National Institute for Health and Care Excellence

Health Technology Evaluation

Olezarsen for treating familial chylomicronaemia syndrome [ID6585]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Sobi	Sobi believes that Olezarsen should be routed through an HST evaluation and has provided an associated HST checklist to support this. Consideration should be provided to the following: - Familial Chylomicronaemia syndrome (FCS) is an ultra-rare disease, with only 115 estimated patients in England. As acknowledged in the latest NICE health technology evaluations manual, evidence generation is challenging in ultra-rare diseases and as a result, the level of evidence for technologies indicated for ultra-rare diseases might not be as high as for other technologies. - Despite Volanesorsen being available via routine commissioning in the UK for the treatment of FCS since 2020, **a large proportion of FCS patients are left without any active treatment.** These patients are only left to be managed by an extremely restrictive, very low-fat diet. There are three distinct reasons for the widespread use of best supportive care with dietary restriction: o 1)The NICE recommendation for volanesorsen is restricted to FCS patients “at risk of pancreatitis, and when response to diet	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist).

Section	Stakeholder	Comments [sic]	Action
		and triglyceride-lowering therapy has been inadequate". In addition, the benefit: risk profile for volanesorsen restricts its use to higher risk patients who have failed on diet alone and have a history of acute pancreatitis episodes. On the other hand, the label for olezarsen is anticipated to include a broader population of patients with FCS, as highlighted in the draft scope. ○ 2) FCS patients who present thrombocytopenia (platelet count<140 x 10E9/L) cannot be offered volanesorsen. On the other hand, there is evidence to demonstrate that olezarsen can be used in patients who cannot be treated with the only authorised medicine (volanesorsen) due to lower platelet counts. (1) ○ 3) Patient Support Programme (PSP) data managed by Sobi for volanesorsen (Waylivra) indicates that volanesorsen has high discontinuation rates due to adverse events such as thrombocytopenia. In addition, patients may discontinue treatment based on criteria laid out in the SmPC (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) or due to the additional burden of platelet monitoring requirements. - **High unmet need**: FCS is an ultra-rare, life-long and burdensome disease that results in an increased risk of morbidity and mortality. 40-76% of patients with FCS have been reported to experience episodes of acute pancreatitis across cohort studies (2); these episodes often require hospitalisation and intensive care, and can result in persistent organ failure and mortality. For example, mortality related to acute pancreatitis has been shown to be as high as 6% in patients with FCS (3, 4). - Even with current best supportive care, quality of life remains severely restricted. Even between pancreatic attacks, the disease is relentless (fatigue, mental strain, and constant planning around diet) (5), affecting the whole family.	

Section	Stakeholder	Comments [sic]	Action
		- Treatments such as volanesorsen are not indicated, tolerated or sustainable for most patients. As a result, FCS patients QoL is severely negatively impacted with 60% of patients (n=100) reporting being on TG-lowering medication that has been proven not effective to manage the disease (6, 7). - **Innovation**: - Olezarsen is an innovative treatment designed to overcome tolerability issues experienced with volanesorsen. In particular, olezarsen reduces the risk of thrombocytopenia and the need for platelet monitoring (15). In addition, thrombocytopenia requiring additional monitoring as standard has not been seen with use of olezarsen. - Olezarsen provides additional benefits to patients and health system: o Reduced treatment frequency, corresponding to a monthly injection rather than injection every 1-2 weeks with volanesorsen (every week, reduced to every 2 weeks after 3 months of treatment). This is expected to improve patient compliance and real-world outcomes in the management of FCS patients. o Reduces the need for close monitoring of patients, generating HRU and cost efficiencies to the health system. **References** 1. Olezarsen CHMP Orphan Medicine designation, (2024). 2. Gaudet D, de Wal J, Tremblay K, Dery S, van Deventer S, Freidig A, et al. Review of the clinical development of alipogene tiparvovec gene therapy for lipoprotein lipase deficiency. Atheroscler Suppl. 2010;11(1):55-60. 3. Gaudet D, Blom D, Bruckert E, Stroes E, Kastelein J, John K, et al. Acute Pancreatitis is Highly Prevalent and Complications can be Fatal in Patients with Familial Chylomicronemia: Results From a Survey of Lipidologist. Journal of Clinical Lipidology. 2016;10(3):680-1.	

Section	Stakeholder	Comments [sic]	Action
		4. Nojgaard C, Becker U, Matzen P, Andersen J, Holst H, Bendtsen F. Progression From Acute to Chronic Pancreatitis: Prognostic factors, Mortality, and Natural Course. Pancreas. 2011($0):1195-200. 5. Williams K, Tickler G, Valdivielso P, Alonso J, Vera-Llonch M, Cubells L, et al. Symptoms and impacts of familial chylomicronemia syndrome: a qualitative study of the patient experience. Orphanet J Rare Dis. 2023;18(1):316. 6. Blom DJ, O'Dea L, Digenio A, Alexander VJ, Karwatowska-Prokopczuk E, Williams KR, et al. Characterizing familial chylomicronemia syndrome: Baseline data of the APPROACH study. J Clin Lipidol. 2018;12(5):1234-43 e5. 7. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Roeters van Lennep J, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907 e2.	
	Action FCS & Metabolic Support UK	The evaluation is very appropriate as many patients with FCS do not have access to the one existing therapy for FCS, volanesorsen (HST13), due to problems with low platelets, injection site issues, large needle phobias, and allergic reactions provoking flu-like symptoms. This means that they live with many of the symptoms of FCS and are in fear of and/or experience bouts of abdominal pain which can be severe, as well as pancreatitis. Patients with FCS are keen for new therapies to help relieve the symptom burden that FCS brings and are hopeful that there will be choices available which means that all patients with the disease can have a therapy that suits them. We have some concerns that using the single technology route for evaluation may not be appropriate. Committees making evaluations through this route may not be as experienced in the ultra-rare disease landscape where there is a paucity of data that can be gathered, and decisions need to be made on a much more marginal evidence base.	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist). However, this topic will be evaluated by the HST (rare diseases) committee.

Section	Stakeholder	Comments [sic]	Action
	Genetic Alliance UK	Genetic Alliance UK welcomes the opportunity from NICE to comment on the draft scope for olezarsen for familial chylomicronaemia syndrome (FCS). In preparation for responding to this draft scoe, we spoke with one of the other stakeholders listed that one of our member organisations, Metabolic Support UK. Please note, we have provided some comments in brief below, but due reduced organisational capacity to respond over the Summer period, we have not completed comments on both therapies in this table, where some of our member organisations with more condition-specific expertise in will be better positioned to elaborate. On review of the draft scope, we suggest that routing olezarsen via the HST pathway would be more appropriate than the STA because as an advanced antisense therapy that selectively targets ApoC-III mRNA, we believe this represents a meaningful innovation for people living with FCS. Phase 3 data suggest it may deliver durable reductions in triglycerides and reduce pancreatitis risk with a favourable safety profile. It is our view that is fulfils the criteria for the HST pathway as: - FCS is ultra-rare, with an estimated prevalence of 1-2/million people in England, equating to 55-110 people (criteria 1 and 2) - The current standard of care is a strict low-fat diet with little effect from lipid-lowering agents, leaving severe unmet need (criterion 3). - Care is delivered through a very small number of highly specialised lipid and metabolic centres (criterion 4)	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist).
	HEART UK – The Cholesterol Charity	N/A	N/A

Section	Stakeholder	Comments [sic]	Action
	NHS England	Appropriate for single technology appraisal	Thank you for your comment.
Wording	Sobi	Sobi considers that the proposed wording of the draft remit fully reflects the proposed indications.	Thank you for your comment.
	Action FCS & Metabolic Support UK	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? It does.	Thank you for your comment.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
Timing issues	Sobi	This appraisal is suitable for prioritisation and expedited process steps where appropriate. As described in the appropriateness for evaluation section above, FCS is a disease with a high burden on patients that increases the risk of morbidity	Thank you for your comments.

Section	Stakeholder	Comments [sic]	Action
		and mortality. The currently established treatment (volanesorsen) has several tolerability issues that limits the use in a broad spectrum of patients.(15) There is an urgent need for a better tolerated treatment that can be prescribed to all patients to improve their symptoms and address the disease.	
	Action FCS & Metabolic Support UK	This evaluation is urgent as there are many patients who have tried volanesorsen and had to stop due to side effects, others , and others who are unable to take the therapy due to the onerous monitoring requirements (affecting especially those from the South Asian community) and are therefore left with no support other than severely reducing their fat, added sugars, and carbohydrates for those with diabetes, and alcohol intake.	Thank you for your comments.
	Genetic Alliance UK	We consider this evaluation urgent, as recurrent pancreatitis drives frequent admissions of people affected by the condition to Intensive Care Units. To our knowledge, there is only one NICE-recommended treatment available on the NHS currently (volanesorsen under HST13 with a commercial arrangement) and additional effective options could reduce the frequency of crises for people living with FCS and their quality of life. We also note rapid regulatory progress for plozasiran and for comparator olezarsen in other jurisdictions.	Thank you for your comments.
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Important but not urgent	Thank you for your comment.
	Sobi	N/A	N/A

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Action FCS & Metabolic Support UK	N/A	N/A
	Genetic Alliance UK	N/A	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	No	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Sobi	In general, the background information provided is appropriate. However, Sobi would like to suggest additional wording for parts of the background section. At the end of the first paragraph outlining the impact of FCS on patients, it would be appropriate to outline that FCS has been shown to have a significant impact on employment (40% of people with FCS report not being employed) (7)	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. A sentence on the psychological impact of the condition has been added. Please include

Section	Consultee/ Commentator	Comments [sic]	Action
		In the third paragraph outlining the management of FCS, Sobi would suggest that it would be appropriate to explicitly state that current treatment options for people with FCS are limited, in particular given the lack of disease modifying treatments. Even between pancreatic attacks, the disease is relentless (resulting from fatigue, mental strain, and constant planning around diet). Even with the best current care, life is severely restricted, and fear of acute pancreatitis dominates patients' lives. As mentioned previously, current treatments like volanesorsen aren't tolerable or sustainable for most, and FCS continues to affect the whole family. Specifically for the technology, olezarsen does not currently have marketing authorisation in the UK for the treatment of FCS, but Sobi feels it is relevant to add that olezarsen does have authorisation in the US via the FDA and has received orphan designation status from EMA(1). The orphan designation recognises the significant patient benefit possible due to the use of olezarsen in patients who cannot be treated with the only authorised medicine (volanesorsen) due to low platelet counts (1). It should also be noted that olezarsen (Tryngolza, Sobi) has been designed to overcome tolerability issues with volanesorsen, specifically the risk of thrombocytopaenia. Olezarsen is designed to bind to the human apoC-III mRNA, as the ASO portion of olezarsen is formulated from volanesorsen. The GalNAc3 conjugate dramatically increases the uptake of the ASO to hepatocytes, thereby decreasing the dose of olezarsen needed to reduce apoC-III compared to the non-conjugated volanesorsen. In fact, similar pharmacodynamic effects are seen for olezarsen at a dose of 80 mg every 4 weeks compared with volanesorsen 285 mg weekly dosing, making the dosing regimen for olezarsen more convenient compared with volanesorsen. Unlike volanesorsen, olezarsen also does not require additional platelet monitoring.	any additional detail in the company evidence submission.

Section	Consultee/ Commentator	Comments [sic]	Action
		Olezarsen offers a treatment option for all patients with genetically confirmed FCS, regardless of previous treatment history. Olezarsen has been studied in a subgroup of patients who have previously received volanesorsen as assessed by a phase 3 open label safety study (NCT05185843). References 1. Olezarsen CHMP Orphan Medicine designation, (2024). 7. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Roeters van Lennep J, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907 e2	
	Action FCS & Metabolic Support UK	Suggestion to update the existing background as follows. FCS is managed by an extremely restrictive, very low-fat diet to keep triglyceride levels low. This involves restricting dietary fat intake to between 10 and 20 g/day, limiting added sugars, and not consuming alcohol. For those patients who have developed diabetes, dietary restrictions become more onerous and other factors like the timing of food intake limiting carbohydrates become relevant. The need to manage insulin levels can become a further burden and a further concern for those around them. .....Symptoms of FCS include…… reduced cognition, fatigue, the constant fear of impending pancreatitis, and depression. (Journal of Clinical Lipidology: The burden of familial chylomicronaemia syndrome: Results from the global IN FOCUS study)	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. A sentence on the psychological impact of the condition has been added. Please include any additional detail in the evidence submission.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	To our understanding, the background is accurate and aligns with HST13. We suggest adding a short sentence that FCS care is typically led by specialist lipid clinics with dietetic expertise to reflect the highly specialised setting needed for treating people with this condition. It may that shared-care for people whose condition becomes more stable is possible later, but most routine follow-up will remain specialist-led given the complexity and rarity of FCS.	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. Please include any additional detail in the evidence submission.
	HEART UK – The Cholesterol Charity	Include psychological impact on the patient and the support needed, even though this is mentioned later in the document. Nicotinic Acid is no longer available in the UK.	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. A sentence on the psychological impact of the condition has been added. Please include any additional detail in the evidence submission. Nicotinic acid has been removed.
	NHS England	Accurate and complete	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Sobi	Sobi believes the population in the scope is defined appropriately.	Thank you for your comment.
	Action FCS & Metabolic Support UK	Once a child begins to be independent from their family (usually when going to secondary school), the dietary restrictions can be harder to manage due to the desire to 'fit in' with their peers and access to inappropriate foods (and potentially alcohol). It would therefore be appropriate to consider the inclusion of children younger than 18 to help them to manage their education without the burden of abdominal pains and pancreatitis.	Thank you for your comment. Olezarsen will be evaluated in line with the current marketing authorisation and the evidence that underpins the marketing authorisation.
	Genetic Alliance UK	Adults with genetically confirmed FCS appears to be appropriate and consistent with HST13. If the marketing authorisation later includes young people/adolescents, NICE might consider making the scope more flexible to include them to avoid the requirement for a second appraisal.	Thank you for your comment. Olezarsen will be evaluated in line with the current marketing authorisation and the evidence that underpins the marketing authorisation.
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	*Is the population defined appropriately?* Yes	Thank you for your comment.
Subgroups	Sobi	In FCS the risk of pancreatitis is primarily defined by severely elevated triglyceride (TG) levels and the presence of chylomicrons in the blood, leading to recurrent episodes of acute pancreatitis. Sobi recommends	Thank you for your comment. "Risk of pancreatitis" has been

Section	Consultee/ Commentator	Comments [sic]	Action
		eliminating the “risk of pancreatitis” subgroup as it represents a group of patients already represented in the first two subgroups (‘TG levels’ and ‘History of pancreatitis’). It is relevant to mention that the EMA approval has removed the ‘Risk of pancreatitis’ from the label, and Sobi would expect MHRA to align with the same wording. Sobi would also like to flag that it will not be possible to provide cost-effectiveness estimates for the subgroup of patients previously treated with volanesorsen. Although this is represented by a small group of patients in the clinical trial, the number of patients (n=24) and resulting evidence lacks robust statistical power to be used in a robust cost-effectiveness model.	removed from the subgroups. The wording of the subgroup “previous treatment with volanesorsen” has been updated to “people who cannot have volanesorsen” based on feedback from NHS England that technology is expected to be especially clinically effective for patients with FCS for whom volanesorsen is contraindicated e.g. because of significant thrombocytopenia or who can’t take volanesorsen for any other reason.
	Action FCS & Metabolic Support UK	Other subgroups to be added are: Patients who have diabetes. People from the South Asian community of whom there is a relatively large population of patients due to consanguinity. These patients have a higher risk of developing diabetes and often their cultural norms make managing food restrictions very difficult. Many of these patients have strong family links in	Thank you for your comments. The suggested subgroups have been added.

Section	Consultee/ Commentator	Comments [sic]	Action
		South Asian countries and travel to see family making it difficult for them to take volanesorsen due to the onerous monitoring requirements. Pregnant women. Pregnancy is a high stress period for women with FCS as triglyceride levels rise naturally during the third trimester increasing the risk of pancreatitis which is dangerous for both mother and unborn baby. For women who develop gestational diabetes the impact can be very negative and add huge amounts of stress to the pregnancy as high blood glucose leads to higher triglycerides, Women can often be recommended plasmapheresis (where available) which is a time-consuming, draining and very short-term intervention with some women having the procedure two or three times a week.	
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	Triglyceride levels are included but this needs to be clearer what range or above what level you are referring to This is an adult treatment only Consideration needs to be given to effects of injection site or people with needle phobia	Thank you for your comments. This has been left intentionally broad so the company can propose a cost-effective range. If a recommendation in this subgroup is considered appropriate, this will be specified in the final guidance recommendation wording.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	Subgroups are appropriate. Additionally, the technology is expected to be especially clinically effective for patients with FCS for whom volanesorsen is contraindicated e.g. because of significant thrombocytopenia or who can't take volanesorsen for any other reason	Thank you for your comment. The suggested subgroup has been added.
Comparators	Sobi	Although the list of comparators are broadly aligned the expected options for patients with FCS, it is important to note that the label for volanesorsen, which is the only disease-modifying treatment on the list, is restricted to FCS patients "at risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate". Sobi believes it would be appropriate to acknowledge this in the scope by stating the subgroup that volanesorsen is indicated in, since the anticipated label for olezarsen includes a broader population. In this broader population of patients, diet is the only comparator (as indicated by its inclusion as a comparator in the pivotal trial). Sobi also does not believe it will be possible to provide evidence versus plozasiran, which is not currently part of established UK clinical practice. Based on submission timelines, Sobi anticipates that it will not be possible to include this treatment in modelling scenarios, particularly as the list price is currently not published. As such, Sobi would request plozasiran be removed from the final scope.	Thank you for your comment. The trial for olezarsen includes people with a very high triglyceride level of 880mg/dl (10mmol/L) or above with a history of pancreatitis. In the final guidance for HST 13, the committee concluded that 'high risk of pancreatitis' is likely to include anyone with high triglyceride levels. Therefore, it is expected that olezarsen would be used in people with a high risk of pancreatitis similarly to volanesorsen. Note: In the APPROACH trial for volanesorsen, part of the inclusion criteria

Section	Consultee/ Commentator	Comments [sic]	Action
			was: “fasting triglyceride (TG) level ≥ 750 mg/dL (8.4 mmol/L) at screening”. This threshold is lower than that used in the olezarsen trial. Plozasiran has been included as a comparator subject to NICE evaluation. If plozasiran has a recommendation at the time of the committee meeting for olezarsen, plozasiran would be considered a comparator.
	Action FCS & Metabolic Support UK	*The comparators are comprehensive.*	Thank you for your comment.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England	*Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?* Yes	Thank you for your comment.
Outcomes	Sobi	Most of the outcomes listed are considered appropriate to capture the benefits of treatment for these patients. Sobi recommends removing "cardiovascular diseases" and "fatty liver disease" from the fifth bullet in the list: - Cardiovascular disease is not a feature of familial chylomicronaemia syndrome, as triglycerides tend to exceed 10 mmol/L and form chylomicrons, which are not associated with cardiovascular disease. - Despite a single study reporting an increased rate of hepatic stenosis in the FCS population versus the general population; this outcome was not collected in the olezarsen pivotal trial and will not be possible to provide data on.	Thank you for your comment. Cardiovascular disease and fatty liver disease outcomes have been removed.
	Action FCS & Metabolic Support UK	The following should be added: **The ability to adhere to the treatment regimen.** From volanesorsen we know that treatment adherence in people with FCS is problematic, regularly leading to discontinuation, due to the numerous side effects associated with volanesorsen. It would be valuable for the community of people living with FCS to understand to what extend adherence would be impacted when treated with olezarsen. **Need for plasmapheresis and stress levels in pregnant women.** The rise in triglyceride levels during pregnancy raises the risk of pancreatitis which is potentially life-threatening for both mother and unborn child and can result in premature birth. This leads to substantial stress, as well as the need for	Thank you for your comments. Adherence has been added as an outcome. Any evidence on the impact of this condition and treatment on carers will be considered during the appraisal. Health-related quality of life (for patients and carers) is included as an outcome in the scope. The outcomes listed in the

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		plasmapheresis in pregnant women. It would be valuable to understand how olezarsen impacts this. **Time spent in good health.** People with FCS experience frequent, sudden bouts of severe abdominal pain, or in hospital due to pancreatitis. This affects their ability to work, attend school/university (i.e. young adults) and increases social isolation. It would be valuable to understand how olezarsen impacts this. **Impact on caring responsibilities** Living with or being a parent to a patient who is liable to develop severe abdominal pain/pancreatitis or is always fatigued, leaves carers and parents constantly concerned about their loved one. For adult partners it can mean they have to carry out family responsibilities, and miss, or attend social events alone. The children of patients can become stressed about their parent's health, and potentially take on extra responsibilities with younger siblings, and taking on the role of a young carer. Parents of patients who do or don't live with them can devote a lot of time to caring for their child with FCS, leaving other siblings without the parental support they may otherwise have had. It would be valuable to understand how olezarsen impacts this.	scope are not expected to be exhaustive and additional outcomes may be presented.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A

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	NHS England	*Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	Thank you for your comments.
Equality	Sobi	Sobi is not aware of particular equality considerations that are likely to impact the recommendations and their appropriateness. However, it should be noted that in a recent publication from the UK FCS National Registry, Bashir et al. highlighted a higher incidence of FCS in non-European patients, as well as those with parental consanguinity. Sobi is also aware of anecdotal evidence that there may be instances where the additional monitoring associated with current treatment for FCS may be stigmatised within tightknit communities. In addition, it may also be appropriate to give special consideration 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(7). There are currently no data available regarding the use of olezarsen in pregnant women, but it is not contra-indicated and the biochemistry suggests that it doesn't cross the blood placenta barrier. **References** 7. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Roeters van Lennep J, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907 e2.	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	Action FCS & Metabolic Support UK	We would like to highlight that people with FCS from the South Asian community in England may be disproportionately affected by the current draft	The equalities issues raised here have been recorded in the

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		remit and scope. This group forms a relatively large proportion of the FCS population in England, in part due to higher rates of consanguinity. Several factors create specific equality challenges for this group: - Higher risk of comorbidities: People of South Asian heritage are at greater risk of developing type 2 diabetes. The combination of FCS and diabetes compounds the burden of disease, dietary restrictions, and health risks. - Cultural barriers to dietary management: Traditional South Asian diets often include foods that are particularly challenging to restrict for someone living with FCS. This makes adherence to the extremely strict dietary requirements potentially more difficult in practice than for some other groups. - Monitoring requirements and international travel: Many patients maintain strong family links in South Asia and travel abroad regularly. Current onerous monitoring requirements for volanesorsen can make it difficult for this group to access or remain on treatment compared with other groups. These issues mean that the draft scope could inadvertently disadvantage people of South Asian heritage.	equalities impact assessment and will be considered by the committee during the evaluation.
	Genetic Alliance UK	To our knowledge, no protected group appears to be excluded by the current wording, although we defer to condition-specific groups for direct of experiences that may be overlooked. For example, there is likely to be a number of practical concerns around regional access to genetic testing, lipid clinics and dietetic support. The committee may therefore need to consider evidence on geographic and socio-economic factors affecting adherence to very low-fat diet, and ensure arrangements for home administration or shared-care is available, where appropriate.	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.

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	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Route of administration may be a consideration. Self-injection favours people better able to self-manage, hospital injection may favour those better able to travel (especially if administered in tertiary care).	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
Other considerations	Sobi	None	N/A
	Action FCS & Metabolic Support UK	Action FCS would welcome the assessment of the socio-economic impact of FCS on people with FCS and their families, including the impact on social isolation felt by patients, the ability of patients to maintain regular employment, uninterrupted by visits to hospital or sick days at home and the impact on carers and children of the patient.	Thank you for your comment. Please include these details in the evidence submission for consideration by committee.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A

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	NHS England	Incidence of significant thrombocytopenia with prolonged use compared with volanesorsen	Thank you for your comment. “Incidence of severe thrombocytopenia” has been included as an additional outcome.
Questions for consultation	Sobi	**Question 1: Please select from the following, will olezarsen be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** Olezarsen will be prescribed and managed in secondary care. Treatment should be initiated and remain under the supervision of a physician experienced in the treatment of patients with FCS. **Question 2: For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** The setting for treatment initiations is anticipated to be the same for all comparators. Following initiation, olezarsen is expected to have a less burdensome follow-up compared with volanesorsen. The latter has a requirement for platelet monitoring at least every 2 weeks, dependent on platelet levels, throughout the treatment. This monitoring is not expected to be required for olezarsen given the improved tolerability observed in the clinical trial.	Thank you for your comments. “Monitoring requirements” has been added as an additional outcome.

Section	Consultee/ Commentator	Comments [sic]	Action
		Question 3: Would olezarsen be a candidate for managed access? Sobi does not believe that olezarsen will be a candidate for managed access. **Question 4: Do you consider that the use of olezarsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** FCS has been shown to have a large indirect burden as a result of impaired workplace ability, including presenteeism (lost productivity) and absenteeism, and ability to work at all. In the IN-FOCUS study, 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 (8). These impacts are not fully captured within traditional QALY measures. The high burden associated with the symptoms and management of FCS affects multiple aspects of patient's lives, including the ability to perform activities of daily living, family life and personal relationships. (9). In the IN-FOCUS study, approximately one third of patients (32%) reported that FCS greatly or significantly interfered with their life (>=6 points on a 1-7 scale. In the same study, less than 10% of patients considered FCS to have low interference in their life. These improvements are anticipated to translate into economic benefits through increased productivity and reduce caregiver burden. Sobi intends to clearly highlight, within its submission, data demonstrating health-related benefits that are not fully captured by the QALY calculation.	

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		Question 5: Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. No **References** **8.** Gardner T, Kennedy A, Gelrud A, Banks P, Vege SS, Gordon S, et al. Chronic Pancreatitis and its effect on employment and health care experience: Results of a prospective american multicenter study. Pancreas. 2010;39:498-501. 9. Sikora Kessler A, Brown TM, Bratlee-Whitaker E, Fehnel S, Vera-Llonch M, Arca M, et al. Patient experience with familial chylomicronemia syndrome before and after olezarsen treatment: Qualitative interviews with clinical trial participants. J Clin Lipidol. 2025.	
	Action FCS & Metabolic Support UK	Regarding the care pathway for olezarsen we would defer to the clinical experts. Regarding olezarsen as a candidate for managed access, we would defer to the company and Action FCS would fully support this outcome. The substantial health-related benefits unlikely to be included in QALY calculation are the socio-economic impacts of FCS on people with the condition and their families, including the impact on social isolation felt by patients, the ability of patients to maintain regular employment, uninterrupted	Thank you for your comments.

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		by visits to hospital or sick days at home and the impact on carers and children of the patient. Action FCS would defer to the pharmaceutical company and to the medical community as to the nature of the data available to take account of these benefits and information Action FCS will gather for our submission.	
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	This treatment should be prescribed and managed in secondary care	Thank you for your comment.
	NHS England	**Questions for consultation** Where do you consider olezarsen will fit into the existing care pathway for familial chylomicronaemia syndrome? Please select from the following, will olezarsen be: D. Other (please give details): **prescribed in tertiary care (specialist FCS centres) with follow-up in tertiary care or as shared care between tertiary centre and local (secondary care) clinic.** Would olezarsen be a candidate for managed access? **Yes** For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Comparators – tertiary care.**	Thank you for your comments. “Monitoring requirements” has been added as an additional outcome.

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		Subsequent treatment of FCS complications such as pancreatitis and diabetes may take place in secondary care settings more local to the patient. Do you consider that the use of olezarsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **If routine platelet monitoring is not required this could represent a significant health (and quality of life) -related benefit compared with volanesorsen** Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **Publications arising from the Balance trial.** **Long term adverse effects including risk of thrombocytopenia not known (NB small reductions in platelets were observed in clinical trials)** Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice.	

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		In practice, volanesorsen is rarely discontinued in patients who fail to achieve a reduction in serum triglycerides >25% or below 22.6 mmol/L – this is because the benefit of volanesorsen in reducing incidence of pancreatitis is evident at higher triglyceride concentrations (and may not be directly related to triglycerides but rather the effect on chylomicrons which is not readily quantifiable). If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. ***Atherosclerosis* 375 (2023) 67-74**	
Additional comments on the draft scope	Sobi	N/A	N/A
	Action FCS & Metabolic Support UK	None	N/A
	Genetic Alliance UK	A Managed access agreement (MAA) could help collect further evidence on pancreatitis incidence, hospital admissions, durability of effect and patient-reported outcomes in NHS practice. Specialist networks are well placed to support this. An MAA arrangement could also help address residual uncertainty on long-term clinical outcomes, real-world adherence and impact on carer burden. Specialist lipid clinics could contribute to national data collection.	Thank you for your comments. The company can submit a managed access proposal if they consider the treatment a candidate for managed access. Sobi has not indicated that this topic will be a

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			candidate for managed access.
	HEART UK – The Cholesterol Charity	None	N/A
	NHS England	None	N/A

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A