, so he didn't eat it, we stopped using the oil and cooked his food with tiny amounts of olive oil.'

There was little to no information or support about how the patient was supposed to manage the extreme restrictions the diet imposed. One parent recounts

> 'I felt very lonely and guilty, that he had to spend the rest of his life struggling with his diet, because I was finding it difficult to cook for him. I had a minor episode of depression, but snapped out of it when I realised that I had to be there for him and try to understand how best to feed him.'

There is currently no effective drug treatment available for FCS. Many patients have been prescribed a range of different medications for the condition – all of which are now considered to have very limited, if any effect

> 'I've been on every fibrate going and any statin going and they haven't really done anything. Medication never worked.'

Others have been given omacor, nicotinic acid, antox, insulin and other diabetes medications used specifically to manage triglycerides. The experience of things being tried to see if they would work was common, often with the expectation of slight or no clinical benefit. Often these medications carry side effects

> 'they gave me muscle ache and pain.'

There is ongoing debate amongst the patients about the efficacy of fish oils. One patient, who was prescribed 10 capsules a day, feels that his numerous episodes of pancreatitis were as a result of this high dose and refuses to take it. Others did not connect their experiences in this way but gave voice to the effect of taking them

> 'Maxepa, ten a day at 17, burping fish oil, which was delightful!'

> 'I was given fish oils but they made me bloated and repeated on me. There never seemed to be a definitive opinion about their value and I worried about taking capsules that are essentially full of oil, so I stopped.'

One patient recounted that her medications were

> 'Too many to count as a child and up to my mid to late teens when I became more knowledgeable about the condition.'

For many, the knowledge that something was wrong but not knowing the cause has created much stress and anxiety and feelings of being fobbed off

> 'They say, have something for the anxiety and depression – I'm not ill in my mind… it's chronic pain… One doctor told me it's in the mind and I thought well you live in my body for one day and you see what chronic pain is like. I even moved doctors because of it. That's how you get treated. The ignorance of someone who doesn't know anything about it.'

(ii) Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects:
- physical health
- emotional wellbeing
- everyday life (including if applicable: ability to work, schooling, relationships, social functioning)
- other impacts not listed above (any impact the condition has had on carers and family members, specifically the ability to work and requirements to update the family home)

Living with FCS is an all-embracing experience which affects every aspect of the patient's life and impacts on the lives of their partners, their children, their parents and their friends. It has ramifications on their ability to work and to engage in the normal flow of events and participate fully in social occasions.

Burden of dietary restrictions

All patients said that the condition is all-consuming with the adherence to a very strict diet having constant and continual ramifications

> 'It's always there – every time you eat, you're thinking about how much fat there is in it and what you've already had that day.'

This near-obsession with food, anxiety about how much fat there is in what they're eating, and concern about its impact on their triglyceride levels, often replaces enjoyment of food with feelings of stress and anxiety about the possible onset of pain, which is hugely disabling and can remove much of the pleasure of the experience of eating. Patients often expressed anxiety about their triglyceride levels as evidence that the condition was not being adequately controlled.

> 'If I know my triglyceride levels are high I'm really anxious about what's around the corner and I get paranoid every time I feel a twinge.'

The severe dietary restrictions mean that eating well means eating from a very limited choice. Most protein sources are beyond the reach of patients leaving them

with a limited 'safe' choice of the breast of chicken or turkey (with skin and all visible fat removed), white fish, seafood (only the white meat of lobster and crab) and pulses (other than soy beans and limited amounts of chickpeas).

Other protein sources are possible but extremely limited and it is vital that the nutritional analysis is checked, as fat content can vary widely.

Eating out is extremely difficult and often impossible. Patients often avoid joining friends or colleagues eating out, as the effort of finding and ensuring food is suitable is far too stressful and difficult to manage.

> 'My heart sinks if the plans revolve around eating first. I'll often miss that bit and join my friends later. I feel left out and like I only have half the social experience.'

All food needs to be cooked without added fat (just one teaspoon of oil is approximately 5g fat). Although some patients use MCT oil, not every patient can tolerate it or like the taste of it, and some find that they are unable to get it on prescription or have not been offered it.

It is vital to check the nutritional analysis of everything. The fat content of bread is an example. One slice of one loaf can contain 0.7g while one slice of another can be as high as 5g, meaning that the fat content of a simple sandwich, even with a no-fat filling, can vary widely.

Analyses can change over time as recipes are changed. 'New and improved' often means the addition of fat meaning that the product is no longer suitable, and the fat content of same product from different suppliers can vary, meaning patients need to go to different shops to buy different foodstuffs. Most pre-prepared foods, even if designated very low fat, do not often meet the stringent requirements of the diet and are often full of sugar.

FCS patients talk about the difficulties of finding or making food that excites them and makes eating enjoyable

> 'I have to take the approach of food being a fuel rather than a pleasure. It gets really boring.'

Adhering to the diet means a life lived outside of the flow of 'normality'. All patients do their best to stay within the recommended amounts of fat but can often be tripped up by the impossibility of finding suitable food when they are not catering for themselves, or being given inappropriate food by someone who hasn't understood the severity of the restrictions.

One patient reports numerous occasions when ordering a skinny cappuccino has been served a coffee with semi-skimmed milk 'because it's the same thing'. The extra 3g of unnecessary fat can make a big difference to what can then be eaten for the rest of the day when the total aimed for is only 10g.

At occasions where food or alcohol is present at a social gathering, which for some can be most social occasions, many chose not to attend and are left feeling isolated and lonely, or do attend but are unable to eat

> 'Eating out or with the kids I think, I can't have that, I can't have that – I don't even have a pint of beer…. If you go out with your friends and they all have glass of wine and you can't have a glass of wine, then you've missed the social experience.'

Parents of young children need to eat separate food so as not to deny their children a normal diet.

The stringent requirements of the diet means there is very little spontaneity around food: there are no easy takeaways for when cooking seems a chore and very limited opportunities to buy something off the shelf. Patients report having little confidence in the ability of someone who doesn't understand the condition to be able to cater effectively and safely. One patient says

> 'I only trust about four people to cook for me without incessantly checking what's in things. That's my husband, my sister-in-law and two friends who really enjoy cooking and have embraced the challenge.'

Eating out successfully – whether at a friend's house or at a restaurant, necessitates forward planning and creates stress. Often the food provided by the host/restaurant can be boring and bland. There is also a degree of trust needed that what is provided has been cooked as requested. A lack of trust can create stress and mar the enjoyment of eating.

The degree of impact the condition imposes in relation to engaging with the 'normal' flow of things can be seen to be more acute at different points in the lives of patients, with a key time being at the point of leaving home - perhaps to go to university

> 'It's huge not to be able to do the things that other people do, forming relationships and making friends at that time in your life.'

Holidays and travel, especially travelling abroad can be almost impossible, and it is difficult to go anywhere even overnight, without having some facility to self-cater.

Physical Health

Many patients experience many episodes of pain, severe pain and pancreatitis attacks, despite being on the restricted diet. These attacks often lead to hospital admissions. Fatigue which impacts on their ability to live their lives fully was mentioned frequently.

Pancreatitis can be a life-threatening event, it can trigger chronic pancreatitis, and lead to permanent damage to the pancreas

> 'I woke up one Saturday morning and collapsed and two weeks later I woke up in intensive care, they nearly lost me twice, it was that severe.'

We are aware of at least two patients who have had a pancreatectomy due to repeated pancreatitis, and two patients who had pancreatic necrosis and were severely ill in hospital for many months.

The onset of pancreatitis is reported as being unpredictable

> 'I had pancreatitis - the day before I was absolutely fine. I don't build up a pain, I just get ill.'

Visits to A&E with severe pain and any resulting hospital admissions are very disruptive to daily functioning for all members of the family

> 'The big problem is that even though my partner sticks rigidly to the diet, attacks still occur. Not often but there is usually no warning and they are totally incapacitating. When this happens, plans have to change.'

Nearly all patients report having had at least one episode of pancreatitis with a hospital admission at one point in their lives, with frequency varying. The GP of one patient reports

> 'Her first attack of pancreatitis occurred in her first pregnancy in 1986 and there is documentation in her records of 38 further admissions with acute pancreatitis…. Despite careful adherence to a very low-fat diet she continues to be at risk of attacks of pancreatitis.'

Another patient stated

> 'My attacks of pancreatitis are too numerous to quantify.'

All of this patient's pancreatitis episodes resulted in a visit to the hospital, the average stay was two weeks and the longest stay was 19 weeks.

A third reports a period in her life when

> 'I was out of hospital every 10-15 days then three days in hospital. I feel tired and felt the effects for at least two days, get eventually better and then go to back to hospital again. Not a normal life.'

Other patients talk of periods of a few years between serious attacks of pancreatitis leading to hospitalisation. Many relate that they manage the pain and sickness of pancreatitis at home and only go to the hospital when the vomiting is out of control

> 'Now when I go in, it's normally only for a few days because I've slightly controlled it myself at home. I have more medication to control pain relief, it's only when I can't control the vomiting that I have to go into hospital. I do have anti-sickness at home...'

One patient mentioned the impact of being sick so much

> 'At one point I did an awful lot of vomiting and had some stomach lining problems.'

Some patients have had negative experiences when arriving at A&E, accused of drug-seeking behaviour and having their pancreatitis attributed to drinking too much alcohol. One reports

> 'I have only admitted myself on two occasions, preferring to manage such attacks at home, as I have always done over the years. The experience in hospital has been unpleasant, with inappropriate remarks from nursing staff about alcoholism, and inappropriate food served up once I could eat again.'

However, not all patients that have suffered from pancreatitis have sought medical attention

> 'I've never been diagnosed with pancreatitis. I'd go into my room and fast for five days, drinking only water and taking pain killers. It was only when I met another patient who had been in hospital with pancreatitis who told me they'd been fasted for five days on a drip with morphine that I thought that maybe I'd had pancreatitis.'

Many patients talk of fasting for a day or more if they feel abdominal pain.

Pancreatitis is a painful and debilitating experience and can take a long time to recover from

> 'However, just one episode of pancreatitis can take a few months to return to full fitness again. It is extremely debilitating. It's not just the stay in hospital, or the initial recovery at home for a few days…. I feel weak for a couple of months and very tired. Generally, I then seem prone to picking up secondary infections from colds etc.'

Other physical effects of the condition create a daily burden. A distended stomach and discomfort around the upper abdomen are frequently reported

> 'I am frequently troubled by a distended abdomen and low-level discomfort and a sense of feeling 'off', quite irritated and that everything is an effort.'

This stomach distension is more pronounced after an attack of pancreatitis

> 'It's only after a couple of months (since a pancreatitis attack) that the swelling has started to go down and I can actually see all the weight I've lost and you can touch my stomach now whereas before it was so sensitive.'

> 'It makes my stomach distended. I'm finding now it doesn't go down as much after an attack. It's staying distended. Clothes-wise, things like that, it affects everything.'

Extreme flatulence and general bowel disorders are a feature

> ‘Terrible flatulence – you end up with more pain trying to control it.’

> ‘My stomach is sometimes churning away producing a lot of evil-smelling wind that is just socially unacceptable.’

> ‘I get a fair amount of pain and become very friendly with the toilet.’

Patients can develop cysts on the pancreas due to the scarring caused by bouts of pancreatitis

> ‘Cysts have also been found on my pancreas, I currently have a large one on the tail of my pancreas which is putting pressure on my kidney and causing me pain and discomfort and worry.’

A number of patients mentioned having joint and lower back pain.

Patients talk of having less energy than people without the condition and feeling fatigued and of feeling very irritated when triglyceride levels are high

> ‘I have always been an emotional person and when my fat levels are not well controlled find that I can be very short tempered, although I have never been violent, I can, however, become very argumentative and very loud.’

Impact on work life

Recurrent pain has an enormous impact on the ability of many patients to work, the choices they have made about which jobs to do, and the number of hours they can manage

> ‘I’d like to do more hours but I can’t because of the tiredness. I do 18 hours but if I’m poorly I don’t get paid. It affects me financially because I can’t do the extra hours.’

One patient, now of retirement age, stopped working at the age of 37 due to the amount of pancreatitis attacks he had experienced which lead to a complete pancreatectomy. Another who has stopped working says

> ‘The stress of trying to work – if you’re at work and you’re in pain – and trying to keep to the diet, whereas at home (not working) I can stop and sit down.’’

The unpredictability of the onset of pancreatitis causes a great deal of stress especially in relation to employment

> ‘..the unpredictability of this condition means you are always worried about the next time you will have to ring in sick, and the patience of your employer. Equally, from the perspective of an employer, especially as you progress in your career, it is hard for them to understand how quickly and how severely you can become ill.’

Patients have varying experiences regarding the understanding of employers. One patient reported having been off work for five months after an attack of pancreatitis that saw her in hospital for two months. On her return to work, she quotes her boss as saying

> '"Your health isn't my problem. Your wellbeing isn't my problem. You're here to do a job". ….It was difficult going back knowing people didn't want you there.'

Another patient says

> 'I've had massive amounts of stress with being off sick and bosses that didn't understand…. A lot of anxiety that goes with my employment and this. This is one of the biggest things with me – being able to hold down a job… it has a huge impact on my employment where I need to be reliable and predictable.'

Many have chosen casual jobs to mask their inability to be consistent and reliable in turning up for work.

One patient talked of choosing to do shift work so she could juggle her work around the attacks of pain

> 'I try and move my shifts around.'

People talked about choosing jobs that were less responsible than they might otherwise have attempted in an effort to balance their health needs against the stresses of work responsibilities

> 'If I didn't have FCS I would be going for a promotion. I'm capable of it, but I have to put my health first…..'

A number of women report having had plasmapheresis on a regular basis whilst pregnant, furthering limiting their ability to work. Plasmapheresis is a very time-consuming intervention.

> 'I was taken into hospital at 16 weeks – the trigs kept going up so had plasmapheresis three times a week. They realised if they took all the fat out it would double so ended up twice a week.'

For nearly all patients their choice of job was limited to a role that did not involve much travel or staying away from home, or roles which did not require them to attend lots of social events, as it was felt that they would be unable to be able to manage the eating out that these would demand of them.

The level of tiredness that people with FCS experience, and the energy needed to manage it, was a factor in many people's choices related to their work

> 'I have now retired, and part of my decision to retire early was awareness that I was more tired than the average, which was attributed to FCS.'

> 'I find it extremely difficult to manage the condition as it requires relentless meal planning and organisation. This is particularly difficult to do when you work long hours in a stressful job. I have tried to mediate this by working less hours.'

Being in pain and unable to be reliable and consistent in their work patterns can have a big effect on the patients' emotional well-being

> 'I feel like I'm not pulling my weight, I'm letting the team down….. I feel separate and isolated – managing what you're coping with sets you apart.'

Impact on the patient's family

Because of the disabling effects of FCS on all areas of the patient's life, the condition also has a huge effect on the patient's family and friends. They place a strain on partners' and their ability to work

> 'He had to take time off work…. Couldn't get paid. For the second baby he had to take time off…. Held him back a little, things he didn't go to, when I was in hospital.'

For children who see their parents in pain or in hospital, the experience can be deeply distressing and can prompt the child taking on the role of a carer.
One daughter (the eldest child now an adult) reports

> 'Now I have the role of looking after my sister – she often gets upset and I have to be her pillar of support. I will often take her and pick up from school, she will stay at mine if Mum is in hospital because Dad will need to get up early – we have to try and keep things normal for everyone because life still goes on and school and work still has to happen.'

The impact of the condition can cause caregivers to be worried about their partners' health and wellbeing

> 'He is constantly concerned about me and what's going to happen. He is thinking about the worst every day…. He keeps on asking me 'How are you feeling, how is your pain?'

The lack of spontaneity and need for careful management of social situations can reduce enjoyment for friends and family members

> 'The condition forces the patient to focus very often on their own needs, in order to ensure their survival and good health in situations where others would simply be at ease and eating as they please. This can have a negative impact on those who are close to the patient.'

> 'Going out for something to eat with family and friends is a very sociable and normal thing to do but actually FCS takes all the enjoyment out of going out with mum. Having to explain to restaurant servers the food needs to be plain

> with zero (or very minimal) fat/oils can be slightly awkward – because who understands FCS?'

Family members and friends can lack understanding of the severity of the condition and be less than supportive to the patient. One patient whose diagnosis came later in life says

> 'my mum doesn't understand it – Sunday lunch – she cooks it all in lard so I take my own dinner with me. It upsets her.'

Patients can be acutely aware of the impact of their FCS on those close to them which can make them feel guilty

> 'I feel bad because I'm imposing my lifestyle on them… it makes me feel bad that they can't eat, or they can't have stuff in the house because I will want to eat it. It puts restrictions on quite a few things.'

Pregnancy

Pregnancy can be difficult for patients with FCS as triglycerides rise naturally in the third trimester (although one reported that they 'skyrocketed' from the outset) and for women with FCS this can be to levels above 60mmol/L. Most women were unaware that there might be complications due to pregnancy.

Some women developed gestational diabetes, making managing the pregnancy even more difficult and stressful as high blood glucose is turned to fat by the body, further raising triglycerides and making managing eating far more problematic.

Women mentioned that in order to manage very high triglyceride levels they limited their fat intake to as little as possible – some patients with gestational diabetes reporting eating as little as 1g – 2g fat per day. One woman with gestational diabetes and following this regime says

> 'I certainly struggled through my pregnancy both times, especially the second time. It was a game changer, I really started feeling sorry for myself…. I was hungry all the time, I couldn't eat. How can you eat when your trigs are around 60 and everything you put in your body converts to fat? Even a banana, which is no fat but high in sugar… so everything I could eat I would panic about…… Pregnancy is huge, another level of worry, diet management and pushing your body.'

The experience of pregnancy was tough both physically and emotionally for most, demanding a high degree of regular monitoring and a huge sense of danger for both the mother and her unborn baby. Both parents report very high stress levels during the pregnancy.

One woman, on her third pregnancy and having developed gestational diabetes from the outset, reported being in constant discussion with her healthcare team

> 'We were seeing if I could manage to control my triglycerides to see if I could manage the pregnancy and didn't fully commit to having the baby until we'd reached 24 weeks on the understanding that if necessary, I could terminate up to that point. After that I was pressured to deliver at 28 weeks, but I refused because I wanted the baby to grow as much as possible in the womb. I eventually managed to get to 39 weeks but afterwards I was exhausted, having panic attacks and I couldn't stop crying. I think it was all due to the strict regime and amount of stress I'd been under'.

The father says

> 'I must confess to having been heedless about any medical complications from the condition in relation to the pregnancy until my wife developed very raised triglycerides in her first pregnancy. In the second she developed high triglycerides and diabetes and the third became dangerous to the point that I was afraid both mother and baby could die. Termination was seriously discussed as a possibility, and there was some pressure for this to happen. Including from me. However, my wife was very keen to have the child, and did so. For which I will always be grateful.'

A number of women reported being sterilised after having particularly difficult pregnancies.

> 'After this pregnancy I was sterilised to be sure that I was not at risk anymore.'

For some the pregnancy was highly medicalised

> 'Pregnancy was my problem. I was pregnant at 19 and the pain started more or less straight away. This along with extreme tiredness and sickness made me feel really ill. The symptoms I had were put down to early pregnancy and I continued to suffer. At around 4 months of pregnancy the pain was severe and I was admitted to hospital with severe pancreatitis. I spent most of the pregnancy in hospital on a drip with a nasogastric tube in situ….. It took me at least 6 months to recover and needed support to raise my child from my husband and family members.

A number of women had had plasmapheresis to manage their very high triglyceride levels.

> 'My trigs were about 70… I would have plasmapheresis every Monday and my trigs would drop to about 20. I would have a blood test on the Friday and they would be rising and then I'd be back in again on the Monday – this was from 16/17 weeks.'

Many of the women we spoke to had had their babies induced because of the joint concerns of the mother and the medical team.

Other women have different experiences

> 'I had no information about the risks of pregnancy, so we just got on with it…. The first two pregnancies were basically fine. They were both on the small side… but it was fine. Not pleasant, but fine.'
>
> 'I had three full term pregnancies without any issues despite my triglycerides rising significantly. I was admitted to hospital for a week to see if their regime would bring down my triglycerides. It did not, they rose further, and I was discharged. I had no special monitoring with the second and third pregnancies.'

For some women having children is not seen as a possibility

> 'It was not even on my radar to consider (having children) as I was unable to stay out of hospital/have a relationship.'

One woman stated

> 'There was no choice. The doctors insisted that having a family was not an option. Consequentially at 18 I was sterilised. Subsequently, we became aware that the advice was flawed.'

FCS associated diabetes

A number of patients develop diabetes as a result of their FCS due to insulin insufficiency caused by decreased insulin production as a result of damage to the pancreas from pancreatitis or insulin insufficient as a result of a diet high in sugar and carbohydrates (eaten to compensate for the lack of fat).

As previously mentioned, high blood glucose levels are turned to fat which then raises triglycerides, as well as loading the symptom burden of diabetes onto the patient. This is well described as fatigue, excessive thirst, dizziness, constant urination and weight loss. Long term complications include possible amputation, neuropathy, retinopathy, cardiovascular disease and kidney disease. For women, menopause can add to the burden as the changes in their hormones can lead to a further increase in blood glucose levels.

Managing diabetes well requires eating a sugar free and low carbohydrate diet at regular intervals throughout the day. For a patient with FCS, the need to eat a regime low in carbohydrate means that their food choice is limited to very low fat, low carbohydrate and no sugar, leaving very few choices to give energy and sustenance.

> 'For years my triglycerides were very low - under five – until I developed diabetes. Since then they're creeping up and I don't seem to be able to do anything about it, despite being on two diabetes medications. I don't know if it's my age or what? I do know that I feel far more tired and frequently have mild abdominal pain that makes me feel crap. For the first time in years I'm scared I'll have pancreatitis.'
>
> 'Throughout my life I have been able to accept my condition and tried, not always successfully, to live on a low-fat diet. However, in 2003 I was

> diagnosed with Type II diabetes brought about by living most of my life on a low fat, high carbohydrate diet. Since then I have found that I am able to either control the fat levels or the sugar levels but not both at the same time.'

The onset of diabetes seemed to have a profound effect

> 'Following the type II diagnosis I have been hospitalised with pancreatitis spending between 6 and 8 days each time.'

This same patient recently developed a foot ulcer

> 'I have been off work since December 2017 with an ulcer under my right foot, which was too deep to allow me to carry on working….. At the time of writing (June 2018) I am still not at work.'

This absence eventually lasted nine months.

Depression and emotional wellbeing

The emotional impact of living with the condition is very pronounced. Most patients felt it impacted on their emotional wellbeing and made them feel isolated from their friends and those around them. Some mentioned that they were depressed and were taking anti-depressants. Some had had suicidal thoughts. Feelings of guilt about eating something 'bad' were often expressed

> 'I became socially isolated over the years and spent large amounts of time in and out of hospital and have continued to do the same. I have felt suicidal at times torn between wanting to live and wanting to die. I am convinced that if I had not got FCS my life would have been different.'

> 'It's made me depressed. I feel very lonely. I'm on anti-depressants at the moment. There's only so many times people can come round and see you and come see you in hospital. Family do, friends not so much. I'm then maybe, pushing people away. I tell people to go out without me and then I'm upset at home on my own. I spend a lot of time on my own feeling lonely.'

> 'I've spent most of my life watching others get on with their lives while I felt completely restricted in the choices I can make and worrying about or being in pain. I have periods of depression where I feel I have nothing to offer anyone and can't see why people would want to have anything to do with me.'

> 'There are days when I get upset and wish I can be the same as everyone else.'

> 'Emotionally FCS poses a constant strain for me. You have to think about absolutely everything you want to eat or drink, day in and day out. You can't throw caution to the wind and not risk being ill…. You have no idea whether you are about to have pancreatitis or not. That unpredictability and fear is very limiting and impacts massively on your social life and life choices. If you have something to eat or drink that you know you shouldn't have, however

small, and just one thing, the guilt can be overwhelming at times. Keeping to the never-ending restrictive diet in itself can be very hard, frustrating and depressing. It feels isolating.'

'I have been really down at times… when you're well you want to make the most of everything because you don't know how long it's going to last..'

'I developed bulimia when I was a teenager. In my twenties I felt guilty and ashamed about struggling so much and indulged in some really risky behaviour because I felt so bad about myself. I had zero self-esteem.'

The restrictions that FCS imposes on patients can create a barrier to building new relationships

'I am reluctant to start dating again as I feel it would be an imposition to expect any future girlfriend to have to change her diet to accommodate me and to restrict the restaurants we can visit.'

What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

2. Advantages
(i) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.

From the publicly available information we expect that the technology will reduce triglyceride levels in patients up to 77% and that this reduction will decrease the risk of damage to the pancreas and reduce the incidence of pain and pancreatitis and therefore the risk that each pancreatic attack brings, including risk of death, the risk of the onset of chronic pancreatitis, and the risk of complications such as diabetes and cysts. We expect this to lead to a healthier and possibly longer life.

We expect that the effect of the reduction of and anticipation of pain and pancreatitis will have a profound effect on the lives of patients improving their ability to work and the choices they make about which job they do.

We expect that the reduction of triglyceride levels will help to relieve the anxiety and anticipation of pain that high triglyceride levels creates in patients, and will reduce the amount of fatigue that patients feel. We think that reduced triglyceride levels will have an effect on patients' xanthoma, which can be painful and unsightly.

We expect that the technology will help patients better engage with their social life, reducing their feelings of isolation and lessening feelings of guilt for cancelling engagements and of unfulfilled promises and will allow them to participate more fully and reliably in their life. We expect all of this to make a massive improvement to their mental health in reducing their episodes of depression and levels of stress and anxiety and thereby improving their sense of wellbeing.

We expect that the improvement in the patient's ability to make choices, in their mental health and their sense of well-being will also have a hugely beneficial impact on those around them. The lives of people close to the patient will not be disrupted by the patient not being able to function well due to their symptoms, or through their emergency visits to and stays in hospital, or by their need to absent themselves to manage their pain at home.

We expect that all the benefits we have described will have a positive impact on all of those around the patient in terms of lives not being disrupted by attacks of pain or by the fear of pain or by changed plans due to the absence of the patient who is dealing with pain, or absent in hospital.

The clinical trial did not address the question of the use of volanesorsen in pregnancy or on lactating women and there is no data on the effect on human fertility. The EMA 'Summary of Product Characteristics' says 'as a precautionary measure it is advisable to avoid the use of this medicinal product during pregnancy'.

We hope that gaining a greater understanding in this area would be a high priority moving forward in order to identify if the therapy could be useful to women who can experience high risk and extremely stressful pregnancies due to raised triglycerides.

(ii) Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on:
- the course and outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example friends and employers)
- other issues not listed above

Ten patients who have taken the drug responded to us, seven of these were on the trial and three have accessed the drug through EAMS. For all but one patent, taking the drug has had a very positive impact on every area of their life. Most importantly has been a huge reduction of pain and the fear of pain. The incidence of pancreatitis among the group had reduced to almost zero (one had a pancreatitis attack after being abroad on holiday).

This huge improvement has allowed them to engage more fully and consistently in their lives, avoiding visits to A&E and hospital stays - or retreating from their daily routine to manage attacks of abdominal pain and pancreatitis. This has massively improved their ability to work, to study and their ability to manage friendships. All of these benefits have reduced the huge amount of stress and anxiety in their daily life, improving their sense of what is possible for their future.

This benefit to the patient has also had an impact on all of those around them, allowing for greater consistency in daily life and the ability to plan, as life is no longer interrupted by the absence of the patient managing severe pain, or through a hospital admission

> 'I feel 100% well with regard to my physical health since starting the treatment. Prior to this I felt about 20% well as I was being admitted to hospital recurrently for severe abdominal pain/pancreatitis. It has improved my emotional well-being ten-fold! I feel happier about myself and Volanesorsen has allowed me to feel less anxious when around food/making decisions around eating out. I don't think without the drug I would be in a long-term relationship which I am now fortunate to be in – when you are being constantly readmitted to hospital there's no way of trying to start a new relationship as that's not a pressure you can put onto a new relationship with someone you don't know well. I have had zero days off work due to FCS. It has enabled me to at least consider being pregnant …. I was previously not well enough to do this.'
>
> 'Keeping my lipid levels low has meant that I am feeling healthy. It means that I won't be so ill that I will not miss work and even have a stay in hospital. The drug trial has shown that with low-fat diet it does lower lipid levels and that results in me feeling healthy.'
>
> 'I'm not tired, not bloated – in a matter of three weeks, I felt better, felt healthier, can I say I felt normal? It made a massive difference, a massive improvement on my life. I felt better in myself, felt more outgoing…. No time off work, no problems with anything at all mentally and physically so good. I felt normal, that I could do anything. I slept better…. I picked up extra hours, they noticed a difference in me. I didn't have to take pain relief….. It was a big relief for all my family – they've all noticed a big difference.'
>
> 'Yes, I feel good taking the drug, feeling better compared to before. People said I looked better. I'm more social – I like social gatherings. I used to avoid them if my mood was not good…. I don't get any pain with the drug.'
>
> 'Feeling physically healthier and feeling better, being able to go to work and therefore receiving money and so less stress about that. Not having so much guilt about letting down my colleagues. Enjoying living day to day. Physical, emotional and mental health all improved.'
>
> I don't get very bad pain now. I mean I used to go hospital at-least 2 times per month before so that's a very big improvement for me. My levels are also low.. It used to be in 20s and go up to 60.. now it's around 10 or below. Again, it's a very big improvement for me.'
>
> 'Ultimately the Volanesorsen seems to be working. Whilst being on the trial I have felt better and not suffered any pancreatitis attacks'.

One caregiver reports

> 'I have seen first-hand the significant improvement in my partner's general day to day life due to participation in this trial. This is through elimination of hospital visits for pancreatitis attacks, ability to work full time and ability to engage in travel and social events with less stress and anxiety. It is difficult to underline how much of a burden this condition is on those who suffer from it.'

All but one of the patients we spoke to felt that the technology would help to improve every area of their lives and would enable them to look to the future with a sense of hope. For a couple of respondents, the issue of mortality was present, one says

> 'I'll be able to have a full life. Everything I do - work, mentally physically, family, workwise, it's going to make my life a lot better, and if the lipids are down, make my life last a lot longer.'

The positive effect of the technology was felt in all areas of the patient's life

> 'Increase of confidence, possibility of having kids more realistic than what it was before even though they don't know how the drug will react – less stress and anxiety… a positive impact -physical, emotional, mental health all improved – in all areas of my life, and maybe over time it will allow me to lead a more regular normal life like others, without the pain.

3. Disadvantages
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

The publicly available information, and the experiences recounted by the patients who have used the drug, show that the problems with the technology centre around the possible reduction in platelets, the subsequent need to monitor the patient closely, and difficulties with the injection site.

Side effects noted were bloating, pain around the injection site and reduction in platelets flagged by blurred vision and headaches

> 'The main problem I suffered with when taking the drug was that I had blurred vision and headaches…. The following day my bloods were done, by the afternoon the hospital contacted me and said that my platelets were low and I shouldn't inject that week. I had to wait three weeks for my platelets level to come up and then I was told to inject every two weeks. My platelets level is checked every week and they have been normal….. I still feel nervous when I inject'.

Another patient reported issues with injections and with the injection site

> 'On a few occasions I have had a virtual paralysis of either the leg or arm for several hours after taking the injection. The injection can be very painful and occasionally has left a rash. I have problems with administering the injection. I cannot carry out the task and rely on my husband. Due to work/travel commitments he's not always available and then I'm reliant on friends and neighbours.'

We are aware of one patient who was on the trial who has subsequently asked to stop taking the therapy after experiencing symptoms which they attributing to the drug. These symptoms have not been identified as side effects but it is worth noting that more information needs to be gathered about the effect of the drug over time, and that the decision about the benefits of the therapy is a very personal one.

As the drug requires regular monitoring, we think that some patients may find this challenging to adhere to. We understand that if the drug were to approved by NICE there could be home visits from a phlebotomist which would mitigate the impact that this has.

We think that patients should be given the opportunity to discuss with their consultant the potential risks of the technology and how the monitoring might affect their lives and that they will know best how the impact of the monitoring will fit into their lives.

Any financial impact of taking the therapy through missed work meaning missed income was felt to be worth the cost, and much more manageable than the financial impact of sudden absences from work that they had experienced through the incidence of pain.

We have some concerns that, once using the technology patients might think they have carte blanche to eat a normal diet. We believe that there would need to be very clear information given to ensure that patients understood fully that the technology is used in addition to the restricted diet.

We recommend that regular monitoring of lipid levels would help to support patients and reinforce this understanding and that access to an expert dietitian should be offered as a matter of routine.

4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

The difference in opinion about the therapy reflected the impact of the symptom burden felt by the individual patient.

Nine out of the ten patients who responded and who have taken the drug were positive about it, despite the concerns and issues detailed above.

Opinions expressed from these patients were reflected in the following quotes

> ‘Notionally, the disadvantages are that there is regular monitoring and injection site reactions, however these are insignificant compared to the regular abdominal pains, pancreatitis and hospital admissions I was experiencing prior to my participation in the trial.’
>
> ‘This drug has helped to lower my lipid levels and has left me feeling a lot happier. I haven’t had to worry about stomach pains and vomiting. It has given me the freedom to go out and socialise with my friends. It has left me with hope that there might not be a cure for my condition - but at least a treatment to make my life happier and easier.’

Everyone who had taken the drug felt that the platelet monitoring was a small price to pay for the benefits that the drug had brought them and that on balance the monitoring requirements hadn’t impeded their lives to any great extent.

For those patients who have not taken the therapy we asked what their opinion was about taking the drug with the knowledge of the potential side effects and monitoring requirements.

Views expressed ranged as follows

> ‘Currently I have a diet and some symptoms. If I could have a diet minus symptoms, it's still a plus. Yes, a less restricted diet would be awesome, but to feel better even with the diet would still be awesome!’
>
> ‘I would definitely accept the monitoring of my bloods and painful injection sites to have some sort of normal life. Preventing pancreatitis by keeping our triglycerides low would be the most important factor for me. Eating is a lifestyle factor as well as necessary for health. I have recently had a set of bloods back where I have low doses of vitamins and minerals associated with having an extremely low-fat diet. This would maybe allow me to eat things occasionally rather than take supplements to counteract this. I would gladly accept the strict monitoring to be able to have this drug!’

At the other end of the spectrum patients who do not suffer from a lot of the physically disabling effects of the condition, e.g. pancreatitis, pain and diabetes, have said that they probably would not choose to go on the drug

> ‘On the condition that a significant reduction in my triglycerides permitted me to be more liberal with my diet, then I would consider the potential close monitoring required and side effects as acceptable. However, without any significant benefit to my dietary regime, for me I anticipate that the close monitoring requirements and the side effects would be too intrusive to my quality of life.’

One patient who had been screened to join the trial said,

> ‘Because my trigs are low I may not be a candidate for this drug - my levels are really low because I’m so restricted on my diet. It was almost like, what if I’d eaten a little bit more fat and my levels were 10 or 20 I’d have been

> allowed to go on, they're only low because it's what I do. It's great when people say well done but it's hard to be in this place. It would be nice to be able to take something and eat more fat, my goodness isn't that a dream! I'd love to be able to take a drug to be able to eat 20g per day. We're never going to get rid of this condition but something that would enable me to eat….'

Another view expressed was

> 'I think I'd at least like to be able to have a full discussion with my consultant about whether, on balance it would be suitable for me. My triglycerides keep rising and I'm struggling to manage them. It's giving me a lot of stress thinking I might suddenly have an episode of pain and if I did have pain, I worry about the impact that might have on me both in the immediate and in the long term…. It's not an easy decision to make.'

The carers view is reflected in the following quotation

> 'I would say that whilst having lived with FCS for many years, if a treatment that would lower or remove the risk of a pancreatitis attack was available, it would be a major benefit to anyone who has the condition. The attacks are totally incapacitating and render the sufferer an invalid for the duration.'

5. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?
(ii) The scope states that if appropriate:

- Consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues.

- Consideration may be given to whether factors contributing to, or exacerbating hypertriglyceridemia are associated with characteristics that are protected under equality legislation (for example, but not limited to, women using oral contraceptives).

Please describe whether people in these subgroups have a different prognosis from the typical patient?

The EMA have licensed waylivra 'as an adjunct to diet in adult patients with genetically confirmed familial chylomicronaemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.' (EMA).

We don't know that there are any sub-groups within these criteria who would benefit more from this therapy than others, although we would like for there to be more exploration of the use of the therapy in pregnant women as we think it could relieve the huge stress and anxiety felt by pregnant women with very high triglyceride levels and for those experiencing pancreatic pain.

Those who might benefit less from the therapy are patients whose platelet levels seem more sensitive to the therapy or who run very low platelet levels and do not meet the threshold to take the drug. We would hope that this could be managed by reduced dosing and that in time there would be a more understanding of the mechanism by which the reduction of platelets occurs and that some mitigating action can be developed to enable the therapy to be an option for these patients.

6. Comparing the technology with alternative available treatments or technologies
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list current standard practice (alternatives if any) used in the UK.

The current standard practice for managing FCS is to follow the recommended highly restrictive and difficult to manage diet which for many patients does not provide respite from the many symptoms of the condition.

There is no other drug that is deemed to benefit patients with FCS even though (as described above), many have been prescribed many different lipid-lowering therapies, most of which have carry an unpleasant side effect burden.

Paramount for patients is preventing abdominal and pancreatic pain and long-term damage to the pancreas, thereby avoiding unnecessary surgical procedures and other complications like diabetes. This therapy overs the only option able to do this.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

The advantages of the technology are that patients who experience the symptoms of FCS despite adhering to the restricted diet would have support to be free of or have a much-reduced symptom burden.

This will make their daily life much more manageable due to pain reduction, no or significantly reduced episodes of pancreatitis involving visits to A&E and possible hospitalisation, and could possibly extend the lives. Reducing the risk of pancreatitis reduces the risk of developing chronic pancreatitis and any complications from pancreatic damage including the onset of diabetes and pancreatic cysts.

Further advantages include greater energy levels, and a reduction in feelings of stress, anxiety and depression leading to better mental health.

These benefits, as well as the benefit of the reduction of the fear of pain and the stress of not knowing when pain may occur, would have a major impact on all areas

of the individual's life in terms of their employment, their social relationships and their choices about having children.

Patients have reported that the technology has also reduced their cholesterol levels.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

The disadvantages of the technology are the potential side effects of a reduction in platelets, (meaning that some patients will not meet the criteria for taking the drug), the need for ongoing monitoring, the potential difficulty for patients self-administering the injection, and injection site reactions.

However, we think that the balance between the advantages and the disadvantages of the technology would vary across patients and is something that each patient should best weigh up and decide upon themselves after a fully informed discussion with their consultant.

We think that the patient will know best if, on balance, they feel the potential negatives are outweighed by the potential positive effects of the technology.

7. Research evidence on patient, family or carer views of the technology
(i) If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their care reflects that observed under clinical trial conditions. Were there any unexpected outcomes for patients?

None that we are aware of.

(ii) Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?

As stated above, one patient has withdrawn from treatment citing symptoms which have not been previously identified which they have attributed to the therapy. More information needs to be gathered before these can be seen as side effects.

(iii) Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

The InFOCUS burden of disease survey and ReFOCUS burden of disease survey both commissioned by Akcea Therapeutics. (InFOCUS: Journal of Clinical Lipidology (2018) 12, 898–907, ReFOCUS ISSN: 1477-9072 (Print) 1744-8344 (Online) Journal homepage: https://www.tandfonline.com/loi/ierk20)

LPLD Alliance was closely involved in setting the questions for the InFOCUS survey to ensure that they properly covered the issues experienced by patients with FCS.

8. Availability of this technology to patients
(i) What key differences, if any, would it make to patients, their families or carers if this technology was made available?

The key differences that this technology would make to patients, their families and carers, is that it would be the first and only medication available offering some relief for those who are currently forced to manage the severe and relentless restrictions and symptom burden of the condition with very little practical support and in the context of virtually no understanding of the impact that it has both on their lives and on the lives of those around them.

The technology would facilitate the reduction of pain and fear of pain and would reduce the risk and incidence of pancreatitis and all the associated risks attached to each pancreatitis episode. It would help to limit damage to the pancreas and reduce the risk of chronic pancreatitis and diabetes offering hope for a healthier and potentially longer life.

These benefits, as well as the benefit of the reduction of the fear of pain and of the stress caused by not knowing when pain may occur, would have a major impact on all areas of the individual's life in terms of their employment, their social relationships, their levels of stress, anxiety and depression, and on their choices about having children.

All of these benefits would allow individuals and families the opportunity to live their lives in a manner that enables forward planning, fulfilled promises and engagements, the opportunity for regular employment, a greater engagement in social opportunities, and lead to a general reduction of the continual and constant stress and anxiety that having FCS creates.

Although not seeming suitable for every patient with FCS, those for whom it is not a possibility would have the benefit of knowing that the plight of fellow patients has been improved. It would also offer some hope that in time developments could be made to the treatment based on further evidence gathered through its use over time, which might allow them to gain access to the treatment in the future.

(ii) What implications would it have for patients, their families or carers if the technology was **not** made available?

Without this technology, patients would be left with little hope of alleviating the symptom burden that the condition imposes and forced to continue to manage the severe and relentless restrictions the condition imposes with little practical support and little understanding, removing hope for the future.

Patients would be left to cope with their lives in fear of, or with unpredictable pain and pancreatitis, with the resulting disruption each episode of pain and pancreatitis causes including hospital admissions and time off work and high levels of fatigue.

Patients' life choices, whether the ability to work, their choice of job and their participation in social occasions would remain severely limited. They would continue to be isolated, stressed and at high risk of depression.

All of this indicates a worsening prognosis in terms of quality of life and life-span, which has an enormous, negative effect on patients' lives and on the lives of all of those around them.

(iii) Are there groups of patients that have difficulties using the technology?

As described above, the platelet levels of some patients mean that this technology may not be an option for them.

(iv) Are there any situations where patients may choose not to use this technology?

As stated above, some patients may choose not to use this technology having weighed up the potential benefits and risks and the impact the monitoring may have on their lives. This is an individual decision and the patient needs to be able to make a fully informed decision when making this choice.

9. Please provide any information you may have on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

We have little information about the number of patients in England with FCS other than from the company who have developed the therapy (Akcea Therapeutics) who estimate the figure to be around 120. However, it is hard to know how many patients there are as the condition is obviously under-diagnosed and as awareness of it grows, so too may the numbers. Having said this, we are certain that the condition will continue to be rare.

As not all patients may choose to take up this technology it would be hard to put a precise number on how many would receive treatment with it.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which volanesorsen will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

We don't believe this evaluation impacts on equalities issues.

Other Issues
Please consider here any other issues you would like the Evaluation Committee to consider when evaluating this technology.

FCS is a little-understood, extremely debilitating and difficult to manage condition for which there is no effective treatment currently available. Patients are desperate for a therapeutic option to help them manage their symptom burden. This burden has ramifications across all areas of their lives and affects the lives of all the people around them.

Awareness of and early diagnosis of FCS needs to improve to ensure that patients have access to the best advice on managing the condition as early as possible and long-term effects on patients can be reduced. We think that the availability of a therapeutic option would improve awareness of the condition, as well as offer much-needed relief for those patients for whom it is suitable.

Dietary advice and access to a dietitian is also varied. One patient diagnosed in her mid-thirties was not offered a dietitian referral on diagnosis and had not seen one a year later. However, many patients who have seen a dietitian express the view that the support they have been offered is limited.

We think that specialist centres will allow all professionals to increase their understanding of the condition and therefore improve the support and resources that they can offer. This would then become more consistently offered to all patients across the board.

Patients do not seem to be offered psychological support. Patients struggling to come to terms with a new diagnosis or patients struggling to manage their dietary restrictions would benefit from some kind of intervention to help them deal with the impact of living with a long-term life-restricting condition. We think that a review of the patients' mental health needs should be part of their treatment plan.

Our last quotation comes from a patient taking volanesorsen.

> 'Please, it has changed my life, literally in the last year – it made me all wobbly and teary just to say that.. (deep breath) ……. it's made a big difference. I'm not great at articulating it.… I'm so sorry. It has made my life a lot better and happier. It's helping me to help myself.'

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted], [redacted] [redacted] [redacted] [redacted] [redacted]
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	None currently
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no specific treatment pathway, NHSE service specification or NHSE clinical commissioning policies for this condition at the moment. Patients are managed via a strict fat restricting diet and restriction of alcohol alongside treatments for hypercholesteraemia.
8. What impact would the technology have on the current pathway of care?	NHS England notes that volanesorsen is likely to be a high cost drug which is given by subcutaneous injection once a week. We would expect prescriptions to be initiated and monitored by a small number of expert lipid centres, likely those centres which already offer lipid apheresis and have participated in the EAMS. After initial dosing we would expect administration of the medicine via home care. We do not think there are any particular difficulties in administration. This technology does not appear to present any particular commissioning challenges beyond its cost effectiveness.
The use of the technology	
9. To what extent and in which population(s) is the technology	Volanesorsen has received a positive Scientific Opinion from the MHRA as part of the Early Access to medicines Scheme (EAMS). To date 29 patients have accessed the treatment under this scheme.

being used in your local health economy?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	To date seven Trusts have accessed volanesorsen through the EAMS. It is likely that only these seven Trusts will be commissioned if the treatment is approved.
• How does healthcare resource use differ between the technology and current care?	See above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	See above
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific facilities as treatment will in general take place in the patient's home. The major cost will the drug itself.
• If there are any rules (informal or formal) for	That will be dependent on what (if any) restrictions are made under a NICE recommendation.

starting and stopping treatment with the technology, does this include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	None made
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that we are aware of
12b. Consider whether these issues are different from issues with current care and why.	n/a

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Fredrik Karpe
2. Name of organisation	Oxford University Hospitals Foundation Trust Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford

3. Job title or position	Honorary Consultant Physician Professor of Metabolic Medicine
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): I have been asked to represent Specialized Endocrinology CRG
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent hypertriglyceridaemia-induced pancreatitis To reduce plasma triglyceride concentrations in patients with extreme hypertriglyceridaemia
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in frequency of hypertriglyceridaemia-induced pancreatitis A very substantial (should probably be 50%) reduction in plasma triglycerides in patients with familial chylomicronaemia syndrome
9. In your view, is there an unmet need for patients and	Yes, the current best treatment is essentially restricted to strict adherence to an extreme low fat diet which is difficult and often unsuccessful.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no guidelines There are individual statements by experts in the literature and as part of medical text books
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No, since the condition is rare and severe, these cases normally find their way to a Lipid Clinic with time. There is unanimous agreement that an extreme low fat diet is helpful. Other treatment options are non-evidence-based and will differ between clinicians.
• What impact would the technology have on the current pathway of care?	In the best interest of patients, it would be reasonable to concentrate the treatment to a few centres to ensure that good experience is assembled and good practice is adhered to.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	This would be a new treatment requiring resources to be implemented.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	1. There is a significant uncertainty about the diagnosis of the Familial Chylomicronaemia Syndrome, which is best defined by genetics. There is currently no testing centre for this in the UK, but the genes some involved are known and tests can be established. 2. There is need for some resources to train patients in administering the self injection 3. In consideration of the side effect profile of new drug, there will be need for extra monitoring (platelets, for example)
12. Do you expect the technology to provide clinically	Yes

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Possibly, but this will be very difficult to demonstrate due the low number of cases.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Extreme hypertriglyceridaemia that has caused pancreatitis but does not fall within the definition of Familial Chylomicronaemia Syndrome definition.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	The current treatment is restricting lifestyle which is likely to be its downfall. The new technology will be relatively easy to adhere to, but does require intense monitoring.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	1. Absence of triglyceride lowering effect 2. Occurrence of adverse effects, such as low platelet count. They both require multiple testing.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the	Additional frequent blood testing is likely to be an absolute requirement.

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The trials have been conducted in countries/sites where there is an aggregation of cases and a substantial experience in managing familial chylomicronaemia syndrome. In the UK, the cases are spread out. The cases in the trials have similar ethnic background and not a vastly different environment (Canada).
• What, in your view, are the most important outcomes, and were they measured in the trials?	Major reduction in plasma triglycerides Reduced hospitalization for pancreatitis
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The major issue is an apparent off-target effect on platelet count, which became apparent in the clinical trials
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	I am not aware of any such data
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Familial chylomicronaemia is a classic recessive disorder caused by rare gene variants. Homozygosity for recessive disorders are more commonly found with consanguinity, which is more common in certain populations due to culture and habits (for example cousin-marriage). There is need for awareness of the fact that familial chylomicronaemia syndrome more likely to be found in people with distinct cultural/religious/ethnic background.

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Uncertainty of the definition and diagnosis of Familial Chylomicronaemia Syndrome
- Reduction of extreme hypertriglyceridaemia vs reduced incidence of hypertriglyceridaemia induced pancreatitis
- Volanesorsen is a completely new therapy for a severe clinical condition that is otherwise intrinsically difficult to manage, potential for life-changing improvement for patients
- The importance of monitoring of platelets

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Charlotte Dawson**
2. Name of organisation	**Queen Elizabeth Hospital Birmingham**

3. Job title or position	**Consultant physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent complications of familial chylomicronaemia syndrome (FCS)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in hospital admissions for acute pancreatitis; reduction in complications of acute and chronic pancreatitis (pain, requirement for analgesia, development of pancreatic insufficiency and diabetes); improved quality of life to include improved pain, increased freedom with dietary choices, fewer days 'lost' to illness In the long term, a clinically significant reduction of incidence of pancreatitis and its complications
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes definitely
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Very low fat diet; fibrates and statins (minimally effective); medication to treat complications of pancreatitis (analgesia, digestive enzymes, insulin)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No – it varies considerably depending on the resources of the lipid clinic in which a patient is seen. In particular the expertise of dietitians - lipid clinic dietitians primarily provide advice for a 'cardioprotective' diet which is not sufficiently fat-restricted for an FCS patient, and may not include consistent advice around the additional supplements required to support a severely fat-restricted diet (fat-soluble vitamin supplements and MCT)
• What impact would the technology have on the current pathway of care?	FCS is a very rare condition and ideally patient care should be concentrated into a few 'specialist centres' (currently very small numbers of patients are widely dispersed in lipid clinics across the country). High cost drug may help with development of specialist centres with access to resources for accessing the drug. This would improve the consistency of care provided (including dietetic support as described above) and help to develop expertise. Requirement for platelet monitoring would be an addition to the current pathway.
11. Will the technology be used (or is it already used) in the same way as current care	No – there is no current effective medical treatment for FCS, the most effective treatment currently is dietetic (very low fat diet)

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	This would be a high cost drug
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics ideally
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Multidisciplinary team support (doctor, nurse, dietician) in every clinic. Training patients in self-injection and support for platelet monitoring.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than	Yes

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	No existing effective medical treatment therefore more difficult than current treatments. Practical implications: training in self-injection, logistics of delivery and storage of drug, disposal of needles, requirement for fortnightly platelet monitoring and reporting results back to patients prior to next dose

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Rules around altering dose and potentially stopping treatment if thrombocytopenia develops
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unsure
17. Do you consider the technology to be innovative in its potential to make a	Yes – reduces morbidity and mortality associated with pancreatitis

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Injection site reactions – requires patient training and ongoing support to minimise the risk Thrombocytopenia – requires platelet monitoring
Sources of evidence	
19. Do the clinical trials on the	Yes

technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in number of episodes of acute pancreatitis – yes this was measured
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Reduction in triglycerides – hypertriglyceridaemia is assumed to be a predictor of risk of acute pancreatitis but this has not been definitively proven in FCS
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic	Anecdotal evidence from patients regarding quality of life and non-pancreatic symptoms of FCS (eg 'brain fog)

review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Good so far
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Women – may be at increased risk if taking hormonal contraception and at particularly high risk during pregnancy Postcode – see 22b
22b. Consider whether these issues are different from issues with current care and why.	This will be a high cost drug directly reimbursed by NHSE (PbR excluded) therefore patients in lipid clinics in smaller hospital trusts without the mechanisms in place to obtain re-imbursement may not be as readily able to access the drug
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Reduced morbidity associated with pancreatitis
- Improved quality of life for patients
-
-
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Dr Karishma Patel**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	LPLD Alliance (And Akcea Therapeutics)
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I was diagnosed in 1987 when very little was known about FCS (then called hypertriglyceridaemia). Fortunately for me, my parents have a medical background, and invested a lot of their own time trying to understand this condition, and consequently how best to handle the severe dietary restrictions that the condition demanded. Information from hospital was scarce and I fear that not all patients are as fortunate as me to have parents that have good basic understanding of FCS and what it takes to control it. My mother gave up her work to look after me - something she did not have to do for her first 2 children. So little was known about FCS that it would have been impossible to try and manage my condition safely without her being able to devote her full attention on how to manage the condition and how to accommodate and meet my dietary requirements, Fortunately this was a financially viable option for my family, but other families may not have been so lucky, and I can only imagine how hard it would be to do

	this without having that dedicated carer in the early stages. As a baby, my parents were given a prescription milks to use, after trial and error with different milks, MCT peptide was the formula they used.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in	When I was 17, I had an unnecessary appendicectomy as my first episode of pancreatitis was mistaken for this. I also came close to having a cholecystectomy as it was suggested that this might reduce my pancreatitis attacks. Throughout my 20s, I had 13 episodes of pancreatitis; the longest of which was 2 weeks. I studied Medicine away from home at Sheffield University and relied on my friends to call ambulances and visit me in hospital. My parents would take time out of their work to visit me in hospital and look after me post pancreatitis. The situation became so bad that my parents pleaded with me to move from Sheffield and transfer to Birmingham University to look after me. I resisted this as I wanted to have a "normal" university experience and retain my independence. I did not want to be succumb to my FCS controlling my life and thus let it limit my life experiences. I was however considering a move to Birmingham after my pancreatitis started to occur every 2 months, despite dietary adherence, whilst I was practising as a Junior Doctor; luckily for me this new technology, Volanesorsen came my way and to say it has been life-changing would be an understatement. Recurrent hospital admissions are frustrating and depressing for patients and worrisome for parents/ friends and have a severe impact on work/study. I was initially considering a hospital medical career but I found the antisocial hours and long days were not conducive to helping me manage my FCS. In retrospect, I think I felt more fatigued than my colleagues did and did not adapt to changing in shift pattern and 12 day stretches of work as well as they did; perhaps due to high triglyceride levels, "brain fog", recurrent abdominal pain and recovery from recurrent episodes of pancreatitis. Even now, I have opted to work part-time as a GP as I think that's necessary to keep me well and be able to give enough time to meal planning, food shopping, preparation of meals and regular exercise. The lack of information and its rarity makes it incredibly difficult to manage. Furthermore the fact that people cannot see the condition makes them take liberties with the food they give despite you explaining

school and social life. What is the effect on any siblings?	in restaurants etc “no oil/ cheese etc”. Even my sister has forgotten to buy me skimmed milk in the past despite me having had this condition from birth/ and she has seen me hospitalised with pancreatitis. This leads to me think that no matter how much you educate about this condition it’s almost impossible for non sufferers to understand it and the world is not built to accommodate a patient with FCS needs. Given that many people opt to follow diets on a non medical basis, this makes eating out particularly hard as chefs/ waiters often perceive you to be ‘fussy’ rather than understanding the importance of the food restriction requests. Unfortunately, my experience is eating anything outside your own kitchen, incurs more fat despite best efforts to explain to people what you can / cannot have. Every time I am invited out by friends, I dread them suggesting a event revolved around drinking/ eating (which is most social events!) as this feels me with anxiety. I am never spontaneous when it comes to eating out – I have to plan in advance if I am going out for dinner and I will eat meticulously low fat meals 2-3 days before – and even skip meals to reduce the burden on my pancreas.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	There are no current treatments that are effective for FCS; I have tried omega 3 capsules, fenofibrate, nicotinic acid, statins, insulin – none of which were effective, but tried out of sheer desperation from myself and my physicians. I have visited consultants in different regions of the UK ; Birmingham, Sheffield and Bristol all of whom gave me the same advice ; keep to a low fat diet. I found them to be empathetic in understanding how difficult this is to do in practice – the nature of any dietary restriction is hard to achieve, especially long term. I think that both the consultants and I found these appointments frustrating as there was nothing more they could offer me and despite my adherence to a low fat diet, I was still getting recurrent pancreatitis.

	I found that dietician input was not helpful and they would often suggest things I was already doing – like using MCT oil for all my cooking. I would go as far to say the consultant / dietician outpatient appointments are almost pointless.
11. Is there an unmet need for patients with this condition?	Certainly – there is no medication currently available to help sufferers with FCS to control their condition. Without this medication, I cannot imagine how I would have continued in the vein I was in, and I certainly wouldn't be the happy, confident, independent, successful person I am today. People sometimes take for granted the freedom they have to socialise, eat whatever they want, go on holiday etc, but for me these only represented additional sources of stress and potential for flares in my condition, not the enjoyable experiences they are supposed to be. Thankfully, that has all changed since Volanesorsen came along. It has given me the opportunity to live my life the way I had always hoped. I am aware that this drug is not a cure but it does enable to live well with FCS.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If	I have not any abdominal pain since starting this treatment in December 2015 and zero days off work. I am able to participate in social events – it still requires the same checks with regards to the food you are being brought, and the pre-preparation in making sure I have been ultra low fat before I go out but I do not get abdominal pain now when I go out for dinner; this I can only attribute to the drug as I am not doing anything different to what I was doing before in terms of my diet. I am also able to travel abroad now which before I was not doing through fear of getting pancreatitis. The holidays are still restricted to 2 weeks as I am not confident to be away from my kitchen for more than this time, but I am certainly more adventurous in where I can travel to.

you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	Now that I am not getting pancreatitis every 2 months or so I feel well in myself, and can consider starting my own family. As a doctor myself, I worried that recurrent pancreatitis would ultimately lead to me developing type 2 diabetes/ pancreatic cysts and organ failure. I also worried that every time I had pancreatitis this one could be my last and ultimately this could kill me.
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	I find the treatment easy to use. At the moment I travel from Birmingham to London to get the treatment every 3-4 months and though this does require me to take a day off work, I find it is completely worth it as it has kept me well. 1 day out of work every 3-4 months is better than having 7 days or more out of work every 2 months due to pancreatitis! There is also a plan in place to move my care from Birmingham to London (where I live now) This has greatly alleviated the care burden for my parents who were worried about travelling abroad themselves should I get hospitalised when they were away. They no longer need to take time off to look after me when I was recuperating after pancreatitis attacks.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is	Both my parents and my boyfriend have commented on the frequent monitoring this drug requires, however ultimately this comes down to individual patient choice and we all agree, that despite the biweekly blood tests, this is much lesser price to pay than having lots of bloods/ scans during long hospital admissions, time off work, anxiety about participating in social events and ultimately is a small price to pay to stay well.

taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Patients that are not suffering from recurrent abdominal pain/ pancreatitis may not feel that injectable drug is necessary as they are already keeping well. I think it is great disservice to not offer this treatment to those patients though as I believe they are living a very restricted life, this drug offers opportunities to have more flexibility with low fat foods and opens up life opportunities; from simple things like being able to attend a social event and not end up in A&E the next day with pain/ pancreatitis, to major decisions like being able to attend University away from home.

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**No**
Other issues	
17. Are there any other issues that you would like the committee to consider?	If the drug cost is a factor on whether or not this should be used I would like the committee to consider that • To receive an ambulance and be taken to hospital costs approx £254 (something I have done at least 5 times) • A single visit to A&E can cost £124 just to be seen (something that I have done 15 times) • Hospital overnight stay is around £400 per day (I have had over 10 hospital admissions; the longest of which was 2 weeks) • ITU bed costs approx £1932 per night (I have been admitted to ITU/ HDU 3 times) • Prescription costs for medications; including opioid analgesia, antiemetics, creon capsules, buscopan, omeprazole. Since starting Volanesorsen I have not required any other prescription other than that of the drug itself and all the listed medications have been stopped • The cost for me personally to not be at work as GP – and extend that to the cost to the NHS where GPs are in shortage • Increasing frequency of Lipid Outpatient appointments but with no new treatments to offer Imagine the above bullet points occur every 2 months and that cost is easily into the £100,000s to the NHS.

	There is also financial ramification to family members / carers to take time off work to look after me / and for their employers

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- Stability and sustained reduction in my triglyceride levels which in turn has improved my physical health and my mental health. In turn my personal relationships have all improved
- Opened up new opportunities to me ; starting my own family, travelling abroad, attending social events
- Working as GP without any days off sick
- Volanesorsen if a life changing and life prolonging drug and the impact on my life has been nothing short of revolutionary
- I dread going back to the life I was leading before Volanesorsen came along.

Thank you for your time.

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Highly Specialised Technology Evaluation - Patient expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	**x**☐ a patient with the condition? ☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	LPLD Alliance
4. Did your nominating organisation submit a submission?	**x**☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	x☐ I have personal experience of the condition x☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I was diagnosed aged two. Since birth I had had episodes where I stopped feeding and assumed contorted stretched positions through abdominal pain. At two my mum gave me chocolate buttons to 'stop my incessant crying' and I came out in yellow spots and was hospitalised for three months at GOSH. My parents were told I had hypertriglyceridaemia and that I needed to eat a low-fat diet. My mum was given many recipe sheets and MCT oil by the dietitian at GOSH. She did her best but hated cooking. There was no nutritional analysis on foods and virtually no understanding of the impact of such a restricted diet on daily living. My mum had no support from her family. My nan used to give me cream cakes when I went to visit 'because it wouldn't hurt'. We were not well off and low-fat meat was expensive. MCT oil used to repeat on me and leave a nasty taste. The impact on me was to develop a very bad relationship with food and eating and a sense that the food that I could eat didn't taste nice and that everything I couldn't eat, did.

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	My life has been completely shaped by having FCS. It has hugely restricted the choices I have been able to make, made me fearful of attacks of pain and pancreatitis and made me really suspicious of food and what it contains. Until my early thirties I had virtually no support in managing my eating and although I did my best, I also took many risks with my health in the attempt to be able to participate in a life that mirrored that of my friends. My attempts to be 'normal' would always lead to periods of pain, fatigue and self-hatred. This left me feeling isolated and poorly understood and impacted heavily on my self-esteem. Particular periods of difficulty were adolescence when I developed bulimia in an attempt to control my eating, and leaving home to go to University where I was completely at sea and found it very difficult to manage eating well. Although I always had a job, I shied away from jobs with any responsibility because I was concerned about having time off with pain, and not being able to think clearly because of the brain fog due to high triglyceride levels. As a result I felt very frustrated in the jobs that I did and often bored. I always wanted to be a nurse, but felt that I was unable to look after my own health so shouldn't try to look after others. I also couldn't see how I would be able to feed myself while I was training. I was very ashamed of how badly I managed my health and it was not until I met my husband that I really found support with managing the diet. A very good cook, he took the challenge of cooking gourmet very low-fat food, and became 'the fat police' which really helped me to begin to feel well. His support and understanding helped me to be assertive about what I could and couldn't eat and we always had people to us if we socialised or did things which didn't revolve around food. When we started a family the dangers of FCS became apparent. My three pregnancies were more and more difficult to manage and I developed gestational diabetes in the third trimester of the second, and from the beginning in the third. This necessitated injecting insulin and eating a diet of negligible fat and I was asked to seriously consider terminating my pregnancy and encouraged to do so by my family and my husband. I felt unable to do this and managed to take the pregnancy to 39 weeks when I had my third induction due to raised triglyceride levels and fear for my health. After this third pregnancy I developed post-natal depression (and had a milder form after the second pregnancy). I think the stress of the pregnancy played some part in this. Four years after my third pregnancy I was diagnosed with diabetes. Initially I was able to manage my triglyceride levels and keep the diabetes under good control but I found that as time went by and I got older and went through the menopause, my triglyceride levels kept rising and I could not manage them through diet and exercise. I found that I was having low-level pain regularly and my fear of pain of pancreatitis, and my subsequently raised stress around food returned to the same levels as before I met my husband, although this time I couldn't see how I could take any action to improve my situation. I felt very hopeless and depressed.

	One of my brothers also has FCS (diagnosed aged 11 when the rest of the family were checked after my diagnosis). His clinical manifestation has been very different and so I found it hard to understand what about my experience was due to the condition and what was 'just me.' There was absolutely no information available from the patient perspective and nobody else to talk to. It was not until I met other patients through creating LPLD Alliance that I found that many of my symptoms are shared and I felt empowered to be honest about the impact the condition has on me, and be vocal about its effect.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Current treatments for FCS are maintaining a diet of less that 20g fat and avoiding sugar and alcohol. Lipid lowering medications are prescribed, but their efficacy is at best very limited. I had been prescribed fibrates and Omacor but I experienced unpleasant side-effects with both and was never convinced that there was any benefit for me. I was always very suspicious of the fish oils as they didn't seem to lower my triglyceride levels and yet they were full of oil. I only became pain free when I began to eat around 10g fat (half the recommended amount). Over the years I have found that the medical professionals with whom I have come into contact have never really understood the daily impact of the condition and what it involves to try and live with such a restricted diet, let alone the fear of pain and pancreatitis and the brain fog and fatigue. I would have benefitted hugely from psychological support at an early age to help me to come to terms with living with a life-long, life-limiting condition. I would also have benefitted from meeting other patients and some attempt to connect patients would have been useful. Hopefully this is improving for new patients as LPLD Alliance becomes more known about. I also think that more discussion about pregnancy and the risks of pregnancy would have helped me, and that support with managing FCS and diabetes and the impact on diet should be offered as a matter of course.
11. Is there an unmet need for patients with this condition?	I think there is a huge unmet need for patients with this condition. I was lucky enough to have been able to manage my experience of pain and pancreatitis by hugely restricting my life (and being lucky enough to find a husband who was willing to share the restrictions and support me by working hard to create very low-fat dishes). However, as I've got older the condition has taken over and I have seen my health deteriorate despite my best efforts. I am aware that just a single attack of pancreatitis can severely damage my pancreas and make managing symptoms even more difficult, despite adherence to diet. It's hard to know what to do if there's little you can do yourself to mitigate the effects of FCS.

Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	I have been on EAMS since February this year and the treatment has made me feel so very, very much better. My triglycerides have reduced by about 60% and with that reduction I have felt much more alert, do not feel fatigued, have not had any pain at all which. I am therefore no longer feeling paranoid about the onset of pancreatitis. I have not changed my eating habits at all, but my fear and stress around eating has largely disappeared and I am generally far more relaxed than I ever have been in my life. Consequently, I am more able to participate in social events, am more able to work, and have the ability to keep in touch with and see my friends. My diabetes is also looking better controlled and I feel in control, rather than out-of-control and anticipating the next 'off day' or period of abdominal pain. Feeling so well has made me be able to manage the restrictions of FCS and diabetes far more effectively as I feel I am better able to plan ahead and be creative in my thinking. An unforeseen effect (for me) is that my cholesterol has also reduced by about 50%.
13. How easy or difficult is it to take the treatment? What is the impact you and the family	I do not have any problem with injecting the treatment which I manage myself at home. On the EAMS I need to travel to the hospital every two weeks for a blood test and once a month I also pick up the volanesorsen. Keeping in touch with the clinic to monitor my platelet levels has worked smoothly. I live very close to my hospital and find the benefits of being on the drug outweigh the inconvenience of this. I understand that should the treatment become available there will be home visits which will minimise the time taken to do this, even if there will be some

in terms or travel and receiving the treatment?	restriction on my life. I think this is a small price to pay for the benefits of feeling so well.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	Disadvantages of the treatment are mostly the platelet monitoring which obviously has to be factored in to my schedule every fortnight. So far, I haven't had a problem with my platelet count and understand that if my platelets should go too low then I will have to miss a dose to allow them to rise again. I can foresee that being away on holiday might impact on a dose and my ability to be monitored but currently there is no issue with this for the foreseeable future. Injections are mildly painful for a few minutes and I have had some injection site reactions - red marks on my stomach at the injection sites which seem to be permanent. These don't hurt and they don't bother me aesthetically.

Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Patients who would benefit more from the treatment are those at risk of pancreatitis because of high triglycerides. Patients who are able to manage their symptoms on diet alone as I was for a number of years, would benefit less but they are not within the licensing criteria, although the question arises for me whether for those patients taking the therapy might offer them some leeway to eat more fat as the restrictions on daily living in order to do this are so onerous. However, when I was able to manage my symptoms, I would not have wanted to take on fortnightly monitoring and I suspect that these patients, even if they were given the choice, would probably opt not to take it.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	There are none that I can see.
Other issues	
17. Are there any other issues that you would like the committee to consider?	It seems miraculous that there is finally a licensed therapy for people with FCS, and I feel very lucky that I have been able to take it. It's been very hard and isolating to live with an ultra-rare condition that few people know about and even fewer actually understand. It's even harder when there is also no treatment available so that the whole burden of managing symptoms falls on the patient. I have been lucky to find someone so supportive and willing to restrict his life in order to be with me. The burden of self-

	management is huge and life-diminishing, and sits on top of the symptom burden experienced by patients and many patients feel judged, or judge themselves harshly when they become ill. Eating a high carbohydrate and sugary diet, and attacks of pancreatitis can lead to the onset of diabetes. Diabetes in itself is a horrible and life-changing condition but for people with FCS, to have both conditions is a near disaster. Together the two conditions add an even greater burden as high blood glucose turns to fat, and dietary choices become even further reduced. Avoiding the onset of diabetes needs to be a priority.

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- FCS has negatively shaped my life, limiting nearly every choice that I have made and action I have taken.
- Abdominal pain and pancreatitis and the fear of the onset of both has been ever-present.
- I have struggled with low self-esteem and depression throughout my life as a result of FCS.
- Despite having learned to manage the condition by eating less than 10g fat per day, as I got older my triglycerides rose and my health deteriorated.
- Taking volanesorsen has completely transformed my life. I no longer feel any pain, have far more energy and no brain fog. This has all contributed to my feeling far more in control of my life and relieved me of a great deal of stress and anxiety making my outlook on life to be much more positive than for many, many years.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Simon Williams**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ x a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	HEART UK- The Cholesterol Charity
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ **x** no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **x** other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ **x** I am drawing on others' experiences. Please specify how this information was gathered: HEART UK have held and attended workshops for patients with FCS, in addition to having a close working relationship with LPLD Alliance.
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?	The condition is poorly recognised, particularly when a patient attends A&E and in severe pain. Many patients report accusations of being a drug abuser or alcoholic and the pain is not managed appropriately or taken seriously. There is very little information about the condition other than that produced by HEART UK and LPLD Alliance. There is very poor dietetic support, with the quality of advice variable across the country with

What was the impact of this you and your family?	little understanding about the limits to fat intact in particular. There is no training available for dietitians on the condition and no support for health care professionals other than a few specialist lipidologists.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in	The impact on the life of someone with FCS and those around them, particularly the family cannot be underestimated. There is a fear of eating food that has not been prepared by the individual and a life-long fear of a life threatening attack of acute pancreatitis. The quality of life for someone with FCS is severely affected due to their limited ability to socialise in any situation that may involve eating, which will include lifetime events such as Christmas and birthdays. The ability to keep to such a strict diet is very challenging for most people and will often mean not eating enough calories to maintain normal energy levels and nutrients for overall wellbeing. There is little guidance other than what is mostly available from HEART UK and LPLD Alliance on eating a healthy, very low fat diet. The frequent and severe abdominal pains will necessitate the need for frequent the self medication of pain relief and there is an ever present threat of hospitalisation. The lifetime of pain becomes part of daily life and an episode would not be tolerated by most people without FCS. Frequent periods of illness has an adverse effect on employability and education. Frequent absent days from work due to sickness will affect someone with FCS ability to develop a career and indeed keep any form of steady employment and will have a detrimental impact on financial income. The impact of FCS on someone's employability often results in a reluctance to speak out about the condition and publicly share their experience.

school and social life. What is the effect on any siblings?	FCS can be isolating and lonely. Mental health is often overlooked as many people with FCS are also affected by depression due to the limitations on their quality of life caused by the condition.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	Treatment is usually one of lifestyle and eating a very low fat diet. However there is a lack of understanding about FCS amongst all but a few dietitians in the NHS and there is a lack of guidance and support available for them. The result can be that inappropriate advice is given and a misunderstanding to what a very low fat diet is, which leads to illness and pain for someone with FCS. There is currently no effective medical intervention. There is little consideration for the impact on mental health and no support readily available by the NHS.
11. Is there an unmet need for patients with this condition?	The unmet needs have already been stated- the lack of knowledge amongst health care professionals, the lack of support for those with FCS, insufficient dietetic support, lack of mental and emotional support and no medication.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and	This treatment offers some hope to people with FCS and lessens the fear of pancreatitis. Although diet and lifestyle will still be limited, medication will offer relief to many.

emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology?	

Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	

Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	People, in particular women from some religions do not access health services and readily seek out treatment.
Other issues	
17. Are there any other issues that you would like the committee to consider?	

Key messages

18. In up to 5 bullet points, please summarise the key messages of your statement:

- FCS is poorly recognised and the hardship of living with the condition is often underestimated
- FCS is a lonely and isolating illness, due to the limitations on socialising and getting tired
- Patients are often stigmatised and discriminated against when presenting to health services and accused of alcohol or substance abuse
- There is little dietetic support and no training for dietitians
- Living in pain and fear of an attack of acute pancreatitis is daily and life-long.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Handrean Soran MBChB MSC MD FRCP**
2. Name of organisation	**Manchester University NHS Trust**

3. Job title or position	
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Control the condition Improve life quality of the patients Prevent complications
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reducing triglyceride below 22 mmol/L or by 25%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes Currently, there is no other effective treatment options. Other lipid lowering therapies are not effective.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Very low fat diet, less than 15-20 grams/day dietary fat. This is not enough.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	None currently available.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Generally yea. No major differences in opinion as the only option currently available is very low fat diet which is not enough to control triglycerides.
• What impact would the technology have on the current pathway of care?	Provides a treatment option. This is the first effective treatment.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Already used as part of early access medicine scheme.

• How does healthcare resource use differ between the technology and current care?	No other effective available options
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Lipid clinics (tertiary clinics who has experience in managing the condition). Preferably the clinics who already use high cost medications for hyperlipidaemia like Lomitapide treatment for Homozygous Familial Hypercholestrolemia.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Not much. Only support the centres.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Volanesorsen reduces triglycerides significantly compared, by 77%.
• Do you expect the technology to increase length of life more than current care?	Yes. But this is an opinion as no clinical trials outcome to support this. It would be difficult to produce such evidence for very rare diseases.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with history of previous pancreatitis or at high risk.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Requires close monitory and more frequent blood tests to monitor response and side effects (in particular decrease in platelet count). This should be done by a clinical team with expertise in this field.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	If side effects for example very low platelets If suboptimal response.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. Control the disease and its complications. Improves quality of life
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes First available effective treatment
• Does the use of the technology address any particular unmet need of the patient population?	Ye. No other available effective treatment options
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Close monitoring and patients should get more supply only if they comply with the monitoring and engage with the clinical team.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in triglyceride level.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Frequency of acute pancreatitis or severe abdominal pain Quality of life
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Low platelet count Injection site reactions

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Improves patients QoL
21. How do data on real-world experience compare with the trial data?	Generally comparable
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- FCS is a very rare and severe disease
- A part from very low fat diet which is not enough to control the disease, no other effective treatment is available
- Volanesorsen reduce triglyceride (main outcome) by more than 70%.
- Some evidence to support improvement in QoL
- Some evidence that treatment reduce the risk of acute pancreatitis.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Volanesorsen for treating familial chylomicronaemia syndrome: A Highly Specialised Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors and clinical advisors

Anthony Wierzbicki was a site investigator for the Volanesorsen CS7 study in familial chylomicroneamia syndrome (Akcea), the evanicumab R1500-TG studies in familial chylomicroneamia syndrome (Regeneron) and the evolocumab VESALIUS trial in cardiovascular disease. He also has publications relating to treatment of familial chylomicronaemia syndrome and high triglycerides. Paul Downie has received consultancy fees from Akcea for attending advisory boards. No other authors or clinical advisors declared competing interests.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Sue Harnan was the project lead. Sue Harnan summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren and Martin Orr critiqued statistical analyses submitted by the company. Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategy. Graham Bayly, Anthony Wierzbicki and Paul Downie provided clinical advice to the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse event
AFT	Accelerated failure time
ANCOVA	Analysis of covariance
AP	Acute pancreatitis
APOA5	Apolipoprotein A-V
APOC2	Apolipoprotein C-II
AUC	Area under curve
CI	Confidence interval
CP	Chronic pancreatitis
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CS6	APPROACH study, ISIS 304801-CS6
CS7	COMPASS study, ISIS 304801-CS16
CSR	Clinical Study Report
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 dimensions
EQ-5D-5L	EuroQol 5 dimensions 5 levels
ERG	Evidence Review Group
FCS	Familial chylomicronemia syndrome
GLMM	Generalised linear mixed model
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
ICER	Incremental cost-effectiveness ratio
LPL	Lipoprotein lipase
LPLD	Type 1 hyperlipidaemia lipoprotein lipase deficiency
MAA	Managed access agreement
MCS	Multifactorial chylomicronaemia syndrome
mg	Milligram
mg/dL	Milligram per decilitre
mL	Millilitre
mm	Millimetre

mmol/L	Millimoles per litre
NA	Not applicable
NB	Nota bene
NHLBI	National Heart, Blood and Lung Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR-HTA	National Institute for Health Research – Health Technology Assessment
NIH	National Institute of Health
OLE	Open-label extension
PAS	Patient Access Scheme
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Medical Outcomes Study 36-Item Short Form Survey Instrument
SmPC	Summary of product characteristics
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TG	Triglyceride
UK	United Kingdom

1 SUMMARY

Familial chylomicronaemia syndrome (FCS) is a rare, genetic disease characterised by high levels of triglycerides (TGs) in the plasma and a build-up of chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body). Patients often experience abdominal pain, fatigue, impaired cognition, numbness or tingling sensations, and acute pancreatitis (AP), which may lead to chronic pancreatitis (CP), diabetes or, infrequently, death through necrosis, sepsis and mulit-organ failure. Volanesorsen (Waylivra®), is an antisense oligonucleotide that inhibits the production of apolipoprotein C-III (apoC-III), a key regulator of plasma TG levels.

1.1 Critique of the decision problem in the company's submission

The company has submitted a decision problem that reflects the licensed indication for the treatment but the ERG notes a few points.

The license stipulates volanesorsen should be used as "an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride TG lowering therapy has been inadequate."

In the company's economic model, "high risk" patients are defined as those with a prior history of pancreatitis. The clinical studies were conducted in a wider population, and only some subgroup analyses relating to the population used in the model were provided. Clinical advisors and the company recognise that "high risk" could be defined in many different ways and that at its most inclusive it could mean any patient with FCS as all have raised TG levels putting them at risk of pancreatitis.

The licensed dose is for weekly dosing (285 mg in 1.5 ml injected subcutaneously) in the first three months, followed by every two weeks thereafter. The license includes a stopping rule at 3 months and optional dose escalation at 6 months. The three clinical studies (APPROACH, COMPASS and APPROACH OLE) planned doses every week and did not have a stopping rule at 3 months. The company have presented subgroup analyses from the clinical studies of patients who conformed to the licensed dose but these are subject to limitations such as small numbers, being *post hoc* in nature, and being subject to selection bias since all patients reduced their dose due to adverse events. The model assumes that volanesorsen is given according to the licensed dosing schedule.

Efficacy estimates are based on TG levels, which is a surrogate for clinical outcomes such as AP, CP, type 2 diabetes and death. The model uses absolute TG levels to define health states.

1.2 Summary of clinical effectiveness evidence submitted by the company

Three clinical studies were included. APPROACH, a randomised controlled trial (RCT) (n=66), a subgroup analysis of patients from COMPASS, an RCT (n=7) and APPROACH OLE, which is described by the company as an open-label extension (OLE) of patients who received volanesorsen in APPROACH (APPROACH-volanesorsen patients), patients who received volanesorsen in COMPASS (COMPASS-volanesorsen patients) and treatment-naïve patients.

The studies all recorded TG levels and demonstrated a statistically significant ($p<0.05$) and clinically meaningful decrease in TG levels in response to volanesorsen. However, not all patients achieved TG levels below 8.4 mmol/L (the protocol-defined responder analysis in APPROACH). Results relating to AP event rates, abdominal pain and health-related quality of life (HRQoL) were uncertain, only significant in subgroup analyses or showed no effect. There were high rates of discontinuations in the clinical studies, mostly due to adverse events (AEs) (especially thrombocytopaenia and injection site reactions) and the burden of monitoring.

[redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The major limitation of the evidence base is that the studies did not use the dose that has been licensed. The studies were based on a weekly dose, whereas the license is for a weekly dose for three months, followed by doses every two weeks. At the licensed dose, the extent to which TG levels reduce is uncertain due to problems with the subgroup analyses including their small sample sizes and *post hoc* nature. The impact of using the licensed dose on safety outcomes and discontinuations is also uncertain

since patients who entered these analyses had generally reduced their dose due to adverse events, thus leaving the analyses at high risk of bias.

In addition, the studies measured a surrogate outcome (TG levels) and used cut-off values for which there is some uncertainty about the clinical significance. The effect on the clinical outcome AP rate is uncertain since no analyses were presented at the licensed dose and other AP analyses were limited due to being underpowered, exploratory, retrospective, single-armed and/or post hoc in nature. Long-term response to and tolerance of treatment with volanesorsen is also uncertain.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's submitted model evaluated the clinical- and cost-effectiveness of volanesorsen used at its licensed dose for treatment of FCS. It was clearly reported and generally well programmed, with minor errors amended in the clarification process. The model had an initial three-month phase in which a patient's responses was assessed and a decision to continue on volanesorsen, or not, was made. Following this, there was a longer-term Markov model that simulated the numbers of AP events, CP events, number of patients with diabetes, and deaths over a patient's lifetime with costs and benefits discounted at 3.5% per annum using an NHS perspective. The model was populated using data from APPROACH, APPROACH OLE, published literature, and from expert clinical judgement. Clinical outcomes were better for patients receiving volanesorsen due to assumed lower TG levels with conferred lower risks of AP, and by implication CP, type 2 diabetes and death, and an additional assumed protective effect of volanesorsen for AP. The company's base case probabilistic incremental cost-effectiveness ratio (ICER) was approximately £220,000 per quality adjusted life year (QALY) gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The evidence review group (ERG) identified a number of apparent limitations within the company's base case analysis. The most important related to: (1) using an acquisition price for volanesorsen that is yet to be formally agreed; (2) an incorrect estimate of the distribution of patients amongst TG-risk bands on model entry; (3) the assumed utility for patients receiving volanesorsen being greater than for patients receiving standard of care (SoC) despite being in the same health state; (4) the assumed discontinuation rates for patients on long-term volanesorsen treatment being over-estimated; (5) underestimation of the acquisition costs of volanesorsen due to the methodology used to half-cycle correct; (6) the impact of volanesorsen treatment on AP independent of changes in TG levels; (7) the assumed level of CP against which the model was calibrated being too high; (8) the disutility associated with type 2 diabetes; (9) the disutility associated with carers; and (10) the costs of treating CP.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The RCT studies were generally well conducted and are commendable in a rare condition.

The submitted mathematical model was well-programmed. The company responded well to the clarification questions raised and provided a revised model and undertook the analyses requested.

1.6.2 Weaknesses and areas of uncertainty

The studies were conducted using a higher dose than has been licensed. Whilst subgroup analyses have been submitted, these are subject to limitations such as small sample sizes, being *post hoc* in nature and risk of selection bias. There is therefore a great deal of uncertainty relating to the likely clinical effectiveness, treatment discontinuation rate and safety of volanesorsen at the licensed dose in clinical practice.

Aside from these clinical limitations, the major evidence gaps relate to the utility values associated with the TG-risk bands for patients and for their carers. Obtaining further data on the costs of treating FCS patients with CP would also reduce the uncertainty within the model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG identified a number of limitations within the analyses which collectively increased the ICER to approximately £490,000 per QALY gained. There was no single factor that caused this marked increase. The four most impactful changes in one-way sensitivity analyses from the deterministic company base case were (approximate increase in the ICER contained in parentheses): using the ERG-preferred utility (£60,000); excluding the utility benefit to carers (£45,000); and assuming that the reduction in AP through volanesorsen independent of TG-level changes was not as large as the company estimated (£25,000). There was substantial uncertainty around the utility values associated with each TG-risk band; if a flat rate utility of 0.7 across all TG health states is assumed, the ICER further increases the ERG base case by approximately £100,000. There was considerable uncertainty related to the relative protective effect of volanesorsen compared with SOC following an AP; if this was removed the base case ICER increases by over £40,000. There also remains considerable uncertainty related to the robustness of the clinical evidence.

2 BACKGROUND

Akcea made a submission to the National Institute for Health and Care Excellence's (NICE) for volanesorsen in 2018. However, a European Medicines Agency (EMA) license was not acquired in 2018 and the submission was paused. An EMA license was acquired in 2019, for a different dosing and monitoring schedule than originally proposed, or used in the pivotal trials. A revised submission was made to NICE in 2019. The Evidence Review Group (ERG) have referred to documentation from both the 2018 and 2019 submissions when preparing this report. Throughout, "company submission" (CS) and "clarification response" refer to the 2019 submission, unless stated otherwise.

2.1 Critique of company's description of underlying health problem

The CS provides a detailed description of familial chylomicronaemia syndrome (FCS), which is relevant to the decision problem under consideration. FCS is described as a rare, genetic disease characterised by high levels of triglycerides (TGs) in the plasma and a build-up of chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body).[1] Patients often experience abdominal pain, fatigue, impaired cognition, numbness or tingling sensation,[2-4] and 65-80% of patients with FCS will experience pancreatitis.[5, 6] Pancreatitis is characterised by inflammation of the pancreas. The CS describes how patients who experience recurrent episodes of acute pancreatitis (AP) may develop chronic pancreatitis (CP), type 2 and 3C diabetes mellitus and pancreatic insufficiency,[7-10] and that pancreatitis may be fatal as a result of necrosis, sepsis and multi-organ failure.[8]

In their background section, the CS states that there is evidence of a dose-response relationship (p38 and p172 of the CS) and a causal dose-response relationship (p186 of the CS) between raised TG levels and AP, citing evidence from a number of sources including a non-systematic review (Valdivielso *et al.*)[11] and four published primary studies, Pedersen *et al.*, Rashid *et al.,* Murphy *et al.* and Toth *et al.,* [12-15] and the company's own analysis of CALIBER data.[16] CALIBER linked electronic health records in England (1997-2016) from the Clinical Practice Research Datalink (CPRD), from Hospital Episodes Statistics (HES) and from the Office for National Statistics (ONS). CALIBER includes 15 million patients in total, approximately 1.8 million of whom had at least 1 TG measurement. The relationship between TG levels and risk of AP is important, since TG levels are the primary efficacy endpoint in the pivotal trials (i.e. a surrogate endpoint), and are used to define health states in the model. The ERG considered the evidence relating to the relationship between TG levels and AP risk, and identified two further, recent studies.[17, 18] Across the five studies[12-16] identified by the company, five additional studies[19-23] cited in Valdivielso *et al.* (an expert review),[11] and the two further studies[17, 18] identified by the ERG, all except for one[13] were retrospective in nature and may be subject to biases related to this

study design (e.g. information bias). All were from western nations including the UK[16], Scotland,[12] Canada[23] and the USA,[15, 17] except for one from Israel,[18] and drew their samples from a widely inclusive population such as insurance claims records or regional and national databases. All adjusted for important covariates in their analyses. Nearly all included >1000 patients (and up to 271,571),[16] and recruited patients with any TG measurement, some restricted to only patient with TGs above a certain threshold (e.g. >1000 mg/dL)[18] and/or before a certain age (e.g. before 40 years).[16] The main limitation across the evidence base is that none report data for FCS patients exclusively, or as a subgroup. The ERG was unable to identify any studies that reported data exclusively for FCS patients, and clinical advice to the ERG indicated that there are no such studies. Clinical advice was a little divided on the generalisability of this data to FCS patients, with one advisor suggesting that FCS patients may experience AP at lower TG levels than patients with raised TG levels by other causes, and another suggesting the relationship should be generalisable.

The CS uses a cut-off of 22.6mmol/L to define the stopping rule in the license, and to define certain health states in the model. They have also used ≥10 mmol/L to <22.6 mmol/L in the model to define a moderate risk health state. The company base the 22.6mmol/L cut-off on the analysis by Toth *et al.*[15] and their analysis of CALIBER data[16] (see Figures 1 and 2 of the CS). Toth *et al*. states that there is a "*pronounced risk increase for TG levels >2000 mg/dL [22.7 mmol/L] (OR 12.8; 95% CI 8.8,18.6; p <0.0001…)*". The company's analysis of CALIBER data reports that [redacted]. The ERG notes that similar results are reported by Zafir 2018[18] , with HRs of 3.22 (95% CI 2.21,4.70) and 5.55 (95% CI 3.53, 8.71), $p<0.0001$ for TG levels 2000-2999 mg/dL and ≥3000 mg/dL respectively, compared to 1000-1999 mg/dL, and Amblee 2018[17] with an HR 4.8 (3.1-7.4), $p<0.001$ for ≥2000mg/dL compared to 1000-1999 mg/dL. The ERG notes that it is not clear how the cut-off value of 2000 mg/dL (22.7mmol/L) quoted in Toth *et al*. was derived, but it would seem most likely this was an arbitrary cut-off based on incremental categories of 250mg/dL. It should also be noted that the category in Toth *et al.* included all values above 2000 mg/dL, and this may account for the "pronounced" increase since theoretically patients with extremely high values would have been included in this category. The ERG further notes that the relationship between TG and AP risk appears to extend to low TG levels; studies which defined categories in the range 0-500mg/dL (0 to ~5.7mmol/L), and/or one category at or around >500mg/dL (e.g. Murphy *et al.*, Pedersen *et al.*, Christian *et al.*)[12, 13, 19] also reported statistically significant HRs in these lower TG categories (e.g. HR 1.50 (95% CI, 1.14-1.97) and 3.20 (95% CI, 1.99-5.16) for TG 150-499 mg/dL and ≥500mg/dL respectively, compared to <149 mg/dL)[12]. Clinical advice also indicated that the relationship was linear from <2mmol/L all the way up to values in the 200's, and that whilst

values such as 10mmol/L and 20mmol/L are used within the literature, these are a little arbitrary. Furthermore, the clinical advisors to the ERG suggest that whilst there is a general linear relationship between TG levels and risk of AP, there is substantial variability between patients, such that some patients with low TG might have recurrent AP whilst some patients with high TG might never have AP. One clinical advisor noted that chylomicron TG levels are considered a better clinical indicator of risk of AP, as these are directly responsible for causing AP. Clinical advice indicated that, although imperfect at an individual level, the relationship between TG levels and AP was an acceptable surrogate at a population level.

The ERG concludes that there is some uncertainty around the exact cut-point at which AP risk increases in FCS patients. However, given that similar results and conclusions were drawn across several independent studies, and that values of 10 and 20 mmol/L, or 1000 and 2000mg/dL are used across the literature (e.g. Endocrine Society's guidelines[24]), and since there is a lack of a better estimate, the ERG agrees that the use of the cut-off points 10 and 22.6 mmol/L are appropriate for the decision problem.

The CS cited evidence[25, 26] that patients with TG levels >11.4 mmol/L had more severe AP with worse outcomes than those with normal TG levels (<1.7 mmol/L), including greater need for intensive care, and higher rates of pancreatic necrosis, persistent organ failure and mortality. The ERG notes that only one study cited to support this statement used these precise cut-offs,[25] whilst the other used 2648 mg/dL, approximately 30 mmol/L.[26] Both studies were based on relatively small numbers of patients (N=201[25] and N=144[26]) and the proportion in each study with FCS was unclear. The ERG note that at least one study did not find a relationship between TG level and AP severity, though this study was also based on small numbers (N=129).[21] ERG concludes that the cut-offs at which more severe consequences of AP arise in FCS patients is uncertain, as are the magnitude of the difference at the cut-offs stated.

The CS also notes that women with FCS may have additional risks since oestrogen can increase TG levels, and since AP can lead to pre-term delivery, loss of foetus or maternal death.

The CS describe other symptoms of FCS, which include fatigue, lack of energy, impaired cognition, numbness or tingling, and poor mental health. The impact on patients' quality of life is extensively described in Section 7 of the CS, and includes a description of the frequency and severity of physical symptoms, emotional symptoms and cognitive symptoms obtained from a sample of 166 FCS patients worldwide (IN-FOCUS study).[4] The ERG agrees that the condition affects patients' quality of life and that the descriptions seemed largely fair. The CS describes non-health impacts of FCS including unemployment, lower workplace productivity and absenteeism, as well as limits on patients' social lives

due to fatigue and dietary considerations, and the impact on families and carers. The clinical advisors to the ERG agree that FCS has an impact on all elements of patients' lives.

The CS provides a description of the diagnosis of FCS patients, which in the past relied on symptoms such as abdominal pain or AP, and raised TG levels refractory to lipid-lowering therapy and not due to other causes (such as type 2 diabetes mellitus or hypothyroidism). Genetic diagnosis, a condition of the license, is becoming more usual and identifies homozygous, compound or double heterozygous mutations in LPL, APOC2, APOA5, LMF1 or GPIHPB1 genes, which code for proteins involved in lipoprotein lipase activity. Clinical advisors to the ERG noted that not all patients will have a known genetic mutation and some patients have single nucleotide polymorphism where only one nucleotide is replaced by another. All genetic mutations cause a severe though variable phenotype, but apoC2 and LMF-1 mutations tend to be associated with milder disease. Clinical advisors noted that patients presenting with severe FCS tend to present with recurrent AP from childhood or teenage years.[27,28] Whilst genetic confirmation is a condition of the license, clinical advisors to the ERG expressed interest in being able to provide treatment to patients without genetic confirmation as alternative causes including mutations in unidentified genes may exist for FCS.

The CS states that FCS affects approximately 2 people per million, and estimates there to be 120 cases in England, of which approximately 60 patients have genetic confirmation. The CS further states that approximately 65-80% have a documented history of AP (the license is for patients at high risk of AP, and this is one possible definition of high risk, see Section 3.1), and concludes that 80-100 patients would be eligible for treatment with volanesorsen in England. The CS also notes that genetic testing for FCS will be available in England through the NHS England genetic testing service (CS p53). Clinical advisors to the ERG did not agree that the term "*at high risk of pancreatitis*" in the license necessarily implies a prior history of AP, and in clinical practice could be interpreted as any patient with elevated TG levels, which all FCS patients necessarily have. The estimate of 80-100 eligible patients would therefore be an underestimate in this respect. Clinical opinion was divided as to whether the introduction of genetic testing and the emergence of a treatment (volanesorsen) would increase the number of FCS diagnoses over the 120 cited by the company. One clinician thought that more cases would emerge, another thought that patients currently diagnosed with multifactorial chylomicronaemia syndrome (MCS), a similar condition, would be found to have a genetic component, and the third thought that most FCS patients have probably already been identified clinically. However, clinicians also noted that volanesorsen is unlikely to suit all patients with FCS due to the requirements for monitoring and adherence to diet. As such, the estimated number of patients who will be eligible in England is somewhat uncertain.

2.2 Critique of company's overview of current service provision

The ERG agrees that the description of current service provision is largely appropriate and relevant to the decision problem under consideration. The CS describes how there are limited treatment options for FCS patients. The main standard of care is strict fat intake restrictions, limited to 10-15 grams per day (equivalent to one tablespoon of olive oil), as well as avoidance of alcohol.[11] The company is clear that volanesorsen will be used alongside dietary control rather than as a replacement for it. The CS also describes that lipid-lowering drugs (including fibrates and statins) may be given to patients, and state that these are generally ineffective. The clinical advisors to the ERG added that fat-soluble vitamin supplements such as fish oils are often prescribed since the reduced fat diet can lead to deficiencies, and additionally the use of medium chain triglyceride fat substitution can allow patients to eat a more varied diet as these fats are less problematic for patients with FCS.

The CS notes that there are a limited number of centres and clinicians with the expertise to treat FCS patients, and there are no specific national clinical guidelines though international consensus statements are widely accepted.[29-31] This seems an accurate reflection of practice in England.

The CS also notes that volanesorsen is being provided free of charge in the UK since March 2018 under the EAMS programme (Early Access to Medicines Scheme). The company describes 20 patients who are currently on treatment (range from 1 month to 15 months in the EAMS programme), and a further five who have been identified to start (or in the case of one patient, continue after APPROACH OLE study completion) treatment. These patients were generally selected by clinicians for treatment on the basis of having genetically proven FCS, a poor current symptomatology or clinical history (recurrent abdominal pain and acute pancreatitis (clarification response[32] A12)); however, some have been on treatment in APPROACH and APPROACH OLE previously. Patients treated through this scheme had a similar dosing schedule as the license (see Section 3.5), except that patients only received a dose every two weeks for the first three months, not every month (clarification response A12).[32] Patients were not subject to the treatment-response stopping rule at 3 months (see Section 3.5).

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

The company's statement of the decision problem is provided in Table 1. The license[33] granted to volanesorsen by the EMA differed from the NICE scope[34] (which was published several months before the license) in several key respects. The company's definition of the decision problem appropriately reflects the licensed indication.

Table 1 Comparison of the final scope issued by NICE and the company's submission (replication of Table A1 from the CS)

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	Adults with familial chylomicronaemia syndrome	The population is patients with genetically confirmed FCS and at high risk for pancreatitis in whom response to diet and triglyceride-lowering therapy has been inadequate.	In line with the final indication.
Intervention	Volanesorsen in combination with established clinical management (including dietary fat restrictions)	None	
Comparator(s)	Established clinical management without volanesorsen (including dietary fat restrictions)	None	
Outcomes	The outcome measures to be considered include: • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability)	Data gaps and limitations, and concerns regarding double counting mean that some outcomes are not explicitly considered in the model: e.g. pancreatic necrosis and fatty liver disease.	

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	• incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions) • mortality (including all-cause and pancreatitis related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers).	Cardiovascular disease is not in the economic model as there is no clinical consensus regarding the impact of FCS on CVD outcomes. Chylomicrons are not considered to be involved in the atherosclerotic process due to their large particle size. Data relating FCS and CVD are limited.	

CVD, cardiovascular disease

3.1 Population

The initial scope issued by NICE was for "Adults with familial chylomicronaemia syndrome".[34] However, the EMA licensed indication is for "an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate."[33] The CS uses this population in its decision problem.

The license does not define "high risk". As noted in Section 2.1, clinical advisors to the ERG believed that the term was somewhat redundant as any patient with a high TG level is clinically considered to be at high risk of pancreatitis, and the company also recognise that the phrase is open to interpretation (clarification response A6).[32] Within their health economic model, the CS defines a "high risk" population as patients with prior AP, and further subdivided these patients into historic patients (an AP event more than 5 years ago) or recurrent patients (an AP event within the last 5 years). The model also has the facility to restrict the population further to those with two or more APs in the past five years. Within the clinical evidence, the CS presents a small number of analyses for patients who had a prior AP and patients who had two or more APs in the past five years (see Section 4.2.4.3 and Section 4.2.4.6). However, clinicians in England may have widely differing interpretations of the license, as indicated in Section 3.5 below; hence, patients in clinical practice may not be restricted to those meeting the definitions provided in the model, or the clinical analyses.

The studies included in the company's clinical review did not recruit solely genetically-confirmed patients; this is discussed further in Section 4.2.3.3.

3.2 Comparators

The comparator listed in the NICE scope was "Established clinical management without volanesorsen (including dietary fat restrictions)". This includes strict dietary control of fats and alcohol, use of lipid-lowering therapies such as fibrates and statins, substitution of dietary fats with medium-chain triglycerides and dietary supplements to ensure intake of fat-soluble vitamins. For patients with pancreatic insufficiency and diabetes, treatment may also include enzyme replacement therapy and insulin, respectively. This reflects established clinical practice in England, although the use of fibrates and statins is not routinely recommended in these patients. The pivotal trials included dietary advice as detailed in Section 3.2.3.

3.3 Outcomes

The outcomes listed in the NICE scope were:

- Chylomicron and triglyceride levels
- Abdominal pain
- Fatigue
- Neurological and psychological impact of disease (including depression and cognitive ability)
- Incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease)
- Hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions)
- Mortality (including all-cause and pancreatitis related mortality)
- Adverse effects of treatment
- Health-related quality of life (HRQoL) (for patients and carers).

The CS includes clinical and economic evidence relating to most of these outcomes. The clinical studies did not record neurological and psychological impacts such as depression and cognitive ability, though [redacted] used to value the health states in the model. Hospitalisation was not included as an outcome in the clinical section; however, the proportion of patients requiring hospitalisation was estimated for use within the health economic model. The model captures key clinical outcomes including TG levels, AP events, CP, diabetes and death, but did not include other complications such as pancreatic necrosis, fatty liver disease and cardiovascular disease. [redacted] and is therefore included in the model health states along with HRQoL.

The primary outcome of all three studies related to TG levels, and this is also used in the model to define different health states and risk of AP events. As discussed in Section2.1, TG levels are a surrogate for the hard clinical outcomes of AP and CP, diabetes and death. In the model, the company assumes the following thresholds to define AP risk: low risk (<10 mmol/L), medium risk (≥10 mmol/L to <22.6 mmol/L) and high risk ≥ 22.6 mmol/L) (p164 of the CS). The stopping rule uses 22.6 mmol/L and 25% reduction in TG. In the trials, responders were defined as those who achieved TG <750mg/dL (~8.5 mmol/L) in APPROACH and APPROACH OLE, but <150 mg/dL (~1.7mmol/L) in COMPASS. The company supported the use of the cut-offs in the model with evidence from various sources, which is described in Section 2.1, along with the opinions of the clinical advisors to the ERG. The ERG concludes that there is some uncertainty around the clinical relevance of the cut-offs used, but that these are the best available estimates.

The company has submitted some additional analyses relating to hard clinical outcomes, including the rate of APs in APPROACH and APPROACH OLE patients for the five years before treatment, and whilst on treatment. Fatigue, diabetes and mortality were only measured as adverse events in the trials. No deaths were reported in the studies.

The health economic outcome employed is the incremental cost per quality-adjusted life year (QALY) gained, as set out within the NICE Reference Case. The model is critiqued in Chapter 5.

3.4 Other relevant factors

The CS includes a section on equity (Section 5.1 and 5.2 of the CS, p35). It highlights that prevalence is higher in South Asian communities. It also highlights that there is an increased risk of FCS during pregnancy, and FCS may affect patient decisions around having a family. They also note that there are no data in pregnant women, but the treatment is not expected to cross the blood-placenta barrier.

The list price is £11,394 per syringe. A patient access scheme (PAS) has been approved with a discounted price of £[redacted] per single-use syringe. [redacted]

3.5 Intervention

The NICE scope defines the intervention as "Volanesorsen in combination with established clinical management (including dietary fat restrictions)." Volanesorsen is marketed as Waylivra® by Akcea.

3.2.1 Posology

According to the license, volanesorsen should be given weekly (285 mg in 1.5 ml injected subcutaneously) for the first three months. At three months, patients with an adequate TG response should down-titrate to doses every two weeks, and patients with an inadequate TG response (serum triglycerides fall by <25%, or patient fails to achieve serum triglycerides below 22.6 mmol/L) should stop treatment. At six months, patients who continue on treatment, but who still have an inadequate TG response (not defined) can up-titrate to weekly dosing if their platelets are in the normal range. If their TG levels remain elevated at 9 months, treatment should be down-titrated to every two weeks. The dosing schedule is summarised in Table 2.

Aside from the three-month stopping rule, the CS states p153, that "*If patients fail to maintain TG levels consistently below 22.6 mmol/L, they should cease treatment with volanesorsen*", and that "*In discussion with clinical experts it seems likely that in the UK patients who experience multiple AP events or develop chronic pancreatitis would be removed from treatment on the basis that the treatment is not efficacious for that patient.*". However, because the company's model assumed that patients remained in the same TG band low risk (<10 mmol/L), medium risk (≥10 mmol/L to <22.6 mmol/L) and high risk ≥ 22.6 mmol/L) after three months, stopping due to TG levels has not been included. Patients discontinue treatment due to CP, but not due to multiple APs. Interestingly, in the 2019 clarification response to question A6,[32] the company indicates that clinicians felt that CP would be a definition of "high risk of pancreatitis" and an indication for initiating treatment. This illustrates that there appears to be a great deal of uncertainty about how clinicians will select patients for treatment and treatment discontinuation.

The ERG notes that the clinical studies relating to volanesorsen (APPROACH, APPROACH OLE and COMPASS) did not use the same dosing schedules as the license, and this is described in Section 4.2.3.4. In the company's model, the trial data was analysed using a generalised linear mixed model (GLMM) approach to predict the effect on TG levels beyond 3 months; this is described in Section 5.2.5.1.

Clinical advisors to the ERG were generally happy with the new dosing schedule, as licensed, and believed that this was likely to achieve the aim of reducing thrombocytopaenia events and discontinuations whilst maintaining some efficacy. One advisor stated that they would like to be able

to dose some patients even less frequently (monthly), and another stated that they would like to keep patients on treatment if they had achieved a large absolute drop in TGs (from a very high baseline TG level), even if their baseline level did not fall below 22.7 mmol/L at 3 months.

When asked about the likelihood of dose escalations at 6 months when the "TG response is inadequate", and what would constitute an inadequate response, one advisor stated that patients who repeatedly had TG levels >10mmol/L, or ever had >20mmol/L on treatment should be escalated, whilst another believed that an average over months prior to and after treatment initiation should inform the decision. One noted that none of the patients he had seen (approximately 20) had experienced an inadequate response, and as such escalations were unlikely.

3.2.2 Monitoring and dose adjustments

Treatment with volanesorsen has been associated with low platelet counts and thrombocytopaenia. Thrombocytopaenia can lead to serious bleeding events. Patients with low platelet counts at baseline and at a repeat measurement one week later (below 140 x 10^9/L) should not start volanesorsen treatment. All patients on treatment should be monitored at least every two weeks depending on platelet counts, and treatment dose should be adjusted in response to decreases in platelet counts, as shown in Table 3. The CS describes that platelet monitoring will be via a service provided by Akcea at patients' homes. No starting dose adjustment is required for elderly patients. Patients with renal or hepatic impairment should be closely observed, as safety and efficacy has not been established in these patients. The CS notes that "*volanesorsen is not metabolised via the cytochrome P450 enzyme system in the liver, therefore dose adjustment is unlikely to be required in patients with hepatic impairment*." (p30 of the CS).

3.2.3 Dietary restrictions

The license also stipulates that patients must adhere to dietary recommendations, and the CS emphasises that patients should be supported to do so (p153 of the CS). The CS further describes that the company has worked with the Patient Advocacy Group LPLD Alliance/Action FCS to develop dietary materials for patients and is continuing to work on improving ways to provide dietary support. [redacted]

3.2.4 Genetic confirmation of disease

A condition of the license is genetic confirmation of disease. Within the model, the company has not included this as an intervention cost, as this will be conducted on the NHS under the new NHS England genetic testing service (see Section 2.1).

Table 2 Posology of volanesorsen as described in the company submission[38] and SmPC[33]

Time	EMA license
0 to 3 months	285 mg in 1.5 ml injected subcutaneously once weekly
3 months	Down-titrate to 285 mg every 2 weeks Or Stop treatment if reduction in serum triglycerides is <25%, or patient fails to achieve serum triglycerides below 22.6 mmol/L
6 months	Option to up-titrate to weekly dosing if serum TG response is inadequate, and platelets normal
9 months	If TG response on weekly dosing still inadequate, down-titrate to every two weeks.

Table 3 Volanesorsen monitoring and treatment recommendations.

Platelet count (x10^9/L)	Dose (285 mg prefilled syringe)	Monitoring frequency
Normal (>140)	Starting dose: weekly After 3 months: every 2 weeks	Every 2 weeks
100 to 139	Every 2 weeks	Weekly
75 to 99	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Weekly
50 to 74[a]	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Every 2-3 days
Less than 50[a,b]	Discontinue treatment Glucocorticoids recommended	Daily

[a]Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels <75 x 10^9/L. Treatment with these medicinal products must be discontinued at platelet levels <50 x 10^9/L. [b]Consultation with a haematologist is required to consider the benefit/risk of possible further treatment with volanesorsen.

Source: Data taken from Table B2 of the CS and APPROACH CSR

4. CLINICAL EFFECTIVENESS

This chapter presents a review of evidence relating to the clinical effectiveness of volanesorsen for the treatment of FCS patients alongside standard of care. Section 4.1 presents a critique of the company's systematic review methods and Section 4.2 provides a summary and critique of the trials of volanesorsen. Section 4.3 describes the reasons why the company did not undertake an indirect treatment comparison and summarises the ERG's view about this. Section 4.4 provides the conclusions of the clinical section.

4.1 Critique of the methods of review

The CS includes a systematic review of evidence relating to volanesorsen. Details were limited, but on the whole, the review appears to have been undertaken to a good standard, though the following points are noted by the ERG (Sections 4.1.1 to 4.1.5).

4.1.1 *Searches*

Appendix 1 of the CS reports a systematic literature review of published and unpublished evidence on the treatment of FCS.

Literature searches were conducted on 19th March 2018 then subsequently updated on 7th June 2019 and covered the following sources from inception: MEDLINE (via Ovid) including Medline-in-Process; Embase; and the Cochrane CENTRAL register of randomised trials. The CS gives a slightly different list of sources, but the above account reflects what was confirmed by the company response to the ERG's clarification letter (A1).

The searches are generally well-designed, including subject headings and free text terms for all the interventions for FCS. Although the inclusion criteria (CS, p325) state no restriction by study design, and on p60 of the CS it is stated that case reports and case series were searched for, the ERG notes that a search filter has been applied to some of the searches limiting results to RCTs or observational studies, whilst excluding case reports. This did not affect the utility of the review to the submission, as the submission identified RCTs and an observational study and did not need to resort to case reports. The CS states that the search terms are based on unvalidated but widely-used filters developed by the Scottish Intercollegiate Guidelines Network (SIGN), with some modifications (clarification response A4).

No date limits have been applied, although an English language limit was applied to some of the searches (in accordance with the specified inclusion criteria). Additional searches were conducted of

several trials' registers and websites for the purpose of identifying unpublished ("grey") literature and ongoing studies. Reference lists of included studies and relevant systematic reviews were checked for any papers missed by the searches.

Taking into account the use of these complementary methods in addition to the searches, the ERG is broadly satisfied that the SLR is unlikely to have missed any relevant studies.

4.1.2 *Inclusion criteria*

The inclusion criteria and process of selecting studies seemed largely appropriate, though no details were given relating to whether study selection was double checked by a second reviewer. The ERG asked for clarification on some points, as follows:

The outcomes of fatigue, neurological and psychological impact and HRQoL did not appear in the PICO for the company's review (Table C1 of the CS), but they are part of the NICE scope. The company clarified in their 2018 clarification response[39] that studies reporting on these outcomes would not have been excluded.

English language studies only were eligible for inclusion. During the 2018 submission clarification process, the company clarified that no non-English language studies were excluded.[39]

4.1.3 *Data extraction*

The CS describes that data were extracted by one reviewer and checked by a second reviewer (p326 of the CS). This is a good quality methodology. However, it was not clear what data were extracted, nor how the data extraction form was created. These details are not crucial, as the data presented in the report tables appear to be complete.

4.1.4 *Quality assessment*

The CS did not describe whether quality assessment was checked by a second reviewer. Assessments were made for all three included trials using the Centre for Reviews and Dissemination (CRD) handbook criteria. The ERG considers that the use of the CRD criteria was appropriate for the RCTs (APPROACH and COMPASS), but was not an appropriate tool for APPROACH OLE. The study was not randomised, and did not have a comparator arm of patients not treated with volanesorsen. It did comprise two groups – treatment-experienced and treatment-naïve, but comparisons of these groups did not appear to be the hypothesis being tested.[35] Categorisation of this study is difficult. The term "open label extension" may be misleading for the treatment-naïve patients, since they were not all enrolled in a trial prior to enrolment in APPROACH OLE. The term "before-after study" may also be inappropriate

since the baseline measurement for some patients was not taken from OLE but from APPROACH or COMPASS. The term "case-series" may be considered synonymous with "before-after study" in the context of the analyses performed, since patients had the same outcomes measured before and after treatment, even though this was in two different trials for APPROACH-volanesorsen and COMPASS-volanesorsen patients. As such, the ERG concludes that the analyses reported in APPROACH OLE are equivalent to a before-after study, or a case-series, and should have been assessed as such. The quality of all three studies is discussed in more detail in Section 4.2.3.2.

4.1.5 Evidence synthesis

No evidence synthesis was provided. The ERG agrees that data from APPROACH and COMPASS should not be synthesised because COMPASS recruited a wider population but did not stratify patients by FCS status; use of the FCS subgroup from COMPASS would break the randomisation.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Which studies were included in the clinical effectiveness review and which were excluded?

The CS describes three key efficacy trials (Table 4). These comprise: APPROACH, a pivotal RCT; COMPASS, an RCT that recruited a wider population than just FCS patients (7 patients in this trial had FCS); and APPROACH OLE, an open-label extension of FCS patients from APPROACH and COMPASS, which also recruited additional treatment-naïve FCS patients.

There was also an additional study identified by the review, Gaudet *et al*.[1] This study was a Phase II, open-label, single-arm study of volanesorsen in 3 patients all of whom had FCS. This was excluded in the CS as it was "*not considered to address the decision problem*" (p62 of the CS). The ERG has looked at this study and believes that it is of some relevance to the decision problem. However, a brief assessment of the results reported for TG levels and safety outcomes suggests that the study outcomes largely agree with the data reported in the included studies, and its exclusion is not particularly problematic, especially given the small sample size (n=3) and single-arm design. Ideally, this study would have been included in the company's review.

In addition, a retrospective web-based survey of APPROACH OLE patients (ReFOCUS)[40] was reported to capture the burden of disease associated with FCS. Patients were surveyed after at least 3 months of treatment in APPROACH OLE, and asked about their experiences for the three months before treatment with volanesorsen, and during the most recent three months whilst on volanesorsen.

Table 4 Clinical evidence and burden of disease evidence relating to volanesorsen, included in the CS

Study name (acronym)	Study design	Population	Intervention	Comparator	Study type
Efficacy and safety studies					
APPROACH[41, 42] NCT02211209	**PIVOTAL** RCT (n=66)	FCS patients with fasting triglycerides >=8.4 mmol/L (>=750 mg/dL)	52 weeks of weekly SC volanesorsen (285 mg)	Placebo	Efficacy & safety
APPROACH OLE (Approach Open Label Study)[35] NCT02658175	Open-label, Phase 3 (ongoing, aims to recruit 70 patients)	Patients with FCS	52 weeks of weekly SC volanesorsen (285 mg)	None (single-arm)	Efficacy & safety
COMPASS [43, 44] NCT02300233	RCT (n=113 total, n=7 with FCS)	Patients with hypertriglyceridemia including FCS with fasting triglycerides +/- 500 mg/dL	26 weeks of weekly SC volanesorsen (285 mg)	Placebo	Efficacy & safety
Gaudet et al. 2014[1]	Single-arm, open-label, n=3	FCS patients, homozygous or compound heterozygous null LPL mutations	13 weeks of 300mg volanesorsen	None (single-arm)	Pharmacodynamics and safety
Effect on burden of disease					
ReFOCUS[45]	Retrospective web-based survey (n=22)	Patients who received at least 3 months of treatment with volanesorsen in APPROACH OLE	See APPROACH OLE	NA	Burden of disease before and after treatment

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The CS provides a list of nine excluded studies (Table C5 of the CS), and the ERG agrees that the exclusions were appropriate.

4.2.3 Description and critique of the design of the studies

4.2.3.1 Design of the key studies

4.2.3.1.1 APPROACH was a Phase 3, multicentre (including 4 UK centres), randomised, double-blind, placebo controlled, 52-week study which recruited patients with FCS. The primary objective of the study was to evaluate the efficacy of volanesorsen (285 mg once weekly) as compared to placebo with standard of care (SoC) on the percent change in fasting TG from baseline to Month 3 in patients with FCS. Patients had to undergo a screening period of diet stabilisation to qualify for entry into the study.

Patients in the active treatment arm received volanesorsen 285 mg, given as a single 1.5 mL subcutaneous injection once a week; patients in the placebo arm received placebo, given as a single 1.5 mL subcutaneous injection once a week. All patients received dietary interventions as detailed in Section 3.2.3. There were stopping rules and dose adjustment/dose pause rules for liver chemistry elevation; renal function test results, and platelet count results (see Section 4.2.3.4). Dose adjustments were allowed for other safety and tolerability concerns. Outcomes are listed in Section 4.2.3.6.

4.2.3.1.2 COMPASS was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 26-week study in patients with hypertriglyceridemia, including FCS patients. The CS (p74) provides very brief details of the study methodology. The study did not seek to exclusively recruit FCS patients, and only 7 were recruited in practice. "*Following screening, patients were randomised 2:1 to SC volanesorsen 285 mg once-weekly or placebo. However, a protocol amendment saw the dose of volanesorsen adjusted to 285 mg every 2 weeks at or after 13 weeks of treatment (patients who had already received at least 5 months of dosing when this amendment came into effect were exempt). As for APPROACH, the primary efficacy outcome was the percent change from baseline in fasting TG levels at Month 3, defined as the average of the Week 12 and Week 13 assessments*." (p74 of the CS). The ERG noted that the dose adjustment would not have affected the primary efficacy outcome, since the dose adjustment was indicated at or after 13 weeks, and the primary results were collected at weeks 12 and 13. Outcomes measures included in this study are listed in Section 4.2.3.6.

4.2.3.1.3 APPROACH OLE is an ongoing, multicentre (including three UK centres) open-label descriptive study. A detailed table of study methodology is provided in Table C7 of the CS. The ERG note difficulties with categorising the study design (see Section 4.1.4). Briefly, the study aims to recruit 70 patients of three types: Group 1: FCS patients rolling over from APPROACH (referred to as

APPROACH-volanesorsen patients); Group 2: FCS patients rolling over from COMPASS (referred to as COMPASS-volanesorsen patients, see below for a description of the COMPASS trial); Group 3: Patients who did not take part in either APPROACH or COMPASS (referred to as treatment-naïve patients).

[redacted]

[redacted]Treatment periods were similar to APPROACH: for patients in groups 1 and 2, patients underwent a qualification period of two weeks, whilst group 3 patients underwent an eight-week screening period, with six weeks of diet stabilisation. Treatment was then given for 52 weeks, after which patients could receive treatment through an expanded access programme, or until such a programme becomes available (for a maximum of 52 additional weeks), or alternatively enter a 13-week follow-up period.

Dosing and stopping rules were very similar to APPROACH (see Section 4.2.3.4). Outcomes are listed in Section 4.2.3.6.

4.2.3.1.4 ReFOCUS[45] was a retrospective web-based survey of patients who had received volanesorsen for at least 3 months in APPROACH OLE. Twenty-two patients were recruited and asked to recall and rate their symptoms for the 3 months before treatment and the most recent 3 months whilst on treatment. The company present this study as evidence on the effect on burden of disease.

4.2.3.2 Critical appraisal using established checklists

Appendix 1 presents the company's critical appraisal of the trials, alongside the ERG's own judgement of the quality of the trials for APPROACH (Table 21) and COMPASS (Table 22) and APPROACH OLE. In summary, the two RCTs were judged by the ERG to be at generally low risk of bias overall, but the open label extension (case-series or before-after study) was judged to be of poor quality to address questions of efficacy.

APPROACH. The CS reports that all items were scored as low risk. The ERG agreed with most scores, but sometimes with different rationales. The ERG disagreed with the score relating to baseline imbalances, since the ERG notes that there are apparent imbalances between volanesorsen and placebo groups in: abdominal pain during screening (21% vs 30%, respectively); previous treatment with alipogene tiparvovec (Glybera®) (6.1% vs 15.2%, respectively); genetic variants with potentially different severities; some lipid lowering therapies (respectively, HMG-CoA reductase inhibitors 27% vs 12%; fish oils 9% vs 3%); and platelet aggregation inhibitors (24% vs 15%, respectively). However, it was not possible to determine the overall effect that these imbalances may have had on estimates of efficacy. In other respects, the study appeared of good quality.

COMPASS. The CS reports that all items were scored as low risk. The ERG agreed with nearly all scores, except that the ERG judged that the groups were not similar at the outset, as fasting TG levels were higher in the placebo arm. This may be caused by the fact that FCS was not a stratification factor, and as such the randomisation has been broken by performing this subgroup analysis.

APPROACH OLE. As noted in Section 4.1.4, the CRD tool for quality assessment was reported in the CS, but the ERG considered this to be an inappropriate tool, as APPROACH OLE was not a comparative study and the CRD checklist is intended for the critical appraisal of RCTs. The ERG has assessed the study using the NIH National Heart, Lung, and Blood Institute's (NIH NHLBI) tool for assessing before-after studies.[46] As the study is designed "*to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen administered subcutaneously to patients with FCS*" (p76 of the CS), the single-arm design is of a low quality in the hierarchy of evidence (see CRD handbook Box 1.3, p10). The ERG further judged the study to be of poor quality (Table 5) for a before-after study, based on the NIH NHLBI assessment tool criteria. The study scored poorly on several items (numbers relate to items listed in Table 5: 3) it was unclear whether patients were representative of those who would be eligible for treatment in England, since it was not clear if all patients had a genetic confirmation, nor whether the proportion with a prior history of AP was similar to that in England (see Section 4.2.4.1), though it should be noted that clinicians believed that AP history was unlikely to impact on generalisability; 4&5) it was not clear from the submission if all eligible patients were enrolled, or on what basis the sample size was decided; 8) the study was open-label, and outcome assessors did not appear to be blind to participants' exposure to the intervention; 9) there was a high level of withdrawals from treatment (>20%), it was not clear whether patients who withdrew were also lost to follow-up, and in the main analysis no substitutions were made for missing data (i.e., percentage change from baseline in TG levels); 10) *p*-values were not reported for change from baseline results.

Table 5 ERG's judgement of APPROACH OLE using the NIH National Heart, Lung, and Blood institute's tool for assessing before-after studies.[46]

Criteria	Yes	No	Other
1. Was the study question or objective clearly stated?	Yes		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			Unclear, genetic confirmation? Proportion with no prior AP history?
4. Were all eligible participants that met the prespecified entry criteria enrolled?			Unclear
5. Was the sample size sufficiently large to provide confidence in the findings?			Unclear
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		No	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			Unclear. It is not clear if patients who withdrew from treatment also withdrew from follow-up, or how missing data was handled in the analysis.
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *p*-values for the pre-to-post changes?		No	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		No	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

4.2.3.3 Population

The CS provides a detailed table of recruitment criteria in Table C6 and C7 of the CS.[47] Briefly, APPROACH recruited 66 FCS patients (33 to each arm), who: could be diagnosed either genetically or clinically; had to have fasting TG ≥750 mg/dL (8.4 mmol/L) at screening; had a documented history of chylomicronaemia; and agreed to follow a diet comprising ≤20 g fat per day. Patients with a documented history of no pancreatitis were capped at 28%, whilst it would appear from the clarification response provided in 2018 (question A17)[39], [redacted]. Exclusion criteria were: diabetes mellitus if newly diagnosed or if HbA_{1c} ≥9.0%; other types of severe hypertriglyceridemia; active pancreatitis within 4 weeks of screening; acute or unstable cardiac ischaemia within 6 months of screening; major surgery within 3 months of screening; treatment with alipogene tiparvovec (Glybera®) therapy within 2 years of screening; previous treatment with volanesorsen; any other conditions that, in the opinion of the investigator, could interfere with the patient participating in or completing the study.

In APPRROACH OLE, key inclusion criteria were similar to APPROACH, but differed in that patients in groups 1 and 2 had to have satisfactorily completed APPROACH or COMPASS. The definition of satisfactory completion given to question A12 of the 2018 clarification response[39] [redacted]. Also, patients had to have a genetic confirmation of FCS (APPROACH allowed inclusion of patients on the basis of a clinical diagnosis) and there was no capping of the number of patients who had a documented history of no pancreatitis.

COMPASS recruited a wider population of patients with hypertriglyceridaemia, a subgroup of whom had FCS. FCS was defined as per APPROACH inclusion criteria.

According to clarification response A16,[32] the company state that all of the 92 patients recruited across the three studies had genetic confirmation in accordance with the license. The clarification response states that 82 of 92 (89.13%) patients were genetically confirmed. Clinical advisors to the ERG indicated that in England, diagnosis of FCS is usually done clinically, and only a proportion of patients undergo genetic testing. They believed that the introduction of a) a treatment requiring genetic confirmation and of b) the NHS England genetic testing service is likely to result in more patients receiving a genetic confirmation. Clinical advice also indicated that not all patients with FCS will have a known mutation so may not receive genetic confirmation if tested (see Section 2.1) and will then not be eligible for treatment. Such patients may have entered the trial. Clinical advice indicated that the

inclusion criteria for the trials may also have allowed inclusion of patients with MCS. Regardless of both these issues (the inclusion of patients without a known genetic mutation, and of patients with MCS), clinical advice to the ERG indicated that the results were still likely to be generalisable to the FCS population indicated by the license.

Patients could be included in the trial if they had treatment with alipogene tiparvovec (Glybera®) therapy more than 2 years before screening. Clinical advisors indicated that, as a gene therapy, AP events could be reduced in previously treated patients, even several years after treatment.[48] This may affect the generalisability of the study to patients in England, since clinical advice to the ERG indicates that no patients in England had received alipogene tiparvovec (Glybera) treatment to date, and the treatment has been withdrawn. Section 4.2.3.2 discusses an imbalance between APPROACH arms in patients previously treated with alipogene tiparvovec (Glybera).

Patients without prior pancreatitis were capped at 28%. As clinical advisors indicated that around 75% of FCS patients would have pancreatitis in their lifetime, and further indicated that they did not expect AP history to be a treatment effect modifier, this is unlikely to have affected the generalisability of results.

Overall, the clinical advisors were not concerned with the inclusion criteria for the studies.

4.2.3.4 Intervention

The dosing schedule in APPROACH, APPROACH OLE and COMPASS did not match the licensed dosing schedule, as detailed in Table 6 and Table 7. This is probably due to changes made during the EMA licensing process to find a balance between adverse events (especially thrombocytopaenia) and efficacy. In all three trials, patients were to receive volanesorsen weekly throughout the trial with no down-titration at three months to doses every two weeks, and there was no stopping rule except a safety stopping rule in response to platelet counts or other adverse events/laboratory measurements. During COMPASS, a protocol amendment mandated a move to two weekly dosing after 13 weeks (unless already on weekly dosing for ≥ 5 months as of 27 May 2016), but it would appear no volanesorsen patients in COMPASS received the licensed posology (i.e., reduced their dose at precisely 3 months, see clarification response A10, though three did reduce their dose at some point after 13 weeks (CS p108)).[32] Patients in any trial may have received the licensed schedule in terms of down-titration at 3 months if they experienced adverse events that necessitated a dose reduction at that time point. The CS presents some results from a subgroup analysis of [redacted].

The platelet count monitoring schedule was also different in the SmPC[33] than in the trials (Table 2 of APPROACH CSR,[36] Table 2 of APPROACH OLE CSR,[35] Table 3 of COMPASS CSR[37]).

Table 7 details the schedule for APPROACH and APPROACH OLE; the schedule for COMPASS was only slightly different than for APPROACH and APPROACH OLE. Generally, the schedules kept patients on higher doses/frequencies of treatments within each platelet count range, but also indicated dose discontinuation at higher platelet counts, compared with the SmPC. The SmPC also allows patients to resume treatment in some circumstances, where the trial schedule indicates permanent discontinuation.

The ERG expects the likely effect of the dosing and monitoring schedules in the trial, compared with dosing and monitoring according to the the SmPC, to be to keep patients in the studies on more frequent doses for longer, with fewer and potentially shorter dose pauses, but with more permanent discontinuations. The effect of being on a more frequent dose is likely to be a greater reduction in TG levels, but possibly more adverse events and discontinuations. These impacts will be explored in Section 4.2.4 (study results).

Table 6 Comparison of the EMA licensed dosing schedule and the schedule used in APPROACH and APPROACH OLE, and initially in COMPASS

Time	EMA license	APPROACH, APPROACH OLE
0 to 3 months	285 mg in 1.5 ml injected subcutaneously once weekly	300 mg* in 1.5 ml injected subcutaneously once weekly. Titration, pauses and discontinuation in accordance with **Table 7** or for other adverse events such as injection site reactions.
3 months	Down-titrate to 285 mg every 2 weeks Or Stop treatment if reduction in serum triglycerides is <25%, or patient fails to achieve serum triglycerides below 22.6 mmol/L	
6 months	Option to up-titrate to weekly dosing if serum TG response is inadequate, and platelets normal	
9 months	If TG response on weekly dosing still inadequate, re-down-titrate to every two weeks.	

* equivalent to 285 mg of licenced formulation

Table 7 Comparison of EMA licensed monitoring schedule and that used in APPROACH and APPROACH OLE

Platelet count (x10^9/L)	**SMPC dose (285 mg prefilled syringe)**	**Monitoring frequency**	**APPROACH and APPROACH OLE dose (300 mg)***	**Monitoring frequency**
Normal (>140)	Starting dose: weekly After 3 months: every 2 weeks	Every 2 weeks	No action	Every 2 weeks
100 to 139	Every 2 weeks	Weekly	No action	Weekly
75 to 99	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Weekly	Permanently reduce dose to 300 mg every 2 weeks or to 150 mg weekly	Weekly
50 to 74†	Pause treatment for ≥4 weeks and resume after platelet levels ≥100 x 10^9/L	Every 2-3 days	If on 300 mg every 2 weeks or 150 mg every week, permanently discontinue, otherwise dose pause. When platelet count returns to > 100,000/mm3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor† If less than 25,000, permanently discontinue treatment	Every 2-3 days
Less than 50	Discontinue treatment Glucocorticoids recommended†,††	Daily		Daily

*300mg in its formulation as volanesorsen sodium, which is equivalent to 285 mg volanesorsen as licensed.
†Discontinuation of antiplatelet medicinal products/NSAIDs/anticoagulants should be considered for platelet levels <75 x 10^9/L. Treatment with these medicinal products must be discontinued at platelet levels <50 x 10^9/L. ††Consultation with a haematologist is required to consider the benefit/risk of possible further treatment with volanesorsen.

4.2.3.5 Comparator

In the APPROACH and COMPASS trials, patients in the placebo group were allowed to continue other treatments, and were expected to comply with diet and lifestyle advice. The ERG agrees that this is an appropriate comparator. It was not entirely clear what diet and lifestyle advice was provided or how this compares to practice in England (see Section 3.2.3).

4.2.3.6 Outcomes

The outcomes reported in the three trials are summarised in Table 8.

Triglyceride as a surrogate outcome, and selected cut-off levels: The primary or main outcome in all three trials was % change from baseline in fasting TG levels. Several other outcomes related to TG levels, including responder analyses using an absolute (e.g. <750 mg/dL (8.4 mmol/L)) or relative (e.g. 40%) cut-off, percent change in area under the curve (AUC) analyses and absolute change data. The relationship of TG to clinical outcomes, and the selection of cut-offs has been discussed in Section 2.1 and Section 3.3, and these issues (uncertainty around the clinical relevance of the cut-offs selected and the sometimes unpredictable relationship of TG levels to AP events in individuals) are relevant here. Clinical advice to the ERG further suggested that chylomicron TG levels are a better surrogate. These were reported for APPROACH. Clinical advisors also emphasised the relevance of assessing the percentage change from baseline, even if TG cut-offs are not achieved. For example, a change from a very high baseline TG level was thought to be clinically useful even if the patient did not achieve levels below 22.6 mmol/L. As such, percentage change data and absolute change data are of clinical relevance.

Pancreatitis and abdominal pain outcomes: These were included in all three trials, but with different definitions and analyses performed, indicating some lack of standardisation in this outcome. In APPROACH, there were two secondary analyses relating to abdominal pain and/or pancreatitis: the average maximum intensity abdominal pain on treatment, and a composite outcome, the incidence of AP and/or moderate/severe abdominal pain. Adjudicated AP events were listed as an exploratory analysis where the event rate was estimated from chart review for the five years prior to treatment, and compared to treatment emergent events. In APPROACH OLE, outcomes were average maximum intensity, worst severity and average pain intensity, rates per patient year of adjudicated AP events, and a retrospective before-after analysis similar to the APPROACH analysis. For COMPASS, whilst pancreatitis and abdominal pain outcomes were planned for the whole trial population, they were not reported for the FCS patients of relevance to this appraisal.

Table 8 Key outcomes from APPROACH, COMPASS and APPROACH OLE reported in the CS

Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives*	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
TG levels						
% change from baseline: Months 3,6 and 12	✓ Months 3,6 and 12 Primary; Secondary 2; Secondary 3 respectively		[redacted]	[redacted]†	[redacted]	[redacted]
Responder analysis (endpoint fasting TG <750 mg/dL (8.4 mmol/L) at Month 3) ††	✓ Secondary 1				[redacted]	

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Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives*	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
Responder analysis (endpoint fasting TG <500 mg/dL (5.7mmol/L) at Month 3		✓		[redacted]	[redacted]	
Responder analysis (≥40% reduction in fasting TG at Month 3)		✓ [redacted]			[redacted]	
Responder analysis (≥70% reduction in fasting					[redacted]	

Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives[*]	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
TG at Month 3)						
% change from baseline in postprandial TG AUC (0-9h)		✓ [redacted]				
Absolute change from baseline in fasting TG (mg/dL) at Month 3		✓ [redacted]	[redacted]		[redacted]	
Pancreatitis and abdominal pain						
Average maximum intensity abdomin	✓ Secondary 4	Pre-planned exploratory subgrou			[redacted]	

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Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives[*]	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
al pain on treatment		p analysis of pts with pain at baseline				
Incidence of AP and/or moderate /severe abdominal pain		✓ [redacted]				
Adjudicated AP events[¶]		✓ Retrospective before-after analysis in patients at "high risk"[§]			[redacted]	[redacted]

Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives*	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain and severe abdominal pain					[redacted]	
Other outcomes						
% change in chylomicron TG (Months 3,6 and 12)		✓				
% change in chylomicron AUC (0-9h)		✓ [redacted]				
Various other lipid parameters		✓			[redacted]	

Outcome	APPROACH		COMPASS[#]		APPROACH OLE	
	Primary and secondary objectives[*]	***Post hoc*, tertiary or exploratory analyses**	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in hepatic fat volume (cm3) at Week 52		✓ [redacted]				
Quality of life		✓ EQ-5D and SF-36			[redacted]	

[redacted]. All analyses after [redacted] were considered exploratory since secondary outcome 4 was not statistically significant._[†] dose change not necessarily at 13 weeks. [††] Among patients who had baseline fasting TG levels ≥750 mg/dL. [¶] adjudicated by a blinded, independent review committee. [§] high risk defined as having at least 2 adjudicated pancreatitis events in the 5 years preceding randomisation. [‖] unclear if this analysis was pre-planned.

Given AP is a key clinical outcome, and an important modelling parameter, it is of concern to the ERG that the analysis used in the modelling was only planned as an exploratory analysis or a *post hoc* analysis, and that the event rate prior to treatment was based on retrospective chart review; for both APPROACH and APPROACH OLE, this analysis should be considered to come from a before-after study, not an RCT.

Outcomes listed in the NICE scope[34] but only measured as adverse events in the trial: Several other outcomes that were listed in the NICE scope were not measured as efficacy outcomes, but as adverse events. These were: fatigue; incidence of diabetes; other complications, and mortality.

4.2.4 Description and critique of the results of the studies

4.2.4.1 Baseline characteristics

Baseline characteristics for all three studies are summarised and presented in Appendix 2: Key patient demographics and baseline characteristics in APPROACH, APPROACH OLE and COMPASS, synthesised from Tables C8-C10 of the CS.

Table 24. In terms of generalisability (external validity) and balance between arms (internal validity) in APPROACH, the ERG noted the following.

In their responses in 2018, clinical advisors to the ERG thought that the levels of abdominal pain reported were high in comparison to the English population, but TG levels were thought to be lower on average than those expected in patients seen in clinical practice in England. A similar observation was made in the EPAR Public Assessment Report.[33] It is not clear if this would affect generalisability.

As noted in Section 4.2.3.2, there was a small imbalance in several baseline factors, but the impact of these imbalances is unclear.

As noted in Section 4.2.3.2, inclusion/exclusion criteria included a cap on patients with no history of pancreatitis at 28% in APPROACH. APPROACH recruited 24% patients without prior history of AP. As clinical advice to the ERG indicated that 75% of patients would experience AP in their lives, this cap and proportion recruited seemed reasonable.

In APPROACH, seven patients (11%, n=7/33) overall received alipogene tiparvovec (Glybera) and may therefore have lower baseline levels of pancreatitis compared with patients in England, of whom the ERG believes none received alipogene tiparvovec (Glybera) (see Section 4.2.3.3). There is also a small imbalance between arms in patients, with more patients in the placebo arm (five, versus two in the

volanesorsen arm). It is unclear if these patients will respond to treatment in a similar way to those who did not receive alipogene tiparvovec (Glybera), and the small imbalance may disadvantage volanesorsen in comparative analyses of AP rates. The extent to which these factors have biased results is unknown.

Clinical advice indicated that in approximately 25% of patients, a known mutation is not found. The trial recruited 23% such patients, which is therefore in keeping with levels in England. In Table C8 of the CS, the genetic variants for APPROACH patients are listed. There were some imbalances between types of genetic variations. The ERG asked the company if there was any evidence that genetic variant could affect prognosis or treatment response. They responded that whilst some variants had higher TG levels at baseline, this did not appear to affect treatment response, and they are not aware of any data relating genetic variant to other aspects of disease prognosis (response A16, 2019 clarification response).[32]

In the case of use of some treatments at baseline (see Appendix 2), small imbalances between treatment groups were reported, but the clinical advisors to the ERG were not concerned about these. [redacted]

[redacted]

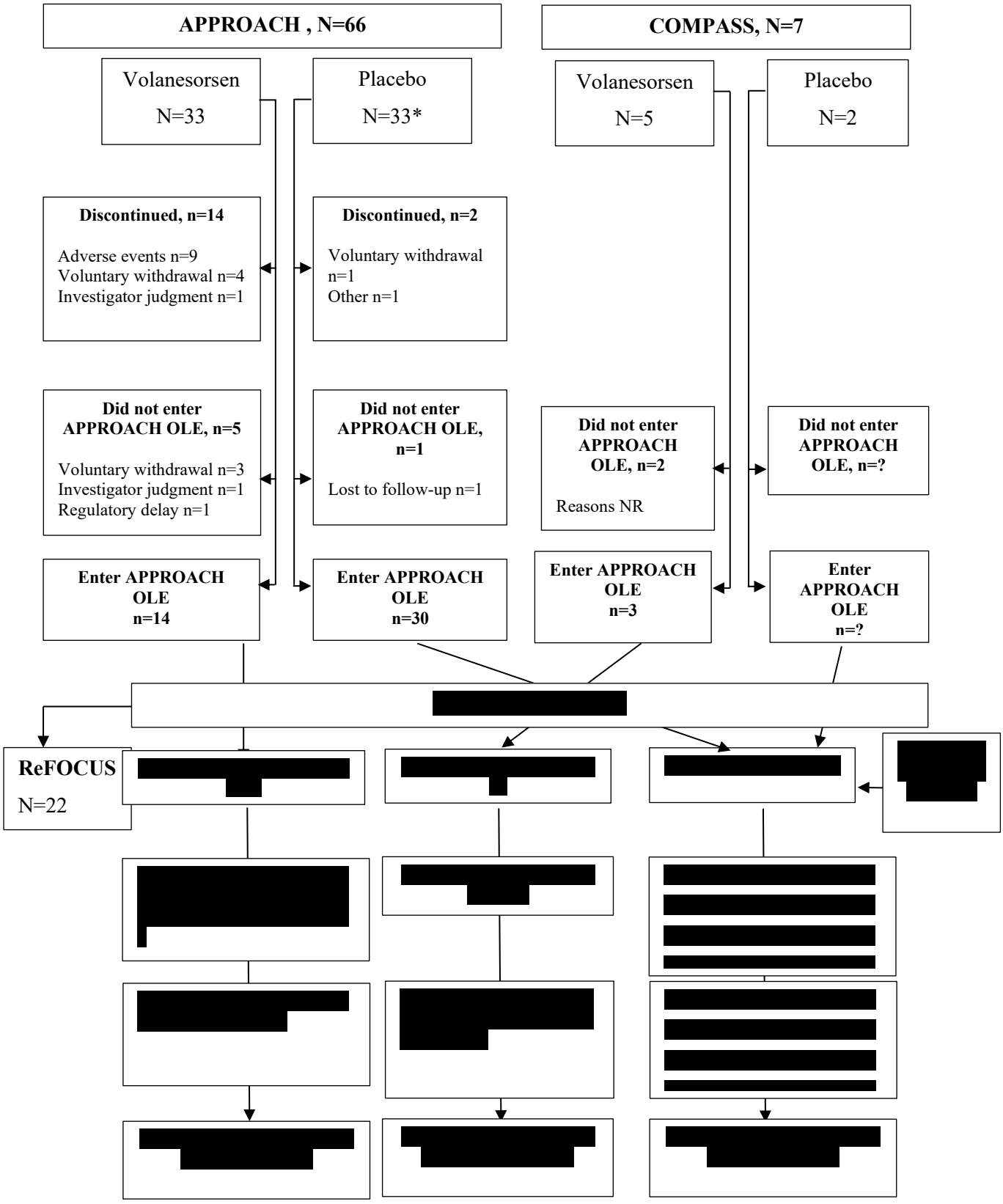
4.2.4.2 Patient flow through the studies

The CS reports the flow of patients through the studies in Figure 11 (APPROACH), Table C11 (APPROACH OLE), and on p86 of the CS (COMPASS). The ERG has compiled a patient flow chart which is presented in Figure 1, and a detailed breakdown of discontinuations by time for patients entering APPROACH in Table 9. There was a relatively high rate of discontinuations in APPROACH (42% at or before Month 12) and [redacted]

[redacted]

The CS also reports some data on dose pauses and reductions in APPROACH OLE (Table C11 of the CS), which showed [redacted].

Figure 1 Flow of patients through APPROACH, APPROACH OLE and COMPASS



* n=34 were initially randomised, but one patient did not receive placebo since their stratification information was wrongly entered into the system. ** The ERG were not clear why the number of patients continuing and the number of patients discontinuing does not sum to the number recruited.

The ERG considered whether discontinuations could be expected to remain high in clinical practice, given the reduced dosing of the EMA license, which could in theory reduce the adverse events that lead to discontinuations. The ERG notes that for treatment-naïve patients in APPROACH OLE, where monitoring schedules were established earlier in the trial (they were a protocol amendment in APPROACH), discontinuations were somewhat attenuated, with 32% discontinued at 12 months compared with 42% in APPROACH, and 61% compared with 79% respectively at 104 weeks. In addition, the CS states that there has only been one discontinuation in the EAMS programme (EAMS described in Section 2.2), and this was due to cancer recurrence. However, the ERG notes that the EAMS programme uses a lower dose than has been licensed by the EMA (dosing every two weeks from inception, 2019 clarification response A12b), may have selected for patients who are tolerant to treatment since some completed APPROACH and APPROACH OLE, and may not include a treatment-response stopping rule at three months. Furthermore, in their 2019 clarification response to question A10f, the CS notes that of the 14 patients who conformed to the licensed dose of every two-week dosing from 3 months onwards, [redacted] In the analysis of 36 patients from APPROACH (number not reported) and APPROACH OLE (number not reported) who changed to every two weeks dosing any time after 3 months, 39% discontinued (time point unclear). The ERG notes that the patients in both these analyses are patients who had an AE, which may select for patients more likely to discontinue. The ERG concludes that the discontinuation rate that will be seen in clinical practice is currently unknown, but believes it is unlikely to be zero. Clinical advisors to the ERG were also of the opinion that there would likely be discontinuations in clinical practice, with estimates up to 10% per annum and 20% in total. The main reasons for these were thought to be the burden of monitoring and adverse events including injection site reactions and thrombocytopaenia.

Figure 2

Table 9 Discontinuation (with reasons) for APPROACH volanesorsen patients from enrolment in APPROACH to treatment in APPROACH OLE, compared with discontinuations in APPROACH OLE naïve patients

Time	Reason	Number	Number left on-treatment in a study	Running total % discontinued	% discontinued in APPROACH OLE naïve
Entered APPROACH			N=33 at baseline		N=51
Discontinued before 13 weeks of APPROACH	AEs (n=9): platelet count/thrombocytopaenia, n=5; injection site reaction & fatigue, n=1; fatigue, n=1; chills and sweating, n=1, generalised erythema, n=1) Voluntary withdrawal (n=4) (dehydration, n=1; study visit duration, n=1; heard volanesorsen does not work, n=1; wished to go travelling, n=1)	2	31	6%	NR
Discontinued before 13-26 weeks of APPROACH		7	24	27%	NR
Discontinued before 26-52 of APPROACH		5	19	42%	32%
Did not enter APPROACH OLE					
Between APPROACH and OLE	Voluntary withdrawal	3	16		
	Investigator judgement	1	15		
	Regulatory delay	1	14	58%(WCS)* 45% (BCS)*	NR
Entered APPROACH OLE			N=14 at OLE baseline		
[redacted]					
[redacted]					

WCS, worst case scenario; BCS, best case scenario

* WCS assumes voluntary withdrawal and regulatory delay patients discontinued treatment; BCS assumes they did not discontinue, e.g. continued on EAMS

4.2.4.3 Results: Percent change from baseline in fasting TG levels

This was the primary efficacy outcome in APPROACH and COMPASS (APPROACH OLE did not define a primary objective). The percent change from baseline in fasting TG levels for APPROACH, APPROACH OLE, the *ad hoc* subgroup analysis of [redacted] who conformed to the licensed indication and the subgroup [redacted]) are presented in Table 10 and Figure 3 to

Figure 5. A substantial reduction was observed in APPROACH at Month 3, (percentage change from baseline was -76.5%, and a statistically significant relative change from placebo of -94.1% (95% confidence interval (CI): -121.7, -66.6)), and [redacted] and COMPASS (-73%, compared with a mean increase of +70% in patients who received placebo; *p*-value not reported). SDs and 95% CIs were wide, where reported. [redacted] The CS also reports a graph of patients from APPROACH and APPROACH OLE who had a mixed dose (n=36, patients who started on once-weekly treatment, had their dose reduced at some point during the study to once every 2 weeks and remained on this dose for more than 3 months) and a graph comparing those who completed the trial with no dose adjustments, those with dose adjustments and non-completers: these are presented in Appendix 3.

At subsequent time points, the response was generally lower than at Month 3 (see **Figure 3** (APPROACH)), with a few exceptions. In the subgroup of patients who conformed to the licensed dose (see Figure 5), [redacted]). In the mixed dose

population, TG levels remained fairly stable from Month 12 to 24, at around -40% change from baseline (Figure 11). In the comparison of patients with no dose adjustments, those with dose adjustments and non-completers (Figure 11), dose pauses lead to a lower reduction in TG levels. In a subgroup of three patients from COMPASS who reduced to every two week dosing after 13 weeks, percentage change from baseline at Month 6 was -69%, compared to -78% for those who remained on weekly dosing.

TG levels rose and fell in patients in the placebo arm of APPROACH, up to 25.3% at Month 6, and down to 8.9% at Month 12.

Table 10 Percent change from baseline in fasting TG (mg/dL) for APPROACH, APPROACH OLE and the subgroup analysis of 14 patients who conformed with the licensed indication

	APPROACH*		APPROACH OLE†					
			Whole trial population			Subgroup of patients with licensed dose	Subgroup of patient with history of pancreatitis	
Timepoint	**Volanesorsen (n=33)**	**Placebo (n=33)**	**APPROACH-Vol (n=14)**	**COMPASS-Vol (n=3)**	**Naïve (n=51)**	**Naïve (n=14)**	**APPROACH-Vol (N=23)**	**Naïve (N=11)**
Month 3	-76.5	17.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	-52.5	25.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	<0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	-40.2	8.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0347 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	See Month 6 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	See Month 12 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vol, volanesorsen; n, number; ANCOVA, analysis of covariance; SD, standard deviation

* Least squares mean; † APPROACH-volanesorsen and COMPASS-volanesorsen patients baseline values were those when they entered the index trial.

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Because responses seemed generally lower in later Months (see **Figure 3** to Figure 5), the ERG asked the company and clinical advisors about the possibility of a waning effect of volanesorsen. Clinical advisors to the ERG indicated that they did not expect the effect to wane. The company responded (2019 clarification response A18) that any apparent waning of effect seen in the results could be "almost entirely" explained by dose pauses and reductions. However, no analysis was presented to support this explanation.

[redacted]. The data submitted for the "mixed dose" population has higher patient numbers (n=36), however, it is unclear when patients discontinued, and the "stable" period from Month 12-24 may include some patients still on the higher dosing regimen or "washing out" from the higher dose. In the analysis of COMPASS patients who reduced to every two weeks dosing (n=3), the Month 6 data remains quite high (-69%), though the ERG note it is not clear when these patients switched treatment, and that treatment effect of weekly dosing is unlikely to have fully washed out at Month 6.

Clinical advisors to the ERG indicated that they did not expect to see a greater effect in patients with a prior history of pancreatitis, or by any other definition of "high risk", though such a group may be the most likely to be cost-effective.

Clinical advisors were not surprised to see a 25% fluctuation in TG levels in the placebo arm, and the ERG speculates that this may in part be due to patients relaxing dietary restrictions after the period of diet stabilisation needed to qualify for the trial.

The ERG noted that the analysis of patients who met the licensed dose was not pre-planned, and did not have a comparator arm. However, based on observations in APPROACH, TG levels were likely to be stable or increasing without treatment.

The ERG concludes that: (a) any waning of effect, if present, is probably small, though the ERG notes that as follow-up and clinical experience with the treatment currently do not appear to go beyond around three to four years, there is some uncertainty about long terms effects; (b [redacted] The extent to which dose pauses will be required at the new dose is unclear: clinical advisors were divided in opinion as to whether rates of thrombocytopaenic adverse events will be lowered at lower doses, since it is unclear how volanesorsen lowers platelets, whilst all agreed they were unlikely to be prevented altogether.

Figure 3 [redacted]

Figure 4 Mean percent change from baseline fasting triglyceride levels (replication of "Revised Figure 20" from the 2019 clarification response)

Figure 5 [redacted]

[redacted]

4.2.4.4 Results: absolute change in TG levels

In APPROACH, at Month 3, there was a mean absolute reduction in the volanesorsen group (n=33) of 1712 mg/dL (19.4 mmol/L), compared with a mean absolute increase of 92 mg/dL (1 mmol/L) in the placebo group (n=33) (Table C15 of the CS). The least squares mean difference was -1804 mg/dL (95% CI: -2306, -1302) (-20.5 mmol/L, 95%CI -26.2, -14.8). Mean change values were also presented for APPROACH OLE (n=68) in Table C19 by treatment group and time point (Months 3, 6, 12, Weeks 76 and 104) of the CS. Nearly all were [redacted]

[redacted]

The ERG notes that a substantial mean absolute change in TG levels appears to be made through treatment with volanesorsen. However, the standard deviations indicate a great deal of variation. This may reflect the very variable baseline TG values of patients, or may be due to dose pauses and reductions meaning treatment effect varies. Clinical advisors to the ERG indicated that nearly all patients, in their experience, have a substantial TG response to treatment.

4.2.4.5 Results: Responder analyses (TG levels)

The company presented some responder analyses (see Tables C15 and Table C19 of the CS). In APPROACH, this was secondary outcome [redacted] and defined as an endpoint fasting TG <750 mg/dL at Month 3 (approximately 8.5 mmol/L). This outcome was met, with 76.7% (n=23/33) of volanesorsen patients and 9.7% (n=3/33) of placebo patients meeting the endpoint (odds ratio 186.16 (95% CI: 12.86, N/A; *p*-value <0.0001). Twelve-month data were not reported.

[redacted]

The endpoint ≥40% reduction in fasting TG at Month 3 was also statistically significant in APPROACH (87.9%, n=29/33, and 9.1%, n=3/33, in volanesorsen and placebo arms respectively; odds ratio 99.69 (95%CI: 15.75, 631.06; *p*-value<0.0001)), and [redacted]

The ERG notes that this indicates that most, but not all, patients appear to achieve a low absolute TG level at month 3, and/or a moderate-to-high relative reduction in TG levels. This indicates that a good proportion of patients are likely to continue on treatment after assessment of the treatment-response stopping rule in the license, where patients must have both TG levels <22.6mmol/L (around 2000mg/dL) and at least a 25% reduction in TG levels

[redacted]

4.2.4.6 Results: Abdominal pain and acute pancreatitis outcomes

The CS reports several analyses of abdominal pain and AP. Key outcomes and analyses are presented in Table 11.

Of the pre-planned secondary efficacy analyses in APPROACH ("average maximum intensity of abdominal pain during on-treatment period" and the composite outcome "incidence of acute pancreatitis and/or moderate/severe abdominal pain"), neither demonstrated a statistically significant difference. However, a pre-planned exploratory analysis showed that volanesorsen-treated patients who had abdominal pain at baseline had a statistically significant reduction in the average maximum intensity of abdominal pain, compared with the equivalent subgroup of patients in the placebo group (p = 0.0227, no further details reported). A safety analysis of pancreatitis events (see Table C17 of the CS) was pre-planned, and did not show a statistically significant difference (one event in one patient in volanesorsen arm (N=33), four events in three patients in placebo arm, N=33, p=0.6132), though this analysis may have been underpowered.

[redacted] Note, abdominal pain was not an outcome measured in COMPASS.

[redacted] These are presented in Table 11. The analysis in APPROACH only included patients with two or more adjudicated APs in the 5 years prior to the study enrolment, (n=7/33 volanesorsen patients, n=4/33 placebo patients), [redacted]. The APPROACH analysis did not account for time on treatment, and the CS acknowledges there may be some bias as discontinuation rates were high. The APPROACH analysis reported a statistically significant difference in favour of volanesorsen (p=0.0242) whilst a statistical test was not reported for the APPROACH OLE analysis, where the rates were 0.23 events per patient year prior to treatment compared with 0.0297 events per patient year on-treatment.

The ERG notes that these results suggest patients continue to experience some abdominal pain whilst on treatment, but may experience fewer AP events, though this is uncertain. However, the subgroup analysis of patients with pain at baseline (number in analysis not reported) showed a statistically significant reduction in abdominal pain. Based on clinical advice to the ERG, which suggests that baseline characteristics are unlikely to predict response to treatment, the ERG does not think this reflects a more responsive subgroup of patients, but may be due to higher baseline events meaning an effect could be detected.

The *ad hoc* analysis in APPROACH patients was restricted to patients with at least two APs in the 5 years prior to treatment (n=11)); this population is used within a scenario analysis reported in the CS.

[redacted] The ERG concludes that treatment may reduce AP events, but this remains uncertain, and the magnitude of any effect is unclear, especially at the reduced dose indicated by the license. The effect on abdominal pain is also uncertain.

It should be noted that in the company's economic model, AP rates are predicted by TG levels (see Section 5.2.5.4.1) as well as using the rate ratio calculated from the APPROACH OLE analysis of AP rates 5 years before treatment and whilst on treatment. This method appears to assume that volanesorsen has a direct effect on AP rates not mediated through TG levels. The ERG discusses this issue with respect to the model in Section 5.3.3.6.

Table 11 Summary of abdominal pain and acute pancreatitis outcomes for APPROACH and APPROACH OLE

	APPROACH		[redacted]			Subgroup of patients with licensed dose
Outcome	**Volanesorsen (N=33)**	**Placebo (N=33)**	**APPROACH – vol (n=14)**	[redacted]	[redacted]	[redacted]
Average maximum intensity of abdominal pain during on-treatment period**			[redacted]			
Mean (SD)	0.38 (0.83)	0.36 (0.79)	[redacted]			
p value	0.8959 (two-sample t-test)					
Incidence of acute pancreatitis and/or moderate/severe abdominal pain†						
n (%) of patients	12 (36)	13 (39)				
Mean (SD) number of events, per patient per year	2.73 (6.57)	2.04 (4.28)				
p-value	0.6131 (two-sample t-test)					

Pancreatitis events††				
Patients (events)	1 (1)**	3 (4)	[redacted]	[redacted]
p-value	P = 0.6132			
Post-hoc analysis of 5-year history of AP compared to on-treatment rate: See Footnotes for APPROACH‖ and APPROACH OLE# analysis details				
Patients in analysis	7	4	[redacted]	[redacted]
Events prior 5 years	24 events =0.69 ppy¶	17 events =0.85 ppy¶	[redacted]	
Events on treatment	0 events§	4 events§	[redacted]	
p-value	0.0242		[redacted]	

NA, not applicable as abdominal pain was not measured in COMPASS; NR, not reported; ppy, per patient year

*secondary outcome, †abdominal pain was not recorded in the COMPASS study; †† safety outcome; ¶rate per patient year calculated by EAG; §exposure time not available for 12-month period on treatment, so rate per patient year could not be calculated; ‖ number of adjudicated acute pancreatitis events within 12 month study period, and the 5-years prior to enrolment (chart review). Only patients with two or more adjudicated pancreatitis events in prior 5 years entered the analysis; # number of adjudicated acute pancreatitis events on treatment to February 28th 2019, and the 5-years prior to enrolment (chart review). All patients included in the analysis.; ** this event occurred after treatment cessation and hence is not counted in the post-hoc analysis of on-treatment events

4.2.4.7 Results: Other lipid outcomes

The CS presents data on other lipid outcomes. Because of their low relevance to the decision problem and the company's model, they are not reported extensively here but can be found in Tables C15, C16 and C20 of the CS, and Figures 18 and 19 of the CS. In summary, the treatment appeared to have a beneficial effect on other lipid outcomes.

Chylomicron levels, which is an outcome listed in the NICE scope, are reported in Table 12 from APPROACH and appear to follow a similar pattern to TG levels over time, i.e., an initial response, somewhat decreasing over time. The same issues relating to TG measurements (see Section 4.2.4.3) apply here, and the ERG conclude that the degree to which chylomicron TG levels will decrease at the licensed dose is unclear.

Table 12 Percent change in fasting chylomicron TG levels over time from APPROACH (replication of Table C16 of the CS).

	% change from baseline, mean (SD)		
	Volanesorsen (n = 33)	**Placebo (n = 33)**	**P value**
Fasting chylomicron TG (mg/dL)			
Month 3	-76.6 (22.1)	+37.7 (112.4)	<0.0001
Month 6	-65.3 (39.1)	+37.7 (75.3)	<0.0001
Month 12	-52.3 (44.9)	+21.9 (79.4)	<0.0001

The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. If one visit was missing, then the other visit was used as the endpoint. The Month 6 endpoint was defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments. If one visit was missing, then the other visit was used as the endpoint. The Month 12 endpoint was defined as the average of Week 50 (Day 344)/Week 51 (Day 351) and Week 52 (Day 358) fasting assessments. If one visit was missing, then the other visit was used as the endpoint.
SD, standard deviation; TG, triglyceride
Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

4.2.4.8 Results: Fatigue, diabetes and mortality

Fatigue, diabetes and mortality were not reported as clinical outcomes in the CS. In APPROACH, [redacted]. In APPROACH OLE, [redacted]. Diabetes rates were only reported for APPROACH, and these were 12% (n=4/33) in the volanesorsen group and 0% (n=0/33) in the placebo group. There were no deaths in APPROACH or APPROACH OLE but the

information was not provided in the CS for COMPASS. [redacted].

4.2.4.9 Results: Health-related quality of life

Health-related quality of life was measured using the EQ-5D and SF-36 in APPROACH and APPROACH OLE. In APPROACH, there was no significant change from baseline for the SF-36 or EQ-5D-5L at Month 3 ($p = 0.6627$ and $p = 0.2920$, respectively), Month 6 ($p = 0.9226$ and $p = 0.5923$, respectively), and Month 12 ($p = 0.7912$ and $p = 0.4079$, respectively). Baseline values were very high (utility >0.97 in both arms). With respect to APPROACH OLE, the CS did not present results but these were given in the CSR and [redacted]

The ERG agrees that the baseline values seem high for the patient group, as clinical advisors to the ERG indicated that FCS has a considerable impact on patients' HRQoL. This would leave very little room for patients to improve (ceiling effect).

To supplement the results measured in the studies, the company conducted a retrospective web-based survey (ReFOCUS) in APPROACH OLE patients (p115 of the CS). Patients had to have been on treatment for 3 months and were asked about the 3 months prior to enrolment and the latest 3 months on treatment. Twenty-two patients took part. More patients believed their FCS symptoms were effectively managed with volanesorsen (40% vs. 19% before treatment). More believed their symptoms were controlled with adherence to diet (90% vs. 55% before treatment). Patients recalled fewer symptoms after treatment than before; 44% reduction from 9 per 3 months before treatment to 5 per 3 months with treatment ($p<0.05$). Patients recalled "no interference" from FCS on their lives more often with volanesorsen (5% before vs. 23% on treatment). More patients reported no interferences from FCS with work or school on treatment (36% before vs. 64% after). The company provided a graphical representation of this data in Figure 22 of the CS, replicated here as Figure 6.

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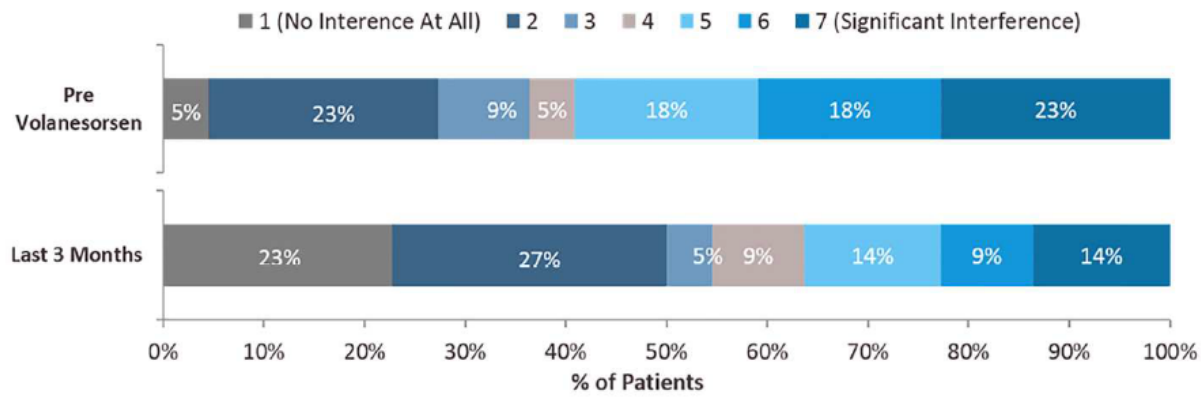
Figure 6 Overall impact of FCS on patients' lives before and during volanesorsen treatment (n = 22) (replication of Figure 7 from the CS)



Source: Arca et al., 2018

The ERG notes that REFOCUS adopted a single-arm, retrospective design asking patients to recall symptoms. The study is therefore at risk of recall bias and in some cases the period of recall would be over a year before (where patients were in APPROACH or COMPASS). The study is also open-label, and as such at high risk of detection bias, which may interact with recall bias in that patients may overestimate pre-treatment symptoms and underestimate current symptoms. Twenty-two patients were enrolled, but it is not clear how many were approached or were eligible; no baseline characteristics were presented in the CS and it is unclear how representative the enrolled patients were of the wider trial and of patients in England. As such, the ERG judges the study to be of low quality and at high risk of bias to answer a question of efficacy.

The company conducted a vignette study to inform their model. This is discussed in Section 5.2.5.5.1.

4.2.4.10 Results: Adverse events

The company summarised treatment-emergent adverse events (TEAEs) related or possibly related to volanesorsen in Table C21 (APPROACH) and Table C22 (APPROACH OLE) of the CS. Table C21 only lists common and very common events, rather than providing event rates per treatment arm. Event rates were provided in the 2018 submission and are included in Appendix 4. Common events (occurring in ≥1/100 to <1/10 patients) in APPROACH were wide ranging, but the most frequent (≥1/10) were limited to injection site reactions [redacted], asthenia [redacted], fatigue [redacted], platelet count decreases [redacted], myalgia [redacted], headache [redacted] and thrombocytopaenia [redacted]. NB: Data in brackets was taken from Table C15 of the 2018 CS, which is all adverse events, not just those potentially

related to study drug. Most TEAEs were mild. In the volanesorsen arm, five events were severe, four of which were potentially related to study drug (severe thrombocytopaenia (n=2), fatigue (n=1) and musculoskeletal pain (n=1)). Three patients in the placebo group had severe TEAEs; none were considered potentially related to treatment. Serious adverse events were experienced by seven patients (21%) in the volanesorsen group who had a total of eight events and five (15%) in the placebo group who had a total of six events. Two of these in the volanesorsen arm were thrombocytopaenia, and led to discontinuation. Others in both arms were not thought to be related to treatment and resolved.

[redacted]

[redacted]

Clinical advisors to the ERG were not concerned about treatment-related adverse events, except for injections site reactions and platelet counts/thrombocytopaenia. Both of these have led to patients discontinuing treatment (injection site reactions led to one discontinuation, and thrombocytopaenia is listed as the discontinuation reason for five patients in APPROACH; a further patient discontinued due to fatigue), and thrombocytopaenia is potentially a serious, life-threatening condition which should be carefully managed and prevented as low platelet counts can lead to bleeding events. Clinical advice to the ERG indicated some optimism that the revised dosing schedule and enhanced monitoring would reduce the events, but also some speculation that as the mechanisms that lead the drug to cause thrombocytopaenia are poorly understood, it is unclear to what extent doses must be reduced to prevent them altogether. Injection site reactions were thought to be cumulative, and it was expected that less frequent dosing may lead to fewer, but probably not zero, events. As such, the ERG concludes that it is

unclear to what extent the licensed dosing schedule and monitoring will prevent the most serious and significant adverse events.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed as there was head-to-head evidence from an RCT comparing volanesorsen versus the only available treatment, SoC.

4.4 Conclusions of the clinical effectiveness section

The CS contained all major studies relating to volanesorsen in FCS patients. In the studies, the treatment statistically significantly (p<0.05) reduced TGs to levels that can be expected to reduce APs. However, not all patients achieved TG levels below 8.4mmol/L. Results relating to AP event rates, abdominal pain and HRQoL were less certain. There were high rates of discontinuations in the clinical studies, mostly due to AEs (especially thrombocytopaenia and injection site reactions) and the burden of monitoring.

The marketing authorisation for volanesorsen states that the patients should be at high risk of AP, but it is unclear how this population will be defined in clinical practice. This is unlikely to affect the generalisability of the study results.

The major limitation of the evidence base is that the studies did not plan to use the dose that has been licensed. The studies were based on a weekly dose, whereas the license is for a weekly dose for three months, followed by doses every two weeks. This is likely to impact on both efficacy and safety outcomes, and consequently on discontinuation rates. The CS reported two subgroup analyses of patients who reduced to every two weekly dosing and these show that TG levels do not reduce to the same extent compared to patients receiving weekly doses. However, the extent by which TG levels are likely to reduce in clinical practice at the licensed dose is uncertain due to problems with the subgroup anlayses including their small sample sizes and *post hoc* nature. The impact on safety outcomes and discontinuations is also uncertain since patients who entered these analyses had generally reduced their dose due to adverse events, thus leaving the analysis at high risk of selection bias. In addition, the primary outcome measure was for the surrogate, TG levels, and the impact on the hard clinical outcome of AP rates is uncertain due to analyses being underpowered, exploratory, retrospective, single-armed and/or post hoc in nature, and being based largely on patients receiving weekly dosing.

5 COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

The company conducted a systematic review to identify relevant studies reporting on the cost-effectiveness of volanesorsen or any other intervention for the management of FCS.

Appendix 3 of the CS reports the searches conducted to identify economic evidence. The company searched the same sources as for the clinical review but not the additional sources recommended by NICE (EconLit and the archive of NHS EED). This was queried by the ERG and subsequently rectified without identifying any additional studies (clarification response A1).[32]

As with the clinical searches, subject headings and free text terms were combined and a filter adapted from SIGN was used to restrict results to economic studies.

In this systematic review, the disease terms were broadened to include diabetes in all forms (as for example in lines 27-38 of the Medline search, p329 of the CS).[38] Additionally, in the same strategy, an attempt is made to limit results to the UK (though not including the MeSH term exp Great Britain/, and with the orphan term "NHS" from line 92 apparently not included in the final sets). The ERG would have preferred to see the use of a validated filter for this purpose, such as that developed by NICE.[49]

There may to be a logic error in line 93 of the Medline search (CS Appendix 3, p331) where the ERG expected to see the following search facets combined thus:
((disease) AND (economic terms NOT (letter or review or comment)) AND (UK))

However, instead they have combined as follows:
(disease AND economic terms AND (letter or review or comment) AND UK

If the search was executed as reported here, it could potentially have resulted in the failure to identify relevant economic studies. It is possible that this is a transcription error though the omission of numbers of results from this search strategy make it impossible to be certain of the impact on retrieval.

Searches were also conducted identify resource utilisation studies. In Section 12.3.2 of the CS (p215) it is stated that "given the lack of published data on the healthcare resource use for UK FCS patients,

the search criteria for the systematic literature review were revised to include resource use in pancreatitis and diabetes".

However, the literature search strategy specifically designed to identify HRQoL was run simultaneously on EMBASE and MEDLINE (presented in Appendix 4 of the CS, p336-339) and does not include any of the diabetes terms used in the economic searches – only terms for FCS and pancreatitis.

Whilst this does not appear to be an optimal means of evidence identification for the stated objectives of the SLR, the ERG understands from the description of the "data abstraction strategy" (CS, p340) that these results were sifted alongside the results of the economic searches, which may have helped to fill some of the gaps for diabetes.

5.1.2 Inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria used by the company were presented in Table D1 of the CS. The ERG believes that these are appropriate.

5.1.3 Findings of the cost effectiveness review

No study was identified that assessed the cost-effectiveness of volanesorsen. Three studies reported economic models assessing different interventions for FCS (one for alipogene tiparvovec (Glybera®), one for a hypothetical TG-reducing intervention and one of a novel treatment); however, all studies were reported in abstract form only.

5.1.4 Conclusions of the cost effectiveness review

The company concluded that '*Given the limitations in the reporting of previous studies and the lack of any published evaluation of volanesorsen, a de-novo model was developed.*' (p157 of the CS). The ERG agrees with the decision made by the company.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

The company submitted a revised model following the clarification question process. Only the revised model is detailed within this report. A simple PAS has been agreed between the company and NICE. However, the base case analysis presented by the company and the majority of scenario analyses included an additional financial arrangement [redacted], despite this not being formally agreed. The company state that "[redacted]

[redacted]

The company's model had the functionality to generate results using the volanesorsen dosing within the APPROACH RCT, but the company did not use that in the base case as this does not meet the finalised SmPC dosing schedule. The ERG agrees that the APPROACH RCT dosing schedule is not appropriate for the decision problem.

5.2.1 Population

The population considered in the company's economic model relates to patients with genetically-confirmed FCS who are at high-risk of pancreatitis, whose response to diet and TG-lowering therapy has been inadequate. High-risk of pancreatitis was defined as having had a previous AP event. The hypothetical cohort of patients are assumed to be 41 years old and are comprised of 54.5% females. Patients are assumed to have the characteristics in terms of AP-history and baseline TG bands (<10 mmol/L (low-risk); ≥10 and <22.6 mmol/L (medium-risk); and ≥22.6 mmol/L(high-risk)) as patients in the APPROACH study.

The split of patients on model entry was: low-risk TG band 4.0%; medium-risk TG band 42.0%; and high-risk TG band 54.0%. The ERG notes that the company assumed that no patients have CP at the start of the model. This is in contrast to the APPROACH study where [redacted] patients randomised to volanesorsen and [redacted] patients randomised to placebo had CP. The company implicitly assumed that the TG levels post-volanesorsen are not affected by CP status.

The model has the facility to analyse high-risk patients by subgroup relating to AP-status: no AP events in the last 5 years; one AP event within the last 5 years, or multiple AP events in the last 5 years. All patients regardless of AP history could also be evaluated.

5.2.2 Intervention and comparators

The intervention is volanesorsen alongside SoC as described in Section 3.2; the comparator is SoC which is described in Section 2.2. The company stated that the placebo arm in the APPROACH study is considered a good reflection of current UK practice. For readability, volanesorsen in conjunction with SoC has been compressed to volanesorsen hereafter.

5.2.3 Perspective, time horizon and discounting

The company's economic analysis adopts an NHS perspective and implements a 59-year time horizon, which was assumed to represent the maximum remaining lifetime of a patient. A discount rate of 3.5% per annum was used for both cost and health outcomes.

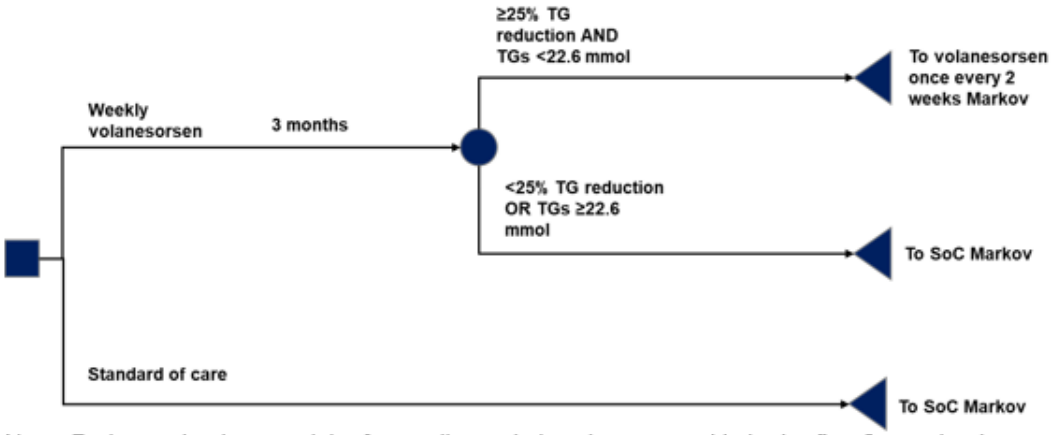
5.2.4 Model structure

The model had two components: (i) a three-month decision tree model and (ii) a long-term Markov model applied to the end nodes of the decision tree. Treatment with volanesorsen was assumed to be weekly within the initial three-month period and fortnightly thereafter until discontinuation or death.

5.2.4.1 Three-month decision tree model

The diagram provided by the company for the decision tree is replicated in Figure 8. All patients who were treated with SoC progressed to the SoC Markov model. In contrast, patients who received volanesorsen had to meet continuation criteria (stopping rule) in order to remain on volanesorsen (and progressed to the volanesorsen Markov model), otherwise the patients discontinued treatment and progressed to the SoC Markov model. A patient continued on volanesorsen treatment only if their TG level had reduced by 25%, or greater, and if their absolute TG level was below 22.6 mmol/L. Within the three-month decision tree, QALYs were half-cycle corrected but costs were not.

Figure 8: The three-month decision tree model (replication of Figure 27A from the CS)



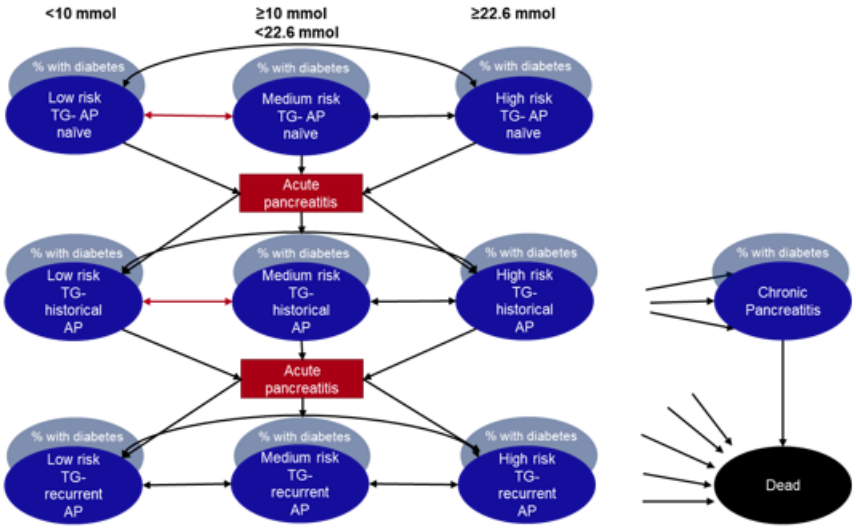
Note: Patients also have a risk of mortality and chronic pancreatitis in the first 3 months, but numbers are small and similar between arms.

5.2.4.2 Longer-term Markov model

The diagram provided by the company for the Markov model is replicated in Figure 9. The structure of the model was identical for the SoC and volanesorsen groups, although components such as the

transition probabilities differed between the two models. Note that within the CS the company only considered those with a history of AP.

Figure 9: The long-term Markov model (replication of Figure 27B from the CS)



Key: TG, triglyceride; AP, acute pancreatitis; Low risk TG is <10 mmol, Medium risk TG is ≥10 mmol and <22.6 mmol and High risk TG is ≥ 22.6 mmol.

Note: There are separate Markov traces for weekly dosing, every 2 weeks dosing and off treatment (SoC) in the volanesorsen arm of the model, to capture the clinical impact of dose. The SoC arm of the model has one trace for SoC.

Patients entered the model in a health state based on their TG band: low-risk (TG level < 10 mmol/L); medium-risk (10 mmol/L ≤TG level < 22.6 mmol/L); or high-risk (≥ 22.6 mmol/L) and based on the number of APs experienced in the last five years: zero; or one or more. The model had the functionality to also select patients with two or more APs in the previous five years; this was explored in scenario analyses.

In each 3-month model cycle, patients moved between TG bands or remained in the same band, experienced an AP, had CP, or died. As the model used a cohort approach, individual patients were not tracked with proportions of patients moving to each health state based on the transition probabilities described in Section 5.2.5. Patients with historical APs moved to the recurrent AP category when experiencing an AP. Within each health state a proportion of patients were simulated to have type 2 diabetes as detailed in Section 5.2.5.4.3.

In the long-term Markov model, both costs and QALYs were half-cycle corrected.

The company provide a full list of the assumptions within the base case model in Table D4 of the CS. Key assumptions include:

- Patients who did not reduce their TG levels by 25% and/or who do not have a TG level < 22.6 mmol/L in the first three months did not continue on volanesorsen treatment
- Patients who developed CP did not continue on volanesorsen treatment
- Patients remain on the fortnightly volanesorsen treatment until discontinuation in the long-term Markov model
- That the risk of an AP event was conditional on TG-risk band
- That volanesorsen treatment was associated with a protective effect with respect to AP events independent of reducing TG levels
- That each AP event was associated with the risk of death
- That each AP event was associated with the risk of developing CP
- That AP history and TG-risk band was associated with the risk of developing type 2 diabetes
- That CP was associated with an increased risk of death
- That type 2 diabetes was associated with an increased risk of death

These assumptions, along with the sources used to parameterise the model, are detailed by the ERG in Section 5.2.5.

The company did not consider the possibility that patients could die of AEs such as Grade 4 thrombocytopaenia and stated that "*we recognise this simplifying assumption is imperfect however, it should have minimal impact on estimates results due to the low likelihood of mortality and the consequent impact on the QALY gain.*"

5.2.5 Evidence used to inform the company's model

5.2.5.1 Treatment effectiveness on TG levels

In the deterministic base case, the company used the actual reduction in TG levels and absolute TG level at three-months to determine whether a patient met the continuation criteria described in Section 5.2.4.1. These values were held fixed in the probabilistic analyses which is likely to underestimate the uncertainty in the decision. The CS did not include a subgroup analysis using data restricted to the 14 APPROACH OLE patients who conformed to the licensed dose in the model because they believed the small numbers "*would likely have resulted in highly unstable ICER estimates*" (clarification response B26).

Beyond three months, the company's base case used the results provided by the GLMM to determine the predicted TG levels at three months associated with patients who received volanesorsen and with patients who received SoC. The data used in the analysis included 1,508 unique TG observations collected in 90 patients up to the February 2019 cut-off from APPROACH and APPROACH OLE. All the analyses were performed in SAS 9.4. The GLMM approach takes into account both within and between patient variability in the TG observations and trends in TG change over time, which is the appropriate method to use for repeated measures data.

The GLMM included 9 dosage regimens (no treatment, every two weeks, every week and 6 other regimes to accommodate periods of kick-in of new treatments and wash-out of old treatments). The principle of maximum likelihood was used to guide the selection of the duration for the kick-in and washout period. An exploratory analysis was conducted to explore the impact of choosing a different kick-in and washout period on the GLMM results. This showed that the change in the length of kick-in or washout period had little impact on the estimates of the coefficients.

For those receiving SoC, all patients are assumed to transition to the high-risk TG band unless another event occurred. These events were: death; CP; or moving to the recurrent AP state for those patients in the historical state.

For those receiving volanesorsen, at the end of the three-month period, a proportion of patients moved to fortnightly volanesorsen treatment whilst the remainder stop treatment. The TG level band for these patients was based on the mean values observed in APPROACH. After three months of treatment with volanesorsen, the model assumed that all patients continuing on treatment were in a medium-risk TG band unless another event occurred. These events were: death; CP; or moving to the recurrent AP state for those patients in the historical state.

Within the company's model the benefit associated with volanesorsen treatment was mainly due to moving patients to a lower TG band (medium-risk) compared with SoC (high-risk) although additional benefits were assumed. The risks of clinical outcomes were dependent on TG band as detailed in Section 5.2.5.4.

5.2.5.2 Treatment safety

Estimating the rate of AEs associated with volanesorsen compared with SoC is difficult as the only RCT did not use the licensed posology of volanesorsen. The company used the rates of AEs associated with the APPROACH OLE study, but commented that "*as AEs were sourced from the entire study population, this includes AEs experienced by patients on long-term weekly dosing and thus may*

overestimate AE frequency." Only AEs affecting 10% or more of patients that were moderate to severe and assessed as treatment-related were included in the model, with the exception of platelet lowering where counts remained above $50*10^9$/L. No AEs were assumed for the comparator arm. The AE rates / probabilities per cycle included in the model are provided in Table 13. For conciseness, the costs and QALY decrement associated with each event are also included in Table 13.

Table 13: The frequency of AEs per three-month cycle assumed for volanesorsen and the costs and QALY decrements associated with each AE.

Adverse Event	**Number per three-month cycle in the base case (scenario analyses)**	**Assumed associated cost per event**	**Assumed associated QALY decrement per event**
Fatigue	Zero (3.559)	Zero	0.004
Injection site reaction	0.130 (4.831)	Zero†	0.00002
Thrombocytopaenia Grade 1	0.070 (0.105)	£70	Zero
Thrombocytopaenia Grade 2	0.017 (0.058)	£70	Zero
	Probability per three-month cycle in the base case (scenario analyses)	Assumed associated cost per event	Assumed associated QALY decrement per event
Thrombocytopaenia Grade 3	0.004 (0.007)	£70	0.004
Thrombocytopaenia Grade 4	0.004 (0.027)	£581	0.038

† Cost assumed to be contained in the home healthcare service provided by the company

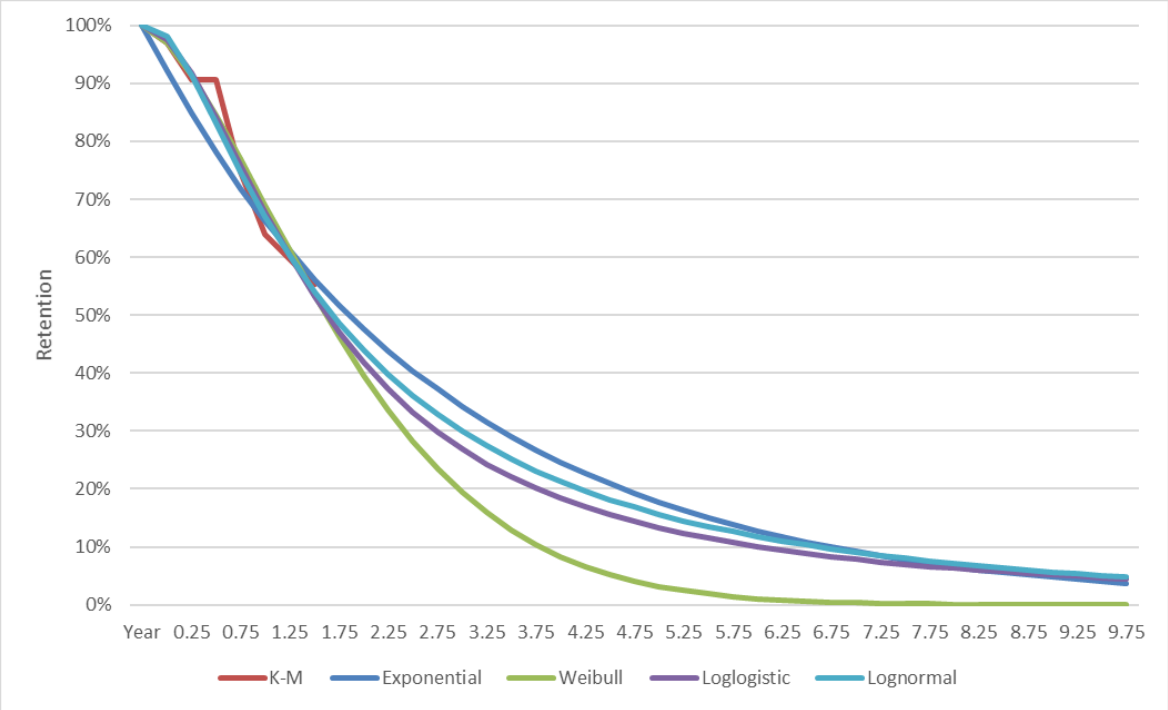
5.2.5.3 Treatment duration

Treatment with volanesorsen was discontinued as a consequence of one of three factors: the patient did not meet the continuation criteria that have been specified in Section 5.2.4.1; the patient died, or the patient discontinued "*due to lack of adherence to the treatment or monitoring regimen or toxicity issues.*" Patients who discontinued volanesorsen treatment received SoC treatment. The company fitted parametric survival functions to time on treatment data for 32 patients within the APPROACH OLE study who had fortnightly treatment, as these were considered more generalisable to the SmPC for volanesorsen. In the base case analysis the company selected the lognormal function in the base case as '*this is a curve with a long tail that best represents a proportion of patients remaining on treatment over the longer term*' and noted that only 1 of 20 patients discontinued treatment in the EAMS, and this was due to recurrence of cancer. The company also provided a scenario analysis whereby no patients discontinued treatment before death provided the continuation criteria were met. The goodness of fit

statistics were provided in Table D6 of the CS. These showed a small range in Akaike Information Criterion values (65.27 (lognormal) to 67.25 (generalised gamma) and in the Bayesian Information Criterion values (68.07 (exponential) to 71.65 (generalised gamma)).

The functions were plotted in Figure 32 of the CS and has been reproduced in Figure 10.

Figure 10: The parametric survival functions of time on treatment presented by the company (replication of Figure 32 of the CS)



The company present a scenario analysis where patients do not discontinue treatment until death or development of CP.

5.2.5.4 Assumed relationships between TG levels / AP status and risk of clinical outcomes

The model submitted by the company simulates the benefits associated with volanesorsen treatments through the favourable impact on clinical output associated with lower TG levels. The benefits took the form of fewer AP events, and based on this: fewer CP events; fewer type 2 diabetes cases; and greater life expectancy. The relationships assumed by the company for each component are detailed in the subsequent sections. Where the ERG believes there are limitations in the approach undertaken by the company these are detailed in Section 5.3.3.

5.2.5.4.1 The relationship assumed by the company between TG band and AP events

5.2.5.4.1.1 The relationship assumed by the company between TG band and AP events in patients with an historical AP who received SoC

The company undertook a retrospective statistical analysis of observational data fitting accelerated failure time (AFT) models using the CALIBER data to estimate the time to a first AP event. All the analyses were performed using R analytics software, although the package was not specified. The CALIBER data (described in Section 2.1) contain linked electronic health records in England between the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics and the Office for National Statistics. The CALIBER 1997-2016 data used for the analyses included around 1.8 million patients aged <40 years with at least 1 TG record in CPRD and included patients with raised TG levels through any cause, not just due to FCS. Covariates included in the analyses were: age; sex; TG band; history of AP, and interaction terms between TG bands and history of AP. The company used the results from this analysis to calculate the probability of an AP occurring in a cycle assuming a constant hazard. The assumed risks per cycle of AP are provided in Table 14. The risks of AP did not change as patients' ages increased. The company states that "*The model therefore under predicts AP rate on SoC, may slightly under predict AP costs, disutility and mortality and therefore may under predict the benefit of volanesorsen. However, these differences are likely to be small given the small absolute differences in AP rate between age 41 and 85, which would increase gradually over time.*"

The ERG notes that although the company called the survival models used to analyse the CALIBER data AFT models, the underlying distribution assumed for data was exponential. It was not clear if the exponential model fits the data the best or whether including other covariates could improve the model fit. The company states in the response to clarification question A25 that "*as Akcea did not have access to the CALIBER datasets, it had limited control in specifying the models*". The ERG believes that the approach taken by the company was reasonable.

5.2.5.4.1.2 The relationship assumed by the company between TG band and AP events in patients with an historical AP who received volanesorsen

The company took the estimated rates of AP in a population with an historic AP from the AFT model to the CALIBER data for SoC (see Section 5.2.5.4.1.1) and assumed that treatment with volanesorsen would reduce the probability of experiencing APs, not only through the lower TG band, but also due to volanesorsen treatment itself. The level of the reduction associated with volanesorsen itself was estimated in a *post hoc* analysis by comparing the rates of AP for patients in the five years prior to entering APPROACH OLE with the rate of APs in APPROACH OLE. These data estimated a rate ratio of 0.13 for people on volanesorsen compared with those on SoC (See Section 4.2.4.3). The assumed

risks per cycle of AP are provided in Table 14. Patients with an historical AP moved to the recurrent AP state following a subsequent AP.

Table 14: Assumed risk of AP per three-month cycle for patients in the company's base case

TG band	Historical AP		Recurrent AP	
	SoC	Volanesorsen	SoC	Volanesorsen
Low	0.88%	0.12%	11.52%	1.51%
Medium	2.13%	0.28%	11.52%	1.51%
High	5.20%	0.70%	11.52%	1.51%

5.2.5.4.1.3 The relationship assumed by the company between TG band and AP events in patients with a recurrent AP who received SoC

The company analysed the AP event rate of patients in APPROACH who had an AP within the previous 5 years to estimate the probability of an AP in a three-month period. The company combined all TG bands as the lower TG bands had a higher rate of AP than higher bands, which was not expected. The company stated that the '*observation may be spurious and may simply reflect the very low patient numbers in APPROACH. Alternative explanations may be that (1) patients with a history of frequent AP may go to greater efforts to control their TGs (2) patients who have had many events in the past are at higher risk of events in the future, regardless of TG levels.*" The assumed risks per cycle of AP are provided in

Table 14.

5.2.5.4.1.4 The relationship assumed by the company between TG band and AP events in patients with a recurrent AP who received volanesorsen

The company took the estimated rates for a population of patients with a recurrent AP for SoC (see previous section) and assumed that treatment with volanesorsen would reduce the probability of APs using the rate ratio of 0.13 described in the previous section. The assumed risks per cycle of AP are provided in

Table 14.

5.2.5.4.2 The relationship assumed by the company between AP events and developing CP

The company identified data contained in Yadav *et al*.[50] which provided rates of CP development based on time since first AP. At 100 months, CP had developed in approximately 2.5% of people following their first AP, which the company assumed was generalisable to AP events experienced by AP naïve patients only, and in approximately 12.5% of those with recurrent AP (defined as a repeat event), which the company assumed was generalisable to AP events experienced by historical or recurrent AP patients. These were translated into rates assuming a constant hazard. However, the company stated that the proportion of patients produced when using Yadav *et al.* were lower than estimated by clinicians. In order to produce a number more concordant with the values estimated by the clinicians, the company multiplied the rates from Yadav *et al.* by a factor of 60.

5.2.5.4.3 The relationships assumed by the company between TG bands, AP events, CP events and developing type 2 diabetes

The company fitted AFT models to the CALIBER data to estimate type 2 diabetes risk. Covariates included in the analyses were: age; sex; TG band; history of AP, and interaction terms between TG bands and history of AP. These models were used to estimate the average time to type 2 diabetes based on TG band assuming a constant hazard and provided the same value whether the patient had an historical or recurrent AP. These predictions were: low-risk TG band [redacted] years; medium-risk TG band [redacted] years; high-risk TG band [redacted] years, which was also assumed to be applicable to patients with CP. The company stated that "*As the diabetes event rate generated by the AFT model resulted in implausibly high levels of diabetes in the model, the prevalence in each health state was capped based on the available literature.*" For those without CP, the company differentiated the cap based on TG band and type of AP, historical or recurrent. For those with an historical AP, the cap was set to: 5.2% for the low-risk TG band; 14.6% for the medium-risk TG band; and 23.0% for the high-risk TG band. For those with a recurrent AP the cap was set to: 5.2% for the low-risk TG band; 14.6% for the medium-risk TG band; and 72.0% for the high-risk TG band. For patients with CP a cap of 80% was set. These caps were applied to the cohort of patients across the entire modelling horizon.

5.2.5.4.4 The relationships assumed by the company between TG bands, AP events, CP events, type 2 diabetes and mortality.

For patients with an historic AP and no subsequent event, the rate of death was taken from England and Wales life tables based on data for the years 2014-2016[51] weighted by the proportion of males and females at the start of the model. For patients who have subsequent APs there was a risk of death, that was assumed independent of the number of previous APs. The risk of death was taken from Gaudet *et al*. and was 4.78% in patients with FCS, although the ERG notes that this appears to be data in abstract form only and is based on a relatively small number of patients, with 12/251 dying from AP. The company assumed that this risk of death would also be reduced by volanesorsen treatment; that is, the

use of volanesorsen would both reduce the number of APs, and the risk of the AP resulting in death. The company estimated the impact of volanesorsen on the mortality rate following AP by using data from a retrospective cohort study presented by Wang *et al*.[26] where 1/66 patients with low TG levels died compared with 7/78 in the high TG group. The company assumed that all SoC patients would have high TG levels whereas those on volanesorsen would have low TG levels and that the relative risk of death would be 0.17 on volanesorsen compared with SoC. The Wang *et al*.[26] study was retrospective, with small event numbers and set in Taiwan which increases uncertainty in the value although clinical advice to the ERG suggested that volanesorsen would have a protective effect following AP compared with SoC.

The company assumed that the relative risk of death following a CP was 5.83 based on Nojgaard *et al*.[52] This value was based on weighted estimates of relative risks for males and females following diagnosis of CP in Denmark, although the majority of patients with CP did not have FCS. Whilst the exact value of increased mortality is uncertain analyses by the ERG showed that this parameter did not strongly affect the results of the cost-effectiveness analyses.

For patients with type 2 diabetes, the relative risk of mortality was assumed to be 1.28 based on data from NHS Digital.[53]

5.2.5.5 Health-related quality of life

5.2.5.5.1 The utility associated with health states

EuroQol 5 dimensions 5 level (EQ-5D-5L) data were collected in the APPROACH study. The company summarise these data as "[redacted]" The company also stated that the EQ-5D-5L scores were "*notably very high in both treatment groups ([redacted] in the volanesorsen and placebo arms respectively)*." Further details were provided in Table C24 and C25 of the CS.

The company claimed that the EQ-5D-5L values were implausible as they are "*notably higher than the average UK index value – which is approximately 0.85 for an adult in their mid-40s*[54]". As such, the company preferred the results from a vignette study that the company had commissioned. These results are only publicly available in abstract form with the conclusion that "*symptoms typically linked to higher triglycerides and history of AP were associated with lower utility*." Detailed descriptions of the vignette study are provided in Appendix 6 of the CS and in a separate report provided to the ERG. [redacted]

[redacted]

The values used in the model are shown in Table 15. This table also includes the assumed utility in the CP state, the QALY decrement of an AP event and the QALY decrement of type 2 diabetes, all of which were assumed independent of treatment.

Table 15: The utility values used in the company's base case.

Health State	Utility value
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	QALY decrement
[redacted]	[redacted]
[redacted]	0.225

5.2.5.5.2 The QALY decrement of AP

The QALY decrement of the AP state was calculated as the average decrement between the value for those in the AP-naïve vignette health states and those in the recurrent AP vignette health states

multiplied by the duration of an AP event in APPROACH, multiplied by two on the assumption that patients only went to hospital on 50% of AP episodes.

5.2.5.5.3 The QALY decrement of CP

The CP state values are calculated as the utility in the AP state minus the disutility of monthly AP flares; in the base case, the company assumed that treatment with volanesorsen would stop if a patient had CP.

5.2.5.5.4 The QALY decrement of type 2 diabetes

The decrement for a patient with type 2 diabetes was assumed to be that associated with uncomplicated diabetes (0.0621) from Sullivan *et al*.[55] plus 50% of the additive decrements of complication of diabetes (hypertension, stroke, congestive heart failure, myocardial infarction, plus additional decrements for five concomitant conditions) which increased the QALY decrement to 0.225.

The decrements are assumed additive, and thus, a person on SoC with an historical AP, in the low-risk TG band, with type 2 diabetes would be assumed in the model to have a utility of [redacted].

The company performed a sensitivity analysis using the EQ-5D-5L data and using a utility of 0.70 for all health states as requested by the ERG in the clarification questions for the initial company submission in 2018.[56]

5.2.5.5.5 The utility decrement estimated for carers

The company also included the disutility for carers of patients with FCS. The company identified no carer disutility related to FCS and used the values in a different NICE HST submission for metreleptin as a proxy.[57] This value was 0.10 and was believed generalisable as the condition (lipodystrophy) is '*another metabolic disease that shares similar outcomes in the scope with FCS and has similar challenges in terms of daily dietary management*'.

5.2.5.5.6 The utility decrement associated with AEs

The disutility associated with each AE in the model is detailed in Table 13 along with the probability of the AE occurring each cycle.

5.2.5.6 Resources and costs

Table D15 of the CS provides the costs used in the company base case. The following notable costs per three-month period were included: the acquisition costs of volanesorsen ([redacted]) which include a pricing scheme that has not been finalised; costs of hospital admissions (ranging from £717 for a person with a low-risk TG band to £1070 for a person with a medium- or high-risk TG band); specialist visits ranging from £308 (low-risk TG band) to £316 (medium- and high-risk TG bands) and CP (£12,668).

Cost per annum of background treatment for FCS were assumed to be £372 for all patients in all health states. The costs associated with each AE in the model is detailed in Table 13.

5.2.6 Model validation and face validity check

The company stated that they have conducted a number of separate steps to validate the modelling within their submission. These included: two advisory boards where the model structure and key assumptions were presented to clinical experts and health economics experts; a review of the model in February 2018 by an independent, experienced, health economics consultant following which a workshop was convened to identify model amendments and improvements; further model checking in May 2018 and July 2019; and calibration of the model to outcomes not captured in APPROACH or APPROACH OLE, such as CP and type 2 diabetes, to literature-based estimates. The ERG believes that the calibration was undertaken manually by adjusting input parameters until the desired target was reached.

5.2.7 Cost effectiveness results

The results reported by the company are shown in Table 16. The deterministic and probabilistic results are similar with incremental cost-effectiveness ratios (ICERs) of £216,565 and £220,056 per QALY gained respectively; the company performed sensitivity analyses on the deterministic model only. The company estimated that in its base case the undiscounted QALYs gained through the use of volanesorsen was less than [redacted] in both the deterministic and probabilistic results.

Table 16: The company's base case results

Description	Discounted Costs	Discounted QALYs	Incremental Discounted Costs	Incremental Discounted QALY	Cost per QALY gained
Deterministic					
SoC	[redacted]	[redacted]			
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	£216,565
Probabilistic					
SoC	[redacted]	[redacted]			
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	£220,056

5.2.8 Sensitivity analyses

The company undertook a large number of sensitivity and scenario analyses. In the majority of one-way sensitivity analyses the incremental cost-effectiveness ratio (ICER) remained stable between the £200,000 and £240,000 with the exception of the analysis in which the company assumed that patients missed over 7 doses per year without affecting the efficacy of volanesorsen, where the ICER dropped to approximately £196,500. The full results of the one-way sensitivity analyses are provided in Table D25 of the company's response to clarification questions.[32]

The majority of the company's scenario analyses increased the ICER, many of which were greater than £240,000 per QALY gained. These scenarios, extracted from Table D26 of the company's response to clarification questions[32], and some of which were requested by the ERG are shown in Table 17.

Table 17: Scenario analyses which increased the ICER above £240,000 per QALY.

Scenario name	Base case assumption	Scenario assumption	Incremental discounted costs	Incremental discounted QALYs	Incremental cost per QALY gained
Starting population	Genetically confirmed with a history of AP	Any genetically confirmed FCS patient	[redacted]	[redacted]	£247,652
Dosing schedule	285 mg weekly for three months followed by every 2 weeks maintenance dosing	APPROACH ITT analysis (note that weekly dosing is not assumed to incur additional drug costs over once every 2 weeks dosing in this scenario)	[redacted]	[redacted]	£260,587
Choice of HRQL inputs	Vignette study	All health states have utility of 0.7	[redacted]	[redacted]	£279,539
Calibration of risk of CP	60% lifetime risk of CP	42% lifetime risk of CP	[redacted]	[redacted]	£241,099
		30% lifetime risk of CP	[redacted]	[redacted]	£248,104
Inclusion of CP as health state	Include CP	Exclude CP	[redacted]	[redacted]	£269,167
Carer utility gain	Include	Exclude	[redacted]	[redacted]	£261,999
Cost of CP	£50,671	£9,465	[redacted]	[redacted]	£249,079

Cost of first 3 months volanesorsen	Same as every 2 weeks dosing	Cost doubled	[redacted]	[redacted]	£244,522

Whilst it did not move the ICER outside of the £200,000 - £240,000 range, the company provided a scenario analysis entitled the '*EAMS Scenario*' which requires further discussion. In this scenario it was assumed that no patient would discontinue volanesorsen treatment unless CP was developed, or death, that a patient would not have an AP whilst on treatment and that there would be no grade 4 thrombocytopaenia events. The ICER for this scenario was [redacted]. [redacted] However, the ERG believes that this scenario is implausible with expert clinical opinion suggesting a 10% discontinuation rate per year (see Section 5.3.3.4) and with AP events being observed in APPROACH OLE.

The company also provided analyses described as structural sensitivity analyses in Table D28 of the clarification response.[32] The ICERs did not change markedly, but the scenario in which it was assumed that patients would not discontinue volanesorsen treatment until CP or death resulted in a large increase in the undiscounted QALYs gained, which became [redacted].

5.3 Critique of the company's submitted economic evaluation

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Re-running the deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) presented within the CS.
- Where possible, checking the parameter values used in the company's model against their original data sources.

- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

During this process, the ERG identified minor implementation errors, which were addressed by the company in the model submitted following the clarification process.

5.3.2 Adherence of the company's model to the NICE reference case

As shown in Table 18 the company's economic evaluation is generally in line with the NICE reference case.[58]

Table 18: Adherence of the company's model to the NICE reference case

Element	Reference case	ERG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The CS met the NICE reference case.[58]
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS met the NICE reference case.[58] A time horizon of 59 years was adopted. By this point, almost 100% of simulated patients were dead.
Synthesis of evidence on health effects	Based on trial outcome data and systematic review	The CS met the NICE reference case.[58] However, the company used GLMM techniques to estimate the TG-risk band for patients on volanesorsen and patients on SoC rather than the raw data. The simulated clinical outcomes were estimated from literature reviews for each TG-risk level. A further protected benefit was assumed for volanesorsen.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	The CS met the NICE reference case.[58]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS did not meet the NICE reference case.[58] Whilst EQ-5D-5L scores were collected in APPROACH the company believed these to be '*implausible*' and commissioned a vignette study. The results of the vignette study were further adapted to provide a utility gain for those on volanesorsen treatment.

Element	Reference case	ERG comments
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	It is unclear whether the CS met the NICE reference case.[58] Participants of the vignette study [redacted]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS met the NICE reference case.[58]
Evidence on resource use and costs	Costs should relate to NHS and personal social services (PSS) resources and should be valued using the prices relevant to the NHS and PSS	The CS partially met the NICE reference case.[58] PSS costs were not included but not thought to be significant by the company.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The CS met the NICE reference case.[58]

5.3.3 Limitations identified by the ERG in the company's modelling

The ERG identified a number of limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the ERG believes are more plausible. These are detailed in the following sections.

5.3.3.1 The acquisition price of volanesorsen

In addition to the PAS, the company want to provide an additional reduction in price to the NHS but this has not been formally agreed. The company presented their base case results incorporating this additional reduction in price. In line with the NICE process, the ERG has produced results which do not include this additional price reduction as it has not been formally agreed.

5.3.3.2 The proportion of patients entering the model in each TG-risk band

The ERG believes that the method for estimating the distribution of patients entering the model in terms of AP history and TG-risk band was incorrect. The ERG used the absolute counts as it preserved the integrity of the data and ensured that the numbers were integers.

5.3.3.3 The utility assumed for health states with and without treatment

The ERG notes that the vignette undertaken by the company did not distinguish between patients who were on treatment and those who were not. As such, the ERG believes that the underlying utility for a patient within a health state should not depend on whether a patient is on treatment as assumed by the company in its base case (Table 15). The ERG prefers utilities more aligned to the vignette results than used by the company, whilst also assuming, as the company arbitrarily did, that the values for patients with an historical AP lie halfway between those with no prior AP and those with an AP with lingering effects.

[redacted]

The ERG identified potential limitations in the vignette study. [redacted]

Table 19: The utility values used in the company's base case

Patients receiving:	Utility value used by the company	Utility value preferred by the ERG
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.3.3.4 The assumed level of discontinuation whilst on volanesorsen treatment

The company contend that the level of discontinuation from volanesorsen treatment will be lower than that seen in APPROACH and APPROACH OLE as after the three-month period volanesorsen would be taken fortnightly rather than weekly. A scenario analysis was run by the company assuming no discontinuation. The ERG believes that an assumption of no discontinuation is not plausible, having noted that one patient had discontinued in the EAMS, albeit for cancer-related reasons, and that [redacted] patients who conformed to the licensed dosing schedule had discontinued at [redacted] years, although these patients had reduced their dose due to an AE and may therefore be more likely to discontinue. Following discussion with clinical experts, the ERG deemed that 10% per year, whilst subjective, would not be an unreasonable estimate of the discontinuation rate.

5.3.3.5 The half cycle-correction of volanesorsen acquisition costs

In calculating the costs of volanesorsen acquisition, the company used a half-cycle correction in the longer-term Markov model. Whilst this is appropriate for continuous treatment, it is not appropriate when doses are given at fixed intervals. As an example, if all patients received an intervention on day 1 of a cycle, then the cost of the intervention in that cycle is unaffected by the events experienced by the patient in the subsequent days of the cycle. The ERG believes that a more accurate way of estimating the acquisition costs of volanesorsen would be to add the costs of half a dose in the discontinuation cycle for each patient who discontinues treatment in that cycle.

5.3.3.6 The assumed reduction in APs associated with volanesorsen treatment additional to TG reduction

The company assumed that volanesorsen would reduce AP events by reducing the TG risk-band of a patient and also by applying a factor to the rate within the TG risk-band as described in Section 5.2.5.4.1.2. The ERG believes that as the factor has been calculated from a population who have already had a potential reduction in TG levels then this represents double-counting of the benefits. Furthermore, the reduction may be an overestimate of the impact of a patient enrolling in a study (albeit open-label), by regression to the mean or through a higher dose of volanesorsen being administered in APPROACH OLE. The ERG calculated that the multiplication factor required to produce a total reduction of 0.13, when it was assumed that the reduction in AP risk between the high-risk TG band and the medium-risk TG band was 59% (1-(2.13/5.20 – see Table 14), would be 0.32 [0.13/(1-0.59)]. In discussion with clinical experts, and considering the potential impact of a study effect and regression to the mean, the ERG believes that a multiplication factor related to the rate of APs within a specific TG-risk band of 0.50 through the use of volanesorsen would be more appropriate than the 0.13 used by the company, although the ERG recognises that this value is subjective. In order to run the probabilistic analyses, the ERG assumed a standard error of 0.10.

5.3.3.7 The assumed level of CP within the model

The company identified data from Yadav *et al*. that provided information on the time to development of CP. However, the company believed this to underestimate the level of CP and multiplied the rates calculated by 60 to arrive at an estimate that was more aligned to a 60% probability of CP that had been raised by clinical experts to the company. The ERG reviewed the documentation related to the probability of CP and noted that: one clinician felt that left untreated 60–70% would develop CP; another stated that all patients with recurrent AP would develop some form of chronic symptomatology; a third thought that the risk of AP was 80% and that of these, at least 60% (so, at least 48% of the total) would go on to be recurrent or chronic, and a fourth thought that the lifetime risk may be nearer 20%. Using information provided by our clinical experts, the ERG assumed that a multiplication factor of 28, which would be aligned with a lifetime CP prevalence of approximately 40%, may be more reasonable as a base case.

5.3.3.8 The disutility associated with type 2 diabetes

The company increased the disutility associated with uncomplicated diabetes by adding 50% of the disutility associated with four major conditions and five concomitant conditions as described in Section 5.2.5.5.4. The ERG believes it implausible that 50% of the population in the model with diabetes would

have all nine conditions. Instead the ERG assumed that 50% of patients had congestive heart failure, which was the most impactful condition with a decrement of 0.1034. The ERG prefers a disutility value of 0.114 rather than the estimate of 0.225 used in the company base case.

5.3.3.9 The disutility associated with carers

As detailed in Section 5.2.5.5.5, the company assumed a disutility of 0.10 for carers assuming that a value within the ongoing HST of metreleptin[57] would be generalisable in FCS as lipodystrophy is '*another metabolic disease that shares similar outcomes in the scope with FCS and has similar challenges in terms of daily dietary management*'. The ERG notes that it is unclear whether the 0.10 has been accepted by the committee which stated in a Final Evaluation Document[59] that "*The committee also noted that no specific carer-related utilities were included in the model, so encouraged the company to explore the effect of including carer utilities, including variation with age.*" The ERG also notes that FCS patients in the model are assumed to be 41 years of age, whereas in the metreleptin HST the "*The committee noted that the population for which metreleptin is indicated includes children and young people*." The ERG is not convinced that the burden on carers in FCS is substantially larger than that of other conditions from which the money to fund volanesorsen, if recommended, would be diverted. As such, the ERG prefers excluding utility gain for carers to represent no net change in carer utility between diseases.

5.3.3.10 The costs of treating CP

The company assumed that patients with CP cost, on average, £50,671 per year. This was taken from Hall *et al*.[60] which the company state "*includes all direct healthcare costs relevant to the management of CP*". The ERG identified an alternative paper by Dennison *et al*.[61] which reported a direct cost of £9,465 per year, which the company state excluded community costs, follow-up costs and the costs of type 2 diabetes. In the Hall *et al*. paper the authors conclude that "*CP is costly but precise costs are difficult to make due to the paucity of available data*" and the ERG notes that the costs calculated appear to be dependent upon an assumed prevalence of CP. Given that the clinical experts to the ERG believed that, on average, the costs used by the company were too high, the ERG has arbitrarily used £30,000 per annum for CP patients which lies between the company's estimated value and £10,000, a value thought more appropriate by some clinical advisors to the ERG.

Additional areas of uncertainty remain, such as whether volanesorsen has a beneficial impact on mortality associated with AP (see Section 5.2.5.4.4) as the study from which the estimate of benefit was derived was a retrospective cohort study that was undertaken in China.[26] Retrospective cohort studies may be confounded or have missed collecting important variables and the generalisability of treatment in China with the UK is uncertain. However, the ERG has left this value at that selected by the company.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has operationalised the changes described in Sections 5.3.3.1 to 5.3.3.10. Each change has been made individually, before being combined into the final ERG-preferred ICER. The results of the ERG's exploratory analyses are provided in Table 20.

It is seen that the ICER preferred by the ERG is in excess of £490,000. No single factor was the driver for this increase in ICER. The undiscounted QALY gain for this scenario was [redacted] in the deterministic model and [redacted] in the probabilistic model. Sufficient PSA iterations (2000) were conducted to be certain the conclusion is robust as the 95% confidence interval in the probabilistic mean ICER was £490,025 to £494,730 using the Hatswell *et al.*[62] method. The 95% confidence interval of the ICER using a percentile method ranged from £449,032 to £643,991.

The component with the largest effect on the estimated QALYs gained was [redacted] which had a discounted QALY gain of [redacted] and an undiscounted QALY gain of [redacted].

Table 20: The exploratory analyses undertaken by the ERG

Scenario description	ERG Report Section	Incremental Discounted Costs	Incremental Discounted QALY	Cost per QALY gained
Deterministic				
Company base case	5.2.7	[redacted]	[redacted]	£216,565
Using the currently agreed price of volanesorsen	5.3.3.1	[redacted]	[redacted]	£244,522
Amending the proportions in each TG-risk band	5.3.3.2	[redacted]	[redacted]	£216,260
Using the ERG's preferred utility values	5.3.3.3	[redacted]	[redacted]	£277,720
Assuming 10% discontinue treatment per year	5.3.3.4	[redacted]	[redacted]	£207,876
Amending the half-cycle correction of volanesorsen drug costs	5.3.3.5	[redacted]	[redacted]	£218,400
Assuming an additional 50% reduction in AP due to volanesorsen treatment	5.3.3.6	[redacted]	[redacted]	£240,595
Calibrating the lifetime probability of CP to 40%	5.3.3.7	[redacted]	[redacted]	£226,926
Amending the disutility associated with type 2 diabetes	5.3.3.8	[redacted]	[redacted]	£231,030
Excluding the utility benefit to carers	5.3.3.9	[redacted]	[redacted]	£261,999
Changing the cost of CP care to £30,000 per year	5.3.3.10	[redacted]	[redacted]	£232,876
ERG-preferred deterministic ICER, incorporating all of the above changes	-	[redacted]	[redacted]	£483,814

ERG-preferred probabilistic ICER, incorporating all of the above changes	-	[redacted]	[redacted]	**£492,364**

The ERG further explored the impact of assuming no decrease in underlying utility associated with either TG-band or treatment, assuming a value of 0.70 for all patients but maintaining all other values in the ERG base case. In this analysis the deterministic ICER increased to £580,226 showing the model is sensitive to assumptions in the underlying utility. An additional analysis was undertaken where the protective effective of volanesorsen on mortality following an AP was removed, with the relative risk changed from 0.17 to 1.00. This increased the deterministic ICER to £525,440 per QALY gained.

Furthermore, the ERG investigated the impact of a scenario analysis added by the company during the clarification process.[32] This analysis evaluated the joint impact of assuming that patients receiving SoC would be distributed amongst TG-risk bands after 3 months as they were when entering APPROACH, and that patients receiving volanesorsen were not all allocated to the medium TG-risk band but were distributed using the predicted TG values from the GLMM for patients receiving volanesorsen. The ICER increased by approximately £14,000 to £497,186 per QALY gained when these assumptions were used in the ERG-preferred base case. Clinical advice provided to the ERG suggested that in the long-term the TG levels for patients on volanesorsen could be lower than that assumed in the company base case and that more patients on SoC would be in the high TG-risk band than on entry to APPROACH. Given this clinical feedback the ERG did not incorporate this scenario analysis into its base case ICER.

The ERG comments that there remains considerable uncertainty in the ICER related to the robustness of the clinical evidence.

6 END OF LIFE

The company made no claims that volanesorsen would meet the end of life criteria. The ERG concurs with the company's view noting that in the company's base case patients on SoC are estimated to live for greater than 20 years.

7 OVERALL CONCLUSIONS

The clinical evidence base has serious limitations in that the pivotal study and supporting studies did not plan to use the dose that has been licensed. The studies were based on a weekly dose, whereas the license is for a weekly dose for three months, followed by doses every two weeks. This is likely to impact on both efficacy and safety outcomes, and consequently on discontinuation rates. The CS reported two subgroup analyses of patients who reduced to every two weekly dosing and these show that TG levels do not reduce to the same extent compared to patients receiving weekly doses. However, the extent by which they do reduce is uncertain due to problems including their small sample sizes and *post hoc* nature. The impact on safety outcomes and discontinuations is also uncertain since patients who entered these analyses had generally reduced their dose due to adverse events, thus leaving the analysis at high risk of selection bias. In addition, the primary outcome measure was for the surrogate, TG levels, and the impact on the hard clinical outcome of AP rates is uncertain due to analyses being underpowered, exploratory, retrospective, single-armed and/or post hoc in nature, and being based largely on patients receiving weekly dosing.

There was a considerable difference in the company's and the ERG's probabilistic estimate of the ICER: the company's value was approximately £220,000 per QALY compared with the ERG's value of approximately £490,000 per QALY. There was no single factor that caused this marked increase. The four changes having greatest impact in one way sensitivity analyses from the deterministic company base case were (approximate increase in the ICER contained in parentheses): using the ERG-preferred utility (£60,000); excluding the utility benefit to carers (£45,000); and assuming that the reduction in AP through volanesorsen independent of TG-level changes was not as large as the company estimated (£25,000). There was substantial uncertainty in the utility associated with each TG-risk band; if a flat rate utility of 0.7 across all TG health states is assumed the ICER further increases by approximately £100,000. There was considerable uncertainty related to the relative protective effect of volanesorsen compared with SOC following an AP; if this was removed the base case ICER increases by over £40,000. There also remains considerable uncertainty related to the robustness of the clinical evidence.

7.1 Implications for research

From a clinical perspective, evidence relating to the actual reductions in TG levels achieved at the licensed dose would help to clarify the clinical efficacy of volanesorsen. Similarly, the rates of adverse events, especially thrombocytopaenia, and discontinuations at the licensed dose would be useful.

The major evidence gaps, aside from the clinical limitations listed above relate to the utility values associated with the TG-risk bands for the patient and for carers. Obtaining further data on the costs of treating FCS patients with CP would reduce the uncertainty within the model.

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9 APPENDICES

Appendix 1: Quality assessment of key efficacy trials

Table 21 Quality assessment of APPROACH; CS and ERG judgements using the CRD handbook criteria[63]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomised to treatment using an interactive voice/web response system. Pati	Yes	1:1, stratified by prior history of pancreatitis and concurrent treatment with fibrates and/or prescription omega-3 fatty acid. Patients were allocated to treatment using an Interactive Voice/Web-Response System. (p67 of the CS)[47] A permuted block schedule was used.

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		ents were stratified by: • • •		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		A permuted block schedule was used.		
Was the	Yes	The study	Yes	Patients were allocated to treatment using an Interactive Voice/Web-Response System. (p67 of the CS)[47]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
concealment of treatment allocation adequate?		was double-blind.		
Were the groups similar at the outset of the study in	Yes	As described in Section 9.4.3, patients' baseline charact eris	[redacted]	[redacted]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
terms of prognostic factors, for example, severity of disease?		tics were well balanced between the treatment groups		
Were the care providers, participant	Yes	The sponsor, patients, monitors and study	Yes	Double-blind. Patients and study personnel were blinded until all patients had completed treatment and the database was locked. To maintain blinding, study personnel were not allowed access to any lipid panel results, including apoC-III. (p67 of the CS)[47]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
s and d outcome assessors blind to treatment allocation? If any of these people were not blinded,		centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apo		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
what might be the likely impact on the risk of bias (for each outcome)?		C-III, were not availble to any of these individuals. An independent review committee adjudicated all SAEs that wer		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		e consistent with a major cardiovascular event, and all AEs and SAEs that were consistent with acute pancreatitis.		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		The committee members were blinded to treatment allocation.		
Were there any unexpected imbalances in dr	Yes	Fourteen patients (42.4%) in the volanesorsen group withdr	Yes	Fourteen patients (42.4%) in the volanesorsen group withdrew from the study, compared with 2 (5.9%) in the placebo group. The most common reason for withdrawal from the study in the volanesorsen group was AEs: 9 patients (27.3) withdrew for this reason. No patients in the placebo group withdrew because of AEs. 5 patients who discontinued because of thrombocytopaenia did so before an enhanced monitoring system was put in place. (p82 of the CS)[47]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
op-outs between groups? If so, were they explained or adjusted for?		ew from the study, compared with 2 (5.9%) in the placebo group. The most common reason for withdrawal from the		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		study in the volanesorsen group was AEs: 9 patients (27.3) withdrew for this reason. No patients in the placebo group withdrew bec		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		ause of AEs. 5 patients who discontinued because of thrombocytopaenia did so before an enhanced monitoring system was		

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
		put in place.		
Is there any evidence to suggest that the authors measured more outcomes	No	All the outcomes measured are fully documented in the study report.	No	All relevant outcomes measured in the trial were reported in the CS.

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
than they reported?				
Did the analysis include an intention-to-treat analysis? If so, was this ap	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-	[redacted]	[redacted]

	CS response		ERG response	
Question	**Response**	**How is the question addressed in the study?**	**Response**	**How is the question addressed in the study?**
proportiate and were appropriate methods used to account for missing data?		to-treat population as defined in ICH Guidelines.		

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care.[63] York: Centre for Reviews and Dissemination

Table 22 Risk of bias assessment for COMPASS as reported in the CS (Table C13), and as judged by the ERG, using the CRD handbook's criteria[63]. Partial reproduction of CS Table C13.

	CS response		ERG response	
Question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomised 2:1 to receive either volanesorsen or placebo using an interactive voice/web response system. Patients were stratified by: • prior history of pancreatitis; • concurrent use of fibrates and/or prescription omega-3 fatty acids. A permuted block schedule was used.	Yes	Patients were randomised 2:1 to receive either volanesorsen or placebo using an interactive voice/web response system. Patients were stratified by: • prior history of pancreatitis; • concurrent use of fibrates and/or prescription omega-3 fatty acids. A permuted block schedule was used.
Was the concealment of treatment allocation adequate?	Yes	The study was double-blind.	Yes	An interactive voice/web response system was used.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	As described in Section 9.4.3 of the submission, baseline characteristics and demographics were balanced between treatment groups in the subset of 7 patients with FCS, although there were no male patients in the placebo group.	No	Fasting TG levels were higher in the placebo group than in the volanesorsen group. Other baseline characteristics were not reported.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	The sponsor, patients, monitors and study centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apoC-III and TGs, were not available to any of these individuals. An independent review committee adjudicated all SAEs that were consistent with either a major adverse cardiovascular event or acute pancreatitis. The committee members were	Yes	The sponsor, patients, monitors and study centre personnel were blinded throughout the study. To ensure the blind was maintained, lipid panel results, including apoC-III and TGs, were not available to any of these individuals. An independent review committee adjudicated all SAEs that were consistent with either a major adverse cardiovascular event or acute pancreatitis. The committee members were

	CS response		ERG response	
Question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
		blinded to treatment allocation.		blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	All 7 patients in the FCS subset completed the study. Five of these patients received volanesorsen and 2 received placebo.	No	All 7 patients in the FCS subset completed the study. Five of these patients received volanesorsen and 2 received placebo.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All the outcomes measured are fully documented in the study report.	Yes	Multiple outcomes are reported in the CSR that are not reported in the CS.[47]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.	Yes	The definition of FAS was all randomized patients with baseline TG. Multiple imputation was used for missing data. (p62 and p75 of the COMPASS CSR[35])

N/A, not applicable; FCS, familial chylomicronaemia syndrome; TG, triglycerides; SAE, serious adverse events; CSR, clinical study report; CS, company submission; ITT, intention to treat; FAS, full analysis set; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination[63]

Table 23 Reproduction of Table C14 of the CS. Critical appraisal of APPROACH OLE, using the CRD handbook[63] criteria.

Study name	**APPROACH OLE**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	N/A	The study was open-label. All patients received volanesorsen.
Was the concealment of treatment allocation adequate?	N/A	The study was open-label. All patients received volanesorsen.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Data were analysed for two patient groups: those who had previously received volanesorsen in APPROACH or COMPASS and those who were treatment-naïve (i.e. received placebo in either APPROACH or COMPASS, or did not take part in either of these studies). As described in Section 9.4.3, at the interim analysis, patients' baseline characteristics were broadly similar between the two groups. However, as would be expected, patients in the treatment-naïve group had higher TG levels at study entry than those who had previously taken volanesorsen.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N/A	The study was open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	At data cut off on 6th January 2017, [redacted]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The interim study report does not report on all outcomes, as there were insufficient data for some outcomes at the time of the analysis. However, all the outcomes measured will be fully documented in the final study report.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	The primary analysis was carried out on the FAS, which represents the practically-feasible intent-to-treat population as defined in ICH Guidelines.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Appendix 2: Key patient demographics and baseline characteristics in APPROACH, APPROACH OLE and COMPASS, synthesised from Tables C8-C10 of the CS.

Table 24 Key patient demographics and baseline characteristics in APPROACH, APPROACH OLE and COMPASS, synthesised from Tables C8-C10 of the CS.

	APPROACH				[redacted]			COMPASS	
	Volanesorsen (n = 33)		**Placebo (n = 33)**		[redacted]			**Volanesorsen (n = 5)**	**Placebo (n = 2)**
Age, mean (range) years	47	(22 – 75)	47 (23 – 73)	(20 – 68)	[redacted]			47 (33 – 54)	51 (43 – 58)
Gender, % M/F	48.5/51.5		42.4/57.6		[redacted]			40.0/60.0	0.0/100.0
Fasting TG, mean (range) mg/dL	2267 (347 – 5660)		2152 (631 – 5475)		[redacted]			2134 (1074 – 3998)	2644 (2422 – 2867)
History of acute pancreatitis, n (%)	24	(72.7)	9 (81.8)	(78.8)	[redacted]			NR	NR
Abdominal pain*	7	(21.2)	3 (27.3)	(30.3)	[redacted]			NR	NR
Lipid lowering therapies, n (%)									
Fibrates	17	4 (36.4)	15	(45.5)	[redacted]			NR	NR

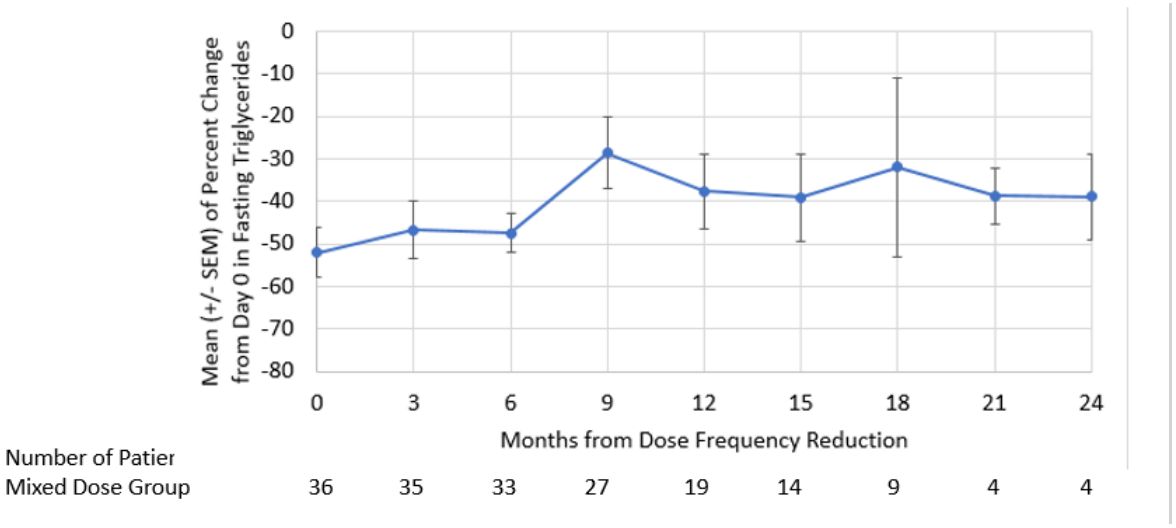
	HMG-CoA reductase inhibitors	9	3 (27.3)	4	(12.1)	[redacted]	[redacted]	[redacted]	NR	NR
	Fish oils/Other ***	3	3 (27.3)	1	(3.0)	[redacted]	[redacted]	[redacted]	NR	NR
Platelet aggregation inhibitors		8	(24.2)	1 (9.1)	(15.2)	[redacted]	[redacted]	[redacted]	NR	NR

HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-coenzyme A; TG, triglyceride; M/F, male/female; NR, not reported
* APPROACH, during screening and Week 1, n (%); [redacted]
** APPROACH reported fish oils; [redacted]

Table of Contents

Appendix 3 Change in TG levels over time after dose adjustment in APPROACH and APPROACH OLE

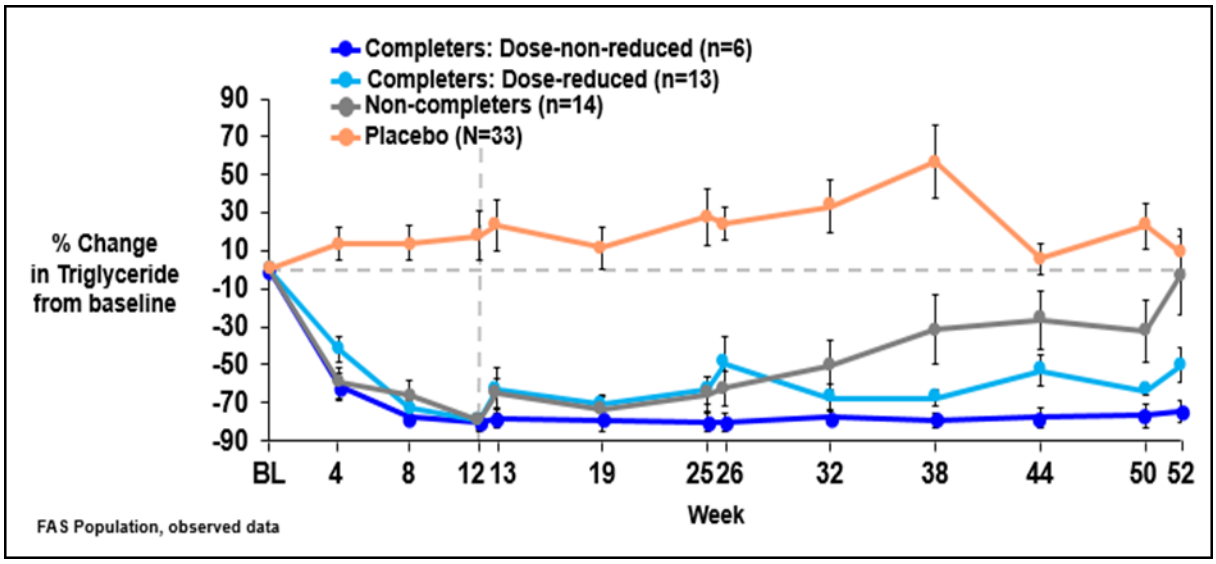
Figure 11 Change in TG levels over time after dose adjustment in APPROACH and APPROACH OLE (replication of Figure 12 from the CS)



Day 0 is defined as the last TG assessment before or on the date of first dose adjustment. SEM, standard error of the mean

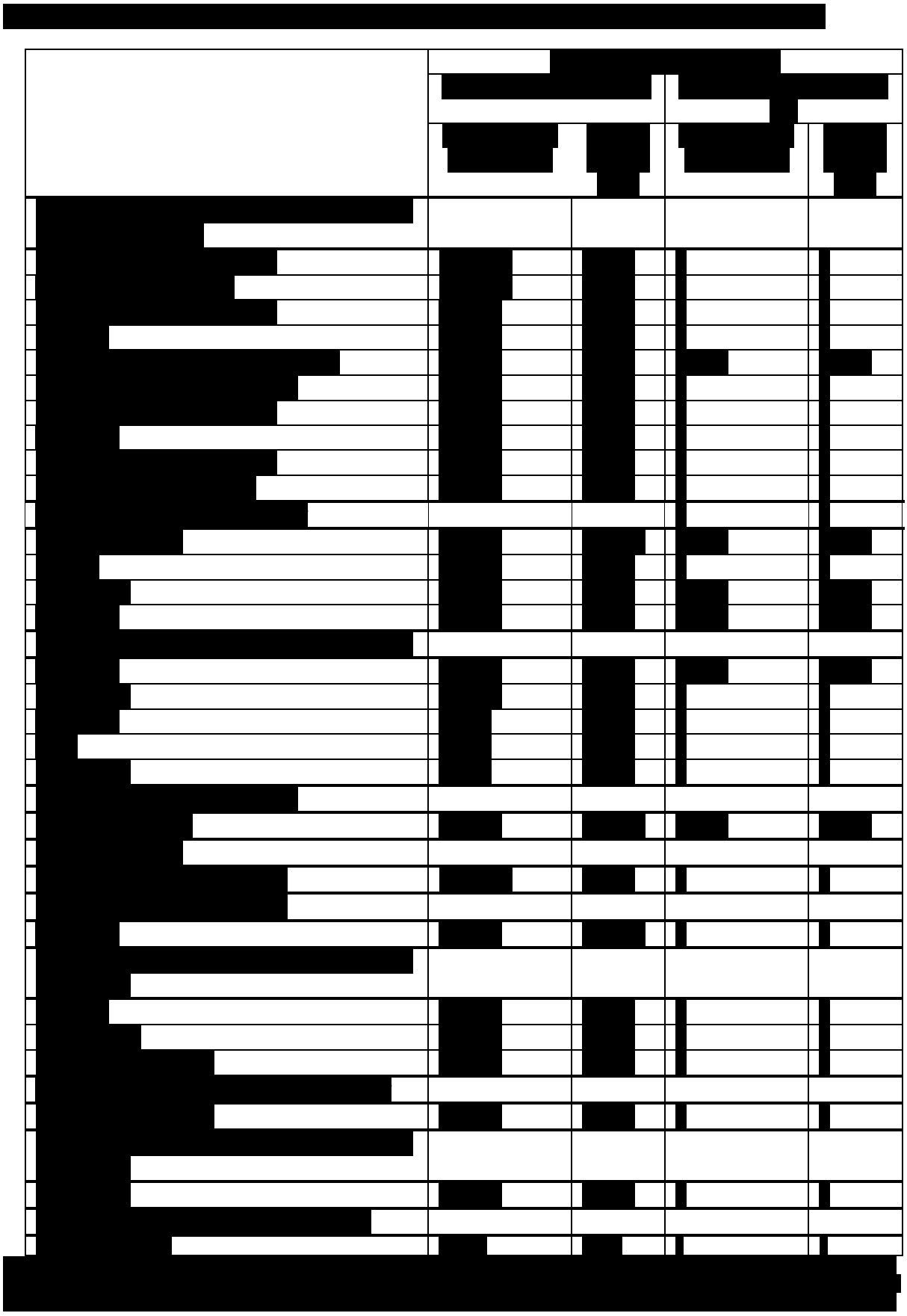
Source: Volanesorsen Type A briefing book, November 2018, Akcea data on file[64]

Figure 12 TG levels over time in APPROACH, including dose adjustments and non-completers (replication of Figure 13 of the CS)



Source: ID1326 volanesorsen ERG clarification responses, July 2018, Akcea data on file

Appendix 4: Adverse event rates for APPROACH, from 2018 company submission.



[redacted]

Source: APPROACH clinical study report, 23rd June 2017, Akcea data on file

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Tuesday 12 November 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ICER using a flat rate utility across all health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 last paragraph, “if the EQ-5D data collected in APPROACH were used, the ICER further increases the ERG base case by approximately £100,000.”	Change to “if a flat rate utility of 0.7 across all TG health states is assumed, the ERG base case ICER further increases by approximately £100,000.”	The company was not able to replicate this analysis. We sought clarification of the details behind the conclusion that this ‘increases the ERG base case by approximately £100,000’. It would be more accurate to state that this (increase of £100,000 on the ICER) is a result of applying a flat rate utility value of 0.7 across all health states. The company found that using the APPROACH EQ-5D data actually decreased the ICER	Thank you, this has been amended.

Issue 2 EAMS stopping rule

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15, last paragraph. “It is also not clear if these patients were subject to the treatment-response stopping rule at 3 months.”	These patients were not subject to the treatment-response stopping rule at 3 months (see Section 3.2).	Clarification: there was no stopping rule in EAMs.	Thank you for the clarification. This has been amended.

Issue 3 Typographical error 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
At the bottom of page 24 trial is misspelt “trail”	Correct to “trial”	Typographical error	Thank you, amended.

Issue 4 Clinical evidence relating to volanesorsen, included in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 4 page 27. The ReFOCUS study is included within table 4 of the ERG report. This study was not included within tables C3 or C4 that summarised the clinical evidence presented in the company submission. Rather, it was presented as complementary data describing the burden of disease. ReFocus was only described within the clinical efficacy section because it recruited patients from APPROACH OLE.	Exclude this study from table 4 and describe it separately under a section relating to evidence presented by the company on burden of disease and/or quality of life.	Clarification: As it stands the ERG report suggests that the company presented evidence from ReFOCUS as a “key efficacy trial”. In the CS the intent was that the APPROACH and APPROACH OLE trials presented the key clinical efficacy evidence. IN-FOCUS and ReFocus were presented in the CS to provide evidence for burden of disease and QoL.	The study is described as “Effect on burden of disease”, which implies efficacy. However, we have divided Table 4 into two sections – “Efficacy and Safety”, and “Effect on burden of disease” to reflect the less robust methodology of this study. We have added a sentence to section 4.2.3.1.4 “The company present this study as evidence on the effect on burden of disease.”

Issue 5 Reference to stopping rule 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Second to last paragraph, page 50. “indicates a good proportion of patients are likely to meet the stopping rule in the license”.	Amend to: ‘indicates a good proportion of patients are likely to continue on treatment after assessment of the treatment-response stopping rule in the license’	Clarification: This statement is open to misinterpretation – and potentially reads as meaning the opposite of what we think is intended. General comment on continuation rule/stopping rule: The NICE HST dossier template refers to a ‘continuation rule’ whereas the SmPC has a ‘discontinuation rule’. One being the opposite of the other. They are not consistently applied in the ERG report (or the CS submission) but we kindly request that any reference in the ERG report to this rule is double checked to ensure accuracy and minimise risk of misinterpretation.	Thank you, this amendment has been made. We have checked for other instances referring to the stopping rule or continuation rule and ensured language is clear.

Issue 6 Reference to stopping rule 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Second to last paragraph, page 50. “[redacted].”	Amend to:“[redacted].”	Clarification: As per the previous issue, to clarify how many patients met the treatment-response	This amendment has been

		stopping rule (and stopped or continued on treatment).	made. Thank you.

Issue 7 Calculation of AP rates on volanesorsen

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 52, “[redacted].”	Request to delete the sentence regarding the lack of clarity regarding pauses. After the sentence: “[redacted].” Write: “[redacted]”.	Clarification: Akcea did not realise that this specific information was required. It can be confirmed that exposure time included periods with dose pauses.	Thank you for the information, this has been amended.

Issue 8 Reference to pricing used in economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Last paragraph of page 60 "The base case analysis presented by the company and the majority of scenario analyses have not used the list price, despite no formal agreement being in place."	Amend to "A simple PAS has been agreed between the company and NICE. However, the base case analysis presented by the company and the majority of scenario analyses included an additional financial arrangement whereby [redacted]."	Clarification: Currently the text does not make clear that a simple PAS has been agreed. It is the mechanism to manage the cost of every week dosing that is still to be finalised. Amending the text would clarify the situation for stakeholders.	This amendment has been made. Thank you.

Issue 9 Subgroup analysis of 14 patients who conformed to SmPC posology

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 64, first paragraph of 5.2.5.1 "The CS did not use data from the APPROACH OLE subgroup analysis of patients who conformed to the licensed dose in the model"	Amend to "The CS did not include a subgroup analysis using data restricted to the 14 APPROACH OLE patients who conformed to the licensed dose in the model"	Clarification: this text could be interpreted such that this subgroup of patients who conformed to the licensed dose were excluded from the modelling. A subgroup analysis of these 14 patients alone was not undertaken. However, these 14 patients are contained within the dataset used in the regression	This amendment has been made. Thank you.

		model that underpins this aspect of the economic model	

Issue 10 Description of how the chronic pancreatitis data from Yadav was used

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Last paragraph, bottom of page 69 “At 100 months, CP had developed in approximately 2.5% of people without recurrent AP, which the company assumed was generalisable to historical AP, and in approximately 12.5% of those with recurrent AP”	This should read “At 100 months, CP had developed in approximately 2.5% of people following their first AP, which the company assumed was generalisable to AP events experienced by AP naïve patients only, and in approximately 12.5% of those with recurrent AP (defined as a repeat event), which the company assumed was generalisable to AP events experienced by historical or recurrent AP patients”.	Clarification: The definition of recurrent AP in Yadav related to any repeat AP event. Historical AP patients in the model had had a previous AP event and therefore can be considered as ‘recurrent’ with respect to Yadav’s definition. Changing the text would clarify how the Yadav data were used.	This amendment has been made. Thank you.

Issue 11 Typographical error 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78 section 5.3.3.2. “The ERG used the absolute counts as it preserved the integrity of the data and insured that the numbers were integers.”	“Insured” should be changed to “ensured”.	Typographical error	This amendment has been made. Thank you.