NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Committee Papers

NICE National Institute for Health and Care Excellence

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COST COMPARISON APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Bayer plc:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Amyloidosis UK
   b. Cardiomyopathy UK
   c. Kidney Research UK
   d. The British Association for the Study of the Liver (BASL)
   e. The Royal College of Ophthalmologists

4. **External Assessment Report** prepared by PenTAG (Peninsula Technology Assessment Group)

5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy (ATTR-CM) [ID6354]

Document B

Company evidence submission

August 2025

File name	Version	Contains confidential information	Date
ID6354_Acoramidis_Document_B_05082025_CON	Final	Yes, Commercial in Confidence	5 August 2025

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Abbreviations

Abbreviation	Definition
6MWD	6-minute Walk Distance; distance achieved in a standardised 6MWT
6MWT	6-minute Walk Test
ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting-enzyme inhibitor
ACM	All-cause mortality
AE	Adverse event
AF	Atrial fibrillation
AGM	Adjusted geometric mean
AHA	American Heart Association
AIC	Akaike information criterion
AL	Amyloid light chain
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARR	Absolute risk reduction
AST	Aspartate aminotransferase
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRm	Mutant Transthyretin amyloidosis (referred to as ATTRv)
ATTRm-CM	Mutant Transthyretin amyloid cardiomyopathy (referred to as ATTRv-CM)
ATTR-PN	Transthyretin amyloid polyneuropathy
ATTRv	Variant transthyretin amyloidosis
ATTRv-CM	Variant transthyretin amyloid cardiomyopathy
ATTRwt	Wild-type transthyretin amyloidosis
ATTRwt-CM	Wild-type transthyretin amyloid cardiomyopathy
BIC	Bayesian information criterion
BID	Twice daily
BNF	British National Formulary
BNP	Brain natriuretic peptide
CEC	Clinical Events Committee
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIC	Confidential in confidence
CIR	Copy increments in reference
CKD	Chronic Kidney disease
CMAD	Cardiac mechanical assist device
CMH	Cochran-Mantel-Haenszel
CMR	Cardiac Magnetic Resonance
COVID-19	Coronavirus disease 2019

Abbreviation	Definition
CRISPR	Clustered regularly interspaced short palindromic repeats
CSR	Clinical study report
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease;
CVH	Cardiovascular-related hospitalisation
CVM	Cardiovascular-related mortality
dl	decilitre
DMC	Data Monitoring Committee
DSA	Deterministic sensitivity analysis
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
ECV	Extracellular volume
eGFR	Estimated glomerular filtration rate
EM	Effect modifier
EMA	European Medicines Agency
EMB	Endomyocardial biopsy
EOCI	Events of clinical interest
EPAR	European Public Assessment Report
EQ-5D-5L	EuroQol 5-dimensions 5-levels Health Outcomes Assessment
ESC	European Society of Cardiology
ESS	Effective sample size
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPE	Fluorescent probe exclusion
F-S	Finkelstein-Schoenfeld
GCP	Good Clinical Practice
HCl	Hydrochloride salt
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HMDP	Hydroxymethylene diphosphonate;
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Hypothetical strategy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IQR	Interquartile range
IRB	Institutional Review Board
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
IV	intravenous
IXRS	Interactive Voice / Web Response System
J2R	Jump to Reference

Abbreviation	Definition
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire Overall Summary Score
KM	Kaplan-Meier
LS	Least squares
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MAIC	Matching-adjusted indirect comparison
MAR	Missing At Random
MAS	Midlands Amyloidosis Service
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified Intention-to-treat
ml	millilitre
MMRM	Mixed model repeated measures
MNAR	Missing Not At Random
MRA	Mineralocorticoid receptor antagonist
NAC	National Amyloidosis Centre
ng	Nanogram
NHS	National Health Service
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
PAS	Patient access scheme
PBO	Placebo
PD	Pharmacodynamic
Pg	Picogram
PH	Proportional hazard
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
Q	Quartile
QALY	Quality-adjusted life-year
QoL	Quality of Life
QRS	Q wave, R wave and S wave complex
RCT	Randomised controlled trial
RD	Risk difference
RDI	Relative dose intensity
RMST	Restricted mean survival time
RNA	Ribonucleic Acid
RRR	Relative risk reduction

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SM	Symptomatic management
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPECT	Single photon emission computed tomography
SUSAR	Suspected unexpected serious adverse reaction
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIA	Transient ischaemic attack
TSH	Thyroid stimulating hormone
TTD	Time to discontinuation
TTDD	Time to treatment discontinuation or death
TTR	Transthyretin
TIA	Transient ischaemic attack
TnI	Troponin I
TTR	Transthyretin
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual Analogue Scale
VAT	Value Added Tax
WB	Western blot
WHO	World Health Organization
Yr	year

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The submission covers the full population for the comparator, as recommended by NICE.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)	Adult patients with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	Slightly amended wording to reflect the marketing authorisation
Intervention	Acoramidis	Acoramidis	N/A
Comparator(s)	Tafamidis	Tafamidis	N/A
Outcomes	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as global longitudinal strain or brain natriuretic peptide [BNP] level) • outpatient diuretic intensification • serum transthyretin and transthyretin stabilisation • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers)	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as brain natriuretic peptide [BNP] level) • serum transthyretin and transthyretin stabilisation • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients)	The following outcomes are not addressed as these are not reported within the study data: • outpatient diuretic intensification • global longitudinal strain (although there was an exploratory Cardiac Magnetic Resonance [CMR] Imaging sub-study of ATTRibute-CM, which is briefly reported in the submission) The following additional measure is reported: • Troponin I
Economic analysis	As the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out	As the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison has been conducted	N/A

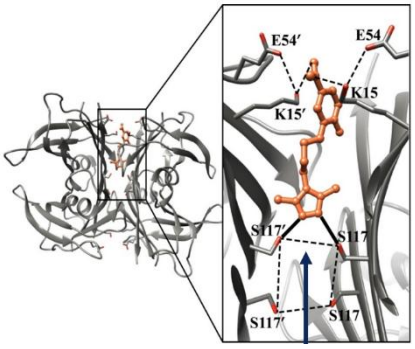
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • severity of heart failure (such as by New York Heart Classification class or National Amyloidosis Centre staging) • wild-type or hereditary ATTR-CM	Bayer do not believe that any subgroups should be considered in this appraisal.	Bayer consider that the subgroups suggested would not be relevant for this appraisal due to insufficient trial data which could lead to conclusions based on underpowered analysis. Specifically: • only 9.7% of the ATTRibute-CM study population had a variant transthyretin genotype, with the remainder wild-type • when considering NYHA classification, the majority of patients in the ATTRibute-CM study had NYHA Class II at baseline (72%), with fewer in Class III and even fewer in Class I. Tafamidis was recommended as a treatment option by NICE in accordance with the marketing authorisation without any reference to subgroups.

B.1.2 Description of the technology being evaluated

See Appendix C for the summary of product characteristics (SmPC) and the UK Public assessment report.

Table 2. Technology being evaluated

UK approved name and brand name	Acoramidis (Beyonttra)
Mechanism of action	Acoramidis is an oral, selective, second-generation stabiliser of transthyretin (TTR) which inhibits the dissociation of tetrameric TTR. TTR (also known as prealbumin) is produced by the liver and exists in the body normally as a tetrameric protein that transports both thyroxine (T4) and retinol (vitamin A)-binding protein (RBP) in the bloodstream.(1) Ageing, or - less commonly - a TTR gene mutation, can lead to structural instability of the TTR protein causing its dissociation into unstable monomeric TTR. TTR monomers misfold and deposit as amyloid fibrils in various organs and tissues - the basis of the disease TTR amyloidosis (ATTR).(2) Using the same binding sites as T4, acoramidis binds to the TTR tetramer and prevents dissociation of the tetramer into its constituent monomers, the rate-limiting step in amyloidogenesis.(2) The mode of binding of acoramidis is enthalpy-driven and involves hydrogen bonding and strong interactions with specific amino acid residues (Serine117) and was specifically designed to mimic the stabilising effects of the disease-protective TTR variant, T119M.(2, 3)

	Acoramidis binding to TTR Strong intermonomer H-bonds observed via X-ray crystallography enable a unique binding mode (graphic from Miller et. al 2018 (3))  As assessed in vitro, acoramidis has a higher binding affinity for TTR than other known TTR stabilisers, including diflunisal and tafamidis,(4) achieving a near-complete (≥ 90%) and sustained TTR stabilisation.(3, 5) Acoramidis also stabilises TTR more effectively than T4, its natural ligand.(4) In line with its mechanism of action, serum free thyroxine may decrease with acoramidis treatment. This is not accompanied with changes in thyroid stimulating hormone (TSH) or thyroid dysfunction.(2) Also, decreases in measured serum RBP in the acoramidis group in the ATTRibute-CM study, were not accompanied by any clinical evidence of AEs that would be associated with Vitamin A deficiency.(6)
Marketing authorisation/CE mark status	• The EU MAA procedure started on 1st February 2024 (EMA centralised procedure). The applicant was Bridge Bio. • Positive CHMP opinion was received 12th December 2024. The European Commission granted Marketing Authorisation for the indication *Treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)* on 10th February 2025. • The UK MAA submission was made to MHRA on 7th February 2025. The application was filed as an International Recognition Procedure, using the EU as the reference regulator. • The UK marketing authorisation was granted on 24th April 2025.
Indications and any restriction(s) as described in the SmPC	The indication for acoramidis in the UK is 'treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).'(2) See Appendix C for SmPC and UK Public Assessment Report.
Method of administration and dosage	The recommended dose of acoramidis is 712 mg (two tablets, 356 mg) orally, twice daily, corresponding to a total daily dose of 1,424 mg. Tablets should be swallowed whole, with or without food.
Additional tests or investigations	Patients with ATTR-CM receive regular tests and investigations (every 6-12 months) to monitor the course of their disease (see Section B1.3 Monitoring). Prescription of acoramidis requires no additional tests to those already performed while monitoring ATTR-CM.
List price and average cost of a course of treatment	The NHS list price is £8,547.60 for a pack of 120 * 356 mg tablets. Treatment will be lifelong until the physician and patient decide to stop.
Patient access scheme (if applicable)	NHS England via the Commercial Medicines and Devices Investment Group (CM&D IG) has agreed that the [redacted] PAS proposal for acoramidis may be considered by NICE as part of the appraisal. The price Bayer have submitted to NHS England is commercial in confidence and aims to target a similar or lower price to the net price of tafamidis (as guided through the HTA process as this is, and will remain, confidential). The proposed confidential PAS price is £[redacted] for 120*356 mg tablets

AEs = adverse events; ATTR = transthyretin amyloidosis; ATTR-CM = Transthyretin amyloid cardiomyopathy; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; EPAR = European Assessment report; EU = European; H-bonds = hydrogen bonds; HTA = health technology assessment; MAA = Marketing Authorisation Application; MHRA = Medicines and Healthcare products Regulatory Agency; RBP = retinol binding protein; PAS = patient access scheme; SmPC = Summary of Product Characteristics; T4 = thyroxine; TSH = Thyroid stimulating hormone; TTR = transthyretin

B.1.3 Health condition and position of the technology in the treatment pathway

Transthyretin amyloidosis cardiomyopathy (ATTR-CM) is a serious clinical manifestation of transthyretin amyloidosis (ATTR), whereby accumulation of amyloid fibrils in the heart causes thickening and stiffening of the heart tissues.(7) ATTR can be hereditary, caused by a mutation in the transthyretin (TTR) gene (variant or ATTRv), or it can occur without a genetic basis because of ageing (wild-type or ATTRwt).(8) Patients with ATTR-CM typically experience progressive heart failure (HF), conduction abnormalities such as cardiac arrhythmias, frequent hospitalisations, irreversible loss of physical function, significantly impaired quality of life (QoL) and high mortality / premature death.(9-14) Caregiver burden is also significant, with caregivers reporting lower health-related QoL (HRQoL), higher rates of anxiety, depression, stress and sleep problems.(10, 15)

Many of the symptoms of ATTR-CM mirror symptoms of other heart disease causes which often leads to misdiagnosis, and hence, underdiagnosis of ATTR-CM. Historically, patients with ATTR-CM had a poor prognosis, surviving a median of 2-6 years from diagnosis if left untreated.(12)

True United Kingdom (UK) prevalence of ATTR and ATTR-CM is unknown. There are thought to be around 1500 people with ATTR-CM in England.(16) An increase in disease awareness and the availability of more conclusive non-invasive diagnostic testing and new disease-modifying therapies means that prognosis is improving as more patients can now receive an earlier diagnosis and treatments which delay disease progression.(12, 17-20) Prevalence and incidence of ATTR-CM is expected to increase as a consequence of improvements in diagnostic techniques, earlier diagnoses and patients surviving longer with new treatments.

With increased recognition of ATTR-CM as a cause of heart failure morbidity and mortality, early identification of patients and treatment with disease-modifying therapies can lessen both the patient and economic impact of ATTR-CM. In particular, this can be achieved by reducing the number of costly ATTR-CM cardiovascular complications and hospitalisations within the NHS, and improving patient QoL, functionality and prolonging independent living.(20-24)

B.1.3.1 Management of ATTR-CM

Management of ATTR-CM was, until recently, symptomatic, focusing on management of heart failure and arrhythmias including diuretics, careful regulation of fluid balance and supportive care.(25) Heart and / or liver transplantation have also been treatment options for ATTR-CM for a minority of patients but rarely in the UK and even more unlikely now with the recent availability of disease-modifying therapies.(26)

The introduction of new therapies has raised awareness of ATTR-CM and stimulated patient referrals with the aim to treat patients early enough to improve prognosis.

The NAC in London provides a highly specialised service for people with amyloidosis and related disorders and UK patients have generally been referred here for assessment, diagnosis, monitoring and treatment. To cope with the increase in patient referrals and continue to provide a timely diagnosis, new hubs are being established around the UK, receiving remote multidisciplinary expertise from the NAC. The Midlands Amyloidosis Service (MAS) was established in 2019, serving as a pilot for a 'hub and spoke' model for a UK Amyloidosis network.(27)

B.1.3.1.1 Monitoring

Patients with ATTR-CM are reviewed every 6-12 months for any signs of disease progression.(28, 29) Measures typically include:

- every 6 months: a medical history to check for any cardiovascular (CV) hospitalisations, new onset of arrhythmic / conduction disturbances, ECG, any changes in New York Heart Association (NYHA) class or NAC staging scores, functional capacity using the 6MWT, NT-proBNP, troponin high-sensitivity assay,
- every 6-12 months: Echocardiogram - LV wall thickness, QoL,
- every 12 months: CMR, Systolic and diastolic function (i.e., LV ejection fraction (LVEF), stroke volume, LV global longitudinal strain).

B.1.3.1.2 Treatment

Treatment of ATTR-CM focuses on 3 main approaches: management of heart failure, management of arrhythmias and conduction disorders, and initiation of disease-modifying therapies to reduce the formation of amyloid / regress existing amyloid deposits.

Management of heart failure can be challenging in patients with ATTR-CM since many of the usual heart failure treatments such as beta blockers, calcium channel blockers, angiotensin-

converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and digoxin can be poorly tolerated due to restrictive cardiomyopathy and autonomic dysfunction.(28-31) ATTR-CM patients are typically managed with dietary sodium restriction, fluid control and the use of diuretics e.g. loop diuretics, mineralocorticoid receptor antagonists.(29, 31) UK clinical experts have also reported usage of sodium-glucose co-transporter 2 inhibitors (SGLT2is) in these patients.

Amiodarone is the antiarrhythmic treatment of choice in patients with ATTR-CM.(28-31) Benefits of other strategies including digoxin, atrial fibrillation (AF) ablation, and electrical cardioversion are less certain. A pacemaker may be considered for bradycardia.(29) ATTR-CM patients are also at high risk of thromboembolism and those with AF should receive an anticoagulant.(28-31)

Disease-modifying therapies

Disease-modifying therapies in ATTR-CM typically fall into three categories of action: TTR gene silencing, TTR stabilisation, and TTR disruption.(32)

- **TTR gene silencers** target hepatic synthesis of TTR. Genetic-based therapies 'switch off' the gene for TTR in liver cells so that they no longer produce TTR. Examples of TTR silencer treatments include small interfering ribonucleic acids (RNAs): patisiran and vutrisiran, and antisense oligonucleotides: inotersen and eplontersen.(8) Other research includes the CRISPR-Cas9 technology (NTLA-2001),(33) where early studies indicate the TTR gene can be knocked-out in patients with ATTR amyloidosis with a single administration.
- **TTR stabilisers** bind to the TTR tetramer, preventing dissociation into monomers and misfolding, and thus deposition of amyloid fibrils. Examples of TTR stabilisers include tafamidis and acoramidis. There has also been some early research with diflunisal (non-steroidal anti-inflammatory drug [NSAID]) but known vascular and renal side effects of NSAIDs may preclude larger scale studies in ATTR-CM.(34)
- **TTR disruptors** target the clearance of amyloid fibrils from tissues, which includes under investigation antibody therapy.(33)

Current management guidelines for ATTR-CM are listed in Table 3.

Table 3. UK, European and North American guidelines on disease-modifying treatment of ATTR-CM

Guideline	Recommendation	Date	Reference
United Kingdom			
NICE			
Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA984) (Re-submission; previous submission TA696)	ATTRv and ATTRwt	June 2024	NICE TA984 (26)
SMC			
SMC2585. Tafamidis (Vyndaqel) For the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (Resubmission; previously rejected in 2021)	ATTRv and ATTRwt	October 2023	SMC2585 (35)
International Guidelines			
World Heart Federation Consensus on Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM) (2023)	Tafamidis NYHA I-III	2023	(28)
iCARDIO Alliance Global Implementation Guidelines on Heart Failure (2025)	Use TTR tetramer stabiliser therapy (tafamidis [partial stabiliser], and acoramidis [near-complete stabiliser]) to improve symptoms, and reduce cardiovascular death and HF hospitalisations in patients with ATTRwt-CM and ATTRv-CM and NYHA class I to III symptoms.	2025	Heart, Lung and Circulation(36)
2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis (2023)	Tafamidis NYHA I-III	2023	Am Coll Cardiology (31)
Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Diseases (2021)	Tafamidis …in patients with reasonable expected survival while patisiran could be considered in ATTRv patients with cardiac involvement in whom gene silencers are prescribed due to symptomatic neurological disease.	2021	ESC (29)
Can. Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis (2020)	Tafamidis for NYHA I-III symptoms	2020	Can J Cardiol (30)

ACC = Am Coll Cardiology = American College of Cardiology; ATTR-CM = Transthyretin amyloidosis cardiomyopathy; ATTRv = variant Transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; Can = Canadian; Cardiol = cardiology; ESC = European Society of Cardiology; NICE = National Institute for Health and Clinical Excellence; NYHA = New York Heart Association; SMC = Scottish Medicines Consortium

The TTR stabiliser, tafamidis (26) is the only disease-modifying therapy available within the NHS in England (see Table 3).

Tafamidis became available within NHS England in 2024 for the treatment of ATTR-CM.(16, 26) Elsewhere in the world, tafamidis is also available as a treatment for hereditary ATTR

polyneuropathy (ATTR-PN). Its registration worldwide for the treatment of ATTR-CM is based primarily on the phase 3 ATTR-ACT trial which enrolled 441 patients with ATTR-CM in 2013 and 2014 and demonstrated a 30% and 32% relative risk reduction (RRR) with tafamidis, relative to placebo, in all-cause mortality (ACM) and CV-related hospitalisation (CVH), respectively, after 30 months.(21) A difference in mortality between treatment groups was only evident after 16 to 18 months of study treatment. A significant treatment effect favouring tafamidis was also observed in functional capacity (measured by 6-minute walk distance [6MWD]) and QoL (as measured by Kansas City Cardiomyopathy Overall Summary Score [KCCQ-OS] questionnaire).(21) An extension study to ATTR-ACT (ATTR-ACT LTE) reveals a clinically significant improvement in survival after 5 years in patients taking continuous tafamidis treatment versus patients first treated with placebo in ATTR-ACT (preliminary 5-year survival rate: 53.2% vs. 32.4%).(19)

Despite this important therapeutic advance, current treatments for ATTR-CM do not provide sufficient improvements in overall survival and health-related quality of life (HRQoL). Untreated ATTR-CM patients have significantly lower survival rates than patients with undifferentiated HF (>50% lower)(37) and - in late-stage HF - a similar symptom burden / mortality to patients with advanced cancer (38, 39). Yet, in the combined active treatment arms, in ATTR-ACT, about 30% of patients died (21), meaning survival in treated patients remains subnormal (e.g.in an age-matched US population, survival rate is 85%.(40)). Also, the annualised rate of CVH remained high at 0.48/year, with a benefit of tafamidis on CVH emerging only after 9 months. Additionally, despite benefits of treatment on QoL, only 41.8% of tafamidis patients experienced an improvement or no change in KCCQ-OS score compared with 21.4% of patients treated with placebo.(24) While the HRQoL declined (LS-mean change from baseline of 15.94) in the QoL domain in the placebo group, the tafamidis group still experienced an overall decline of 1.53 in this domain.(24)

These limitations highlight the need for additional disease-modifying treatment options in ATTR-CM that provide patients with more favourable outcomes for CV-related mortality, hospitalisations and functional capacity while maintaining and improving QoL.

B.1.3.2 Acoramidis – fulfilling an unmet need in ATTR-CM

Acoramidis is a potent, highly selective TTR stabiliser designed to mimic the protective T119M mutation, which hyperstabilises TTR, preventing dissociation into monomers and development of amyloid.(3) Acoramidis is unique in its capacity to form hydrogen bonds with the same serine residues at position 117 that stabilise the T119M variant of the TTR gene.(2, 3) As assessed in vitro, acoramidis has a higher binding affinity for TTR than other

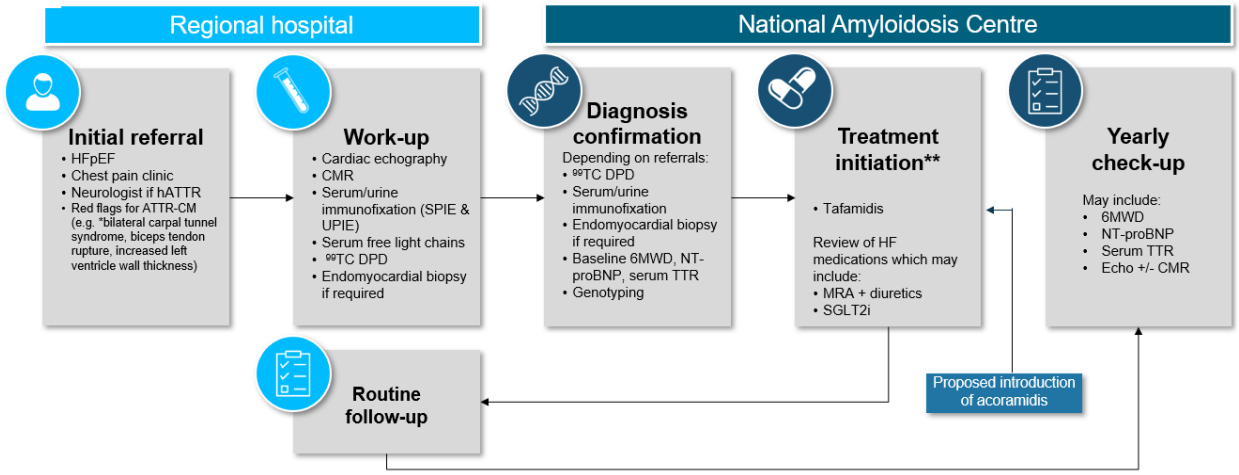
known TTR stabilisers, including diflunisal and tafamidis (4), achieving a near-complete (≥ 90%) and sustained TTR stabilisation.(3, 5) The therapeutic hypothesis that has driven the design of acoramidis is that near-complete (≥ 90%) and sustained TTR stabilisation, above and beyond what is achievable with tafamidis (as demonstrated in three complementary stabilisation assays in both variant and wild-type ATTR-CM), will slow, or stop, ongoing amyloid formation, thus resulting in robust clinical outcomes and further reduction in disease progression.

Acoramidis has been studied within a comprehensive clinical trial programme in ATTR-CM, the pivotal trial of which was ATTRibute-CM, a phase 3 international, randomised, placebo-controlled 30-month trial involving 632 patients. In ATTRibute-CM, compared with placebo, acoramidis significantly improved ACM / CVH, biomarkers (NT-proBNP), functional measures (6MWD) and QoL in patients with ATTR-CM.(20) Acoramidis was well tolerated. Early results (to month 12 i.e. month 42 from start of ATTRibute-CM) from AG10-304, the open-label extension (OLE) study, further confirm the benefits for patients receiving continuous acoramidis treatment compared to the group who received placebo in ATTRibute-CM: ACM or first CVH (0.57 [0.46, 0.72], p-value<0.0001); a 33.7% RRR in ACM; 41% RRR to first CVH alone and a statistically significant (p<0.0001) and clinically meaningful 50% reduction in the annualised frequency of CVH. Favourable treatment effects on functional capacity and QoL also continued into the OLE.

The introduction of acoramidis and its effect on the current management pathway

It is envisaged that, upon introduction within the NHS, acoramidis will provide an effective *alternative* treatment option to tafamidis for clinicians to use in patients diagnosed with ATTR-CM. Use of acoramidis does not require any additional tests or investigations beyond those already used in standard clinical practice.

Figure 1. Overview of current management pathway



*TTR deposition in ligaments starts 10-15 years before the first cardiac symptoms
**For patients unable to travel to London, the NAC offers virtual consultations for treatment initiation
6MWD = six-minute walking distance; ^{99}TC DPD = ^{99}Tc-radio-labelled diphosphono-1,2-propanodicarboxylic acid; ATTR-CM = Transthyretin amyloid cardiomyopathy; CMR = Cardiac Magnetic Resonance; HF = heart failure; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SPIE = serum protein electrophoresis with immunofixation; TTR = Transthyretin; UPIE = urine protein electrophoresis with immunofixation

B.1.4 Equality considerations

Patients affected by ATTR-CM are typically over 70 years of age, which could bring issues for accessibility and attendance at the NAC for diagnosis, treatment and review. A UK Amyloidosis network with regional amyloid services across the England / UK will ensure older patients have equal access to recommended treatments.

Additionally, one of the most prevalent variants of ATTRv in the UK is V142I, which has a primarily cardiac phenotype and is most common in men of Afro-Caribbean origin.(41-43) Patients with V142I ATTRv-CM have the worst prognosis of all forms of ATTR-CM, including ATTRwt-CM and non-Val142I ATTRv-CM (median survival from diagnosis: 31, 57 and 69 months, respectively, p<0.0001).(12) While it is understood that NICE treatment recommendations apply equally, irrespective of ethnicity, the susceptibility of this patient group could be highlighted to facilitate earlier identification and treatment of V142I ATTR-CM mediated HF versus other forms of HF in patients of Afro-Caribbean origin.

B.2 Key drivers of the cost-effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The comparator for acoramidis in this appraisal is tafamidis, which is licensed in the same indication and was previously evaluated by NICE as part of NICE TA984,(26) which updated and replaced NICE's previous guidance on tafamidis from NICE TA696.(44) As in NICE TA696, a cohort Markov state transition model was used in NICE TA984 to capture natural disease progression of ATTR-CM based on NYHA classes (I, II, III and IV) and death.

Overall survival data from the ATTR-ACT trial was extrapolated beyond the observed trial follow-up using parametric survival analysis, with different mortality extrapolations used for tafamidis and best supportive care, and adjusted with relative risk estimates by NYHA class.(21, 24, 45-47) Time to discontinuation (TTD) data for tafamidis from the ATTR-ACT trial was also extrapolated using parametric models to model discontinuation of tafamidis treatment over time. Movement between NYHA class health states was informed by transition probabilities derived from the ATTR-ACT trial, with transition probabilities beyond the available follow-up assumed to be consistent with those observed during the trial.

Treatment-specific health state utility values were also derived from EQ-5D-3L data collected in the ATTR-ACT trial to calculate differences in HRQoL between tafamidis and best supportive care.

CV hospitalisation and adverse event (diarrhoea, nausea, urinary tract infection) rates from ATTR-ACT were also considered to inform quality-adjusted life-year (QALY) losses and costs associated with each event, although CV hospitalisation and adverse event disutility were excluded in the updated company submission in NICE TA984 as it was assumed that they would be captured as part of the treatment-specific NYHA class health state utilities applied.

Overall survival extrapolations, NYHA class health state utilities, CVH event rates and treatment discontinuation assumptions for tafamidis (discontinuation in NYHA IV, treatment effect waning upon discontinuation) were noted as key drivers of the results in NICE TA984.

Key differences between NICE committee and company preferred assumptions in the original NICE TA696 appraisal included:

- Exclusion of a stopping rule for tafamidis for patients reaching the NYHA IV health state, which the committee highlighted was not included in the marketing authorisation and cited difficulties with applying such a stopping rule in clinical practice
- Excluding the company assumption that introduction of tafamidis would reduce ATTR-CM diagnosis delays, which the committee believed there was insufficient evidence to support
- Application of best supportive care inputs for patients discontinuing tafamidis at the point of discontinuation rather than continued use of tafamidis inputs, given uncertainty around duration of tafamidis treatment effect after discontinuation
- Use of best supportive care health state utilities in the NYHA class IV health state for both comparators rather than treatment-specific utilities, given that substantial differences in treatment-specific utility values were observed for this health state (while smaller differences were observed for other health states) and the limited numbers of observations available to inform calculation of NYHA class IV utilities from the ATTR-ACT trial
- Inclusion of drug wastage to occur in clinical practice with tafamidis, which the Evidence Review Group had stated should be included given the application of a relative dose intensity (RDI) parameter for tafamidis based on the number of capsules taken rather than packs dispensed, and estimated to be half a pack over a patient lifetime.

Key differences between the NICE committee and company preferred assumptions in NICE TA984 included the following:

- Use of log-normal OS model instead of generalised gamma OS model (as discussed in NICE TA696)
- Application of best supportive care inputs for patients discontinuing tafamidis at the point of discontinuation rather than continued use of tafamidis inputs (as highlighted in NICE TA696)
- Capping of tafamidis NYHA class I and NYHA Class II health state utilities to prevent them from exceeding utility values for age-matched members of the general population

- Use of best supportive care health state utilities in the NYHA class IV health state for both comparators rather than treatment-specific utilities (as noted in NICE TA696).

B.2.2 Resource use assumptions

Resource use components considered in NICE TA984 and TA696 for tafamidis included:(26, 44)

- Drug acquisition costs
- Disease management costs (electrocardiograms, consultant cardiologist visits, community nurse visits)
- CVH costs
- Adverse event costs (diarrhoea, nausea, urinary tract infections)
- End-of-life care

No comments appeared to be made by the committee during NICE TA984 on the resource use assumptions applied, with tafamidis drug acquisition costs indicated as the primary driver of costs in the cost-effectiveness analysis.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

See Appendix D.1 for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

One phase 3 clinical study (ATTRibute-CM) was identified relating to the efficacy and safety of acoramidis in adult patients with symptomatic ATTR-CM.(20) In addition, the ongoing OLE study (AG10-304) for patients still on treatment at the end of the ATTRibute-CM trial has recently reported the first set of results.(48) See Table 4 for brief details on designs of these studies including study endpoints.

Phase 2 studies (AG10-201; AG10-202) were also identified in the systematic literature review (SLR). Primary objectives of these studies were safety and tolerability of acoramidis in ATTR-CM patients. AG10-201 tested two different dose levels of acoramidis (800 mg BID vs 400 mg BID), establishing the optimal dosing in the target population of ATTR-CM for the phase 3 trial. Results from the phase 2 studies are summarised in Appendix F but not used in evidence synthesis or economic modelling.

B.3.2 List of relevant clinical effectiveness evidence

Table 4. Clinical effectiveness evidence for acoramidis in symptomatic ATTR-CM

Study	**ATTRibute-CM: Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy (20, 49)**	**AG10-304: Open-label extension study for patients completing ATTRibute-CM (48, 50)**
Study design	Prospective, international, randomised, double-blind, placebo-controlled, parallel-group, multicentre phase 3 study	Open-label extension study from the ATTRibute-CM double-blind study
Population	Patients with a diagnosis of symptomatic (NYHA Class I-III) ATTR-CM (either wild-type TTR or a variant TTR genotype).	Patients with symptomatic (NYHA Class I-III) ATTR-CM who have completed 30 months of blinded study treatment and the Month 30 assessments of the double-blind treatment period of the phase 3 ATTRibute-CM trial and who met OLE eligibility criteria
Intervention(s)	Acoramidis hydrochloride (+/- stable heart failure therapy*) 800 mg† BID (administered as two 400 mg tablets) N=421 patients randomised	Acoramidis hydrochloride (+/- stable heart failure therapy*): 800 mg† BID (administered as two 400 mg tablets) N=389 (263 continuous acoramidis, 126 placebo to acoramidis).
Comparator(s)	Placebo (+/- stable heart failure therapy*) N=211 patients randomised	Not Applicable
Supports application for marketing authorisation	Yes	Yes
Reported outcomes specified in the decision problem	ACM by Month 30, including death due to any cause, heart transplant, or CMAD (key secondary endpoint) Other Secondary Endpoints: Cumulative frequency of CVH by Month 30. **Adverse events**	Long-term safety and tolerability (primary endpoint) Secondary endpoints: **Time to ACM** **Time to CVH**
All other reported outcomes	A hierarchical combination of ACM, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD over the 30-month fixed treatment duration (primary endpoint) Change from baseline to Month 30 of treatment in 6MWD (key secondary endpoint) Change from baseline to Month 30 of treatment in KCCQ-OS (key secondary endpoint) Change from baseline to Month 30 in serum TTR level (an in vivo measure of TTR stabilisation) (key secondary endpoint) Other Secondary Endpoints: A hierarchical combination of ACM and cumulative frequency of CVH over a 30-month fixed treatment duration. A hierarchical combination of ACM, cumulative frequency of CVH, and change from baseline in 6MWD over a 30-month fixed treatment duration.	Time to ACM or first CVH ACM or recurrent CVH events Change from Baseline in distance walked during the 6MWT during study period Change from Baseline in KCCQ-OS during study period Change from baseline in NT-proBNP Change from baseline in serum TTR

Study	**ATTRibute-CM: Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy (20, 49)**	**AG10-304: Open-label extension study for patients completing ATTRibute-CM (48, 50)**
	CV-mortality by Month 30. TTR stabilisation measured in established ex vivo assays (FPE and WB) Change in NT-proBNP from baseline to Month 30 of treatment. Exploratory Endpoints: Change from baseline in Troponin I Change from baseline in the EQ-5D-5L.	

* Patients taking cardiovascular medical therapy, except for diuretic dosing, must have been on stable doses for at least 2 weeks prior to screening. †712 mg (equivalent to 800 mg as acoramidis HCl)
6MWD = 6-minute walk distance; ACM = all-cause mortality; ATTR-CM = Transthyretin amyloid cardiomyopathy; BID = twice daily; CMAD = cardiac mechanical assist device; CV = cardiovascular; CVH = cardiovascular hospitalisation; CVM = cardiovascular mortality; EQ-5D-5L = EuroQoL-5 Dimensions; FPE = fluorescent probe exclusion; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; TTR = transthyretin; WB = Western Blot

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

The clinical evidence in this submission is based on results from ATTRibute-CM, a pivotal phase 3 randomised controlled trial (RCT) in patients with symptomatic ATTR-CM and the ongoing OLE study (AG10-304) of ATTRibute-CM. A summary of the methodologies of these studies is presented in Table 5.

Notes:

- *Throughout this submission, use of 'acoramidis' and 'placebo' in relation to ATTRibute-CM refers to the 'acoramidis hydrochloride (acoramidis HCl) plus any cardiovascular medical therapy the patient is taking for heart failure' and 'placebo plus any cardiovascular medical therapy the patient is taking for heart failure' respectively. Except for diuretics, the heart failure medication had to be at a stable dose for at least two weeks prior to screening.*
- *During design of ATTRibute-CM, as part of an Early Scientific Advice Procedure, it was confirmed that enrolling a limited number of patients with severe renal impairment (eGFR < 30 but ≥ 15 mL/min/1.73 m^2) - an understudied subgroup not typically enrolled in heart failure and ATTR-CM trials (51) - would be beneficial in providing preliminary information on the safety and tolerability of acoramidis and that this was an acceptable approach in lieu of a dedicated study in this patient subgroup, due to the rarity of the disease. Therefore, by design, the study enrolled such patients to assess preliminary safety and tolerability and did not intend to evaluate efficacy. Consequently, these patients were excluded from the primary efficacy analysis but were included in an exploratory analysis and represented in the Intention-to-treat (ITT) population in Appendix J.*

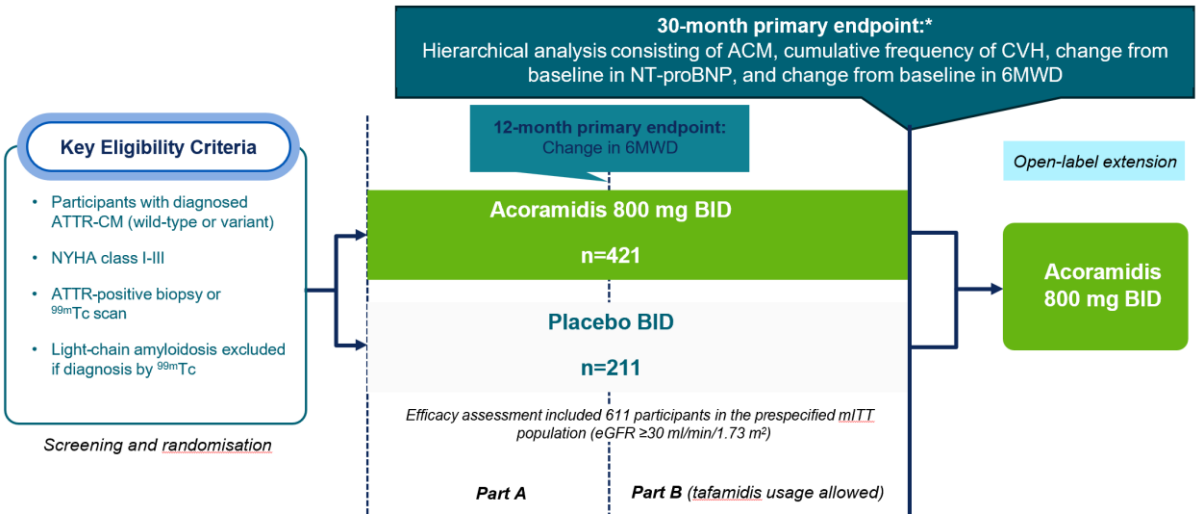
- *At the start of the study, the primary endpoint for Part B (see Figure 2 below) used a two-component Finkelstein-Schoenfeld analysis (F-S test) of ACM and CVH. This was later updated (March 2021) to use three components (ACM, CVH, and change from baseline [CFB] in 6MWD) in the F-S test to mitigate the potential impact on the power of the study of allowing concomitant tafamidis after month 12.; and then further updated to a four-step primary hierarchical analysis of ACM, then CVH, then CFB in NT-proBNP, then CFB in 6MWD in the F-S test (see Appendix K for definitions). NT-proBNP was added as a component of the hierarchical primary endpoint in June 2022 due to recognition of a lower event rate of CVH noted via blinded aggregate review of reported CV outcome events, and the need to preserve the statistical power of the study and mitigate the risk of Type II error. The study sponsors assessed that the lower event rate appeared to be primarily driven by two factors: increased access to tafamidis and recognition of a shift in the ATTR-CM patient population, including increased survival, caused by increased disease awareness, earlier diagnosis, and better disease management, as reported in the literature.(52)*

B.3.3.1 ATTRibute-CM: A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of AG10 in Subjects with Symptomatic Transthyretin Amyloid Cardiomyopathy (Study AG10-301; NCT03860935) (20, 49, 53-55)

Study enrolment started in April 2019 and was completed October 2020, during which time a total of 836 patients underwent screening and 632 patients with symptomatic ATTR-CM were randomised in a 2:1 ratio to receive acoramidis 800 mg BID (n = 421) or matching placebo (n = 211) BID for 30 months. The final patient visit in the study was 11th May 2023.

The study was designed to last a total of 30 months and employed an embedded design consisting of two parts (Part A and Part B) (see Figure 2) each with different primary endpoints. Part A was a 12-month functional readout with analyses of the primary functional (6MWD) and key secondary HRQoL (KCCQ-OS) endpoints. Part B assessed 30-month mortality, morbidity, biomarker and functional outcomes.

Figure 2. ATTRibute-CM study design



* Primary analysis assessed using the Finkelstein-Schoenfeld method.
6MWD = 6-minute walk distance; 99mTc = technetium-labelled pyrophosphate or bisphosphonate (e.g., DPD); ACM = all-cause mortality; ATTR-CM = transthyretin amyloid cardiomyopathy; BID = twice daily; CVH = cardiovascular-related hospitalisation; DPD = 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid; eGFR = estimated glomerular filtration rate; min = minutes; mITT = modified intent-to-treat; ml = millilitres; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

After screening and randomisation, trial visits were conducted at day 1, month 1, month 3 and then every 3 months until trial completion, plus an end of study visit 30 days after the last dose of medication.(49) Patients also had monthly phone contact to discuss concomitant medications, adverse events (AEs) and to assess compliance. Patients were assessed at study visits for outcomes and AEs. Study visits also included assessment of NYHA class, clinical laboratory values (including haematology, chemistry, urinalysis), physical examinations (including vital signs) and 12-lead electrocardiograms (ECG). The 6MWT and HRQoL questionnaires (KCCQ and EQ-5D-5L) were completed at baseline and every 3 months thereafter.(49)

Discontinuation of study drug could occur by patient request, patient choice to initiate treatment with another therapy including tafamidis in the first 12 months of the study, AE, investigator decision, death, protocol deviation, non-compliance, heart or liver transplant or CMAD, a need for medications prohibited during the study or pregnancy. Wherever possible, patients were monitored and followed for efficacy and safety events until the study end, even if study drug treatment had been discontinued. Regardless of discontinuation or withdrawal status all patients were asked to consent to monthly phone contact and determination of vital status (alive, death, heart transplant, receiving CMAD) at Month 30, either via direct contact or through public records.(49)

Patients who completed the 30-month assessments in ATTRibute-CM were offered enrolment in an extension trial (Study AG10-304) of long-term acoramidis treatment.

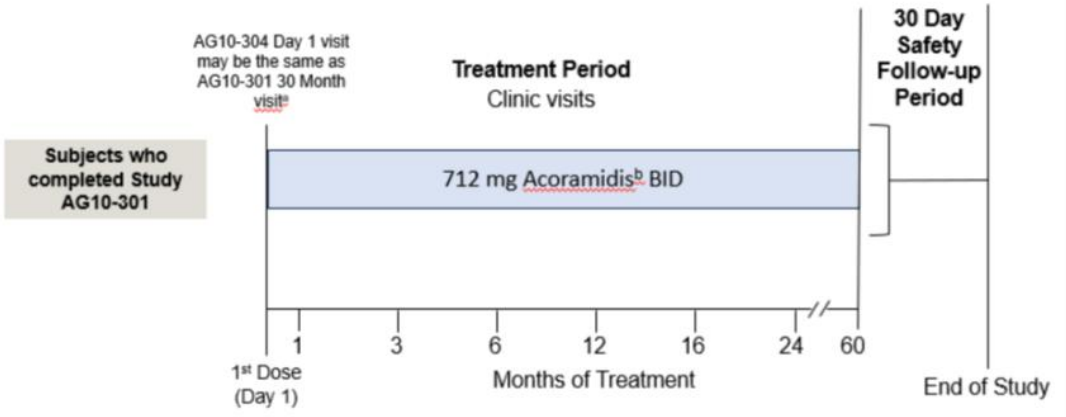
B.3.3.2 Open-Label Extension and Safety Monitoring Study of Acoramidis (AG10) in Participants with Symptomatic ATTR-CM Who Completed the Phase 3 ATTRibute-CM Trial (Study AG10-304; NCT04988386)(48, 50, 56)

The OLE study started in August 2018 and is ongoing. All patients completing 30 months of blinded study treatment (including Month 30 assessments) of the ATTRibute-CM trial *and* who met OLE eligibility criteria (see Table 5) could participate.

Overall, 438 of 632 patients in ATTRibute-CM completed treatment and 389 enrolled in the OLE (263 continuous acoramidis, 126 placebo to acoramidis). Forty-nine of the 438 patients who completed treatment in ATTRibute-CM chose not to enrol in the OLE (34 from the acoramidis group and 15 from the placebo group), the most common reason was related to tafamidis treatment (i.e., choosing to continue tafamidis if they received it as a concomitant medication during ATTRibute-CM, or choosing to initiate tafamidis treatment upon completing ATTRibute-CM).

The study is designed to last a total of 60 months followed by 1 month follow-up (see Figure 3), to provide long-term efficacy and safety data over a period of up to a total of 90 months of acoramidis treatment including the ATTRibute-CM study duration. Patients in the OLE study had planned study visits at 1 month, 6 months, and every 6 months thereafter.

Figure 3. AG10-304 study schematic (56)



AG10-301 = ATTRibute-CM phase 3 study; AG10-304 = OLE study of ATTRibute-CM; BID = twice daily; HCl = hydrochloride; mg = milligrams; OLE = open-label extension
[a] The Day 1 visit may be concurrent with the Month 30 visit of Study AG10-301 and must be completed no later than 30 days after the Month 30 visit. If the delay between studies is more than 14 days, all baseline assessments should be repeated.
[b] 712 mg acoramidis (equivalent to 800 mg acoramidis HCl)

Table 5. Summary of acoramidis trial methodologies

Study	NCT03860935 (ATTRibute-CM; Study AG10-301) (20, 49, 53, 54, 57)	NCT04988386 (AG10-304; ATTRibute-CM OLE) (48, 50, 56)
Data sources	Key results - published January 2024 in NEJM.(20) Trial protocol and statistical analysis plans form part of the supplementary material with the NEJM publication.(49, 58) Other sources: EPAR (57), the manufacturer licence application submission to the EMA (53, 55), CSR (54) and relevant congresses poster or oral presentations.	Early efficacy and safety data of acoramidis in patients who completed ATTRibute-CM and enrolled in the OLE were presented at the American Heart Association meeting (November 2024) and subsequently published.(48, 50) Other elements of the OLE within this submission are **unpublished and remain confidential**.
Location	95 sites in 18 countries: Australia (n = [redacted], [redacted]%), Belgium, Brazil, Canada, Czech Republic, Denmark, Greece, Ireland, Israel, Italy (n = [redacted], [redacted]%), Netherlands, New Zealand, Poland, Portugal, South Korea, Spain (n = [redacted], [redacted]%), UK (n = [redacted], [redacted]%), and United States of America (USA) (n = [redacted], [redacted]%).	As per site / country of recruitment in ATTRibute-CM.
Trial design	International, phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. Eligible patients were randomised on a 2:1 basis, using permuted block randomisation, to receive twice daily treatment with either acoramidis or placebo, with stratification by: (49) • TTR genotype (wild-type or variant) with a target of 20% ATTRv, and • NT-proBNP level (≤3,000 or >3,000 pg per millilitre) • eGFR category at screening (<45 or ≥45 ml per minute per 1.73 m^2). Central randomisation was performed using an IXRS portal. The NT-proBNP and eGFR cutoffs correspond to those used in the NAC Staging system.(25)	Prospective, international, multicentre, open-label study (see Figure 3 for schematic).
Eligibility criteria for participants	**Inclusion criteria** Aged 18-90 with written, informed consent and: • An established diagnosis of wild-type or variant ATTR-CM based on either an endomyocardial biopsy with confirmatory typing or positive results (Perugini grade, ≥2†) on technetium-99m scintigraphy combined with biochemical exclusion of a monoclonal gammopathy characteristic of AL. • Clinical heart failure with at least one previous hospitalisation for heart failure, or signs and symptoms of volume overload, or heart failure that resulted in diuretic treatment. • NYHA Class I-III symptoms due to ATTR-CM.	**Inclusion criteria** Written, informed consent and: • Completed 30 months of the blinded study treatment in ATTRibute-CM and that study's Month 30 visit including assessments and procedures. • Agreement to use highly effective contraceptive method where there is childbearing potential. **Exclusion criteria** • Acute myocardial infarction, coronary syndrome, or coronary revascularisation, stroke, or transient ischaemic attack within 90 days prior to Day 1.

Study	NCT03860935 (ATTRibute-CM; Study AG10-301) (20, 49, 53, 54, 57)	NCT04988386 (AG10-304; ATTRibute-CM OLE) (48, 50, 56)
	• 6MWD of ≥ of 150m on at least two tests performed 24 hours to 3 weeks apart. • NT-proBNP ≥ 300 pg/mL. • Left ventricular wall thickness of ≥12 mm on a previous imaging study. • Stable doses of any cardiovascular medication, except for diuretics (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to screening. • Agreement to use highly effective contraceptive method where there is childbearing potential. **Exclusion criteria** included: • Acute coronary syndrome, coronary revascularisation, stroke, or transient ischaemic attack within 90 days before screening. • Likely heart transplantation within a year after screening. • AL amyloidosis. • Abnormal liver function tests at screening (ALT or AST > 3× ULN or total bilirubin > 3× ULN). • NT-proBNP level ≥ 8500 pg/mL. • eGFR < 15 ml per minute per 1.73 m^2 of body-surface area. • Treatment with tafamidis during the first 12 months of the trial. • Haemodynamic instability at screening or randomisation posing too much risk for study participation. • Treatment with medicines lacking a labelled indication for ATTR-CM within 14 days prior to dosing. Patisiran (within 90 days prior), inotersen (within 180 days), or other gene silencing agent (within 5 half-lives)	• Haemodynamic instability posing too great a risk for study participation. • Has had a heart and/or liver transplant or is on the heart transplantation list within the year prior to Day 1. • Implantation of a CMAD or is scheduled for implantation of a CMAD. • Confirmed diagnosis of AL amyloidosis. • eGFR < 15 ml per minute per 1.73 m^2 of body-surface area at Month 27 of ATTRibute-CM or at any subsequent central lab value prior to Day 1. • Known hypersensitivity to acoramidis or its metabolites, or formulation excipients. • Treatment with prohibited medication at the end of Study ATTRibute-CM or at Day 1 of Study AG10-304 (or any time during the study [see ATTRibute-CM exclusion criteria in this table]) • Pregnancy or breastfeeding. • Any clinically important ongoing medical condition / laboratory abnormality / condition that might jeopardise participation or interfere with the study. • Participation in another clinical trial within 30 days prior to dosing (with the exception of participation in of ATTRibute-CM).
Trial drugs	Patients (N=632) were randomised to receive either: • 800 mg acoramidis [equivalent to 712 mg acoramidis] – taken orally as two 400 mg tablets, twice daily (N=421) or, • Placebo (as two matching placebo tablets) twice daily (N=211). The dose could be reduced to 400 mg (or one matching placebo tablet) twice daily if poor tolerability / AEs.	All patients received acoramidis only (acoramidis HCl 800 mg BID). Patients who previously received acoramidis up to Month 30 in ATTRibute-CM continued to receive it (continuous acoramidis), and those who received placebo in ATTRibute-CM were switched to acoramidis (placebo to acoramidis). Observations were analysed comparing the 'continuous acoramidis' and 'placebo to acoramidis' cohorts.
Permitted and disallowed concomitant medication	Concomitant therapy was assessed at every visit and monthly phone contact.	Patients who received concomitant tafamidis in ATTRibute-CM were required to discontinue to be eligible for the OLE.

Study	NCT03860935 (ATTRibute-CM; Study AG10-301) (20, 49, 53, 54, 57)	NCT04988386 (AG10-304; ATTRibute-CM OLE) (48, 50, 56)
	Tafamidis was not permitted during the initial 12 months of the trial, although could be taken thereafter. **Note:** When the ATTRibute-CM trial was designed, tafamidis was not approved for treating ATTR-CM. To provide optimal care, patients were allowed to start tafamidis therapy once it became commercially available for ATTR-CM. Patients could use tafamidis as a concomitant medication, at the discretion of the treating physician, provided they had completed at least 12 months (Part A) of blinded study treatment. **It is important to note that the treatments would not be used together in clinical practice.**	
Outcomes:	See Appendix K for full list of study outcomes, outcome definitions and assessment.	All ACM and investigator-identified CVH events were adjudicated by a CEC (as per ATTRibute-CM), and without knowledge of prior treatment assignment in ATTRibute-CM. Adjudicated events were the basis for the efficacy analyses of ACM and CVH. An independent Data Monitoring Committee that monitored unblinded data throughout the ATTRibute-CM study continues to monitor the long-term safety of acoramidis in the OLE.
• Primary outcome	**Part A:** Change from baseline in 6MWD **Part B:** The hierarchical combination of ACM, cumulative frequency of CVH*, clinically meaningful difference (≥ 500pg/mL) in CFB in NT-proBNP, and CFB in 6MWD over a 30-month fixed treatment duration.	• Long-term safety and tolerability.
• Key secondary outcomes	• CFB to Month 30 in 6MWD. • CFB to Month 30 in KCCQ-OS. • CFB to Month 30 in serum TTR. • ACM by Month 30.	• Time to ACM • Time to ACM or first CVH • Time to CVH • ACM or recurrent CVH events • CFB in 6MWD • CFB in KCCQ-OS / EQ-5D-5L • CFB in NT-proBNP • CFB in serum TTR
• Other secondary endpoints relevant to decision problem	• A hierarchical combination of ACM and cumulative frequency of CVH over a 30-month fixed treatment duration. • A hierarchical combination of ACM, cumulative frequency of CVH, and CFB in 6MWD over a 30-month fixed treatment duration. • CV-mortality by Month 30. • Cumulative frequency of CVH by Month 30. • TTR stabilisation measured in established ex vivo assays (FPE and WB)	• Shifts in NYHA class from baseline.

Study	NCT03860935 (ATTRibute-CM; Study AG10-301) (20, 49, 53, 54, 57)	NCT04988386 (AG10-304; ATTRibute-CM OLE) (48, 50, 56)
	• CFB to Month 30 in NT-proBNP • CFB in EQ-5D-5L questionnaire • Safety	

99mTc = technetium labelled; 6MWD = 6-minute walk distance; ACM = all-cause mortality; AEs = Adverse events; AL = light chain amyloidosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = variant transthyretin amyloidosis; BID = twice daily; CEC = Clinical Event Committee; CFB = change from baseline; CMAD = cardiac mechanical assist device; CSR = Clinical Study Report; CT = computed tomography; CV = cardiovascular; CVH = cardiovascular-related hospitalisation; DPD = 3-diphosphono-1,2-propanodicarboxylic acid; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; EOCI = events of clinical interest; EPAR = European Public Assessment Report; EQ-5D-5L = European Quality of Life – 5 Dimension questionnaire; FPE = Fluorescent probe exclusion; HMDP = hydroxymethylene diphosphonate; HRQoL = Health-related QoL; IXRS = Interactive Voice/Web Response System; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire, Overall Summary Score; NAC = National Amyloidosis Centre; NEJM = New England Journal of Medicine; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; OLE=open-label extension study; QoL = quality of life; UK = United Kingdom; ULN = upper limit of normal; USA = United States of America; WB = western blot

† **The Perugini grading scale** is a semi-quantitative method of scoring cardiac uptake following injection of 99mTc-DPD, 99mTc-Pyrophosphate or 99mTc-HMDP scintigraphy in the investigation of cardiac amyloidosis (particularly ATTR amyloidosis). The grading scale visually compares tracer uptake in the myocardium and ribs. Grade 0: no cardiac uptake and normal rib uptake; Grade 1: cardiac uptake which is less than rib uptake; Grade 2: cardiac uptake with intensity similar to rib uptake; Grade 3: cardiac uptake greater than rib uptake with mild or absent rib uptake. Visual scores of 2 or greater on planar +/- SPECT/CT imaging are classified as ATTR-positive studies. Scores of less than 2 are interpreted as ATTR negative.

* **CVH:** includes both CVH and EOCIs. CVH was defined as a non-elective admission to an acute care setting for CV-related morbidity that resulted in a ≥ 24 hour stay. An EOCI was defined as an unscheduled medical visit of < 24 hours due to heart failure. The diagnosis and interventions at an EOCI visit were required to document that the purpose of the visit was for intravenous diuretic therapy for management of decompensated heart failure or for a primary diagnosis of heart failure, and the event did not otherwise meet the criteria for CVH. The CEC reviewed and adjudicated suspected CVH and EOCI.

B.3.3.3 Baseline characteristics

B.3.3.3.1 ATTRibute-CM patient baseline characteristics (2, 20, 54)

Patient baseline characteristics for ATTRibute-CM are presented in Table 6 for the overall study population (ITT), and also the primary analysis population (modified ITT; mITT).

Overall study population (ITT)

Baseline demographics were broadly similar between treatment groups in the ITT population. The overall ATTRibute-CM trial population was predominately male (90.2%) and white (87.8%), with a mean age of 77.3 years at randomisation. Almost all patients were ≥ 65 years of age (97.1%) and had been recently diagnosed with ATTR-CM (a mean of 1.2 years [±1.2] since diagnosis).

Baseline ATTR-CM history characteristics and assessment of endpoints were generally well balanced between the treatment groups. Just over 90% patients (90.3%) had wild-type TTR Note, the target was to recruit 20% patients with variant ATTR-CM, however recruitment to ATTRibute-CM may reflect the recently noted upsurge in diagnosis of wild-type ATTR-

CM).(52) Most of the patients had either NYHA Class II (72.0%) or class III symptoms (17.2%). The distribution of NAC stages was 57.1% in stage I, 32.1% in stage II, and 10.8% in stage III.

Overall, [redacted]% of patients had atrial fibrillation, [redacted]% had a permanent pacemaker placed, and [redacted]% had prior carpal tunnel release surgery.

Prior and concomitant medications were balanced between the treatment groups and consistent with ATTR-CM and comorbidities in this patient population. The most reported prior and concomitant medications were diuretics (acoramidis: [redacted]%; placebo: [redacted]%); antithrombotic agents (acoramidis: [redacted]%; placebo: [redacted]%); and lipid modifying agents (acoramidis: [redacted]%; placebo: [redacted]%).

The number of patients who initiated tafamidis at any point during the study (i.e. before or after the Month 12 visit) was greater in the placebo group compared to the acoramidis treatment group ([redacted]% vs. [redacted]%). [redacted] of these patients (acoramidis: [redacted]; placebo: [redacted]) initiated tafamidis prior to the Month 12 visit and were discontinued from study drug, as per protocol.

Modified Intention-to-treat (mITT) population (primary analysis population)

Twenty-one ATTRibute-CM study patients had stage 4 kidney disease (acoramidis n=12; placebo n=9) and were excluded from the primary analysis to form the mITT population (see Section B.3.3). The mITT population of 611 patients (acoramidis n=409; placebo n=202) generally resembled characteristics of the overall population. Generally, baseline demographic and ATTR-CM disease characteristics were well balanced between the two treatment groups and were similar to those observed in the overall study population.

In the acoramidis treatment group, compared to placebo there was a lower proportion of patients with NYHA Class II (70.4% versus 77.2%), and a slightly higher proportion of patients with NYHA Class III (17.1% versus 14.4%). Similar findings were observed in the overall study population.

A total of 107 patients received tafamidis (acoramidis group: 61 / 409 [14.9%]; placebo group:46 / 202 [22.8%]). Median time until the initiation of tafamidis was 17.2 months, and the median duration of exposure was 11.4 months.

Table 6. Baseline demographic and disease characteristics for the mITT and ITT ATTRibute-CM study populations (2, 20, 22, 54, 59-61)

	mITT		ITT	
	Acoramidis (N=409)	**Placebo (N=202)**	**Acoramidis (N=421)**	**Placebo (N=211)**
Age (yr) (mean±SD)	77±6.5	77±6.7	77.4±6.5	77.1±6.8
n (%):				
<65	12 (2.9)	9 (4.5)	[redacted]	[redacted]
≥65 to <78	186 (45.5)	92 (45.5)	[redacted]	[redacted]
≥78	211 (51.6)	101 (50.0)	[redacted]	[redacted]
Male, n (%)	374 (91.4)	181 (89.6)	384 (91.2)	186 (88.2)
Race, n (%) †				
White	358 (87.5)	179 (88.6)	368 (87.4)	187 (88.6)
Black	19 (4.6)	10 (5.0)	20 (4.8)	10 (4.7)
Asian	10 (2.4)	3 (1.5)	10 (2.4)	3 (1.4)
Other	[redacted]	[redacted]	23 (5.5)	11 (5.2)
Not reported	[redacted]	[redacted]	-	-
Transthyretin genotype, n (%)				
Wild-type	370 (90.5)	182 (90.1)	380 (90.3)	191 (90.5)
Variant	39 (9.5)	20 (9.9)	41 (9.7)	20 (9.5)
Transthyretin variant. n (%)				
V30M	[redacted]	[redacted]	1/39 (2.6)	0
V122I (=V142I)	23/37 (62.2)	12/19 (63.2)	24/39 (61.5)	12/19 (63.2)
T60A (=T80A)	3/37 (8.1)	2/19 (10.5)	3/39 (7.7)	2/19 (10.5)
E89Q	0	1/19 (5.3)	0	1/19 (5.3)
Other	11/37 (29.7)	4/19 (21.1)	11/39 (28.2)	4/19 (21.1)
Duration of ATTR-CM (years)	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP (ng/L)				
Mean (±SD)	2865±2150	2650±1899	2946±2226	2725±1971
Median (IQR)	2273 (1315- 3872)	2274 (1128-3599)	2326 (1332-4019)	2306 (1128-3754)
eGFR (ml/min/1.73m^2)				
Mean	62±17.4	63±17.5	61±18	61±19
< 45 ml/min/1.73 m^2, n (%)	65 (15.9)	29 (14.4)	[redacted]	[redacted]
≥ 45 mL/min/1.73 m^2, n (%)	344 (84.1)	173 (85.6)	[redacted]	[redacted]
NAC stage, n (%)				
I	241 (58.9)	120 (59.4)	241 (57.2)	120 (56.9)
II	130 (31.8)	66 (32.7)	134 (31.8)	69 (32.7)
III	38 (9.3)	16 (7.9)	46 (10.9)	22 (10.4)
Mean serum TTR ‡ (mg/dl) (±SD)	n=406 23.0±5.6	n=199 23.6±6.1	23±6	24±6
NYHA functional class, n (%)				
I	51 (12.5)	17 (8.4)	51 (12.1)	17 (8.1)
II	288 (70.4)	156 (77.2)	293 (69.6)	162 (76.8)
III	70 (17.1)	29 (14.4)	77 (18.3)	32 (15.2)
6MWD (metres)	[redacted]	[redacted]	n=419 361.2±103.7	n=211 348.4±93.6
KCCQ-OS	N=408 71.7 (19.37)	N=202 70.5 (20.65)	n=420 71.5±19.4	n=211 70.3±20.5

	mITT		ITT	
	Acoramidis (N=409)	**Placebo (N=202)**	**Acoramidis (N=421)**	**Placebo (N=211)**
Atrial Fibrillation, n (%)	236 (57.7)	117 (57.9)	[redacted]	[redacted]
History of Thromboembolic Event or Stroke/TIA / Reversible Ischaemic Neurological Defect, n (%) Thromboembolic event TIA Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Permanent pacemaker placed	77 (18.8)	38 (18.8)	[redacted]	[redacted]
Implantable cardioverter-defibrillator placed	[redacted]	[redacted]	[redacted]	[redacted]
Prior carpal tunnel release surgery	[redacted]	[redacted]	[redacted]	[redacted]
Patients initiating Tafamidis, n (%) Months to initiation Months of exposure	61 (14.9) [redacted]	46 (22.8) [redacted]	61 (14.5) Not available “	46 (21.8) Not available “

6MWD = 6-minute walk distance; ATTR-CM = transthyretin amyloid cardiomyopathy; dl = decilitre; eGFR = estimated glomerular filtration rate; IQR = interquartile range; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire, Overall Summary Score; mg = milligram; min = minute; ml = millilitre; mITT = modified intention-to-treat; NAC = National Amyloidosis Centre; ng = nanogram; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin; n = number; TIA = transient ischaemic attack; yr = year;
‡ Normal serum TTR range is 18 to 45 mg/dL (62)

Representativeness of ATTRibute-CM population to UK population

[redacted] of ATTRibute-CM trial patients were recruited from the UK. The authors of the ATTRibute-CM results publication (20) confirmed the trial population were reflective of a contemporary ATTR-CM population. Patient baseline characteristics in ATTRibute-CM align with those reported from a retrospective observational cohort study at the NAC in the UK involving 1967 patients (52), where most patients in the ATTR-CM cohort (n=1967) were male (86.3%) and the mean age of all patients was 75.5 years (±8.40).

B.3.3.3.2 OLE patient baseline characteristics

Baseline characteristics of patients entering the OLE study are presented in Table 7. Of note are parameters associated with progression of disease or predictive of mortality (NYHA class distribution, NAC Stage distribution, and NT-proBNP levels), which, relative to baseline at the start of ATTRibute-CM, show a shift towards disease progression in patients who received placebo during the ATTRibute-CM study and also a treatment effect of early and continuous acoramidis treatment in the active treatment arm from ATTRibute-CM.

Table 7. Patient baseline characteristics at entry to the OLE (OLE FAS) (48, 50, 63)

Patient characteristics [a,b]	**Continuous acoramidis n=263**	**Placebo to acoramidis n=126**
Age, years, mean (SD) [c]	78.8 (6.50)	79.7 (6.33)
Male sex, n (%)	244 (92.8)	115 (91.3)

Patient characteristics [a,b]	Continuous acoramidis n=263	Placebo to acoramidis n=126
ATTR-CM duration at time of randomisation in ATTRibute-CM [d,e] years,		
n	262	126
Mean (SD)	1.2 (1.10)	1.1 (1.29)
Transthyretin genotype, n (%) [f]		
Wild-type	242 (92.0)	120 (95.2)
Variant	21 (8.0)	6 (4.8)
NYHA class, n (%) [g]		
I or II	216 (82.1)	79 (62.7)
III	44 (16.7)	45 (35.7)
IV	3 (1.1)	1 (0.8)
NT-proBNP, pg/ml,		
n	252	121
Median (IQR)	2064.0 (1240.5-3442.5)	2905.0 (1624.0-5087.0)
eGFR (ml/min/1.73m^2)		
< 45 ml/min/1.73 m^2, n (%)	[redacted]	[redacted]
≥ 45 mL/min/1.73 m^2, n (%)	[redacted]	[redacted]
NAC stage, n (%) [h]		
I	136 (51.7)	52 (41.3)
II	66 (25.1)	46 (36.5)
III	53 (20.2)	26 (20.6)
Missing	8 (3.0)	2 (1.6)
6MWD (metres)	[redacted]	[redacted]
KCCQ-OS	[redacted]	[redacted]
Serum TTR, mg/dL,		
n	253	120
Mean (SD)	32.8 (6.27)	25.6 (6.61)
Patients who received tafamidis in the ATTRibute-CM study, n (%)	29 (11.0)	23 (18.3)

[a] Data are for all patients who enrolled in the OLE and received at least one dose of open-label acoramidis.
[b] Baseline values are the last non-missing assessment values completed before the first OLE acoramidis treatment.
[c] Age calculated from the first OLE treatment date and date of birth/age.
[d] Data at the time of randomisation in ATTRibute-CM (not at OLE entry).
[e] Calculated as (randomisation date – date of ATTR-CM diagnosis)/365.25.
[f] Genotype based on ATTRibute-CM stratification factors at the time of randomisation (not at OLE entry).
[g] Data missing for one patient in the placebo to acoramidis group.
[h] NAC ATTR Stage: NAC ATTR Stage I, defined as NT-proBNP≤3000ng/L and eGFR≥45 mL/1.73 m^2; Stage III defined as NT-proBNP > 3000 ng/L and eGFR < 45 mL/1.73 m^2; the remainder categorised as Stage II when both NT-proBNP and eGFR are not missing.
ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRwt-CM = transthyretin amyloidosis wild-type cardiomyopathy; eGFR = estimated glomerular filtration rate; FAS = full analysis set; IQR = interquartile range; NAC = National Amyloidosis Centre; ng = nanogram; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension study; SD = standard deviation; TTR = transthyretin; n = number

B.3.4 Statistical analysis and definition of study groups

B.3.4.1 Analysis sets of ATTRibute-CM

The population for primary analysis of ATTRibute-CM was the mITT population, which excluded patients with stage 4 kidney disease (eGFR < 30 mL/min/1.73 m^2). Efficacy results are also presented in Appendix J for the overall ITT population, which is the same population used for the safety analysis.

B.3.4.1.1 Rationale for using mITT Population as the Primary Efficacy Analysis Population

During ATTRibute-CM trial design and discussions with regulatory authorities, the question was raised as to whether concomitant severe renal impairment (i.e., Stage 4 chronic kidney disease (CKD), defined as an eGFR between 15 and 30 mL/1.73m^2) in the context of chronic exposure to acoramidis might generate safety signals of clinical concern. Patients with severe renal impairment (eGFR < 30 but ≥ 15 mL/min/1.73 m^2) are an understudied subgroup not typically enrolled in heart failure and ATTR-CM trials (51), hence it was agreed to enrol a limited number of such patients in ATTRibute-CM to provide preliminary information on the safety and tolerability of acoramidis. There was no intention to evaluate efficacy, hence these patients were excluded from the primary efficacy analysis in the original protocol Version 1.0 (10 January 2019; (49)).

Note: Analyses using the Per Protocol population were only to be performed if the PP population was ≤90% of the mITT population. As the PP population made up a large fraction (>90%) of the mITT population (see Table 8), analyses using the PP population were not conducted.

B.3.4.2 OLE

In the extension study, the full analysis set (FAS) is used for analyses. The FAS included the mITT population in ATTRibute-CM, which was defined as all patients who were randomised to acoramidis or placebo, received at least one dose of acoramidis or placebo, had baseline eGFR rate of ≥30mL/min/1.73m^2 and at least one efficacy evaluation after baseline.

Table 8. Analysis sets in ATTRibute-CM (20, 49) and AG10-304 (the OLE) (64)

Analysis set	Definition	ATTRibute-CM population		OLE (AG10-304)	
		Acoramidis	Placebo	Continuous acoramidis	Placebo to acoramidis
ITT	All randomised patients who have received at least one dose of study drug and have at least one post-baseline efficacy evaluation.	N=421 (100%)	N=211 (100%)	N=421 (100%)	N=211 (100%)
Modified intention-to-treat (MITT)	All ITT patients with baseline eGFR ≥30 mL/min/1.73m^2	N=409 (97.2%)	N=202 (95.7%)	-	-
Full analysis set (FAS)	All patients in ATTRibute-CM mITT population.	-	-	N=409 (97.2%)	N=202 (95.7%)
OLE Full Analysis set (OLE FAS)	All patients who were enrolled in AG10-304 and received at least one dose of open-label acoramidis treatment.	-	-	N=263 [a] (100%)	N=126 [a] (100%)
Safety population	All patients who received at least one dose of study drug.	N=421 (100%)	N=211 (100%)	N=263 (100%)	N=126 (100%)
Acoramidis-treated Safety analysis set	All patients who received at least one dose of acoramidis during either ATTRibute-CM or the OLE study (AG10-304).	-	-	N=421 (100%)	N=211 (100%)
Per protocol (PP)	All patients from the ITT set who did not have major protocol violations or deviations.	N=402 (95.5%)	N=198 (93.8%)	-	-

eGFR = estimated glomerular filtration rate; FAS = full analysis set; ITT = intention-to-treat; mITT = modified intention-to-treat; N = number; OLE = open-label extension study; OLE FAS = open-label extension FAS population; PP = per protocol

[a] Five patients in the acoramidis group and 4 patients in the placebo group were not in the mITT population of ATTRibute-CM (i.e. had baseline eGFR<30mL/min/1.73m^2 when randomised into ATTRibute-CM).

B.3.4.3 Overview of statistical analyses

Table 9. Summary of statistical analyses of ATTRibute-CM and the OLE study (AG10-304) (20, 48, 49, 56, 58)

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Missing data, Data management, patient withdrawals
ATTRibute-CM	The primary hypothesis is: *H_0 (null hypothesis): All four components of ACM, cumulative frequency of CVH, change in NT-proBNP, and change in 6MWD are the same between placebo and acoramidis treatment groups.* *H_a (alternative hypothesis): At least one component of ACM, cumulative frequency of CVH, change in NT-proBNP, and change in 6MWD is different between the placebo and acoramidis treatment groups.*	**ATTRibute-CM employed an embedded study design, that included a Part A and Part B, with different endpoints.** **Part A -** At the end of 12 months of treatment (Part A), efficacy was assessed by the Part A team through analyses of the functional (6MWD change from baseline to Month 12) and health-related QoL (as measured by KCCQ-OS, change from baseline to Month 12). The two-sided alpha for Part A was 0.01. To control alpha, the key secondary endpoint was formally tested if the primary endpoint was statistically significant at the 0.01 level. Endpoints were analysed using a MMRM analysis of covariance (ANCOVA), including terms for randomisation stratification factors, treatment, time, treatment by time interaction. An unstructured variance-covariance model was used. Part A did not meet its primary endpoint at the pre-specified α-level of 0.01.(20) **Part B -** formal statistical tests of the primary and select secondary efficacy analyses were controlled at an α of 0.04 sequentially. For other variables of interest, uncontrolled for Type I error, statistical comparisons used a two-sided significance test evaluated at α level of 0.05. Multiplicity adjustment was applied to the primary and key secondary endpoints only and mITT set only. **Primary Efficacy Analysis** The **primary endpoint** was analysed by the F-S test (Finkelstein and Schoenfeld, 1999 (65)), an established non-parametric test for assessing a treatment effect for an endpoint with several components. Each patient was compared to every other patient within each stratum in a pairwise manner (see Figure 4). The F-S test has been accepted by Health Authorities for prior regulatory approvals.(21, 66) The order of individual components in the hierarchical endpoint corresponds to their clinical impact. ACM and cumulative CVHs were the most clinically important components contributing to the overall clinical benefit-risk assessment within the hierarchical endpoint and were appropriately the first and second components in the hierarchy. Clinically meaningful difference (≥ 500 pg/mL) in change from baseline in NT-proBNP was the third step,	Sample size calculations were based on two-sided alphas = 0.01 for Part A and 0.04 for Part B. The power for Part B was originally estimated based on the primary endpoint of a hierarchical combination of ACM and CVH over a 30-month treatment period. Based on the below assumptions (using estimates of ACM and CVH from ATTR-ACT (21)), a sample size of 460 patients with eGFR ≥30mL/min/1.73m^2 resulted in greater than 90% study power with two-sided alpha = 0.04. Assumptions in sample size calculations included: - a risk of death from any cause of 40% in the placebo group (HR 0.70)	Vital status data (dead, alive, heart transplant, receiving a CMAD) was obtained for patients who discontinued from study treatment and/or study procedures prior to Month 30 either via direct contact or through public records, regardless of discontinuation or withdrawal status. “Unknown” patients were censored at the date last known to be alive or upper bound of the Month 30 visit analysis window, whichever was earlier. Patients without an ACM event were censored at the Min (Last known alive date, Day 907) for the ACM component in the primary analysis and survival analyses. **Rules for Imputation for Missing Data in sensitivity analyses of the Primary endpoint** • any missing data accruing after an ACM event were not imputed. For patients without ACM events and with missing measurements of 6MWD or NT-proBNP at Month 30: • if the patient did not discontinue treatment early and had missing

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Missing data, Data management, patient withdrawals
		and the difference in change from baseline in 6MWD was the fourth and final step. In this stepwise approach, a subsequent step was considered in the hierarchy only when the patient pair being considered could not be differentiated on the basis of the variable in the prior step i.e., potential pairwise comparisons advanced to the next step only if the prior comparison resulted in a tie. Measurements of the components of the primary efficacy endpoint were used as available regardless of whether patients discontinued study drug or initiated concomitant tafamidis. No missing data were imputed for the primary analysis. The F-S procedure does not generate a useful treatment estimate, so win ratios (Pocock et al., 2012 (67)) were calculated to provide a point estimate and corresponding CI of the treatment difference. The stratified win ratio can be expressed as the proportion of pairwise comparisons for which active treatment wins over placebo divided by the proportion of pairwise comparisons for which placebo wins, taking into account both the hierarchical ordering of the comparisons and the strata in which the comparisons are performed.(68) **Sensitivity Analyses of the Primary Endpoint** were conducted to examine the impact of the preset threshold (i.e., ≥ 500 pg/mL) in NT-proBNP and missing data. These analyses included: - the F-S test with different thresholds for the difference in change from baseline in NT-proBNP - imputation for missing data in change from baseline in NT-proBNP and change from baseline in 6MWD - and multiple imputation methods for CVH. **Analysis of Key Secondary Endpoints** To control αB (the available error in Part B of the study, equal to 0.04), the key secondary endpoints were formally tested sequentially in the following order, per the multiplicity adjustment rule: 1) Change from baseline to Month 30 in 6MWD, 2) Change from baseline to Month 30 in KCCQ-OS, 3) Change from baseline to Month 30 in serum TTR level, 4) All-cause mortality by Month 30. An endpoint was only formally tested if the previous endpoint was statistically significant in favour of acoramidis at the αB level. If p-value was ≥ αB, the statistical tests corresponding to all subsequent endpoints were considered not statistically significant. The **6MWD, KCCQ-OS**	- mean number of CVHs of 0.75 in the acoramidis group and 1.15 in the placebo group by 30 months, giving a trial power of more than 90%. - Approximately 10% patients were to have baseline eGFR <30mL/min/1.73 m^2. As described in Section B3.3 changes to key assumptions underlying the study design required that the statistical analysis plan was amended to ensure that the study would have sufficient statistical power to demonstrate treatment effects and avoid a Type II error. The F-S test of the primary endpoint was updated to a hierarchical combination of ACM, cumulative frequency of CVH, clinically meaningful difference (≥ 500 pg/mL) in change from baseline in NT-proBNP, and difference in change from baseline in 6MWD. The number of patients who would	measurements due to CVHs, then the missing measurements were imputed by resampling from the worst 25% in the same arm at a given visit. • Any missing measurements due to early discontinuation of treatment were imputed under MNAR using the J2R method • All other missing 30-month measurements due to protocol deviations or any other reasons were imputed under MAR. **Handling missing data – key secondary endpoints:** Missing data due to reasons other than study drug discontinuation and death were handled by MMRM without imputation. For missing data due to death, the missing value was imputed by sampling with replacement from the worst 5% of observed change from baseline values in the corresponding arm at a given visit. For missing data due to early study drug discontinuation, measurements were imputed using the J2R multiple imputation approach (Carpenter et al., 2013).(69) This method treats intermediate missing values separately from monotone missing values. A missing value was said to be

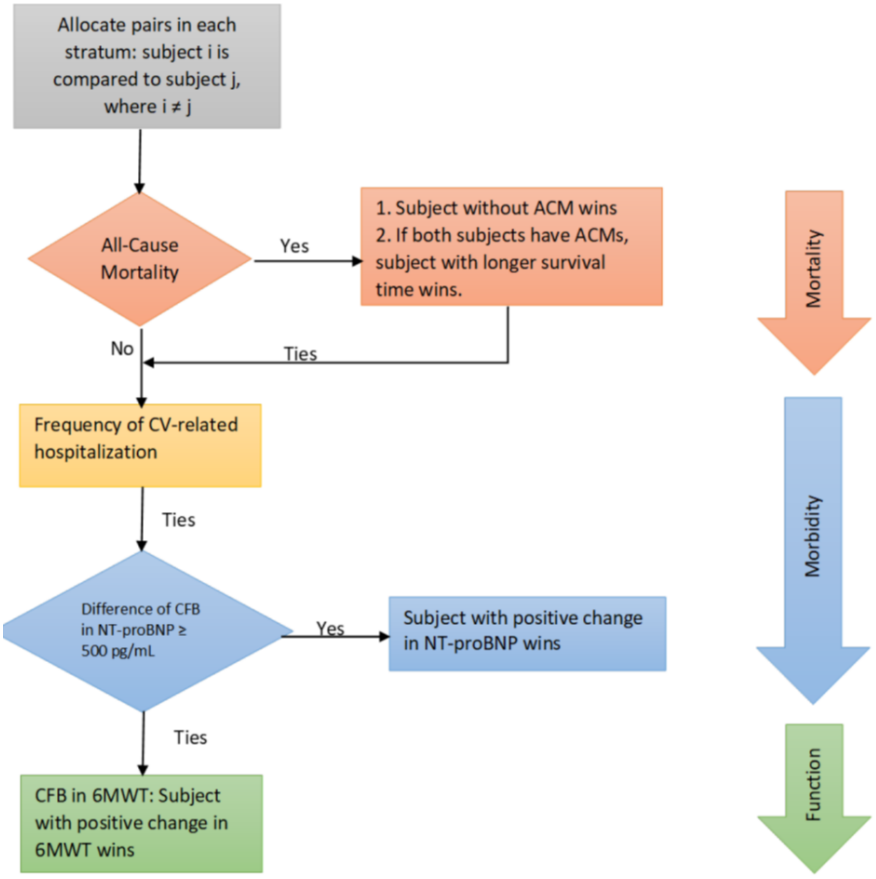
Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Missing data, Data management, patient withdrawals
		score, and serum TTR level were analysed with the use of a MMRM, with an unstructured covariance matrix, including additional terms for randomisation stratification factors, trial visit, and treatment-by-visit interaction. All the patients in the mITT population contributed to each of the analyses of the MMRM as well as to the primary analysis. **ACM by Month 30** was analysed using a stratified Cox proportional hazards model that included treatment as an explanatory factor along with baseline 6MWD. P-values and CIs for the hazard ratio were based on the Wald statistic. A stratified log-rank test was also performed. Treatment differences in the proportion of patient with ACM were tested at Month 30 with the stratified Cochrane-Mantel-Haenszel (CMH) test. The analyses planned for ACM were repeated on the ITT population. **Sensitivity Analyses of Key Secondary Endpoints** conducted to examine the impact of missing data (not performed for all-cause mortality). Four approaches to sensitivity analysis were used: 1. Copy Increments in Reference (CIR) 2. MMRM without imputation 3. Tipping point analysis 4. MMRM with imputation of missing values occurring during a CVH. **Other endpoints (not αB-controlled):** - the F-S test was used to analyse **all other hierarchical combined endpoints** in the mITT population, - **CVM** by Month 30 was analysed as a time-to-event endpoint. The analyses planned for CV-related mortality were repeated on the ITT population. - **Cumulative Frequency of CVH** by Month 30 was analysed using negative binomial regression analysis with treatment, the three stratification factors and an offset term equal to log of each patient's study duration included in the model. If the number of patients with zero CVH was high, a zero inflated negative binomial model was performed to provide further assurance of the results. Stratified CMH row means scores tests were used to analyse the **frequency of CVH by treatment**. - **TTR Stabilisation Measured in Established Ex Vivo Assays** (FPE and WB) – [Only for patients with sufficient data to calculate TTR stabilisation]. Summary statistics of TTR stabilisation were presented for ATTRwt-CM and ATTRv-CM genotype groups. Treatment differences in the proportion of patients meeting ≥ 90% percent stabilisation were summarised by visit and tested at Month 30 nominally (without α control)	initiate, and when they would initiate, tafamidis was unknown and could not be estimated with precision but simulations to assess power for the revised four-component hierarchical endpoint were conducted under various scenarios taking into consideration potential tafamidis use and potentially missing data and the estimated power across the various scenarios remained above 80%.	intermediate if a later response was observed for that patient. The J2R approach imputed intermediate missing values under a randomised-arm MAR assumption. Missing values in the acoramidis arm for visits after study drug discontinuation were imputed under the assumption of MNAR, utilising the J2R approach. The J2R imputation was not used to complete missing data due to death. In the J2R approach, the distribution of missing values in the acoramidis arm for visits once the patient discontinued study drug was set to the distribution of the "reference" group (reference group = patients randomised to placebo). In other words, missing values for patients due to study drug discontinuation in the acoramidis group "jumped" to the distribution expected in the reference group. Missing data post study drug in the reference group were imputed under randomised-arm MAR. There was no imputation for missing CVH values.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Missing data, Data management, patient withdrawals
		with the CMH statistic (two-sided, α = 0.05) adjusting for wild-type/variant genotype TTR, NT-proBNP group, and eGFR group. - **Change From Baseline in NT-proBNP**: analysed as for key secondary endpoints. Event rates/100 patient-yrs were calculated for each treatment group for: ACM, CV death, CVH, and composite of ACM or first CVH. Kaplan-Meier (KM) curves and cumulative incidence function by treatment groups were plotted for ACM, CV death, time to first CVH, and time to ACM or first CVH. **Concomitant Tafamidis - Supplementary Analyses of all endpoints** were conducted to address the potential effect of concomitant tafamidis. These analyses included: **- Hypothetical Strategy** - analyses repeated in the mITT population using observations without any concomitant tafamidis. For patients who had any concomitant tafamidis, observations after tafamidis initiation were not used in analysis. - **Principal Stratum Strategy** - patients from the mITT population who initiated tafamidis were excluded (i.e., acoramidis only versus placebo only). To examine the introduction of tafamidis, the Cox proportional hazards model for the ACM or CV-related mortality or the first CVH with the randomised study drug (acoramidis and placebo) were performed with the addition of the time-dependent covariate for introduction of tafamidis. **Subgroup Analyses** were conducted for the primary endpoint, components of the primary endpoint, and key secondary endpoints using randomisation stratification factors. All statistical analyses were performed with the use of SAS software, version 9.2 or higher (SAS Institute).		
AG10-304 Open-Label Extension study		Data for Study AG10-304 patients were presented by ATTRibute-CM treatment group (i.e. continuous acoramidis and placebo to acoramidis). Time-to-event analyses were performed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomisation stratification factors. The		

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Missing data, Data management, patient withdrawals
		proportional hazards assumption was checked through examination of both Schoenfeld and Martingale residuals. Analyses included time-to-event for ACM or first CVH, ACM alone, CV-mortality, and first CVH alone. KM curves by treatment group were plotted for these analyses. Comparable analyses were examined using data through Month 36 to assess the constancy of treatment effect over varying follow-up time. The annualised frequency of cumulative ACM or recurrent CVH events was analysed using a negative binomial regression model with treatment group, the randomisation stratification factors applied in ATTRibute-CM and an offset term of the logarithm of the follow-up duration. Changes from baseline in NT-proBNP, 6MWD, hsTnI, EQ-5D-5L, and NYHA class were summarised descriptively, and the mean (geometric mean fold-change for NT-proBNP) with error bars for the change from baseline values over time presented. Serum TTR, was also analysed as change from baseline (at entry to the OLE) in the two cohorts. QoL was assessed by KCCQ-OS score. TEAEs were tabulated according to frequency, seriousness, severity, relatedness to study drugs, and discontinuation of study drug. Laboratory data were listed, and values and changes from the baseline summarised.		

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ACM = all-cause mortality; CI = confidence interval; CMAD = cardiac mechanic assist device; CMH = Cochrane-Mantel-Haenszel; CV = cardiovascular, CVH = CV-related hospitalisation; CVM = cardiovascular-related mortality; eGFR = estimated glomerular filtration rate; F-S = Finkelstein and Schoenfeld; HR = hazard ratio; ITT = intention-to treat; J2R = jump to reference; ATTRwt/v-CM = transthyretin amyloid cardiomyopathy wild-type/variant; CFB=change from baseline; CMAD = cardiac mechanical assist device; EQ-5D-5L = European Quality of Life (EQ) – 5 Dimension; FPE = Fluorescent probe exclusion; hsTnI = high-sensitivity Troponin I; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire, Overall Summary Score; KM = Kaplan-Meier; MAR = missing at random; mITT = modified intention-to-treat; MMRM = mixed model of repeated measures; MNAR = missing not at random; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OLE = open-label extension; QoL = quality of life; TEAE = Treatment-emergent adverse event; TTR = transthyretin; WB = western blot; yrs = years

Figure 4. Finkelstein-Schoenfeld Scoring Algorithm used in ATTRibute-CM(20)



6MWD = 6-minute walk distance (i.e., distance achieved in a standardised 6MWT); 6MWT = 6-minute walk test; ACM = all-cause mortality; CFB = change from baseline; CV = cardiovascular; F-S = Finkelstein-Schoenfeld; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
Notes:
1. Positive change in NT-proBNP can be smaller increase or a larger decrease from baseline in paired comparison.
2. Positive change in 6MWT can be a smaller decrease or a larger increase from baseline in paired comparison.
3. The paired comparison for NT-proBNP and 6MWT will use last available non-missing pair for both subjects.
4. A score will be assigned to the subject i within each pair with the following rule: win (+1), tie (0), loss (-1)

See Appendix D1.2 for details of participant flow in the ATTRibute-CM and AG10-304 studies.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

B.3.5.1 ATTRibute-CM

Table 10 presents a brief summary of the quality assessment of the ATTRibute-CM study. ATTRibute-CM was completed to the highest standard with adequate randomisation and blinding procedures. Please see Appendix D.3 for a more detailed assessment.

Table 10. Quality assessment results for ATTRibute-CM

Trial number (acronym)	ATTRibute-CM
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis was a modified intention-to-treat (mITT) analysis. Analyses were also performed in the ITT population, which included patients with eGFR<30mL/min/1.73m^2 in order to gather safety data on this small group of patients. Appropriate methods were used to account for missing data.
Did the authors declare any conflicts of interest?	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).	

B.3.5.2 Quality assessment of AG10-304 – the OLE study of ATTRibute-CM

Note: As this is an (ongoing) extension study, only relevant aspects of quality assessment of a non-randomised study are considered here i.e. recruitment / cohort composition, treatments, confounding factors.

All patients received the same treatment (acoramidis) during the OLE but continued to be analysed as per treatment group in ATTRibute-CM. Enrolment into the OLE study was by patient choice, therefore the final patient cohort for the extension study was arrived at in a non-randomised manner. Of the 421 acoramidis-treated patients in ATTRibute-CM, 62.5% (n=263) opted to enrol into the extension study. A similar proportion of placebo-treated patients in ATTRibute-CM (59.7%, n=126) also enrolled into the extension study. Therefore, analysis groups remained balanced. Patients in ATTRibute-CM who completed treatment to 30 months but did not elect to participate in the OLE reduces the power of the estimates of the treatment effect.

Additionally, although there were fewer patients with exposure to tafamidis than in ATTRibute-CM, a possible confounder in interpretation of the analyses of results of the OLE is any hangover of effect in patients who received concomitant tafamidis in ATTRibute-CM. In ATTRibute-CM, 14.9% (n=61) acoramidis patients and 22.8% (n=46) placebo patients received tafamidis, whereas in the OLE study, only 29 continuous acoramidis patients and

23 placebo to acoramidis patients had previously received tafamidis in the ATTRibute-CM study.

The OLE design is, by definition, unblinded which carries uncertainty regarding the interpretation of efficacy analyses and long-term safety data without a 'true' control group for comparison. However, the trajectories of the effects of continuous acoramidis treatment observed from initiation of therapy in ATTRibute-CM underscore the importance of early and continuous administration of disease-modifying treatment.

The baseline characteristics of patients in the two arms of the OLE were not balanced because patients who received acoramidis for 30 months in ATTRibute-CM derived a treatment benefit, while those who received placebo experienced a greater degree of disease progression, especially for parameters associated with disease progression, which may influence the estimated benefits of acoramidis treatment in the OLE.

It is considered that ATTRibute-CM and the OLE study AG10-304 and the clinical evidence provided by results from these trials, is relevant and applicable to routine clinical practice in England. See Appendix D.3 for further information.

B.3.6 Clinical effectiveness results of the relevant studies

Notes:

1. *The European Commission granted Marketing Authorisation for the indication 'Treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)' on 10th February 2025 based on the original 2-component hierarchical endpoint of ACM and CVH. This was the confirmatory endpoint used by the EMA for assessing efficacy.*
2. *Due to the embedded design employed in ATTRibute-CM, formal statistical tests of the primary and key select secondary efficacy analyses in Part B were controlled at an α of 0.04 sequentially (i.e. use of 96% CI). For other variables of interest, uncontrolled for Type I error, statistical comparisons used a two-sided significance test evaluated at α level of 0.05 (i.e. use of 95% CI). Multiplicity adjustment was applied to the primary and key secondary endpoints only and mITT set only. Where relevant (and available) both 95% and 96% CIs are reported in results tables.*
3. *The primary analysis population was pre-specified as the mITT population, for which a total of 21 patients were excluded based on the concomitant presence of Stage 4 CKD (12 in the acoramidis and 9 in the placebo arm). Sensitivity analyses of primary and secondary endpoints included all randomised patients on an ITT basis. Results in the ITT population are summarised alongside the mITT results in Table 11 and presented separately in more detail in Appendix J.*

4. *At the time of writing this submission first results from the OLE study have become available (12 months; Month 42 when ATTRibute-CM combined with extension). For ease of comparison and continuity, these results have been reported alongside the relevant ATTRibute-CM endpoint results.*
5. *The ATTRibute-CM protocol allowed patients to take concomitant tafamidis alongside study drug (acoramidis or placebo) after the Month 12 visit. Supplementary analyses were performed to adjust for the potential effect of concomitant tafamidis, the results of which are reported in the additional analyses sections under each endpoint.*

B.3.6.1 Part A

The primary endpoint at 12 months was 6MWD, which did not achieve statistical significance, incurring an alpha penalty of 0.01.(20) In the 12-month readout, the two groups had a similar decrease from baseline in 6MWD, with LS-mean change from baseline in the distance walked of −26.51m (95% CI, −37.07 to −15.96) in the acoramidis group and −24.54m (95% CI, −37.26 to −11.83) for placebo. The key secondary outcome,12-month KCCQ-OS score showed a LS-mean change from baseline of −7.00 (95% CI, −9.65 to −4.34) in the acoramidis group and −10.21 (95% CI, −13.45 to −6.96) in the placebo group. The study continued into Part B as planned until the 30-month readout.

B.3.6.2 Part B

Table 11. Summary of Efficacy results for ATTRibute-CM and AG10-304 OLE (6, 20, 48, 50, 54, 57, 61, 63, 70)

	ATTRibute-CM		OLE at Month 42 (FAS) (OLE Month 12 data cut)	
	mITT	ITT	Continuous acoramidis (i.e., Acoramidis in ATTRibute-CM)	Placebo to acoramidis (i.e., Placebo in ATTRibute-CM)
	N=611	N=632	N=409	N=202
4-step hierarchical analysis of ACM, CVH, CFB in NT-proBNP and CFB in 6MWD over a 30-month period	Win Ratio 1.772 96% CI: (1.402, 2.240) 95% CI: (1.417, 2.217) p-value from F-S Method: <0.0001	Win Ratio 1.763 96% CI: (1.399, 2.220) 95% CI: [redacted] p-value from F-S Method: <0.0001	-	-
2-step hierarchical analysis of ACM and CVH over a 30-month period	Win Ratio 1.464 96% CI: [redacted] 95% CI: (1.067, 2.009) p-value from F-S Method: 0.0182	Win Ratio 1.459 (96% CI): (1.055, 2.018) (95% CI): [redacted] p-value from F-S Method: 0.0168	-	-
Time to ACM or First CVH Hazard Ratio (95% CI)[a]	0.645 (0.500, 0.832) p-value: 0.0008	0.661 (0.516, 0.848) p-value: 0.0011	0.57 (0.46, 0.72) p<0.0001	
ACM Hazard Ratio [a] (96% / 95% CI) p-value ARR, RRR (%)	0.772 96% CI: (0.532, 1.121) 95% CI: (0.54, 1.1) p-value: 0.1543 6.4%, 25% (p=0.0569)[c]	0.762 96% CI: (0.533, 1.089) 95% CI: (0.542, 1.072) p-value: 0.1184 7%, 26% (p=0.0390)[c]	0.64 95% CI: (0.47, 0.88) p=0.006	
Time to first CVH Hazard Ratio (95% CI) [a]	0.601 (0.451, 0.800) p-value: 0.0005	0.611 (0.461, 0.809) p-value: 0.0006	0.53 (0.41, 0.69) p<0.0001	
Annualised frequency of CVH Relative risk ratio (95% CI) [b]	0.496 (0.355, 0.695) p-value: <0.0001	0.510 (0.368, 0.708) p-value: <0.0001	NA	NA
CV-related Mortality Hazard Ratio (95% CI) [a] ARR, RRR (%)	0.709 (0.476, 1.054) p-value: 0.0889) 6.4%, 30% (p=0.037)[c]	[redacted]	NA	NA

	ATTRibute-CM		OLE at Month 42 (FAS) (OLE Month 12 data cut)	
	mITT	ITT	Continuous acoramidis (i.e., Acoramidis in ATTRibute-CM)	Placebo to acoramidis (i.e., Placebo in ATTRibute-CM)
	N=611	N=632	N=409	N=202
	LS-Mean Difference at Month 30 (95% CI)		Mean change from baseline (SD)	
6MWD (m) LS-Mean Difference at Month 30: (96% / 95% CI) p-value	39.64 96% CI: (20.18, 59.10) 95% CI: (21.1, 58.2) p<0.001	[redacted]	[redacted] -24.5m ([redacted])	[redacted]
KCCQ-OS LS-Mean Difference at Month 30: (96% / 95% CI) p-value	9.94 96% CI: (5.79, 14.10) 95% CI: (5.97, 13.91) p<0.001	[redacted]	[redacted] -4.0 ([redacted])	[redacted]
Serum TTR (mg/dL)	LS-Mean Difference at Month 30 (96% / 95% CI): Acoramidis-Placebo		Mean change from baseline (SE) to month 31	
	7.10 96% CI: [redacted] 95% CI: (5.79, 8.40) p<0.001	[redacted]	8.9 (0.38)	7.4 (0.55)
NT-proBNP (pg/mL)	Ratio of AGM Fold-change (95% CI)		Geometric mean (Geometric SD) of fold-change	
	0.529 (95% CI: 0.463, 0.604) Nominal p<0.0001	[redacted]	1.10 (1.93)	2.29 (2.19)

6MWD = 6-minute walk distance / distance achieved in a standardised 6MWT; 6MWT = 6-minute walk test; ACM = all-cause mortality; AGM = Adjusted geometric mean; ARR = absolute risk reduction; CEC = Clinical Events Committee; CFB = change from baseline; CI = confidence interval; CMH = Cochrane-Mantel-Haenszel; CV = cardiovascular; CVH = cardiovascular-related hospitalisation; eGFR = estimated glomerular filtration rate; F-S = Finkelstein-Schoenfeld; FAS = full analysis set; ITT = intent-to-treat; IXRS = Interactive Voice/Web Response System; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; LS = Least squares; mITT = modified intent-to-treat; NA = not available; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; RRR = relative risk reduction; SD = standard deviation; TTR = transthyretin.
Full Analysis Set relating to OLE results includes all patients in ATTRibute-CM mITT population.
[a] Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWT as a covariate, and is stratified by randomisation stratification factors of genotype, NT-proBNP level and eGFR level as recorded in IXRS.
[b] Negative binomial regression model with treatment group, randomisation stratification factors of genotype, NT-proBNP level and eGFR level from IXRS, and the offset term is used to analyse the cumulative frequency of CEC adjudicated CVH.
[c] calculated via CMH test;

B.3.6.2.1 Primary efficacy outcome

A hierarchical combination of ACM, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD over the 30-month fixed treatment duration

The primary endpoint was met and showed a statistically significant positive treatment effect of acoramidis relative to placebo in the **mITT population**.(20)

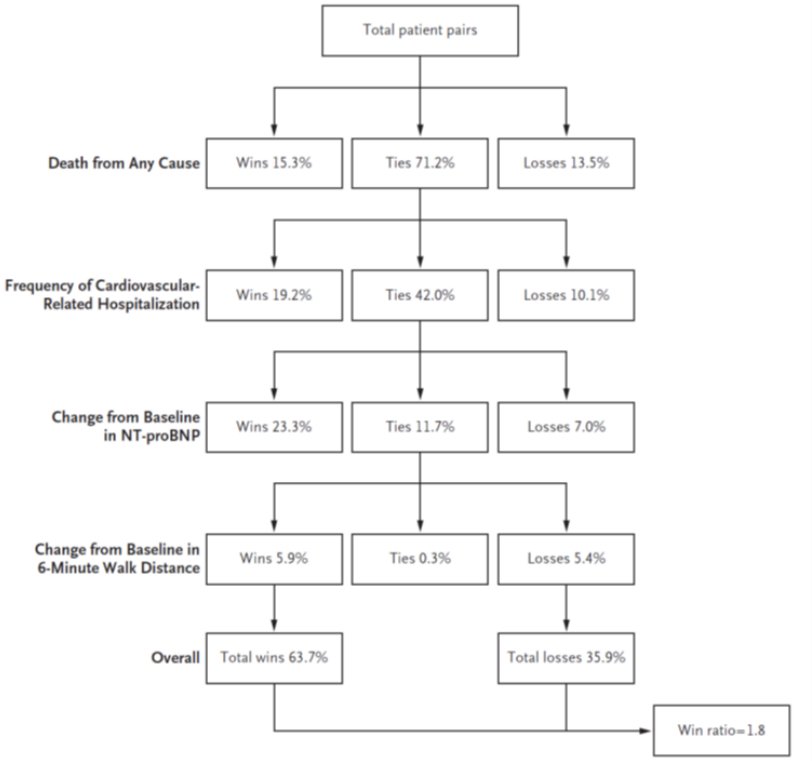
The analysis produced a Finkelstein-Schoenfeld (F-S) test statistic of 5.015 (p<0.0001) (Table 12) and a win ratio in favour of acoramidis of 1.772 (96% CI, 1.402, 2.240) (Figure 5).(53) The corresponding numbers of Pocock wins, ties, and losses at each level is presented in Table 13. The win ratio indicates that an acoramidis-treated patient in ATTRibute-CM had a ~80% higher chance of deriving a treatment benefit than a placebo-treated patient.

Table 12. Finkelstein-Schoenfeld primary analyses for ATTRibute-CM primary endpoint – hierarchical combination of ACM, CVH, change from baseline in NT-proBNP and change from baseline in 6MWD (mITT) (20, 57, 61)

	mITT population		
	Acoramidis N=409		**Placebo N=202**
Patients with ACM at Month 30	79 (19.3%)		52 (25.7%)
Average CVH among those without ACM at Month 30 (per year)			
N	330		150
Mean (SD)	0.132 (0.3257)		0.293 (0.5751)
Median (Q1,Q3)	0.000 (0.000, 0.000)		0.000 (0.000, 0.404)
Min, Max	0.00, 2.03		0.00, 2.95
% of ties after ACM		71.9%	
% of ties after cumulative frequency of CVH		44.9%	
% of ties after CFB in NT-pro BNP		14.7%	
% of ties after CFB in 6MWD [a]		0.4%	
Test Statistic	5.015		
P-value from F-S test	**<0.0001**		

% = percent; 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; CFB = change from baseline; CV = cardiovascular; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; max = maximum; min = minimum; mITT = modified intention-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; Q = quartile; SD = standard deviation;
[a] 6MWD is the distance achieved in a standardised 6MWT.
Note: In FS-test, the comparisons include all pairwise ones (including those between patients within the same treatment group). For win ratio analysis, comparisons only include those between patients from different treatment groups. Therefore, Table 12 (based on FS) and Figure 5 (based on win ratio) are slightly different in the percentage of ties

Figure 5. Stratified win ratio, paired comparisons in the four-step hierarchical analysis of the primary outcome (mITT) (20)



The stratified win ratio can be expressed as the proportion of pairwise comparisons for which active treatment wins over placebo divided by the proportion of pairwise comparisons for which placebo wins, considering both the hierarchical ordering of the comparisons and the strata in which the comparisons are performed. For each element of the hierarchical analysis, percentages of the total pairs that are determined to be wins, ties, or losses are shown. In each subsequent row, the wins, ties, and losses were all categorised as ties in the previous row. Percentages in several categories may not sum to the stated values because of rounding. For numbers of pairs see Table 13 below.

Table 13. Win ratio analysis [number of pairs] for hierarchical combination of ACM, CVH, CFB in NT-proBNP and CFB in 6MWD (mITT) (20, 57)

Details from Win Ratio	Acoramidis N=409		Placebo N=202
Number of pairs		28,794	
Pairs won by ACM	4401		3880
Pairs won by cumulative frequency of CVH	5517		2894
Pairs won by Change from baseline in NT-proBNP	6723		2009
Pairs won by Change from baseline in 6MWD [a]	1705		1568
Total Wins	18,346		10,351
Total Ties		97	
Win ratio (versus Placebo)	**1.772**		
96% CI of Win Ratio	**1.402-2.240**		
95% CI	**1.417-2.217**		

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CFB = change from baseline; mITT = modified intention-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
[a] 6MWD is the distance achieved in a standardised 6MWT.

Additional analyses of the Primary Efficacy Endpoint

The robustness of the primary efficacy analysis in the mITT population was assessed by performing sensitivity and supplementary analyses of the primary endpoint.

A sensitivity analysis of the primary outcome in the ITT population showed a similar outcome ((Finkelstein-Schoenfeld test statistic, 5.045; p<0.001); Win Ratio 1.763 (96% CI, 1.399 to 2.220); p<0.0001).(20, 57) See Appendix J for full results.

Imputation for missing data was performed on three numerical components: CVH, NT-proBNP, and 6MWD to evaluate robustness of the F-S test. These analyses showed [redacted].(53) To evaluate the impact of the preset threshold (i.e., ≥ 500 pg/mL) on the difference in change from baseline in NT-proBNP between patients in each pairwise comparison, the F-S test was repeated for mITT population using different thresholds set to 250 pg/mL, 750 pg/mL, and 1,000 pg/mL. A consistently statistically significant improvement was observed for acoramidis compared to placebo at Month 30 for each test (p<0.0001).(71)

Concomitant tafamidis (mITT): The two supplementary analyses conducted to address the potential effect of concomitant tafamidis use initiated during the study also showed consistent results with the primary analysis.(72) Neither the exclusion of observations post initiation of tafamidis (Hypothetical Strategy) nor the exclusion of patients who initiated tafamidis (Principal Stratum Strategy) altered the statistical significance of the primary efficacy analysis performed with the F-S test (p<0.0001) (Table 14).

Table 14. Supplementary analyses for ATTRibute-CM primary endpoint – hierarchical combination of ACM, CVH, change from baseline in NT-proBNP and change from baseline in 6MWD (mITT) (54, 72)

	Hypothetical strategy (mITT)			**Principal Stratum Strategy (mITT)**		
	Acoramidis N=409		**Placebo N=202**	**Acoramidis N=348**		**Placebo N=156**
Patients with ACM at Month 30	75 (18.3%)		42 (20.8%)	75 (21.6%)		42 (26.9%)
Average CVH among those without ACM at Month 30 (per year)						
N	[redacted]		[redacted]	[redacted]		[redacted]
Mean (SD)	0.136 (0.4019)		0.322 (0.6179)	0.137 (0.3350)		0.301 (0.6133)
Details from F-S test						
% of ties after ACM	77.3%			70.1%		
% of ties after cumulative frequency of CVH	51.1%			44.1%		
% of ties after CFB in NT-pro BNP	18.3%			15.2%		
% of ties after CFB in 6MWD [a]	1.0%			0.5%		

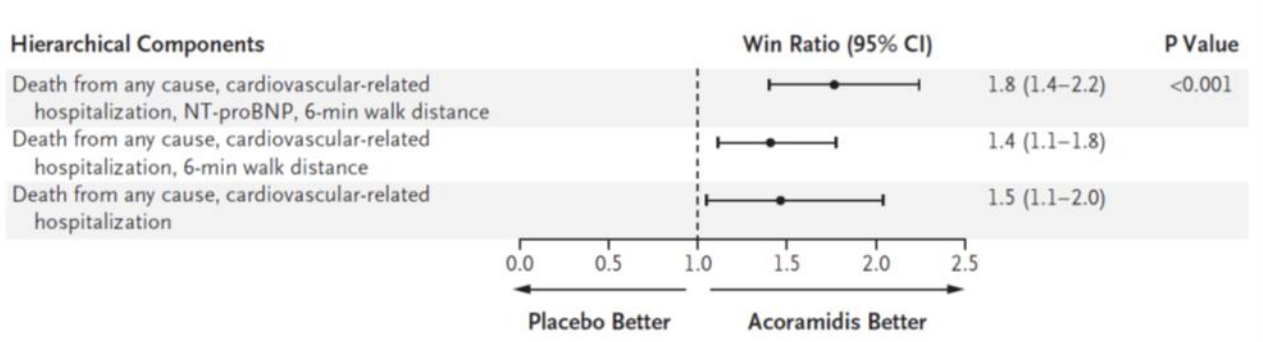
	Hypothetical strategy (mITT)	Principal Stratum Strategy (mITT)
Test Statistic	[redacted]	[redacted]
p-value from F-S test	**<0.0001**	**<0.0001**

% = percent; 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; CFB = change from baseline; CV = cardiovascular; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; max = maximum; min = minimum; mITT = modified intention-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; Q = quartile; SD = standard deviation;
[a] 6MWD is the distance achieved in a standardised 6MWT.

B.3.6.2.2 Analysis of the Consistency of Results of Different Hierarchical Endpoints

Consistently positive findings were observed for the win ratios and F-S analyses across all the hierarchical component analyses as specified by the previous and current versions of the statistical analysis plan (SAP) (two-, three- or four-component F-S primary analysis), indicating the robustness of the observed efficacy. The forest plot of F-S and win ratio analyses for the hierarchical composites is presented in Figure 6. The dual component hierarchical endpoint was the original primary endpoint for ATTRibute-CM and is the endpoint considered by the EMA in the granting of marketing authorisation for acoramidis (see below for results). See Appendix L for three-component endpoint results.

Figure 6. Primary efficacy analysis and pre-specified secondary analyses of hierarchical endpoints (mITT) (20)



6MWD = 6-minute walk distance (distance achieved in a standardised 6MWT); 6MWT = 6-minute walk test; CV = cardiovascular; CVH = CV-related hospitalisation; F-S = Finkelstein-Schoenfeld; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
The initial specification of the primary endpoint: two-component F-S analysis (all-cause mortality and frequency of CVH).
The p-value for the win ratio was calculated with the use of the Finkelstein-Schoenfeld method.
The first revision of the primary endpoint: three-component F-S analysis (all-cause mortality, frequency of CVH, and change from baseline in the 6MWD).
The final revision of the primary endpoint: four-component F-S analysis (all-cause mortality, frequency of CVH, change from baseline in the 6MWD, and change from baseline in NT-proBNP).

B.3.6.2.3 Two-component hierarchical endpoint: A hierarchical combination of ACM and cumulative frequency of CVH over a 30-month fixed treatment duration.

The two-component F-S test for hierarchical combination of ACM and CVH over a 30-month period demonstrated the superior treatment effect of acoramidis compared to placebo (nominal p = 0.0182). Win ratio was 1.464 (96% CI[redacted]) (53, 57) (Table 15). The Kaplan-Meier (KM) curves for time to ACM or first CVH for placebo and acoramidis showed separation as early as 3 months, and steady divergence through Month 30 (Figure 7).(73)

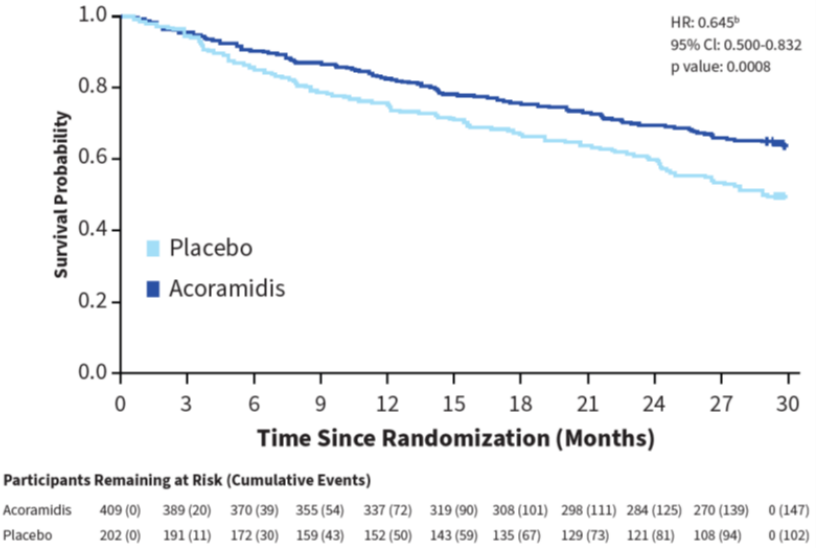
Patients in the mITT population treated with acoramidis experienced a significant reduction in the two-component composite endpoint that included time to ACM or first CVH (acoramidis: n=147 [35.9%]; placebo: n=102 [50.5%], HR=0.645; 95% CI: 0.500, 0.832; p=0.0008),(73) corresponding to a 14.6% ARR.(73)

Table 15. F-S and Win ratio analyses for hierarchical combination of ACM and CVH (mITT) (53, 57, 61)

	Acoramidis N=409		**Placebo N=202**
Details from F-S test			
% of ties after ACM		71.9%	
% of ties after cumulative frequency of CVH		44.9%	
Test Statistic		2.361	
p-value from F-S test		**0.0182**	
Details from Win Ratio			
Number of pairs		28,794	
Pairs won by ACM	4401		3880
Pairs won by cumulative frequency of CVH	5517		2894
Total Wins	9918		6774
Total Ties		12102	
Win ratio (versus Placebo)	**1.464**		
96% CI	[redacted]		
95% CI	**(1.067, 2.009)**		

CI = confidence interval; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; mITT = modified intention-to-treat

Figure 7. KM Curve for Time to ACM or First CVH to Month 30 (mITT)[a] (73)



ACM = all-cause mortality; CEC = Clinical events committee; CVH = Cardiovascular-related hospitalisation; EOCIs = events of clinical interest; mITT = modified intention-to-treat; IV = intravenous; KM = Kaplan-Meier
[a] ACM includes all-cause death, heart transplant, and cardiac mechanical assist device implantation. CVH includes those that were adjudicated as CV-related and non-elective by a CEC, including EOCIs requiring treatment with IV diuretics.
[b] Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWT as a covariate and is stratified by randomisation stratification factors.

Over 30 months, a total of 261 and 222 ACM and recurrent CVH events were reported in 409 acoramidis and 202 placebo patients, respectively; corresponding to a total number of ACM and recurrent CVH events per patient observed of 0.64 (261 of 409) and 1.10 (222 of 202) with acoramidis and placebo, respectively. The negative binomial regression analysis showed that acoramidis treatment led to a 42% risk reduction in ACM and recurrent CVH events over 30 months compared with placebo (RRR: 0.58; 95% CI: 0.43-0.79; p=0.0005).(61)

Additional analyses of the hierarchical combination of ACM and cumulative frequency of CVH over 30-months

For analyses using the ITT population please see Appendix J.

Concomitant tafamidis (mITT): Supplementary analyses also showed a consistent favourable trend for acoramidis compared to placebo for the two-component F-S test. The win ratios were [redacted] with the Hypothetical Strategy and [redacted] with the Principal Stratum Strategy (54) (see Table 16). Additionally, in a sensitivity analysis of Time to ACM or first CVH, conducted with the addition of a time-dependent covariate for tafamidis, the HR of

acoramidis for the risk of ACM or first CVH was 0.65, similar to that observed in the mITT population.(61)

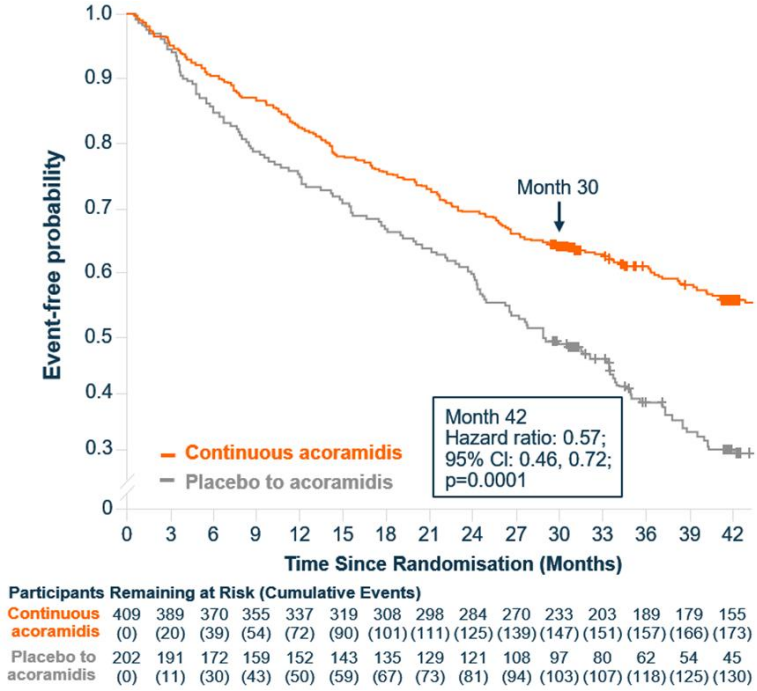
Table 16. Supplementary analyses for two-component hierarchical endpoint of ACM and CVH (mITT) (54)

	Hypothetical strategy (mITT)			Principal Stratum Strategy (mITT)		
	Acoramidis N=409		**Placebo N=202**	**Acoramidis N=348**		**Placebo N=156**
Patients with ACM Month 30	[redacted]		[redacted]	[redacted]		[redacted]
Average CVH among those without ACM at Month 30 (per year)						
N	[redacted]		[redacted]	[redacted]		[redacted]
Mean (SD)	[redacted]		[redacted]	[redacted]		[redacted]
Median (Q1, Q3)	[redacted]		[redacted]	[redacted]		[redacted]
Min, Max	[redacted]		[redacted]	[redacted]		[redacted]
Details from F-S test						
% of ties after ACM		[redacted]			[redacted]	
% of ties after cumulative frequency of CVH		[redacted]			[redacted]	
Test Statistic		[redacted]			[redacted]	
p-value from F-S test		[redacted]			[redacted]	
Win ratio (vs. placebo)		[redacted]			[redacted]	
95% CI of win ratio		[redacted]			[redacted]	

% = percent; CV = cardiovascular; CVH = cardiovascular-related hospitalisation; F-S = Finkelstein-Schoenfeld; max = maximum; min = minimum; mITT = modified intention-to-treat; SD = standard deviation

In the OLE study, time-to-event analysis of the clinical outcome of ACM or first CVH at Month 42, confirms the robust and persistent treatment effect that was observed as early as Month 3 in ATTRibute-CM (Figure 8).(48) ACM or first CVH was reported in 174/409 (42.5%) patients in the continuous acoramidis group and 130/202 (64.4%) patients in the placebo to acoramidis group at Month 42, corresponding to a 33.9% RRR (HR=0.57, 95% CI (0.46, 0.72); p<0.0001).

Figure 8. Kaplan-Meier Curve for Time to ACM or First CVH from Baseline in ATTRibute-CM through Month 42 in the OLE Study (FAS) (48)



ACM = all-cause mortality; CI = confidence interval; CVH = cardiovascular-related hospitalisation; FAS = full analysis set; HR = hazard ratio; OLE = open-label extension
Data are for the full analysis set, which includes all patients in ATTRibute-CM mITT population The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study.

Time-to-event analyses, unlike the win ratio and Finkelstein-Schoenfeld test used for the primary endpoint in ATTRibute-CM, do not account for recurrent CVH events. Therefore, a negative binomial regression analysis was performed. This showed the robust and sustained treatment effect of acoramidis not only on ACM and first CVH, but also on recurrent CVH events. The negative binomial regression analysis of the annualised frequency of cumulative ACM or recurrent CVH events showed that continuous acoramidis treatment led to a reduction in the relative risk of ACM or recurrent CVH by 48.2% through Month 42 (relative risk ratio: 0.52; 95% CI: 0.39, 0.68; p<0.0001) compared with the placebo to acoramidis arm.

B.3.6.2.4 Key secondary efficacy outcomes – testing sequence

The key secondary endpoints were formally tested sequentially in the following order:

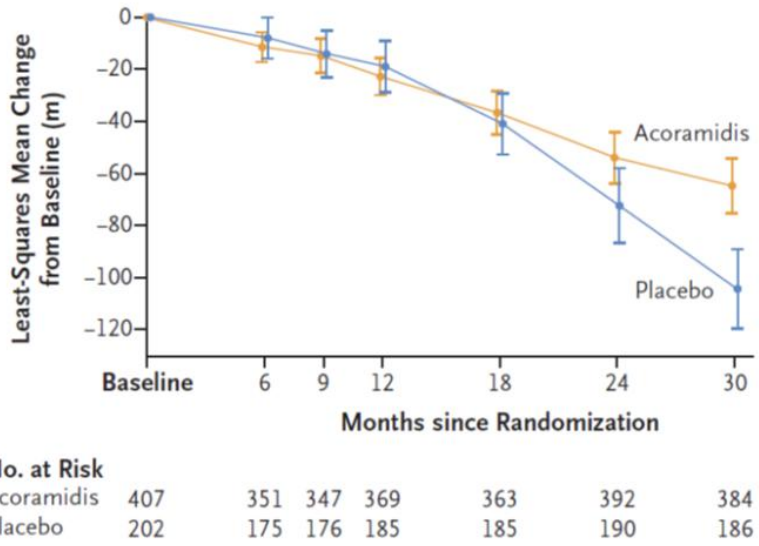
1) Change from baseline to Month 30 in 6MWD,
2) Change from baseline to Month 30 in KCCQ-OS,
3) Change from baseline to Month 30 in serum TTR level,
4) ACM by Month 30 (stratified Cox proportional hazard model).

In the mITT population, results were significant for the 6MWD, KCCQ-OS score, and TTR serum level but not for death from any cause (ACM). The mortality results may reflect the change in the disease landscape in terms of increased disease awareness, earlier diagnosis and better prognosis since the ATTRibute-CM trial design and completion of studies involving other therapies for ATTR-CM.(21) These aspects are discussed in Section B.3.11.

B.3.6.2.5 Change from baseline to Month 30 in 6MWD

In the acoramidis group, at month 30, the decrease from baseline in the 6MWD was less than that in the placebo group, with a LS-mean difference of 39.6m in favour of acoramidis (96% CI, 20.2, 59.1**;** [95% CI, 21.1 to 58.2]; p<0.001; Figure 9).(20, 57) Post-hoc analysis with imputation (that accounted for missing observations), at Month 30, found a net increase in 6MWD relative to baseline, an indication of clinical improvement, in 26.2% of acoramidis-treated patients versus 13.4% in the placebo group (nominal p=0.0002).(57) Curve separation between the acoramidis and placebo-treated populations started at 18 months, illustrating why significance in 6MWD was not achieved at Month 12 in Part A of the study.

Figure 9. Change from baseline in 6MWD at Month 30 in ATTRibute-CM (mITT) (20)



6MWD = 6-minute walk distance; mITT = modified intention-to-treat

Additional analyses of change from baseline to Month 30 in 6MWD

See Appendix J for results of ITT analyses.

Other analyses: Sensitivity analyses - analysis of change from baseline 6MWD by visit using MMRM (with CIR), MMRM, and MMRM (sampling from the worst 25% of observed values was used for imputation of missing values due to CVH) - all showed a statistically significant ($p \leq 0.0001$) and clinically meaningful treatment benefit on 6MWD favouring acoramidis at Month 30, [redacted]

Concomitant tafamidis (mITT): A significant favourable treatment effect of acoramidis over placebo on 6MWD was still observed after controlling for the potential effect of concomitant tafamidis use (Table 17).(57)

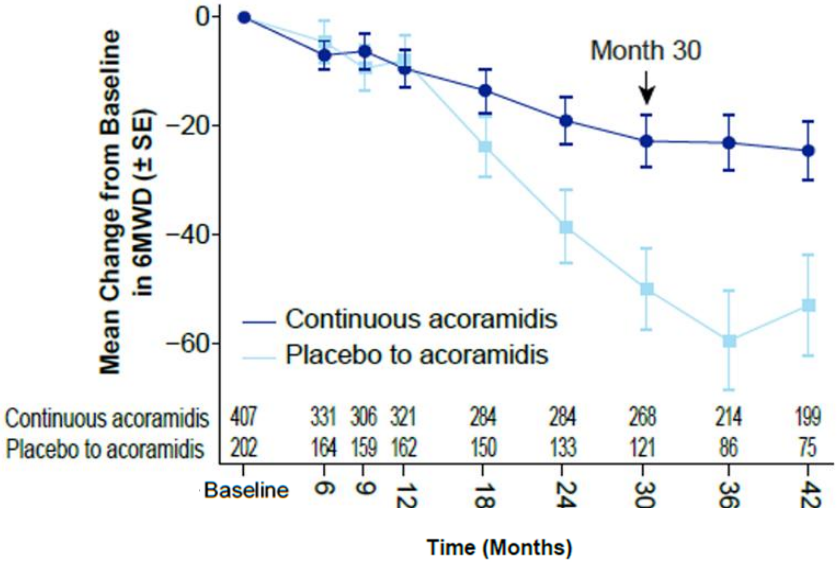
Table 17. Supplementary analyses for change from baseline in 6MWD (mITT) (54)

	Hypothetical strategy (mITT)		Principal Stratum Strategy (mITT)	
	Acoramidis N=409	**Placebo N=202**	**Acoramidis N=348**	**Placebo N=156**
Baseline 6MWD [a] observed value mean [SD]	[redacted]	[redacted]	[redacted]	[redacted]
Month 30 Change from baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Least Squares Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
96% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS-Mean Difference: Active Dose-Placebo	[redacted]		[redacted]	
SE for Difference	[redacted]		[redacted]	
95% CI for Difference	[redacted]		[redacted]	
96% CI for Difference	[redacted]		[redacted]	
p-value	[redacted]		[redacted]	

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; CFB = change from baseline; CI = confidence interval; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error.
[a] 6MWD is the distance achieved in a standardised 6MWT.

Early results in the **OLE study**, suggest a continuing benefit of continuous acoramidis treatment in patient functional capacity (48), with mean (standard deviation [SD]) change from baseline in 6MWD of -24.5m ([redacted]) at Month 42 (Figure 10) versus [redacted] for the placebo to acoramidis group.(63)

Figure 10. Change from Baseline to Month 42 in 6MWD (Observed Values) (FAS) (48)



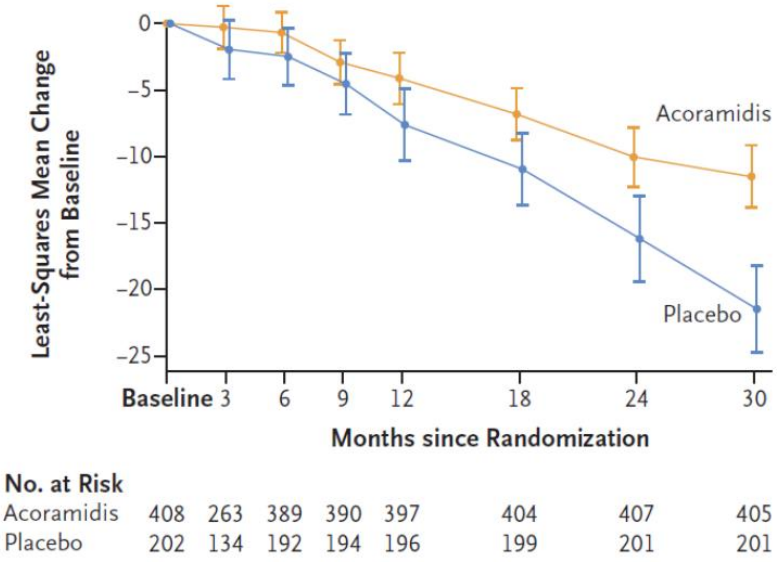
6MWD = 6-minute walk distance; FAS = full analysis set; OLE = open-label extension; SD = standard deviation; SE = standard error.
The baseline values are the last non-missing assessment values done before the first study drug in ATTRibute-CM. Data are for the full analysis set, which includes all patients in ATTRibute-CM mITT population. The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study.

B.3.6.2.6 Change from baseline to Month 30 of treatment in KCCQ-OS

Patients treated with acoramidis also showed significantly improved preservation of QoL from baseline to Month 30 compared to placebo.(20) A statistically significant ($p < 0.0001$) treatment benefit on the KCCQ-OS, was observed favouring acoramidis, with a 10-point increase from baseline LS-mean difference observed between the two treatment groups ((96% CI, 5.79, 14.10); [95% CI, 5.97 to 13.91]; $p<0.001$) (Figure 11, Table 18). The curves started to separate at month 3, indicating an early effect of acoramidis on preserving QoL.

In patients with chronic heart failure, a KCCQ-OS change of five or more points has been shown to be a clinically significant and independent predictor of reduced mortality and reduced CVH (74, 75)].

Figure 11. Change in KCCQ-OS score in ATTRibute-CM (mITT) (20)



KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; mITT = modified intention-to-treat

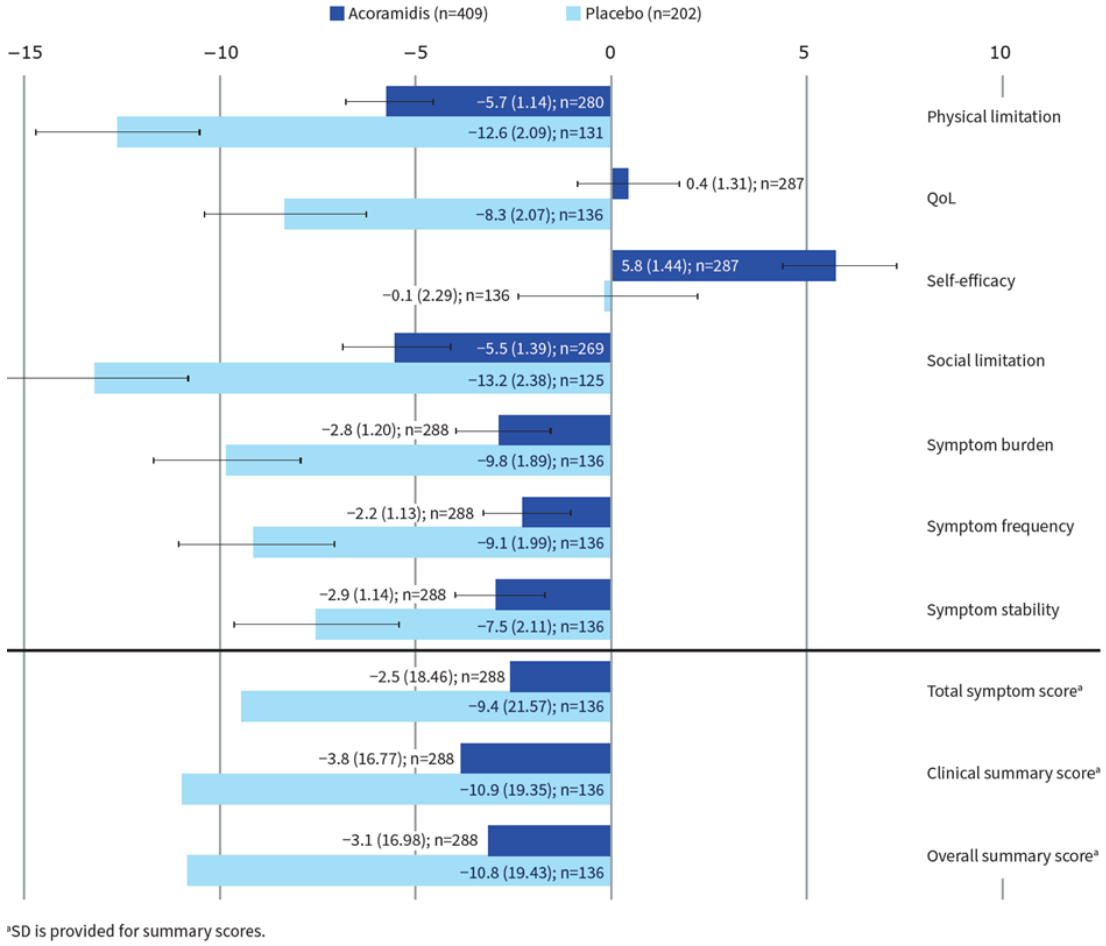
At Month 30, the observed mean (percent) changes from baseline in KCCQ-OS score were -3.1 (-3.0%) and -10.8 (-14.0%) in the acoramidis and placebo groups, respectively.(22) In a post-hoc analysis a net increase in KCCQ-OS relative to baseline, an indication of clinical improvement in health status, was observed in 43.8% of patients in the acoramidis treatment group (vs. 26.5% for placebo). With imputation (that accounted for missing observations), this net increase in KCCQ-OS score relative to baseline was observed in 30.8% of acoramidis patients (vs. 17.8% for placebo (stratified CMH; nominal p-value=0.0005).(22) Improvements were observed numerically across all KCCQ-domains.(22) The impact of acoramidis on health status and QoL, as demonstrated in the KCCQ-OS, underscores the clinical meaningfulness of the 6MWD treatment effect.

Table 18. Analysis of CFB in KCCQ-OS at Month 30 – MMRM (with J2R) (mITT)(57)

	Acoramidis N=409	**Placebo N=202**
Month 30		
Change from baseline		
N	405	201
LS-Mean (SE)	-11.48 (1.18)	-21.42 (1.65)
95% CI	-13.79, -9.16	-24.66, -18.18
96% CI	-13.90, -9.05	-24.81, -18.03
LS-Mean Difference Active Dose - Placebo	9.94	
SE for Difference	2.024	
95% CI / 96% CI for Difference	95% CI: 5.97, 13.91; 96% CI: 5.79, 14.10	
p-value	**<0.0001**	

CFB = Change from baseline; CI = confidence interval; J2R = Jump to Reference; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LS = least squares; MMRM = mixed model for repeated measures; mITT = modified intent-to-treat; Q = quartile; SE = standard error

Figure 12. Change From Baseline (Mean± SE) at Month 30 in KCCQ Domain Scores (mITT, Observed Values) (22)



[a]SD is provided for summary scores.

Additional analyses of change from baseline to Month 30 of KCCQ-OS

See Appendix J for ITT analyses.

Other analyses: All sensitivity analyses of KCCQ-OS [1) CIR; 2) MMRM without imputation; 3) Tipping point analysis; 4) MMRM with imputation of missing values occurring during a CV-related hospitalisation] showed consistent results and, therefore, demonstrated the robustness of the results of the KCCQ-OS.(54)

[redacted]

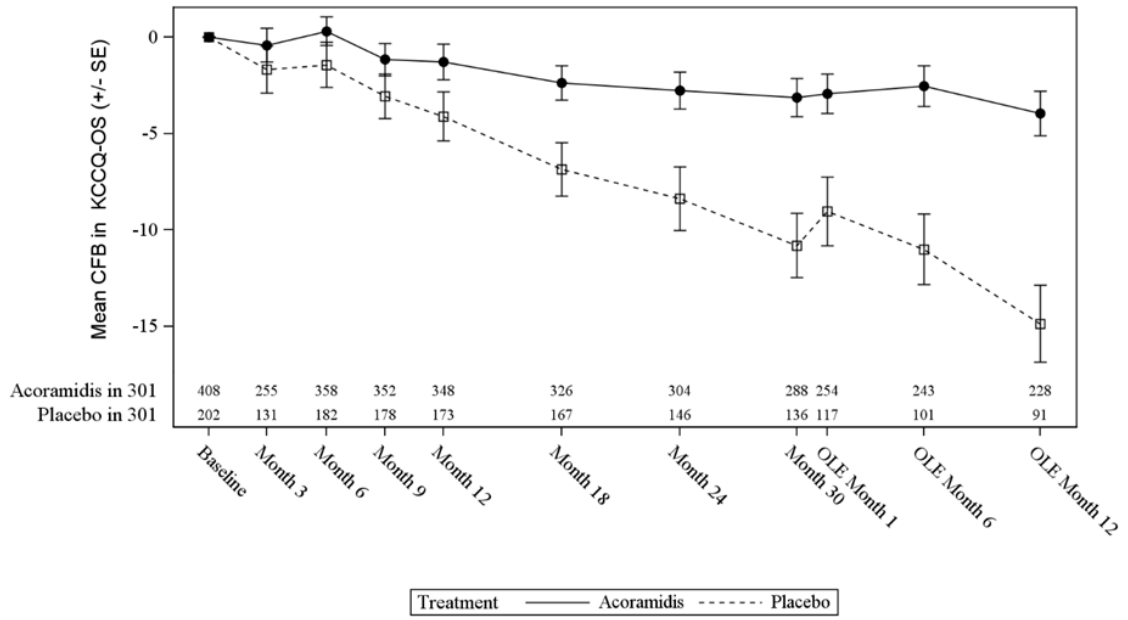
Table 19. Supplementary analyses for change from baseline in KCCQ-OS (mITT)(54)

	Hypothetical strategy (mITT)			Principal Stratum Strategy (mITT)		
	Acoramidis N=409		Placebo N=202	Acoramidis N=348		Placebo N=156
Baseline KCCQ-OS observed value mean [SD]	[redacted]		[redacted]	[redacted]		[redacted]
Month 30 Change from baseline						
N	[redacted]		[redacted]	[redacted]		[redacted]
Least Squares Mean (SE)	[redacted]		[redacted]	[redacted]		[redacted]
95% CI	[redacted]		[redacted]	[redacted]		[redacted]
96% CI	[redacted]		[redacted]	[redacted]		[redacted]
LS-Mean Difference: Active Dose-Placebo	[redacted]			[redacted]		
SE for Difference	[redacted]			[redacted]		
95% CI for Difference	[redacted]			[redacted]		
96% CI for Difference	[redacted]			[redacted]		
p-value	[redacted]			[redacted]		

CI = confidence interval; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Score; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation; SE = standard error

In the **OLE study**, results for the continuous acoramidis arm at Month 42 [mean (SE) change from baseline in KCCQ-OS: –4.0 (1.15)] show that the early separation observed in ATTRibute-CM continues in favour of acoramidis treatment (Figure 13).

Figure 13. Mean (+/- SE) change from baseline in KCCQ-OS (ATTRibute-CM and OLE (FAS)) (48)



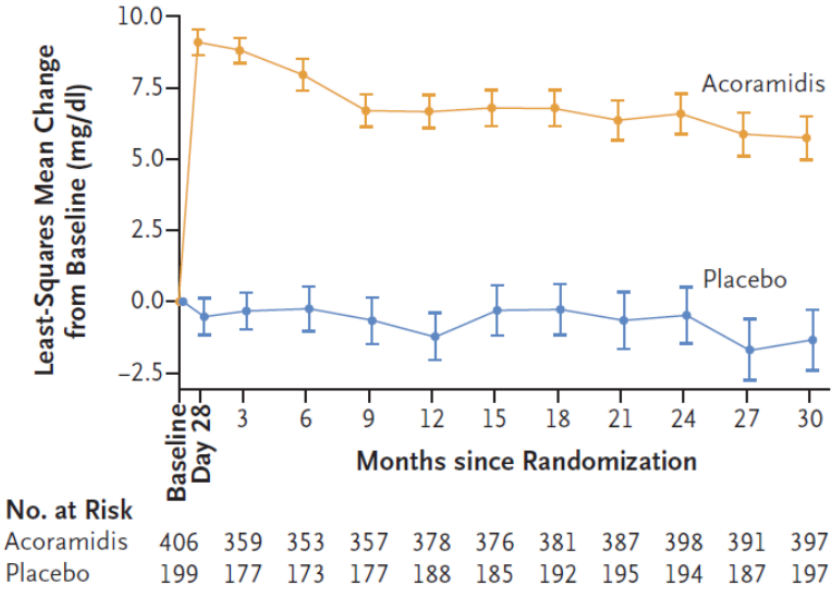
301 = ATTRibute-CM trial; FAS = full analysis set; KCCQ = Kansas City Cardiomyopathy Questionnaire; mITT = modified intent-to-treat; OLE = open-label extension; SE = standard error

B.3.6.2.7 Change from baseline to Month 30 in serum TTR level

Serum TTR is an in vivo measure of TTR stabilisation. In patients with ATTR-CM, serum TTR is typically below normal or in the low-normal range (normal serum TTR range is 18 to 45 mg/dL).

During ATTRibute-CM, serum TTR was consistently higher in patients in the acoramidis group than in the placebo group, with a treatment effect observed early in the study, from the first measurement at Day 28 (Figure 14). At 30 months, the change from baseline in the LS-mean difference in the serum TTR level was 7.10 mg per decilitre in favour of acoramidis ((96% CI: [redacted]); [95% CI, 5.79 to 8.40]; p<0.001).(20, 53)

Figure 14. Change from baseline in serum transthyretin to Month 30 (mITT) (20)



Additional analyses of change from baseline to Month 30 in serum TTR

See Appendix J for ITT analyses.

Other analyses: All sensitivity analyses showed results consistent with the primary analysis of serum TTR.(57) [redacted]

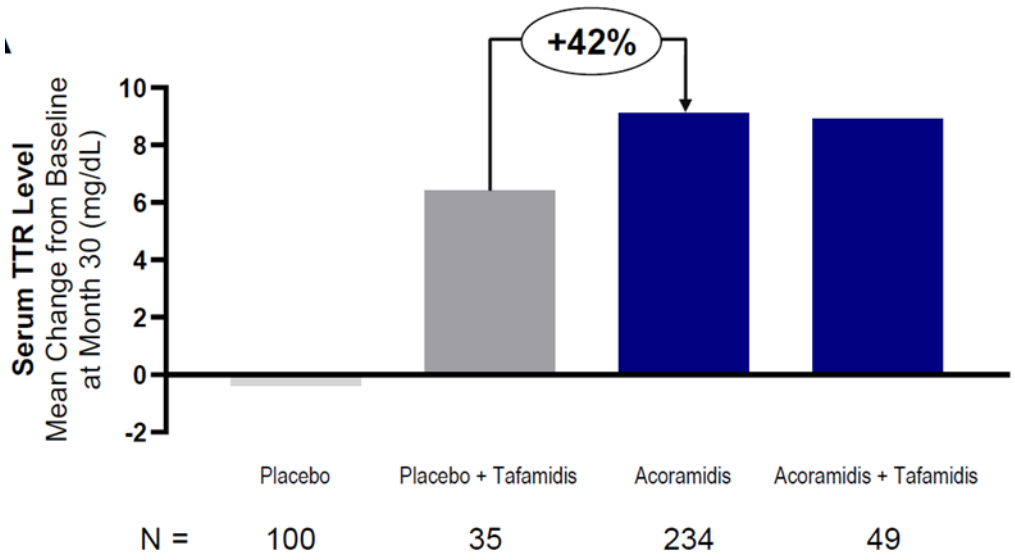
Concomitant tafamidis (mITT): A significant favourable treatment effect of acoramidis over placebo was still observed after controlling for the potential effect of concomitant tafamidis use.(57)

[redacted]

At Month 30, the observed mean increase from baseline in TTR level was 9.07, 8.92, and 6.37 mg/dL in the acoramidis-only, acoramidis plus tafamidis, and placebo plus tafamidis treatment groups, respectively (

Figure 15). These findings demonstrate that (1) acoramidis-only treatment resulted in a 42% greater increase in the mean change from baseline in serum TTR levels than did the addition of tafamidis to placebo, and (2) adding tafamidis to acoramidis did not have an incremental effect on serum TTR level.(57, 76)

Figure 15. Change from Baseline to Month 30 in Serum TTR Level by Concomitant Tafamidis Groups (mITT) (5)



mITT = modified intent-to-treat; N = number of patients with available serum TTR levels at baseline and Month 30; TTR = transthyretin

No influence of genotype (variant vs. wild-type) on the response of TTR levels to therapy was observed.(57)

The raised serum TTR observed in acoramidis-treated patients in ATTRibute-CM was sustained in the continuous acoramidis arm through Month 30 and to date in the **OLE study** (Figure 16). In the placebo to acoramidis arm, mean (SE) change from baseline in serum TTR was 1.3 mg/dL (0.55) at Month 30 and 7.4 mg/dL (0.55) at Month 31.(48) This observed increase in serum TTR in the patients initiating acoramidis in the OLE is consistent with the initial observation at Day 28 of ATTRibute-CM in patients randomised to acoramidis.

Figure 16. Change from Baseline in TTR Level (mg/dL) (ATTRibute-CM and OLE M42) (FAS) (63)

FAS = full analysis set; mITT = modified intention-to-treat; TTR = transthyretin.
Full Analysis Set includes all patients in ATTRibute-CM mITT population.

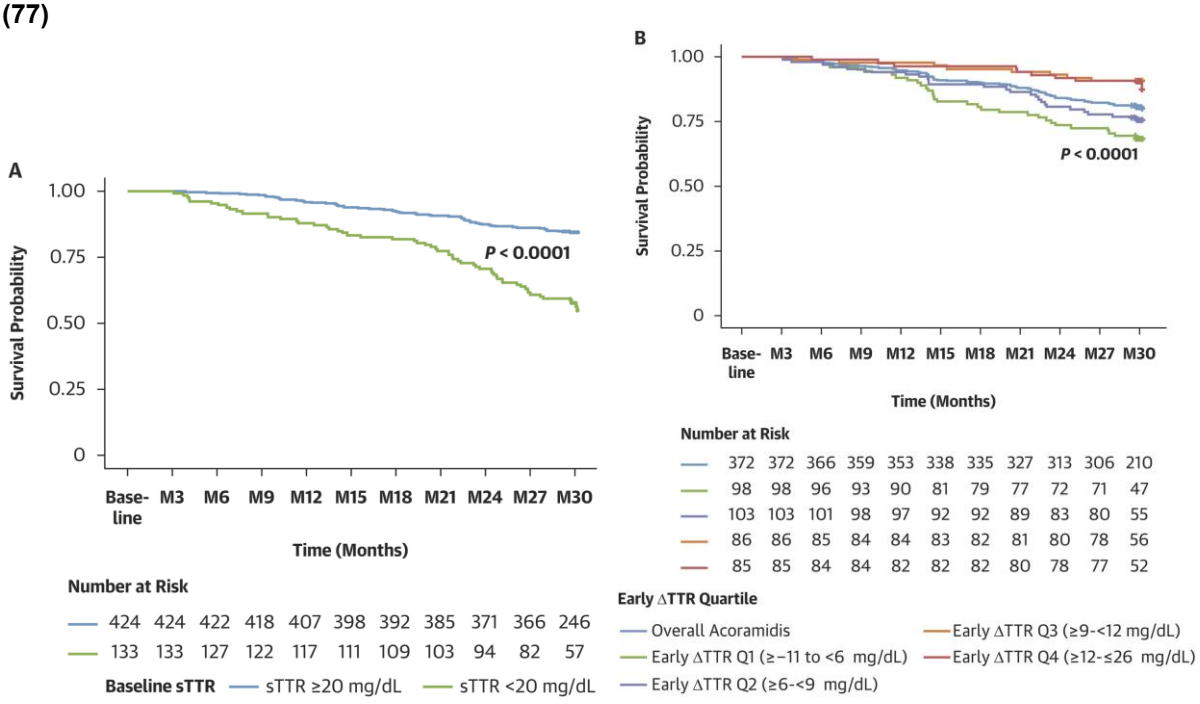
An analysis at month 6 of the OLE, showed a significant increase in serum TTR levels in patients who had switched from 'placebo + concomitant tafamidis' to acoramidis, further highlighting the superior TTR stabilisation properties of acoramidis compared with tafamidis.(76)

B.3.6.2.8 Correlation of TTR stabilisation with clinical outcomes (post-hoc analyses)

Post-hoc analyses investigated any correlations between serum TTR levels and key clinical outcomes such as ACM, CV-mortality and CVH.(70, 77, 78)

ACM (77): Patients with ≥20 mg/dL serum TTR at baseline had significantly greater overall survival probability than those with <20 mg/dL (p<0.0001) (Figure 17). An early increase in serum TTR levels on day 28 of dosing (early ΔTTR) was associated with reduced ACM in univariate analysis (HR: 0.96 per 1 mg/dL increase in early ΔTTR; 95% CI: 0.93-0.98; p=0.002). In the multivariate analysis, after adjusting for known predictors (e.g. TTR variant status, baseline NYHA functional class, baseline NAC stage, and baseline serum TTR level), early ΔTTR remained independently associated with reduced ACM (p<0.001). For every 5 mg/dL increase in serum TTR levels, a logistic model predicted a 31.6% relative reduction in odds of ACM, suggesting increasing serum TTR levels through stabilisation by acoramidis may be protective. No such association was observed in patients treated with placebo.

Figure 17. A. Survival by Baseline sTTR Level Through Month 30 in the Overall Population and B. Survival by Early ΔTTR Quartiles Through Month 30 in the Acoramidis-Treated Population (77)



dL = decilitre; mg = milligram; sTTR = serum transthyretin; TTR = transthyretin.
A Data represent modified intent-to-treat population from ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy) who had serum transthyretin (sTTR) levels available at the corresponding time points. All-cause mortality includes heart transplant, cardiac mechanical assist device, and all-cause death. Solid lines represent median survival probability.
B Data demonstrate survival by early ΔTTR quartiles through month 30 in the acoramidis-treated population.

CV-related mortality (CVM) (70): The relationship between change from baseline in Day 28 serum TTR levels and CVM was analysed using a stratified Cox proportional hazards model. The model included baseline 6MWT and change from baseline in TTR levels at Day 28 as covariates, and was stratified by treatment group, baseline TTR group (≥20 vs <20), and randomisation stratification factors of genotype, NT-proBNP levels, and eGFR levels. For

each 1 mg/dL increase in serum TTR on day 28 after treatment initiation, there was a 5.5% risk reduction in CVM risk over 30 months (HR=0.945 [95% CI 0.901, 0.922]; p=0.021).

CVH (78): Using a stratified Cox proportional hazards model, the association between CFB to Day 28 serum TTR levels and first CVH was analysed. This included baseline 6MWT and CFB in TTR level at Day 28 as covariates, and stratification by treatment group, baseline TTR group (≥20 vs <20) and randomisation stratification factors. For each 1 mg/dL increase in serum TTR on day 28 after treatment initiation, there was a 4.7% lower risk of a first CVH over 30 months.

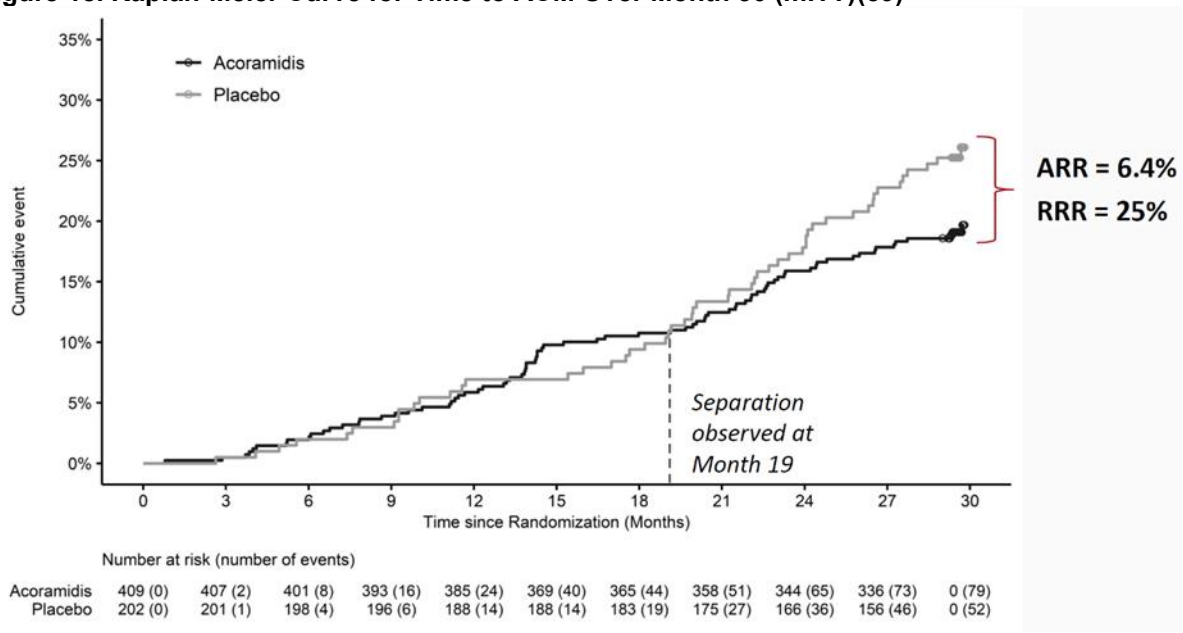
Supportive evidence from phase 2 studies with acoramidis and its effect on TTR stabilisation can be found in Appendix F.

B.3.6.2.9 ACM by Month 30 [including death due to any cause, heart transplant, or CMAD]

A numerically positive treatment effect was observed for acoramidis compared to placebo for ACM by Month 30 (HR: 0.772; 96% CI: 0.532, 1.121 [95% CI: 0.54,1.1]; p=0.1543).(57, 61) The KM curve for time to ACM, including heart transplant and CMAD, is shown in Figure 18. The curves were observed to cross multiple times early in the study before their eventual separation starting at 19 months. The crossing of the curves prior to Month 19 does not reflect a shift towards placebo but rather indicates that there was no meaningful separation between the two groups during that time. At Month 30, a survival rate of 81% was observed in the acoramidis treatment group versus a 74% survival rate for placebo (ARR: 6.4%; RRR: 25%).

The ACM results were also examined using a stratified log-rank test (p=0.0754) and a CMH test (p=0.0569). The hazard ratio from the time-dependent Cox model for acoramidis versus placebo was 0.774 (95% CI: 0.543, 1.104) (Table 20).(57)

Figure 18. Kaplan-Meier Curve for Time to ACM Over Month 30 (mITT)(59)



ARR = absolute risk reduction: CMAD = cardiac mechanical assist device; mITT = modified intention-to-treat; All-cause mortality includes heart transplant, implantation of CMAD, and all-cause death; RRR = relative risk reduction

The majority (104/131; 79%) of mortality events were CV-related (acoramidis group: 14.9%, placebo group 21.3%; [ARR 6.4%, RRR 30%]) (HR=0.709 [95% CI: 0.476, 1.054], nominal p=0.089).(57, 59, 70) The incidence of non-CV-related deaths was comparable in both groups (4.4% versus 4.5%) (Table 20). See later in this Section 'Secondary endpoints – CV-Mortality' for further details regarding CV-related mortality (Section B.3.6.2.11).

Table 20. Summary of All-cause Mortality (mITT)(57, 59, 61, 70)

	Acoramidis (N=409)		**Placebo N=202**
All-cause mortality [a]	**79 (19.3%)**		**52 (25.7%)**
Total Death [b]	79 (19.3%)		50 (24.8%)
CV-related [c]	61 (14.9%)		43 (21.3%)
Non-CV-related	18 (4.4%)		9 (4.5%)
(CMAD implantation)	0		1 (0.5%)
(Heart transplants)	0		1 (0.5%)
Cox Proportional Hazard Model [d]			
Hazard Ratio (versus Placebo)		0.77	
95% CI of Hazard Ratio		(0.54, 1.1)	
96% CI of Hazard Ratio		(0.532,1.121)	
p-value		0.1543	
Log-rank test [e]		0.0754	
Cochran-Mantel-Haenszel test		0.0569	
Time-Dependent Cox Model [f]			
Hazard Ratio (versus Placebo)		0.77	

	Acoramidis (N=409)		Placebo N=202
95% CI of Hazard Ratio		(0.543, 1.104)	
96% CI of Hazard Ratio		(0.533, 1.123)	
p-value		0.1577	

6MWD = 6-minute walk distance; CI = confidence interval; CMAD = cardiac mechanical assist device; CV = cardiovascular; eGFR = estimated glomerular filtration rate; IXRS = Interactive Voice/Web Response System; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide
[a] All-Cause Mortality included all-cause death, heart transplant, and CMAD implantation.
[b] Total death included CV-related and non-CV-related death.
[c] CV-related death included all adjudicated CV-related and undetermined cause death.
[d] Stratified Cox proportional hazards model included treatment as an explanatory factor and baseline 6MWD as a covariate, and was stratified by randomisation stratification factors of genotype, NT-proBNP level, and eGFR level as recorded in IXRS.
[e] Stratified Log-rank test that was stratified by randomisation stratification factors of genotype, NT-proBNP level, and eGFR level as recorded in IXRS.
[f] Stratified Cox proportional model was performed with the addition of the time-dependent covariate for introduction of tafamidis.

ATTRibute-CM ACM results in context

While the benefit in death from any cause for patients receiving acoramidis at 30 months was not significant in ATTRibute-CM, the mortality results observed appear to reflect a lower risk of death for acoramidis and even for patients treated with placebo (survival rates of 80.7% and 74%, respectively, at 30 months) (20) than was observed for patients receiving tafamidis in the ATTR-ACT trial (survival rates of 70.5% at 30 months for the combined tafamidis treatment groups and 57.1% for the placebo group).(21) This improved survival in ATTRibute-CM may reflect the better prognosis for the more recently diagnosed patients in ATTRibute-CM because of greater disease awareness and earlier diagnosis.(20)

A systematic review of clinical trials in ATTR-CM: across 39 publications of studies which enrolled patients between 2008 and 2021 supports this hypothesis.(79) Baseline characteristics of patients in recent ATTR-CM trials have shown lower proportions of patients in NYHA stage III, lower baseline NT-proBNP levels, and higher baseline eGFR levels. Also, ACM rates at 12 months for groups receiving placebo have dropped across studies with later enrolment periods: 12-month mortality was 9% in ATTR-ACT, which enrolled from 2013 to 2015; 6.9% in ATTRibute-CM, which enrolled from 2019 to 2020; and 5.6% in APOLLO-B, which enrolled from 2019 to 2021.(79) In fact, the 30-month survival for patients with ATTR-CM receiving acoramidis (80.7%) in ATTRibute-CM approached that seen in an age-matched cohort of the general population of adults in the US (85%).(40)

Additional analyses of ACM by Month 30

Statistical model diagnostics indicated that the proportional hazards assumption inherent to the Cox model of analysis may not have held, especially with respect to the covariate for

6MWD. This possible departure from model assumptions is also indicated by the observation of the survival curves for the two treatment groups crossing multiple times in the beginning of the study before their eventual separation starting at around 19 months (Figure 18). A post-hoc analysis of ACM using restricted mean survival time (RMST) through day 907 of the study (the end of the Month 30 visit analysis window) was thus performed as a sensitivity analysis. No significant treatment difference was observed in this analysis, with an RMST difference of 6.6 days (95% CI -25.0, 38.2).(20) See Appendix J for ITT analyses.

The 25% RRR in ACM observed in the mITT population was also observed in the 21 patients with eGFR< 30 mL/min/1.73 m^2 (acoramidis: 41.7%; placebo: 55.6%) (post-hoc analysis).(60).

Concomitant tafamidis (mITT): The favourable trend in ACM in the mITT population was also supported by the results of the two supplementary analyses: [redacted] Additionally, in a sensitivity analysis conducted with the addition of a time-dependent covariate for tafamidis, the HR of acoramidis for the risk of ACM was unchanged (compared with that in mITT population) at 0.77.(61)

Table 21. Supplementary analyses for ACM (mITT)(54)

	Hypothetical strategy (mITT)			Principal Stratum Strategy (mITT)		
	Acoramidis (N=409)		**Placebo (N=202)**	**Acoramidis (N=348)**		**Placebo (N=156)**
All-cause Mortality	[redacted]					
Total Death						
CV-related						
Non-CV-related						
CMAD Implantation						
Heart Transplants						
Cox Proportional Hazard Model: p-value						
Hazard Ratio (HR) (versus Placebo)						
95% CI of HR						
96% CI of HR						
Log-rank test						
Cochran-Mantel-Haenszel test						

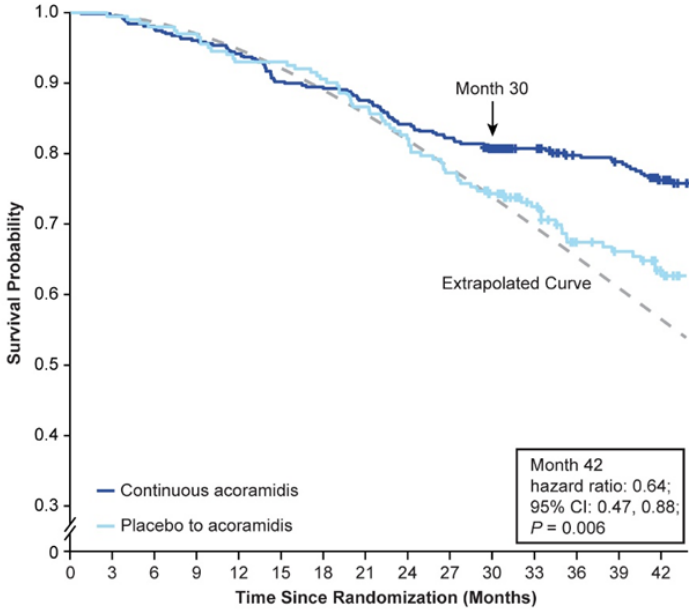
CI = confidence interval; CMAD = cardiac mechanical assist device; CV = cardiovascular; HR = hazard ratio; mITT = modified intention-to-treat
Hypothetical Strategy: For patients who had any concomitant tafamidis, the observations after initiation of tafamidis were not used in the analysis.
Principal Stratum Strategy: The patients who initiated tafamidis were excluded from this analysis.

B.3.6.2.10 ACM Post-hoc analysis for EMA

As a post-hoc analysis for the EMA, a further sensitivity analysis on the ACM endpoint excluding patients who had either a CMAD or heart transplant during ATTRibute-CM was performed. This involved excluding 2 patients, both in the placebo group (1 CMAD, 1 heart transplant). Results were consistent with the main analyses with KM curves showing a separation, starting at Month 24, and increasing in magnitude through Month 30.(57) [redacted].(6)

First results from the **OLE study** show that ACM risk continued to decrease with longer-term treatment of acoramidis. At Month 42 (Month 12 of the extension study), the percentage of patients with ACM was reduced with continuous acoramidis (vs. placebo to acoramidis group) (23.0%, 94/409 vs. 34.7%, 70/202) corresponding to a RRR of 33.7% (HR=0.64; 95% CI:0.47, 0.88; p=0.006).(48) See Figure 19 for KM Curve. There appears to be a trend of reduction in the risk of ACM in the placebo to acoramidis arm from Month 30 following initiation of OLE acoramidis [when compared to the extrapolated curve showing expected results if patients had continued receiving placebo in the OLE study].

Figure 19. Kaplan-Meier Curve for Time to ACM from Baseline in ATTRibute-CM study through Month 42 in the OLE study (FAS) (50)



Participants Remaining at Risk (Cumulative Events)

Continuous acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	297 (79)	260 (79)	247 (82)	243 (85)	216 (93)
Placebo to acoramidis	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	143 (52)	118 (55)	102 (63)	98 (65)	87 (70)

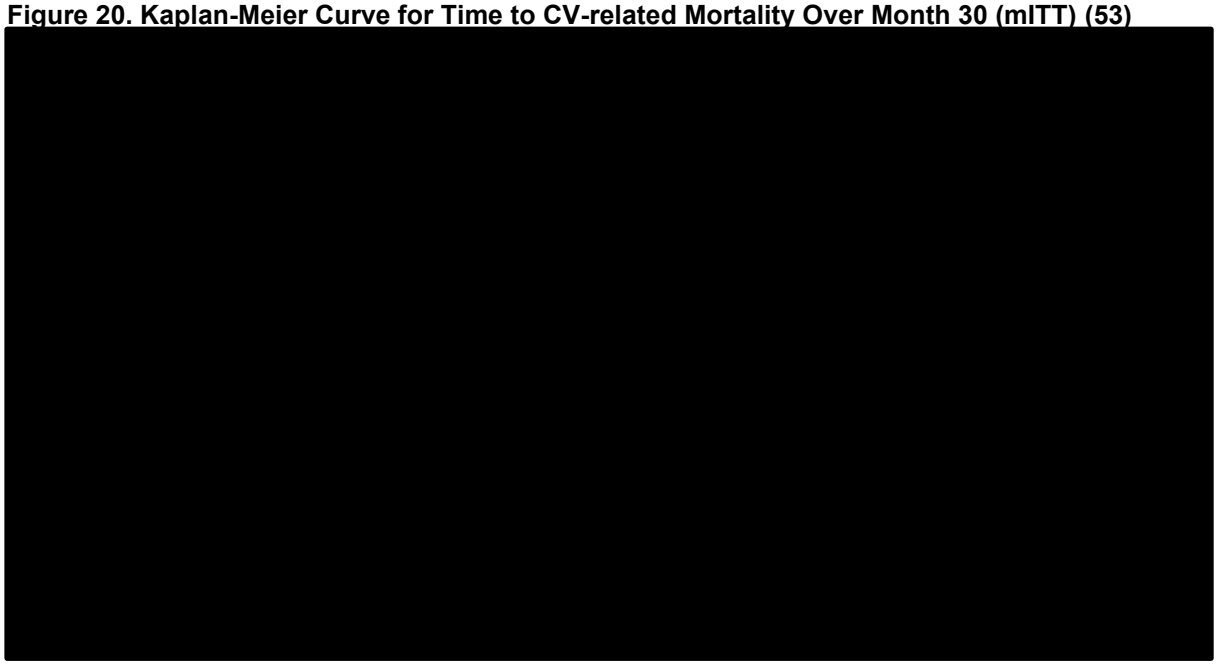
6MWD = 6-minute walk distance; ACM = all-cause mortality; CI = confidence interval; eGFR = estimated glomerular filtration rate; FAS = full analysis set; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OLE = open-label extension
Data are for the FAS which included the modified intention-to-treat population in ATTRibute-CM. The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study. Data were analysed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomisation stratification factors of genotype, NT-proBNP, and eGFR.
The extrapolated curve shows expected results if patients had continued receiving placebo in the OLE study. Survival probabilities for placebo to acoramidis treatment group beyond Month 30, assuming no open-label acoramidis had been taken, were extrapolated based on a Weibull probability model for the time to the ACM event estimated from the data observed in the ATTRibute-CM study and represented by the dotted line.

B.3.6.2.11 Other Secondary endpoints – CV-related mortality by Month 30

The majority (104/131; 79%) of mortality events were CV-related (Table 20).(70) CV-related mortality was reported in 14.9% and 21.3% of patients in the acoramidis and placebo groups, respectively (6.4% ARR; 30% RRR)(HR=0.709 [95% CI: 0.476, 1.054], nominal p=0.089).(57, 59, 70) The CV-related mortality results were also examined using a stratified log-rank test ([redacted]) and a CMH test (p=0.037).(53, 70) The hazard ratio from the time-dependent Cox model for acoramidis versus placebo was [redacted]).(53)

KM curves for time to CV-related mortality showed separation of the curves starting at Month 18 and increasing in magnitude through Month 30, which demonstrated the clinically important treatment effect of acoramidis compared to placebo.

Figure 20. Kaplan-Meier Curve for Time to CV-related Mortality Over Month 30 (mITT) (53)



CV = cardiovascular; mITT = modified intention-to-treat

Additional analyses of CV-related mortality by Month 30

See Appendix J for ITT analyses.

Concomitant tafamidis (mITT): Supplementary analyses showed consistent results with the primary analysis of CV-related mortality (Hypothetical Strategy: [redacted]; Principal Stratum Strategy: [redacted]).(54)

B.3.6.2.12 Other Secondary endpoints – Cumulative frequency of CVH by Month 30

By Month 30, 26.7% of patients treated with acoramidis had experienced a CVH compared with 42.6% of placebo patients.(61) A clinically important treatment effect was observed for acoramidis compared to placebo (Time to first CVH: HR=0.601, stratified Cox proportional hazard model; 95% CI: 0.451, 0.800; nominal p=0.0005).(78)

Relative risk on the annualised frequency of CVH was reduced by 50% in the acoramidis group vs. placebo group at 30 months (imputed: acoramidis: 0.224, placebo: 0.450 (RRR=0.496 [95% CI, 0.355 to 0.695]; nominal p<0.0001))(Table 22).(20, 59, 80)

Table 22. Frequency of CVH (mITT) (20, 54, 59, 61, 80)

	Acoramidis N=409		**Placebo N=202**
Total number of patients with CVH, n (%)	109 (26.7%)		86 (42.6%)
Observed: Frequency of CVH per year[a]; Mean (SD)	0.29 [redacted]		0.55 [redacted]
Modelled (imputed): Frequency of CVH per year[b]; Mean (SD)	0.224 (0.180,0.277)		0.450 (0.347,0584)
Modelled: Relative Risk Ratio (95% CI)[b]	**0.496 (0.355, 0.695)**		
p-value[b]	**<0.0001**		
Number of CVHs			
0	300 (73.3%)		116 (57.4%)
1	70 (17.1%)		47 (23.3%)
2	16 (3.9%)		17 (8.4%)
3	14 (3.4%)		9 (4.5%)
4	7 (1.7%)		7 (3.5%)
5	2 (0.5%)		3 (1.5%)
6	0		2 (1.0%)
7	0		1 (0.5%)
p-value	<0.0001		

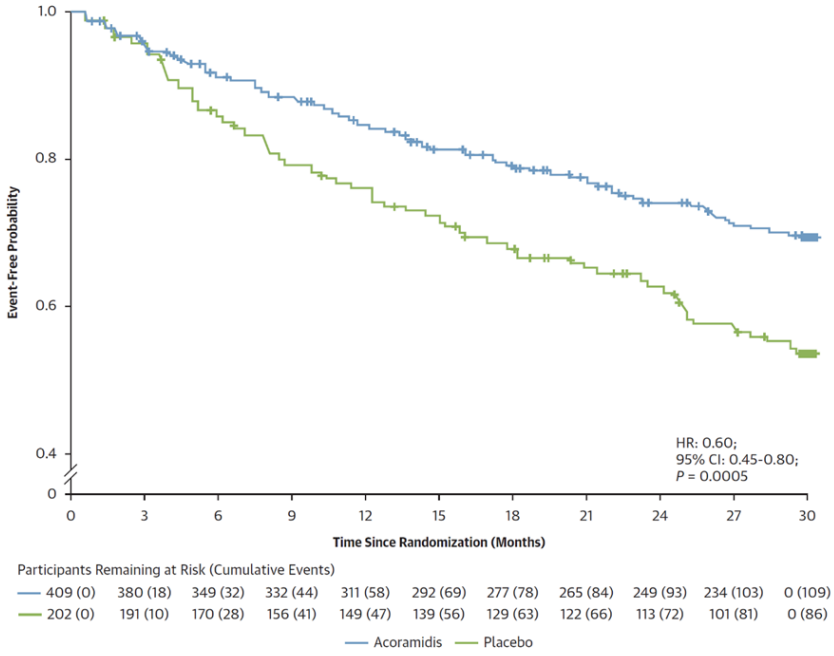
ACM = all-cause mortality; CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; CVH = CV-related hospitalisation; eGFR = estimated glomerular filtration rate; EOCI = event of clinical interest; IXRS = Interactive Voice/Web Response System; mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SD = standard deviation

[a] CVH includes both CEC adjudicated CVH and EOCI. CVH frequency was calculated for the period of (the earlier date of (last dose date+30 days) or Day 907 or ACM date for patients with ACM or Last known alive date - randomisation date +1).

[b] Negative binomial regression model with treatment group, randomisation stratification factors of genotype, NT-proBNP level and eGFR level from IXRS, and the offset term was used to analyse the cumulative frequency of CEC adjudicated CVH.

Acoramidis significantly delayed the first occurrence of CVH in comparison to placebo, with KM curves showing early separation at Month 3 in the ATTRibute-CM study, and increasing in magnitude through Month 30 (Figure 21).(57)

Figure 21. Kaplan-Meier Curve for Time to First CVH Over Month 30 (mITT)(61)



CV = cardiovascular; CVH = CV-related hospitalisation; mITT = modified intent-to-treat

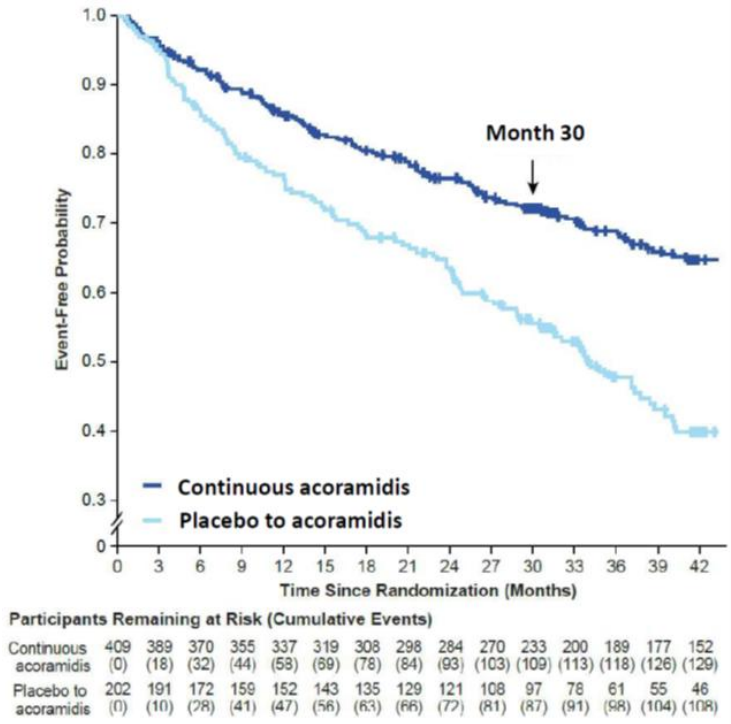
Additional analyses of CVH by Month 30

See Appendix J for ITT analyses.

Concomitant tafamidis (mITT): [redacted] (Hypothetical Strategy: [redacted] Principal Stratum Strategy: [redacted]

In first results from the **OLE study**, 129/409 (31.5%) patients in the continuous acoramidis group and 108/202 (53.5%) patients in the placebo to acoramidis group reported CVH events through to Month 42, corresponding to a 41.0% RRR. The HR (95% CI; p-value) for time to first CVH was 0.53 (0.41, 0.69; p<0.0001) based on a stratified Cox proportional hazards model favouring continuous acoramidis.(48)

Figure 22. Kaplan-Meier Curve for Time to First CVH from Baseline in ATTRibute-CM through Month 42 in the OLE Study (FAS) (48)

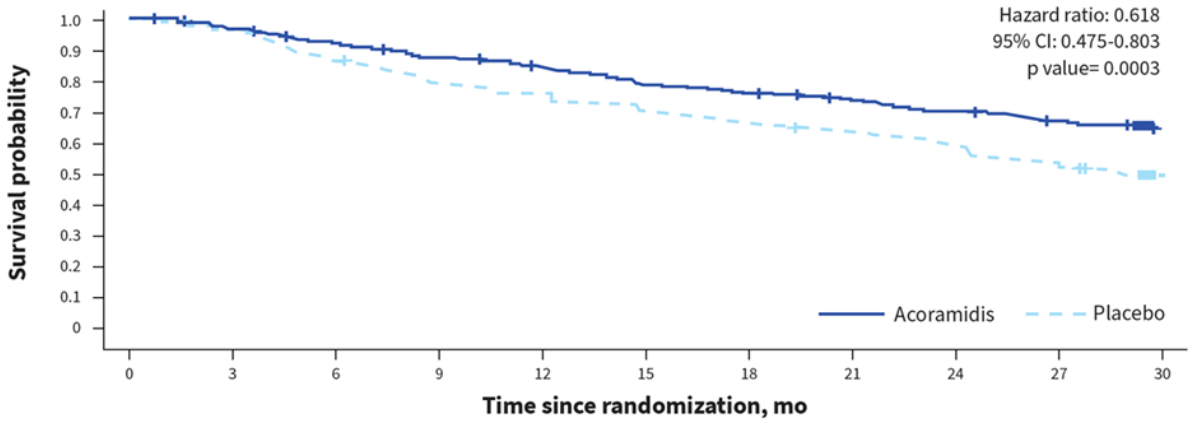


6MWD = 6-minute walk distance; CI = confidence interval; CV = cardiovascular; CVH = CV-related hospitalisation; eGFR = estimated glomerular filtration rate; FAS = Full analysis set; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OLE = open-label extension
The full analysis set included the modified intention-to-treat population in ATTRibute-CM. The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study. Data were analysed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomisation stratification factors of genotype, NT-proBNP, and eGFR.

B.3.6.2.13 Time to CV-related Mortality or First CVH (post-hoc analysis)

Acoramidis significantly improved CV outcomes compared to placebo in an analysis of CV-mortality or first CVH at Month 30. A 38.2% hazard reduction was observed in the acoramidis treatment group compared to placebo (HR=0.618 [95% CI: 0.475, 0.803; nominal p=0.0003]). The KM curves for time to CV-related mortality or first CVH showed early separation and continued to diverge through Month 30 (Figure 23).(81)

Figure 23. Kaplan-Meier Curve for time to CVM or first CVH through Month 30 (mITT) (81)



Subjects remaining at risk (cumulative events)

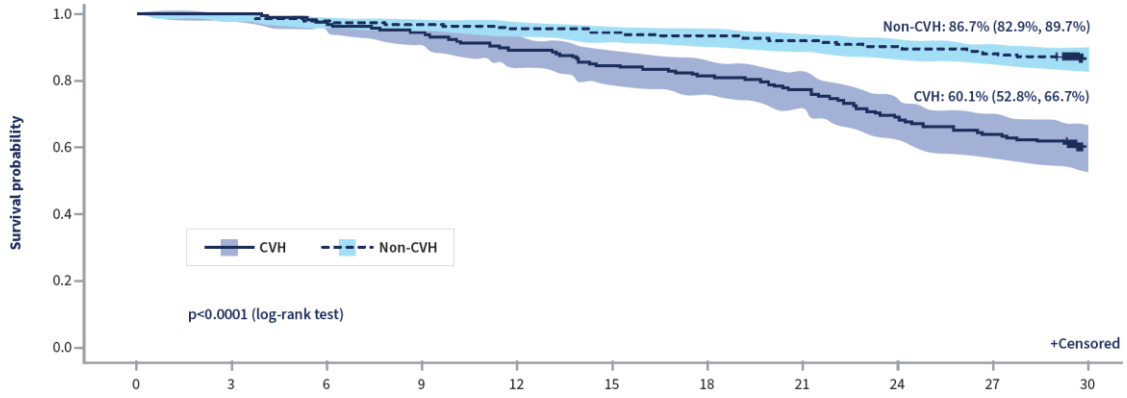
Acoramidis	409 (0)	389 (18)	370 (36)	355 (50)	337 (66)	319 (84)	308 (94)	298 (102)	284 (116)	270 (128)	0 (136)
Placebo	202 (0)	191 (11)	172 (29)	159 (42)	152 (49)	143 (58)	135 (66)	129 (71)	121 (79)	108 (92)	0 (98)

CI = confidence interval; CVH = cardiovascular-related hospitalisation; CVM = cardiovascular-related mortality; HR = hazard ratio; mITT = modified intention-to-treat

B.3.6.2.14 Risk of mortality in previously hospitalised patients (post-hoc analysis)

Post-hoc analysis of ATTRibute-CM results has also demonstrated, for the first time in a clinical study, that CVH may increase the risk of subsequent death in people with ATTR-CM.(82) Patients with no CVH during the study had a 30-month survival rate of 86.7% (95% CI, 82.9%-89.7%) vs 60.1% (95% CI, 52.8%-66.7%) in patients who had at least one CVH during the study (p<0.0001).(82) These results suggest that a treatment that can help reduce CVH is critically important for people with ATTR-CM because it may improve their survival.

Figure 24. Kaplan-Meier Curve for Time to ACM Over Month 30 by CVH Groups (mITT Population) (82)



Patients Remaining at Risk (Cumulative Events)

CVH	195 (0)	195 (0)	192 (3)	185 (10)	174 (21)	165 (30)	159 (36)	151 (44)	135 (60)	125 (70)	0 (77)
Non-CVH	416 (0)	413 (3)	407 (9)	404 (12)	399 (17)	392 (24)	389 (27)	382 (34)	375 (41)	367 (49)	0 (54)

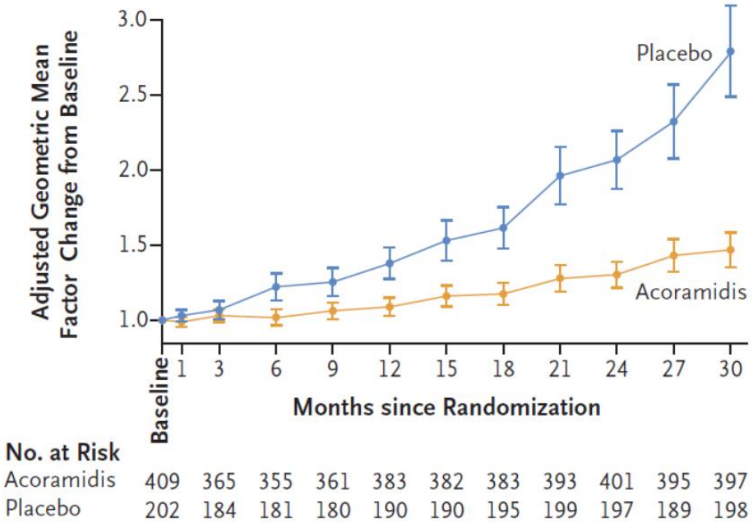
ACM = all-cause mortality; CVH = cardiovascular-related hospitalisation.

B.3.6.2.15 Change in NT-proBNP from baseline to Month 30

At Month 30, a statistically significant treatment effect on NT-proBNP was observed favouring acoramidis with observed mean (percent) changes from baseline in NT-proBNP levels at Month 30 of [redacted] in the acoramidis group compared to [redacted] in the placebo group. The AGM fold-change from baseline reduced from 2.77 for placebo to 1.47 for acoramidis (ratio of the AGM factor change = 0.529 [95% CI: 0.463, 0.604], nominal p<0.0001).(20, 57)

A higher percentage of patients in the acoramidis group had improvements in NT-proBNP from baseline to Month 30 than in the placebo group (45% vs. 9%).(59) In a post-hoc analysis with imputation (that accounted for missing observations) at Month 30, a net decrease in NT-proBNP relative to baseline - an indication of clinical improvement - was observed in 31.1% of patients in the acoramidis treatment group, compared to 5.9% in the placebo group (nominal p<0.0001). (57)

Figure 25. Change from baseline to Month 30 in NT-proBNP (mITT)(20)



mITT = modified intent-to-treat; NT-proBNP = N-terminal prohormone of brain natriuretic peptide

Additional analyses of Change in NT-proBNP from baseline to Month 30

See Appendix J for ITT analyses.

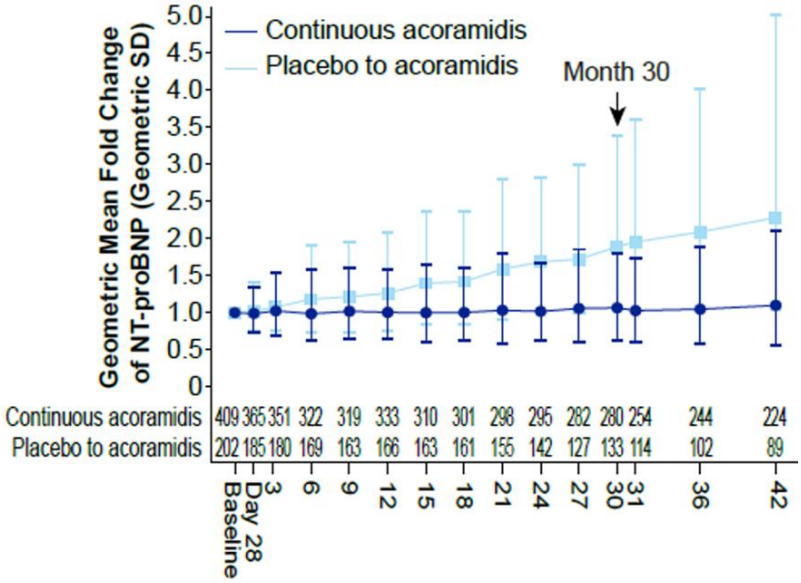
Concomitant tafamidis: Supplementary analyses showed consistent results with the primary analysis of change from baseline in NT-proBNP, which indicates that the positive treatment effect was not affected by concomitant tafamidis (53):

- Hypothetical Strategy - AGM fold-change: acoramidis [redacted]; placebo: [redacted]; (Ratio of AGM Fold-Change [redacted]), nominal p<0.0001).(54)

- Principal Stratum Strategy - AGM fold-change: acoramidis [redacted]; placebo: [redacted]; (Ratio of AGM Fold-Change [redacted]), nominal p<0.0001).(54)

The early separation in change from baseline in NT-proBNP observed in ATTRibute-CM continued into the **OLE study**.(48) At Month 42, the geometric mean (geometric SD) for fold-change from baseline in NT-proBNP was 1.10 (1.93) in the continuous acoramidis group and 2.29 (2.19) in the placebo to acoramidis group (see Figure 26).

Figure 26. Change from Baseline in Geometric Mean of Fold-Change in NT-proBNP in ATTRibute-CM through Month 42 in the OLE Study (FAS) (48)



FAS = Full analysis set; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OLE = open-label extension
The full analysis set included the modified intention-to-treat population in ATTRibute-CM. The arrow at Month 30 indicates the final follow-up time point in ATTRibute-CM and the beginning of the OLE study.

Supportive evidence from phase 2 studies for acoramidis and its effect on NT-proBNP can be found in Appendix F.

B.3.6.2.16 TTR stabilisation measured in established ex vivo assays

Fluorescent Probe Exclusion (FPE), and Western Blot (WB) assays were performed as complementary measurements to serum TTR. Near-complete stabilisation was attained in most patients by both ex vivo FPE and WB assays. At Month 30, mean FPE stabilisation on acoramidis (n=81) was [redacted]% with most patients ([redacted]%) achieving ≥ 90% stabilisation. In contrast, [redacted] patients in the placebo group (n = 29) achieved ≥ 90% FPE stabilisation. Similarly, at Month 30, mean WB stabilisation in the acoramidis group (n = 95) was [redacted]%

compared to [redacted]% in the placebo group (n=37) (p-value for testing using FPE or WB ≥ 90% at Month 30: nominal p<0.0001).(54) Ex vivo assays, support the findings from the in vivo measure of TTR (*key secondary endpoint: Change from baseline to Month 30 in serum TTR level)* and the treatment benefit in TTR level in the acoramidis treatment group compared to placebo was observed in both ATTRv-CM and ATTRwt-CM.(57)

Additional analyses of TTR stabilisation measured in FPE and WB ex vivo assays: Concomitant tafamidis

Adding tafamidis to acoramidis had no additional effect on TTR stabilisation (Figure 27 and Figure 28).(57)

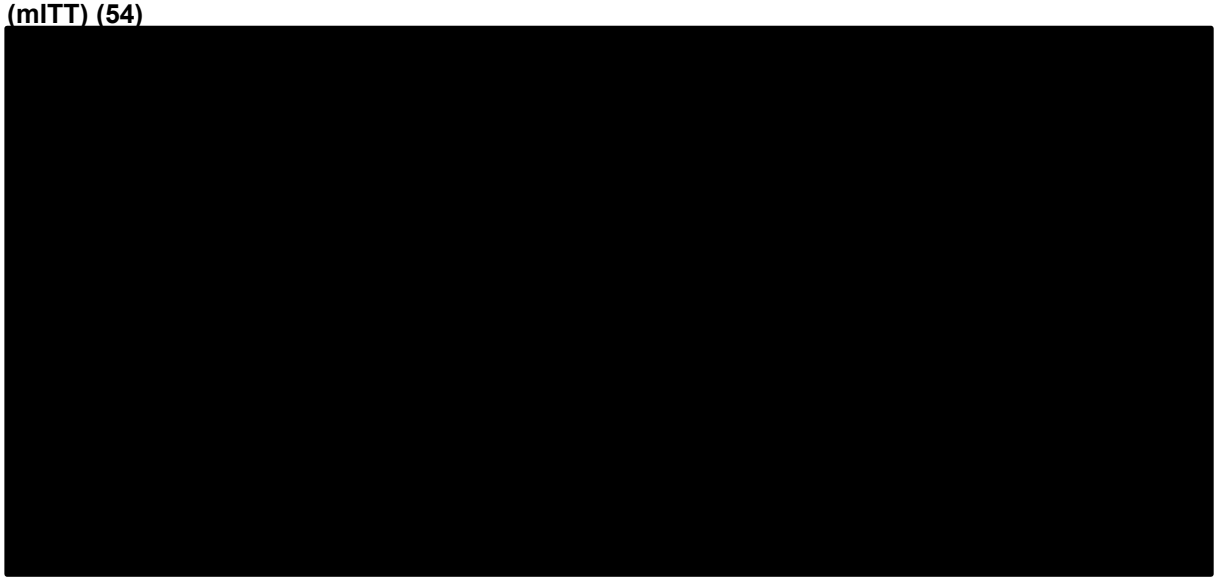
[redacted].(54)

Figure 27. TTR Stabilisation Measured in FPE at Month 30 by Concomitant Tafamidis Groups (mITT) (54)

[redacted]

FPE = Fluorescent Probe Exclusion; mITT = modified intent-to-treat; TTR = transthyretin

Figure 28. TTR Stabilisation Measured in WB at Month 30 by Concomitant Tafamidis Groups (mITT) (54)



mITT = modified intent-to-treat; TTR = transthyretin; WB = Western Blot

B.3.6.2.17 Exploratory Endpoints

Change from baseline in the EQ-5D-5L

Acoramidis significantly reduced the decline in EQ-5D-5L VAS with a LS-mean difference for change from baseline (95% CI) compared to placebo at Month 30 of 9.55 (5.50 to 13.59; nominal p<0.0001). Acoramidis also significantly reduced the decline in EQ-5D-5L Index Score with LS-mean difference for change from baseline (95% CI) compared to placebo at Month 30 of 0.13 (0.07 to 0.18; nominal p<0.0001).(23)

The EQ-5D-5L health status change from baseline in those completing the study at Month 30 was reported as ‘Better’ (i.e., better on at least one dimension and no worse in any other dimension) in a greater percentage of patients in the acoramidis treatment group compared to placebo (acoramidis, 20.4%, placebo, 11.8%); and was reported as ‘Worse’(i.e., worse in at least one dimension and no better in any other dimension) in a smaller percentage of patients in the acoramidis treatment group compared to placebo (acoramidis, 37.3%, placebo, 52.2%). At Month 30, characterisation of health status change from baseline as either ‘Same or Better’ was reported in 35.9% (102 of 284) patients for acoramidis and 18.4% (25 of 136) patients for placebo.(23)

In a context of progressive disease, where ATTR-CM is associated with a poor and declining QoL and severe disease burden, improvement or no change in EQ-5D-5L can represent clinical benefit.

A positive treatment effect of acoramidis over placebo on EQ-5D-5L (both EQ 5D 5L VAS and Index Score) was still observed after controlling for the potential effect of concomitant tafamidis.(53)

B.3.6.2.18 Subgroup analysis

Not applicable. Acoramidis is expected to provide similar or greater health benefits at a similar or lower cost to the comparator in the full population for whom the comparator has been recommended by NICE. Therefore, no subgroup analyses are included in this submission.

B.3.7 Meta-analysis

Meta-analysis is not applicable as a single RCT provided data for acoramidis.

B.3.8 Indirect and mixed treatment comparisons

Please note that the matching-adjusted indirect comparison (MAIC) was performed based on the SLR update on November 1, 2024, and no further data of relevance were identified in the SLR update on March 31, 2025.

As detailed in Appendix D, an SLR performed on November 1, 2024, identified 15 trials (reported across 59 citations) that could be considered for inclusion in indirect treatment comparisons (ITCs) of interest to this appraisal; these trials investigated acoramidis, tafamidis, diflunisal, inotersen, patisiran, and vutrisiran. Thirteen trials were excluded during feasibility assessment due to comparators not being of interest (n=6), due to studies not being randomised (n=6), and due to study duration and sample being insufficient (n=1). Ultimately, two trials provided the evidence for the ITC: ATTRibute-CM for acoramidis and ATTR-ACT for tafamidis.

ATTR-ACT trial (2013-2018) was conducted several years before the ATTRibute-CM trial (2019-2023). Clinical expert opinion indicated that standards and systems of care have significantly shifted in recent years, with patients being diagnosed earlier, which have ultimately led to improvements in overall survival.(52) In addition to the shifting standards of care, the trials differed in several eligibility criteria, baseline characteristics including eGFR, NYHA class, TTR genotype, NT-proBNP and age, which were suspected - and later confirmed using clinical expert opinion - treatment effect modifiers (EMs). The trials also differed in outcome definitions, thus traditional methods for anchored ITCs, such as Bucher's ITC(83) and network meta-analysis (NMA)(84), that do not account for heterogeneity between studies, were deemed not appropriate.

In the absence of head-to-head trials comparing acoramidis and tafamidis, and after a feasibility assessment (please see Appendix D.1.3.1.1), an anchored MAIC(85) approach was used to derive comparative efficacy and safety of acoramidis vs. tafamidis while adjusting for the imbalances in the distribution of EMs between ATTRibute-CM and ATTR-ACT. The specific outcomes selected for comparison were ACM, rate of CVH and commonly reported treatment-emergent adverse events (TEAEs). Treatment estimates for the primary endpoint derived using win ratios were considered not feasible for an ITC. Simulations have shown that the accuracy of an ITC-derived win ratio varied with the relative effect sizes of the treatments and could therefore be prone to bias.(13) Therefore, an ITC of the win ratio was not considered feasible.

ACM and frequency of CVH were both components of the primary endpoint in both trials and were considered the most clinically relevant outcomes for assessing comparative efficacy for clinical benefit assessment, and (in addition to safety outcomes) most directly relevant for a potential cost-effectiveness analysis comparing acoramidis with tafamidis.

B.3.8.1 Matching-adjusted indirect comparison

B.3.8.1.1 Methods

The MAIC analysis utilised individual patient-level data from the ATTRibute-CM study for acoramidis (data cutoff: 06 July 2023),(20, 59, 86, 87) and aggregate data published on effect modifiers from the phase III trial ATTR-ACT for 80 mg tafamidis (data cutoff: 15 February 2018).(19, 21, 24, 45, 46, 66, 88-92). The MAIC was conducted following the guidance from the UK NICE Decision Support Unit (DSU) 18.(93)

For efficacy, all analyses were based on the ITT populations, which included all randomised patients who received at least one dose of study medication and had at least one post-baseline efficacy evaluation and excluded patients with eGFR <15 mL/min/1.73 m^2 at screening to align the inclusion criteria in ATTR-ACT. For safety, all analyses were based on the safety population, which included all patients who received at least one dose of study medication.

The selection of potential treatment effect modifiers for matching was informed by published evidence from each trial (i.e. forest plots) and interviews with UK clinical experts. As a result, NYHA class, eGFR, NT-proBNP, TTR genotype, and age were selected as potential treatment effect modifiers and prognostic factors. Six different matching scenarios (please see Appendix D.1.3.2.1) were conducted to address differences in clinical expert opinion on

potential effect modifiers or to allow for more granular adjustment for some effect modifiers (i.e., age).

Additional exploratory analyses matching on baseline characteristics that were assumed to be prognostic factors only and were imbalanced between the studies (e.g., baseline medications and permanent pacemaker) were also performed. Events of clinical interest (EOCIs) were excluded from the count of CVH to align with the definition in ATTR-ACT, which also excluded them. The use of concomitant tafamidis after month 12 in ATTRibute-CM was adjusted by censoring patients' observations at the initiation of tafamidis for consistency with the hypothetical strategy (HS) applied in the main CSR analyses. Sensitivity analyses without censoring patients' observations at initiation of tafamidis and without excluding EOCIs were also conducted. For ACM, to account for potential non-proportionality of the treatment effect, time-dependent hazard ratios were produced for selected scenarios in the first 18 months and after 18 months. The relative risk ratio for CVH was estimated using a weighted Poisson model with treatment as the sole covariate.

Results from Scenario 3 and Scenario 6 analyses were considered as the primary analyses since in these scenarios, all selected effect modifiers were matched and adjusted. Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max). Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max, mean, and proportion ≥80). Thus, Scenario 6 adjusted for the same treatment effect modifiers as Scenario 3 but with more granular adjustment for age.

B.3.8.2 Results

Baseline characteristics before and after matching and effective sample size

Table 23 presents the baseline characteristics in the ATTRibute-CM and ATTR-ACT trials before and after matching in scenarios 1-3, while Table 24 presents the baseline characteristics in the ATTRibute-CM and ATTR-ACT trials before and after matching in scenarios 4-6. Before matching, the ATTRibute-CM trial enrolled fewer patients with mutant ATTR, fewer patients with NYHA Class III, patients with higher median age, and patients with lower mean NT-proBNP (ng/ml) than those enrolled in the ATTR-ACT trial. After matching, the distributions of these effect modifiers were matched in scenarios in which they were included. The other baseline characteristics, representing prognostic factors, were mostly similar between the trials before and after the MAIC adjustment, except for the use of a permanent pacemaker, diuretics, antithrombotic agents, agents acting on the renin-

angiotensin system, and beta blockers. More patients in ATTRibute-CM used these devices and medications at baseline compared to ATTR-ACT.

In Scenario 3 and Scenario 6, which matched on all potential effect modifiers, the original sample sizes of the acoramidis (N=421) and placebo (N=211) arms were reduced by 50% (ESS=209) and 58% (ESS=89), respectively, in Scenario 3 and by [redacted]% (ESS=[redacted]) and [redacted]% (ESS=[redacted]), respectively, in Scenario 6. All other scenarios had lower ESS reductions.

Weight distribution diagrams for all other scenarios are available in Appendix D. The majority of patients received weights smaller than 1.0. The weight distribution was skewed to the right in all scenarios with only a small number of patients receiving weights as large as 7.7 times the original weight of 1.0. The weight distribution in most scenarios appeared to be typical of MAIC analyses.(93)

Table 23. Baseline characteristics before and after matching ATTRibute-CM to ATTR-ACT (Scenarios 1-3), ITT Population

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 1**	**Acoramidis Matched Scenario 2**	**Acoramidis Matched Scenario 3**	**Placebo Unmatched**	**Placebo Matched Scenario 1**	**Placebo Matched Scenario 2**	**Placebo Matched Scenario 3**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=242.2)**	**(ESS=311.3)**	**(ESS=208.7)**	**(N=211)**	**(ESS=102.7)**	**(ESS=121.7)**	**(ESS=88.7)**	**(N=176)**	**(N=177)**
TTR Genotype, n (%)										
ATTRv	41 (9.7)	**23.9**	8.2	**23.9**	20 (9.5)	**24.3**	9.2	**24.3**	**42 (23.9)**	**43 (24.3)**
ATTRwt	380 (90.3)	**76.1**	91.8	**76.1**	191 (90.5)	**75.7**	90.8	**75.7**	**134 (76.1)**	**134 (75.7)**
NYHA Class, n (%)										
I	51 (12.1)	**9.1**	**9.1**	**9.1**	17 (8.1)	**7.3**	**7.3**	**7.3**	**16 (9.1)**	**13 (7.3)**
II	293 (69.6)	**59.7**	**59.7**	**59.7**	162 (76.8)	**57.1**	**57.1**	**57.1**	**105 (59.7)**	**101 (57.1)**
III	77 (18.3)	**31.2**	**31.2**	**31.2**	32 (15.2)	**35.6**	**35.6**	**35.6**	**55 (31.3)**	**63 (35.6)**
Race, n (%)										
Black	20 (4.8)	9.4	3.9	10.7	10 (4.7)	9.2	3.8	9.5	26 (14.8)	26 (14.7)
White	368 (87.4)	80.2	87.7	80.4	187 (88.6)	82.6	89.1	80.4	136 (77.3)	146 (82.5)
Asian	10 (2.4)	2.7	2.1	2.5	3 (1.4)	0.3	0.4	0.2	11 (6.3)	5 (2.8)
Other	7 (1.7)	3.8	1.7	3	3 (1.4)	4.3	2.7	5.5	3 (1.7)	0
Not Reported	16 (3.8)	3.9	4.6	3.4	8 (3.8)	3.6	4	4.4	0	0
Ethnicity, n (%)										
Hispanic/Latino	8 (1.9)	2.6	2.1	2.8	4 (1.9)	1.4	1.2	1.9	4 (2.3)	7 (4.0)
Not Hispanic/Latino	401 (95.2)	93.9	94	94.2	199 (94.3)	95.5	94.9	94.7	171 (97.2)	170 (96.0)
Not Reported/ Unknown	12 (2.9)	3.4	3.9	3	8 (3.8)	3.1	3.9	3.4	1 (0.6)	0
NT-proBNP (ng/ml)										

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 1**	**Acoramidis Matched Scenario 2**	**Acoramidis Matched Scenario 3**	**Placebo Unmatched**	**Placebo Matched Scenario 1**	**Placebo Matched Scenario 2**	**Placebo Matched Scenario 3**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=242.2)**	**(ESS=311.3)**	**(ESS=208.7)**	**(N=211)**	**(ESS=102.7)**	**(ESS=121.7)**	**(ESS=88.7)**	**(N=176)**	**(N=177)**
Mean (SD)	2.9 (2.2)	**3.9** (2.2)	**3.9** (2.5)	**3.9** (2.1)	2.7 (2.0)	**3.8** (1.6)	**3.8** (1.8)	**3.8** (1.6)	**3.9 (3.1)**	**3.8 (3.0)**
Median (Min, Max)	2.3 (0.3, 15.7)	**3.1 (0.4, 15.7)**	**3.1 (0.4, 15.7)**	**3.1 (0.4, 15.7)**	2.3 (0.3, 8.8)	**3.2 (0.5, 8.8)**	**3.2 (0.5, 8.8)**	**3.2 (0.5, 8.8)**	**3.1 (0.4, 22.0)**	**3.2 (0.3, 16.8)**
Sex, n (%)										
Male	384 (91.2)	90.7	91.8	91.5	186 (88.2)	84.8	86.1	88	158 (89.8)	157 (88.7)
Age (years)										
Mean (SD)	77.4 (6.5)	77.4 (5.1)	78.0 (5.6)	75.5 (5.4)	77.1 (6.8)	77.0 (5.5)	78.2 (5.4)	75.0 (5.1)	**75.2 (7.2)**	**74.1 (6.7)**
Median (Min, Max)	78.0 (50, 91)	78.0 (50, 91)	78.9 (50, 91)	**76.0 (50, 88)**	78.0 (55, 91)	78.0 (55, 91)	79.0 (55, 91)	**74.5 (55, 89)**	**76.0 (46, 88)**	**74.0 (51, 89)**
≥65 years, n (%)	409 (97.1)	96.5	97.8	**90.9**	202 (95.7)	92.5	96.2	**91.5**	**160 (90.9)**	**162 (91.5)**
≥80 years, n (%)	161 (38.2)	39.3	41.3	30.9	83 (39.3)	41.7	47.3	30.9	**51 (29.0)**	**37 (20.9)**
eGFR (mL/min.1.73 m^2)										
Mean (SD)	60.9 (18.2)	58.1 (14)	57.65 (15.6)	58.5 (13.5)	61 (18.7)	56.6 (13.1)	55.9 (14.8)	57.1 (12)	57.5 (17.3) †	55.6 (16.8)
Median (Min, Max)	61 (8, 125)	56 (25, 125)	56 (25, 125)	56 (25, 125)	60 (21, 114)	57 (25, 114)	55.3 (25, 114)	57 (25, 114)	NR	NR
BMI										
Mean (SD)	27.07 (3.793)	26.78 (3.070)	26.88 (3.350)	26.93 (2.939)	27.01 (3.766)	26.17 (2.581)	26.39 (2.860)	26.25 (2.526)	26.32 (3.805)	26.33 (4.277)
Min, Max	18, 43	18, 43	18, 43	18, 43	19, 40	19, 40	19, 40	19, 40	18, 40	16, 48
Duration (years) of ATTR-CM										

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 1**	**Acoramidis Matched Scenario 2**	**Acoramidis Matched Scenario 3**	**Placebo Unmatched**	**Placebo Matched Scenario 1**	**Placebo Matched Scenario 2**	**Placebo Matched Scenario 3**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=242.2)**	**(ESS=311.3)**	**(ESS=208.7)**	**(N=211)**	**(ESS=102.7)**	**(ESS=121.7)**	**(ESS=88.7)**	**(N=176)**	**(N=177)**
Mean (SD)	1.24 (1.203)	1.37 (1.093)	1.35 (1.261)	1.40 (1.046)	1.12 (1.195)	1.34 (0.864)	1.31 (0.975)	1.39 (0.818)	0.93 (1.179)	1.23 (1.439)
Median (Min, Max)	0.84 (0.0, 10.1)	0.96 (0.0, 10.1)	0.91 (0.0, 10.1)	0.98 (0.0, 10.1)	0.71 (0.0, 7.4)	0.91 (0.0, 5.1)	0.83 (0.0, 5.1)	1.01 (0.0, 5.1)	0.56 (0.0, 6.9)	0.67 (0.0, 7.9)
Permanent Pacemaker, n (%)										
Yes	81 (19.2)	23.4	22.8	20.5	39 (18.5)	17.1	19.7	18.8	13 (4.9)†	12 (6.8)
Implanted Cardiac Defibrillator, n (%)										
Yes	26 (6.2)	6.4	6.7	7	17 (8.1)	8.5	8.5	9.2	16 (6.1)†	9 (5.1)
6MWT										
Mean (SD)	361.21 (103.705)	340.73 (78.106)	341.75 (90.094)	348.86 (74.552)	348.37 (93.564)	318.22 (70.970)	315.03 (77.386)	325.25 (69.837)	350.55 (121.296)†	353.26 (125.983)
Median (Min, Max)	363 (151, 696)	335 (159, 696)	336 (159, 696)	342 (159, 696)	349 (151, 598)	328 (151, 560)	317 (151, 560)	338 (151, 560)	342.5 (61, 685)	346 (80, 822)
KCCQ-OS – overall summary score										
Mean (SD)	71.52 (19.39)	67.27 (15.79)	68.15 (18.05)	66.53 (15.10)	70.31 (20.54)	63.20 (16.83)	64.13 (17.70)	62.04 (15.47)	67.28 (21.36)†	65.90 (21.74)
Use of Diuretics, n (%)										
Yes	359 (85.3)	90.1	89.6	89	181 (85.8)	88.2	90.3	88.4	175 (66.3)†	123 (69.5)
Use of Antithrombotic Agents, n (%)										

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 1**	**Acoramidis Matched Scenario 2**	**Acoramidis Matched Scenario 3**	**Placebo Unmatched**	**Placebo Matched Scenario 1**	**Placebo Matched Scenario 2**	**Placebo Matched Scenario 3**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=242.2)**	**(ESS=311.3)**	**(ESS=208.7)**	**(N=211)**	**(ESS=102.7)**	**(ESS=121.7)**	**(ESS=88.7)**	**(N=176)**	**(N=177)**
Yes	342 (81.2)	83.1	83.9	83	169 (80.1)	81	84.8	78.9	105 (39.8)†	72 (40.7)
Use of Agents Acting on the Renin-angiotensin System, n (%)										
Yes	188 (44.7)	45.1	43.3	43.5	88 (41.7)	40.3	39.9	42.3	69 (26.1)†	48 (27.1)
Use of Beta blockers, n (%)										
Yes	194 (46.1)	50.7	49.2	52.4	97 (46.0)	51.4	48.6	53.8	76 (28.8)†	53 (29.9)

6MWT = six-minute walk test; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary transthyretin amyloidosis; ATTRwt = wild-type; BMI = body mass index; ESS = effective sample size; ITT = intention-to-treat; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin

† Reported for the pooled tafamidis (80 mg and 20 mg). Denominator is 264. **Bold** characteristics were matched

Table 24. Baseline characteristics before and after matching ATTRibute-CM to ATTR-ACT (Scenarios 4-6), ITT Population

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 4**	**Acoramidis Matched Scenario 5**	**Acoramidis Matched Scenario 6**	**Placebo Unmatched**	**Placebo Matched Scenario 4**	**Placebo Matched Scenario 5**	**Placebo Matched Scenario 6**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=218.7)**	[redacted]	[redacted]	**(N=211)**	**(ESS=89)**	[redacted]	[redacted]	**(N=176)**	**(N=177)**
TTR Genotype, n (%)										
ATTRm	41 (9.7)	**23.9**			20 (9.5)	**24.3**			**42 (23.9)**	**43 (24.3)**
ATTRwt	380 (90.3)	**76.1**			191 (90.5)	**75.7**			**134 (76.1)**	**134 (75.7)**
NYHA Class, n (%)										
I	51 (12.1)	**9.1**			17 (8.1)	**7.3**			**16 (9.1)**	**13 (7.3)**
II	293 (69.6)	**59.7**			162 (76.8)	**57.1**			**105 (59.7)**	**101 (57.1)**
III	77 (18.3)	**31.2**			32 (15.2)	**35.6**			**55 (31.3)**	**63 (35.6)**
Race, n (%)										
Black	20 (4.8)	11			10 (4.7)	9.5			26 (14.8)	26 (14.7)

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 4**	**Acoramidis Matched Scenario 5**	**Acoramidis Matched Scenario 6**	**Placebo Unmatched**	**Placebo Matched Scenario 4**	**Placebo Matched Scenario 5**	**Placebo Matched Scenario 6**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=218.7)**	[redacted]	[redacted]	**(N=211)**	**(ESS=89)**	[redacted]	[redacted]	**(N=176)**	**(N=177)**
White	368 (87.4)	80.4			187 (88.6)	79.7			136 (77.3)	146 (82.5)
Asian	10 (2.4)	2.4			3 (1.4)	0.8			11 (6.3)	5 (2.8)
Other	7 (1.7)	2.9			3 (1.4)	5.6			3 (1.7)	0
Not Reported	16 (3.8)	3.4			8 (3.8)	4.4			0	0
Ethnicity, n (%)										
Hispanic/Latino	8 (1.9)	2.7			4 (1.9)	1.9			4 (2.3)	7 (4.0)
Not Hispanic/Latino	401 (95.2)	94.3			199 (94.3)	94.7			171 (97.2)	170 (96.0)
Not Reported/Unknown	12 (2.9)	2.9			8 (3.8)	3.4			1 (0.6)	0
NT-proBNP (ng/ml)										
Mean (SD)	2.9 (2.2)	**3.9** (2.1)			2.7 (2.0)	**3.8** (1.6)			**3.9 (3.1)**	**3.8 (3.0)**
Median (Min, Max)	2.3 (0.3, 15.7)	**3.1 (0.4, 15.7)**			2.3 (0.3, 8.8)	**3.2 (0.5, 8.8)**			**3.1 (0.4, 22.0)**	**3.2 (0.3, 16.8)**
Sex, n (%)										
Male	384 (91.2)	91			186 (88.2)	88			158 (89.8)	157 (88.7)
Age (years)										
Mean (SD)	77.4 (6.5)	75.5 (5.4)			77.1 (6.8)	75.0 (5.1)			**75.2 (7.2)**	**74.1 (6.7)**
Median (Min, Max)	78.0 (50, 91)	**76.0 (50, 88)**			78.0 (55, 91)	**74.5 (55, 89)**			**76.0 (46, 88)**	**74.0 (51, 89)**
≥65 years, n (%)	409 (97.1)	**90.9**			202 (95.7)	**91.5**			**160 (90.9)**	**162 (91.5)**
≥80 years, n (%)	161 (38.2)	30			83 (39.3)	30.9			**51 (29.0)**	**37 (20.9)**
eGFR (mL/min.1.73 m^2)										
Mean (SD)	60.9 (18.2)	57.8 (14.3)			61 (18.7)	57.04 (11.9)			57.5 (17.3) †	55.6 (16.8)
Median (Min, Max)	61 (8, 125)	56 (8, 125)			60 (21, 114)	57 (25, 114)			NR	NR
BMI										
Mean (SD)	27.07 (3.793)	26.95 (2.967)			27.01 (3.766)	26.23 (2.509)			26.32 (3.805)	26.33 (4.277)
Min, Max	18, 43	18, 43			19, 40	19, 40			18, 40	16, 48

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 4**	**Acoramidis Matched Scenario 5**	**Acoramidis Matched Scenario 6**	**Placebo Unmatched**	**Placebo Matched Scenario 4**	**Placebo Matched Scenario 5**	**Placebo Matched Scenario 6**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=218.7)**	[redacted]	[redacted]	**(N=211)**	**(ESS=89)**	[redacted]	[redacted]	**(N=176)**	**(N=177)**
Duration (years) of ATTR-CM										
Mean (SD)	1.24 (1.203)	1.40 (1.032)	[redacted]	[redacted]	1.12 (1.195)	1.40 (0.813)	[redacted]	[redacted]	0.93 (1.179)	1.23 (1.439)
Median (Min, Max)	0.84 (0.0, 10.1)	0.99 (0.0, 10.1)	[redacted]	[redacted]	0.71 (0.0, 7.4)	1.02 (0.0, 5.1)	[redacted]	[redacted]	0.56 (0.0, 6.9)	0.67 (0.0, 7.9)
Permanent Pacemaker, n (%)										
Yes	81 (19.2)	19.7	[redacted]	[redacted]	39 (18.5)	18.6	[redacted]	[redacted]	13 (4.9)†	12 (6.8)
Implanted Cardiac Defibrillator, n (%)										
Yes	26 (6.2)	6.8	[redacted]	[redacted]	17 (8.1)	9.1	[redacted]	[redacted]	16 (6.1)†	9 (5.1)
6MWT										
Mean (SD)	361.21 (103.705)	348.45 (76.575)	[redacted]	[redacted]	348.37 (93.564)	326.49 (71.125)	[redacted]	[redacted]	350.55 (121.296)†	353.26 (125.983)
Median (Min, Max)	363 (151, 696)	342 (151, 696)	[redacted]	[redacted]	349 (151, 598)	338 (151, 598)	[redacted]	[redacted]	342.5 (61, 685)	346 (80, 822)
KCCQ-OS – overall summary score										
Mean (SD)	71.52 (19.39)	66.45 (15.38)	[redacted]	[redacted]	70.31 (20.54)	61.96 (15.38)	[redacted]	[redacted]	67.28 (21.36)†	65.90 (21.74)
Use of Diuretics, n (%)										
Yes	359 (85.3)	89.1	[redacted]	[redacted]	181 (85.8)	88.6	[redacted]	[redacted]	175 (66.3)†	123 (69.5)
Use of Antithrombotic Agents, n (%)										
Yes	342 (81.2)	83.4	[redacted]	[redacted]	169 (80.1)	78.9	[redacted]	[redacted]	105 (39.8)†	72 (40.7)
Use of Agents Acting on the Renin-angiotensin System, n (%)										
Yes	188 (44.7)	44.1	[redacted]	[redacted]	88 (41.7)	42	[redacted]	[redacted]	69 (26.1)†	48 (27.1)

	ATTRibute-CM								ATTR-ACT	
	Acoramidis Unmatched	**Acoramidis Matched Scenario 4**	**Acoramidis Matched Scenario 5**	**Acoramidis Matched Scenario 6**	**Placebo Unmatched**	**Placebo Matched Scenario 4**	**Placebo Matched Scenario 5**	**Placebo Matched Scenario 6**	**Tafamidis**	**Placebo**
	(N=421)	**(ESS=218.7)**	[redacted]	[redacted]	**(N=211)**	**(ESS=89)**	[redacted]	[redacted]	**(N=176)**	**(N=177)**
Use of Beta blockers, n (%)										
Yes	194 (46.1)	50.9	[redacted]	[redacted]	97 (46.0)	53.7	[redacted]	[redacted]	76 (28.8)†	53 (29.9)

6MWT = six-minute walk test; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = hereditary transthyretin amyloidosis; ATTRwt = wild-type; BMI = body mass index; ESS = effective sample size; ITT = intention-to-treat; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; TTR = transthyretin

† Reported for the pooled tafamidis (80 mg and 20 mg). Denominator is 264. **Bold** characteristics were matched

ACM

Before the MAIC adjustment and before applying the HS, in the naïve ITC (i.e. Bucher ITC), the overall HR and 95% CI suggested a tendency for a higher risk of death with acoramidis vs. tafamidis; however, the results were not statistically significant (HR: 1.105, [95%CI: 0.678, 1.799]). After weighting and applying the HS the overall HR and 95% CI suggested a tendency for longer survival with acoramidis vs. tafamidis (HR: 0.719, [95%CI: 0.409, 1.264] and [redacted] ([redacted])) in Scenario 3 and Scenario 6 (analyses matching on all effect modifiers), respectively (28% and [redacted]% reduction in the risk of death, respectively); however, the results were not statistically significant. The results obtained in the other scenarios were consistent with the results in Scenario 3 and Scenario 6 (Table 25 and Figure 29).

Table 25. ACM in the ITT population

Comparison	Without HS HR (95% CI)	HS HR (95% CI)	Source
Naïve Acoramidis vs. Placebo	[redacted]	[redacted]	ATTRibute-CM
Naïve Tafamidis 80 mg vs. Placebo	0.690 (0.487, 0.979)		ATTR-ACT
Acoramidis vs. Tafamidis 80 mg	1.105 (0.678, 1.799)	1.268 (0.765, 2.103)	Bucher ITC (Naïve)
Acoramidis vs. Placebo (Scenario 1)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 2)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 3)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 4)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 5)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 6)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Tafamidis 80 mg (Scenario 1)	0.820 (0.481, 1.398)	0.856 (0.493, 1.485)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 2)	0.884 (0.522, 1.497)	0.917 (0.530, 1.587)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 3)	0.681 (0.395, 1.174)	0.719 (0.409, 1.264)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 4)	0.717 (0.418, 1.228)	0.752 (0.430, 1.314)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 5)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 6)	[redacted]	[redacted]	Anchored MAIC

CI = confidence interval; HR = hazard ratio; HS = hypothetical strategy; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Figure 29. ACM in the ITT Population

ACM = all-cause mortality; CI = confidence interval; HS = hypothetical strategy; ITT = intention-to-treat
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype
Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

In ATTRibute-CM, proportional hazard (PH) assumption tests showed that the PH assumption was violated before matching, shown by a statistically significant interaction term of log(time)*treatment ($p<0.0001$) in the Cox proportional hazard model for ACM (Appendix D). The KM curves for acoramidis and placebo overlapped in the first 18-21 months.

In ATTR-ACT, the global Schoenfeld test ($p>0.05$) and a test for interaction of log-time and treatment ($p>0.05$) suggested that PH assumptions could hold (Appendix D). However, the test for PH assumption is likely underpowered in ATTR-ACT and thus results should be interpreted with caution. In ATTR-ACT, the KM curves were overlapping in the first 18 months and started to diverge after months 18 in the double-blind phase of the study. In the OLE, KM curves for ACM continued to diverge over time suggesting that the PH assumption maybe violated.

Therefore, in addition to an overall hazard ratio, time-dependent hazard ratios were also produced for 0-18 months and >18 months (Table 26) for the primary analyses where all selected effect modifiers were matched and adjusted (Scenario 3 and Scenario 6).

Table 26. Time-dependent hazard ratios for ACM for the primary scenarios, ITT Population

	Without HS Time-dependent HR (95% CI) Acoramidis vs. Tafamidis 80 mg	**HS Time-dependent HR (95% CI) Acoramidis vs. Tafamidis 80 mg**	**Source**
Scenario 3			
0-18 Months	[redacted]	[redacted]	Anchored MAIC
>18 Months	[redacted]	[redacted]	Anchored MAIC
Scenario 6			
0-18 Months	[redacted]	[redacted]	Anchored MAIC
>18 Months	[redacted]	[redacted]	Anchored MAIC

ACM = all-cause mortality; CI = confidence interval; HR = hazard ratio; HS = Hypothetical Strategy; ITT = intention-to-treat; MAIC = matching-adjusted indirect comparison
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max, mean, proportion ≥80)

Additional Exploratory MAIC Scenarios for ACM

While clinical experts agreed that use of medications and devices (i.e., pacemaker) are likely only prognostic factors, to assess how large differences in baseline medications and pacemaker presence may affect MAIC results, additional matching scenarios were conducted adding to Scenario 3 matching on various types of medications and whether or not a pacemaker is present (Table 27). The results of these scenarios showed similar and consistent results with scenarios 3 and 6.

Table 27. Additional anchored MAIC analyses for ACM, ITT Population

	ESS, Acoramidis	**ESS, Placebo**	**Without HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg**	**HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg**	**Source**
Scenario 3	209	89	0.681 (0.395, 1.174)	0.719 (0.409, 1.264)	Anchored MAIC
Scenario 3 + RAS	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + RAS + Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + Pacemaker	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + RAS + Diuretics +Beta Blockers +	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC

	ESS, Acoramidis	ESS, Placebo	Without HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg	HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg	Source
Antithrombotic Agents					
Scenario 3 + RAS + Diuretics +Beta Blockers + Antithrombotic Agents + Pacemaker	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC

CI = confidence interval; ESS = effective sample size; HR = hazard ratio; HS = hypothetical strategy; ITT = intention-to-treat; MAIC = matching-adjusted indirect comparison; RAS = agents acting on renin-angiotensin system

Cumulative frequency of CVH

To align with the definition of ATTR-ACT, EOCIs were excluded from the count of CVH in ATTRibute-CM. Before MAIC adjustment and before applying the HS, the results were statistically significant in favour of acoramidis vs tafamidis (RRR: 0.725 [95% CI: 0.540, 0.975]). After MAIC adjustment and applying the HS, the results remained statistically significant in favour of acoramidis compared vs tafamidis for all MAIC scenarios except Scenario 2 (RRR ranged from [redacted] to [redacted]), suggesting a relative risk reduction of between [redacted]% (Table 28, Figure 30).

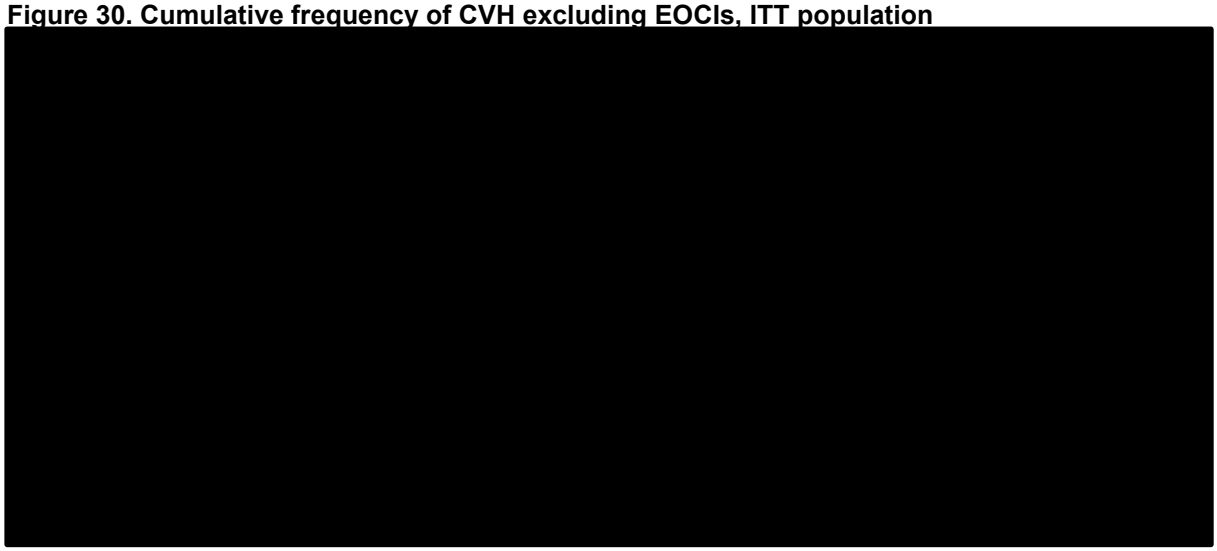
Table 28. Cumulative frequency of CVH excluding EOCIs, ITT population

Comparison	Without HS RRR (95% CI)	HS RRR (95% CI)	Source
Naïve Acoramidis vs. Placebo	[redacted]	[redacted]	ATTRibute-CM
Naïve Tafamidis 80 mg vs. Placebo	0.700 (0.570, 0.850)		ATTR-ACT
Acoramidis vs. Tafamidis 80 mg	0.725 (0.540, 0.975)	0.744 (0.550, 1.008)	Bucher ITC (Naïve)
Acoramidis vs. Placebo (Scenario 1)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 2)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 3)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 4)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 5)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 6)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Tafamidis 80 mg (Scenario 1)	0.748 (0.536, 1.043)	0.703 (0.498, 0.993)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 2)	0.743 (0.538, 1.027)	0.739 (0.531, 1.028)	Anchored MAIC

Comparison	Without HS RRR (95% CI)	HS RRR (95% CI)	Source
Acoramidis vs. Tafamidis 80 mg (Scenario 3)	0.696 (0.494, 0.981)	0.663 (0.463, 0.948)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 4)	0.698 (0.496, 0.983)	0.665 (0.466, 0.949)	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 5)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 6)	[redacted]	[redacted]	Anchored MAIC

CI = confidence interval; CV = cardiovascular; CVH = CV-related hospitalisation; eGFR = estimated glomerular filtration rate; EOCI = event of clinical interest; HS = hypothetical strategy ITC = indirect treatment comparison; ITT = intention-to-treat; MAIC = matching-adjusted indirect comparison; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; RRR = relative risk ratio; TTR = transthyretin
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype
Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Figure 30. Cumulative frequency of CVH excluding EOCIs, ITT population



CI = confidence interval; CV = cardiovascular; CVH = CV-related hospitalisation; eGFR = estimated glomerular filtration rate; EOCI = event of clinical interest; HS = hypothetical strategy; ITT = intention-to-treat; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; TTR = transthyretin
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype
Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Additional Exploratory MAIC Scenarios for CVH Excluding EOCIs

While clinical experts agreed that use of medications and devices (i.e., pacemaker) are likely only prognostic factors, to assess the impact of large imbalance in baseline medications and pacemaker presence between studies, additional matching scenarios were conducted to match on various types of medications and whether or not a pacemaker is present (Table 29). The point estimates from the additional exploratory analyses, before and after applying the HS, were similar to scenarios 3 and 6, suggesting a tendency for lower frequency of CVH.

Table 29. Additional anchored MAIC analyses for CVH excluding EOCIs, ITT population

	ESS, Acoramidis	ESS, Placebo	Without HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg	HS HR (95% CI) Acoramidis vs. Tafamidis 80 mg	Source
Scenario 3	209	89	0.696 (0.494, 0.981)	0.663 (0.463, 0.948)	Anchored MAIC
Scenario 3 + RAS	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + RAS + Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + Diuretics	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + Pacemaker	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + RAS + Diuretics +Beta Blockers + Antithrombotic Agents	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC
Scenario 3 + RAS + Diuretics +Beta Blockers + Antithrombotic Agents + Pacemaker	[redacted]	[redacted]	[redacted]	[redacted]	Anchored MAIC

CI = confidence interval; CV = cardiovascular; CVH = CV-related hospitalisation; ESS = effective sample size; HR = hazard ratio; HS = hypothetical strategy; ITT = intention-to-treat; MAIC = matching-adjusted indirect comparison; RAS = agents acting on renin-angiotensin system

Analyses including EOCIs in the count of CVHs

Analyses were also conducted without excluding EOCIs from the count of CVHs. Before the MAIC adjustment and before applying the HS, in the naïve ITC (i.e., Bucher ITC), the overall RRR and 95% CI suggested a tendency of a [redacted] frequency of CV-related hospitalisations with acoramidis vs. tafamidis; however, the results were [redacted] (RRR: [redacted], [95% CI: [redacted]]). After weighting and applying the HS, the overall RRR and 95% CI suggested a tendency for [redacted] frequency of CVHs for acoramidis versus tafamidis

in all MAIC scenarios (RRR ranged from [redacted] to [redacted]) ([redacted]% relative risk reduction). [redacted]. (Table 30, Figure 31).

Table 30. Cumulative frequency of CVH, ITT population

Comparison	Without HS RRR (95% CI)	HS RRR (95% CI)	Source
Naïve Acoramidis vs. Placebo	[redacted]	[redacted]	ATTRibute-CM
Naïve Tafamidis 80 mg vs. Placebo	0.700 (0.570, 0.850)		ATTR-ACT
Acoramidis vs. Tafamidis 80 mg	[redacted]	[redacted]	Bucher ITC (Naïve)
Acoramidis vs. Placebo (Scenario 1)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 2)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 3)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 4)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 5)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Placebo (Scenario 6)	[redacted]	[redacted]	ATTRibute-CM (weighted)
Acoramidis vs. Tafamidis 80 mg (Scenario 1)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 2)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 3)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 4)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 5)	[redacted]	[redacted]	Anchored MAIC
Acoramidis vs. Tafamidis 80 mg (Scenario 6)	[redacted]	[redacted]	Anchored MAIC

CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = hypothetical strategy; ITT = intention-to-treat; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; RRR = relative risk ratio; TTR = transthyretin

Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis

Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class

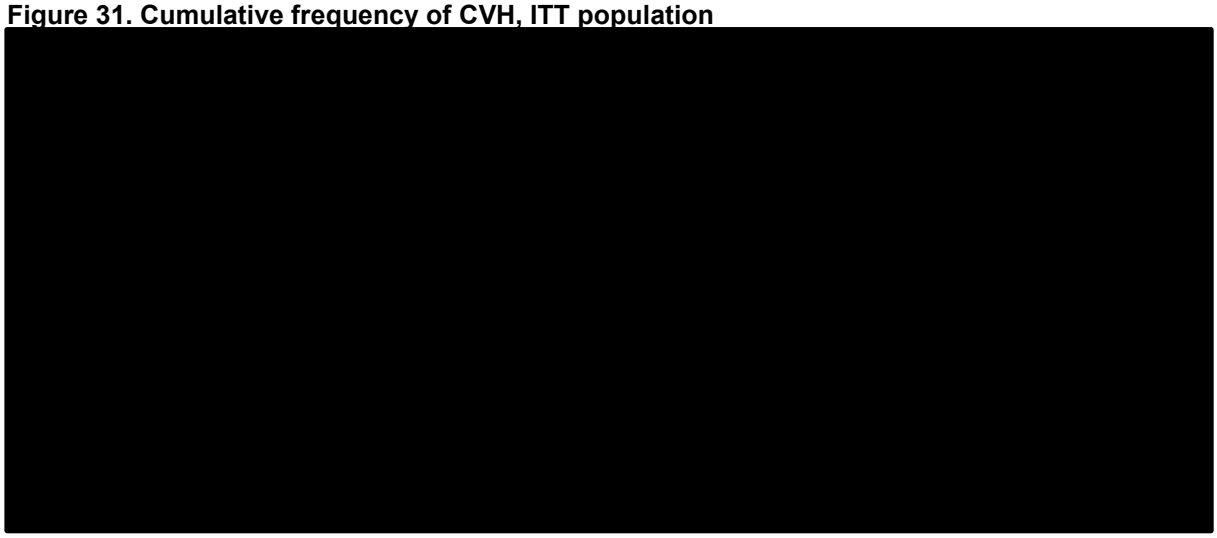
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Figure 31. Cumulative frequency of CVH, ITT population



CI = confidence interval; eGFR = estimated glomerular filtration rate; HS = hypothetical strategy; ITT = intention-to-treat; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; TTR = transthyretin
Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis
Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype
Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class
Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)
Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Safety

For the safety comparisons, all clinical experts agreed that no baseline characteristic represented an effect modifier. Therefore, only naïve Bucher ITC analyses with and without the HS were conducted. Table 31 presents the safety outcomes with the HS. Table 32 presents the safety outcomes without the HS.

After applying the HS, there were no statistically significant differences between acoramidis and tafamidis in any of the compared safety outcomes, except for [redacted]. The results suggested [redacted] of experiencing a [redacted] with acoramidis vs. tafamidis (odds ratios [OR]: [redacted], [95% CI: [redacted]]). However, this result should be interpreted with caution given the large differences in the rates of this event among the placebo arms (>20%), which suggest potential differences in the definitions. For instance, clinical experts suggested that in the ATTRibute-CM trial, a smaller proportion of AEs have been classified as “related to study treatment” in both arms based on improved understanding of the disease in recent years and prior experience treating patients with tafamidis from the ATTR-ACT study. Large differences were also observed in the placebo arms of the two studies in the rates of

TESAEs, severe TEAEs, and TEAEs leading to treatment discontinuation. For these safety outcomes, the results should be interpreted with caution. For safety outcomes, where large differences in rates were observed in the placebo arms, relative effect measures, such as ORs, are preferred over absolute effect measures, such as risk differences (RDs). However, for rare AEs, RDs were presented instead of ORs, which could exaggerate the treatment effect. Results without applying the HS were similar and consistent to those with the HS. The results of the ITC aligned with clinical expectations for similar safety profiles of the two treatments.

Table 31. Safety outcomes with HS, Safety Population

	ATTR-ACT: Observed Incidence and RD or OR			ATTRibute-CM: Observed Incidence and RD or OR			ITC
	Tafamidis 80 mg (N=176)	Placebo (N=177)	RD / OR (95% CI)	Acoramidis (N=421)	Placebo (N=211)	RD / OR (95% CI)	OR/RD (95% CI) (Acoramidis vs. Tafamidis) Bucher Analysis
TEAE	173 (98.3%)	175 (98.9%)	-0.57% (-3.04%, 1.89%)*	[redacted]	[redacted]	[redacted]	[redacted]
TESAE	133 (75.6%)	140 (79.1%)	0.82 (0.50, 1.35)	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	110 (62.5%)	114 (64.4%)	0.92 (0.60, 1.42)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study treatment	79 (44.9%)	90 (50.8%)	0.79 (0.52, 1.20)	[redacted]	[redacted]	[redacted]	[redacted]
TESAE related to study treatment	3 (1.7%)	4 (2.3%)	-0.56% (-3.46%, 2.35%)*	[redacted]	[redacted]	[redacted]	[redacted]
Patients discontinued drug due to TEAEs	40 (22.7%)	51 (28.8%)	0.73 (0.45, 1.17)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose reduced due to TEAEs	2 (1.1%)	4 (2.3%)	-1.12% (-3.82%, 1.57%)*	[redacted]	[redacted]	[redacted]	[redacted]
Common TEAEs (all causalities)							
Cardiac failure	46 (26.1%)	60 (33.9%)	0.69 (0.44, 1.09)	[redacted]	[redacted]	[redacted]	[redacted]
Fall	43 (24.4%)	41 (23.2%)	1.07 (0.66, 1.75)	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	29 (16.5%)	55 (31.1%)	0.44 (0.26, 0.73)	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema	30 (17.0%)	31 (17.5%)	0.97 (0.56, 1.68)	[redacted]	[redacted]	[redacted]	[redacted]

	ATTR-ACT: Observed Incidence and RD or OR			ATTRibute-CM: Observed Incidence and RD or OR			ITC
	Tafamidis 80 mg (N=176)	Placebo (N=177)	RD / OR (95% CI)	Acoramidis (N=421)	Placebo (N=211)	RD / OR (95% CI)	OR/RD (95% CI) (Acoramidis vs. Tafamidis) Bucher Analysis
Dizziness	25 (14.2%)	37 (20.9%)	0.63 (0.36, 1.09)	[redacted]	[redacted]	[redacted]	[redacted]
Congestive cardiac failure	22 (12.5%)	33 (18.6%)	0.62 (0.35, 1.12)	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	35 (19.9%)	33 (18.6%)	1.08 (0.64, 1.84)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	29 (16.5%)	33 (18.6%)	0.86 (0.50, 1.49)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	26 (14.8%)	30 (16.9%)	0.85 (0.48, 1.51)	[redacted]	[redacted]	[redacted]	[redacted]
Cough	16 (9.1%)	30 (16.9%)	0.49 (0.26, 0.94)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	27 (15.3%)	20 (11.3%)	1.42 (0.77, 2.64)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; HS = hypothetical strategy; ITC = indirect treatment comparison; OR = odds ratio; RD = risk difference; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

* Risk Difference (95% CI)

Note: Results shown in red significantly favour comparator

Note: For these safety outcomes, where large differences in rates were observed in the placebo arms, relative effect measures, such as ORs, are preferred over absolute effect measures, such as RDs. For rare adverse events (e.g. <10 events per arms), risk differences were presented

Table 32. Safety outcomes without the HS, Safety Population

	ATTR-ACT: Observed Incidence and RD or OR			ATTRibute-CM: Observed Incidence and RD or OR			ITC
	Tafamidis 80 mg (N=176)	Placebo (N=177)	OR/RD (95% CI)	Acoramidis (N=421)	Placebo (N=211)	OR/RD (95% CI)	OR/RD (95% CI) (Acoramidis vs. Tafamidis) Bucher Analysis
TEAE	173 (98.3%)	175 (98.9%)	-0.57% (-3.04%, 1.89%)*	[redacted]	[redacted]	[redacted]	[redacted]
TESAE	133 (75.6%)	140 (79.1%)	0.82 (0.50, 1.35)	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	110 (62.5%)	114 (64.4%)	0.92 (0.60, 1.42)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study treatment	79 (44.9%)	90 (50.8%)	0.79 (0.52, 1.20)	[redacted]	[redacted]	[redacted]	[redacted]
TESAE related to study treatment	3 (1.7%)	4 (2.3%)	-0.56% (-3.46%, 2.35%)*	[redacted]	[redacted]	[redacted]	[redacted]
Patients discontinued drug due to TEAEs	40 (22.7%)	51 (28.8%)	0.73 (0.45, 1.17)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with dose reduced due to TEAEs	2 (1.1%)	4 (2.3%)	-1.12% (-3.82%, 1.57%)*	[redacted]	[redacted]	[redacted]	[redacted]
Common TEAs (all causalities)							
Cardiac failure	46 (26.1%)	60 (33.9%)	0.69 (0.44, 1.09)	[redacted]	[redacted]	[redacted]	[redacted]
Fall	43 (24.4%)	41 (23.2%)	1.07 (0.66, 1.75)	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	29 (16.5%)	55 (31.1%)	0.44 (0.26, 0.73)	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema	30 (17.0%)	31 (17.5%)	0.97 (0.56, 1.68)	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	25 (14.2%)	37 (20.9%)	0.63 (0.36, 1.09)	[redacted]	[redacted]	[redacted]	[redacted]
Congestive cardiac failure	22 (12.5%)	33 (18.6%)	0.62 (0.35, 1.12)	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	35 (19.9%)	33 (18.6%)	1.08 (0.64, 1.84)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	29 (16.5%)	33 (18.6%)	0.86 (0.50, 1.49)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	26 (14.8%)	30 (16.9%)	0.85 (0.48, 1.51)	[redacted]	[redacted]	[redacted]	[redacted]
Cough	16 (9.1%)	30 (16.9%)	0.49 (0.26, 0.94)	[redacted]	[redacted]	[redacted]	[redacted]

	ATTR-ACT: Observed Incidence and RD or OR			ATTRibute-CM: Observed Incidence and RD or OR			ITC
	Tafamidis 80 mg (N=176)	**Placebo (N=177)**	**OR/RD (95% CI)**	**Acoramidis (N=421)**	**Placebo (N=211)**	**OR/RD (95% CI)**	**OR/RD (95% CI) (Acoramidis vs. Tafamidis) Bucher Analysis**
Pain in extremity	27 (15.3%)	20 (11.3%)	1.42 (0.77, 2.64)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; HS = hypothetical strategy; ITC = indirect treatment comparison; OR = odds ratio; RD = risk difference; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

* Risk Difference (95% CI)

Note: Results shown in red significantly favour comparator

Note: For these safety outcomes, where large differences in rates were observed in the placebo arms, relative effect measures, such as ORs, are preferred over absolute effect measures, such as RDs. For rare adverse events (e.g. <10 events per arms), risk differences were presented.

B.3.8.3 Uncertainties and Limitations in the indirect and mixed treatment comparisons

There were several uncertainties and limitations to the MAIC analysis. The ATTR-ACT trial included some patients with NT-proBNP ≥8.5 ng/mL at screening, while the ATTRibute-CM trial excluded patients with NT-proBNP >8.5 ng/mL. However, the proportion of these patients in the ATTR-ACT trial was not reported and could not be adjusted for. It is only known that the maximum baseline NT-proBNP levels with tafamidis and placebo in the ATTR-ACT trial were 22.0 ng/mL and 16.8 ng/mL, respectively, while the maximum NT-proBNP levels after matching for acoramidis and placebo were [redacted] ng/mL and [redacted] ng/mL, respectively.

The ATTRibute-CM trial selected patients with 6MWD≥150 m at screening, while the ATTR-ACT trial selected patients with 6MWD>100 m at screening. It was not possible to adjust for the 6MWT score since the ATTRibute-CM trial was more restrictive. However, 6MWD was not determined to be a treatment effect modifier, suggesting that this difference should not bias the current results.

For eGFR, only exclusion criteria were matched as this factor was determined to be an effect modifier at the extreme end of the distribution. However, after matching on effect modifiers included in the primary scenarios (3 and 6), the baseline mean eGFR became similar to that of ATTR-ACT (Table 23). Although the ITT population used for the MAIC differed from the primary analysis population (mITT) for the ATTRibute-CM study based on eGFR criteria, the results of the MAIC were anticipated to be generalisable to the mITT population due to the small differences in patient numbers between the “restricted ITT” population excluding patients with eGFR between 15 and 25 mL/min/1.73 m^2 used for the MAIC (N=621) and the mITT population (N=611), and because the results from ATTRibute-CM were similar between ITT and mITT populations. This assumption was also validated during discussion with two UK clinical experts (see Section B.4.2.7).

Some baseline characteristics were reported only for the pooled tafamidis dose (e.g., permanent pacemaker and KCCQ-OS score). It was assumed that the distribution of these would be similar for the 80 mg dose, given that the 80 mg and 20 mg doses were randomised arms in the ATTR-ACT trial.

It was not possible to fully adjust for concomitant tafamidis after month 12 in the ATTRibute-CM trial. The HS, which excludes observations after tafamidis initiation, represents

informative censoring rather than random and may still cause bias or may dilute the treatment effect of acoramidis.

In addition, the clinical experts consulted indicated that standards and systems of care could have significantly shifted in recent years. Improvement in supportive care and earlier diagnosis have likely led to improvements in overall survival in recent years.(52) Since the ATTR-ACT trial (2013-2018) was conducted before the ATTRibute-CM trial (2019-2023), patients could have had more advanced cardiac disease when they started treatment; thus the population enrolled in ATTR-ACT might no longer be representative of the current disease landscape in ATTR-CM. Differences in standards of care cannot be fully adjusted for in an ITC; however, in the anchored setting, such bias is expected to be offset due to the comparison of relative rather than absolute effects, unless differences in standard of care could modify the effect of treatment. It should also be noted that the two trials were only powered to detect statistical significance in their primary composite endpoints, rather than individual endpoints such as ACM and rate of CVH. Since the ITC analysis accounts for uncertainties arising from both studies, the estimated treatment effects for ACM and rate of CVH have wide confidence intervals, reflecting the inherent uncertainty.

Finally, the MAIC only produced estimates that are valid in the ATTR-ACT population in this two-study indirect treatment comparison.

B.3.8.4 Conclusions of indirect and mixed treatment comparisons

The anchored MAIC approach is a form of population adjusted indirect comparison designed to mitigate between-study differences in eligibility criteria and adjust for the difference in the distribution of effect modifiers across studies, resulting in a fairer comparison between interventions. A variety of scenario analyses were conducted to help address or mitigate some potential concerns associated with the limitations of MAIC, which further supported broad similarity in key efficacy and safety outcomes: For efficacy outcomes, treatment effect modifiers that were not in balance between ATTR-ACT and ATTRibute-CM included TTR genotype, NYHA class, eGFR, NT-proBNP, and age. For safety outcomes, no baseline characteristics were identified as effect modifiers.

To address differences in clinical expert opinion on potential effect modifiers and to assess robustness of the results to adding baseline characteristics that are prognostic factors or more granular adjustment for some effect modifiers (i.e., age), multiple matching scenario analyses were conducted. To adjust for initiation of concomitant tafamidis after month 12, the HS was applied, where patients' observations were censored at the start of concomitant

tafamidis. Analyses were also performed without applying the HS to assess the impact on the results.

Matching Scenario 3 and Scenario 6, which adjust for all potential effect modifiers and applying HS were considered primary analyses. After matching, the effective sample sizes of acoramidis and placebo were 209 (50% reduction) and 89 (58% reduction), respectively for Scenario 3 and [redacted] ([redacted]% reduction) and [redacted] ([redacted]% reduction), respectively for Scenario 6. After applying the HS, the results suggested a statistically significantly lower cumulative frequency of CVH (RRR: 0.663 [95% CI: 0.463, 0.948] in Scenario 3 and RRR: [redacted] [95% CI: [redacted]] in Scenario 6) for acoramidis vs. tafamidis and a tendency for lower ACM (HR: 0.719, [95%CI: 0.409, 1.264] in Scenario 3 and HR: [redacted], [95%CI: [redacted]] in Scenario 6). Time-dependent hazard ratios were derived to address potential violations of the PH assumption for ACM. These were: 0-18 months: [redacted] [95%CI: [redacted]] and >18 months: [redacted], [95%CI: [redacted]] in Scenario 3 and 0-18 months: [redacted] [95%CI: [redacted]] and >18 months: [redacted] [95%CI: [redacted]] in Scenario 6. Results of the analyses including EOCIs in the count of CV-related hospitalisations also suggested a tendency for [redacted] of CV-related hospitalisation with acoramidis, with results [redacted] (RRR: [redacted] [95% CI: [redacted]].

Before and after applying the HS, there were no statistically significant differences between acoramidis and tafamidis in any of the compared safety outcomes, except for [redacted]. The results [redacted] of experiencing a [redacted] with acoramidis vs. tafamidis (OR: [redacted], [95% CI: [redacted]]). However, this result should be interpreted with caution given the large differences in the rates of this event among the placebo arms (>20%), which suggest potential differences in the definitions.

Overall, results across all matching scenarios indicated that acoramidis tends to have a comparable ACM, a lower frequency of CVH, and a similar safety profile compared to tafamidis. It is important to note that both ATTRibute-CM and ATTR-ACT were not powered to detect statistical significance for ACM and rate of CVH as individual outcomes, and since the ITC accounts for uncertainties arising from both studies, the estimated treatment effects for ACM and frequency of CVH had wide confidence intervals.

The present study has various strengths. First, the selection of potential treatment effect modifiers for matching was informed by published evidence from each trial and interviews with clinical experts. Second, a formal ITC feasibility assessment was conducted to

comprehensively compare trial designs, eligibility criteria, baseline characteristics, and outcomes definitions. Third, population-adjustment ITC methods were used following the guidance from the UK NICE Decision Support Unit (DSU) 18.(93) Fourth, anchored MAIC was conducted because a common comparator arm (i.e., placebo) was available. Anchored comparisons are expected to result in less biased comparisons than unanchored forms because the anchored approaches rely on fewer assumptions.(93)

As noted in Section B.3.8.3, some limitations were present with the MAIC analyses, such as differences in trial design as well as inclusion and exclusion criteria, availability of patient characteristics for the ATTR-ACT trial and potential changes in standard of care over time. However, a variety of scenario analyses were also conducted to help address or mitigate some potential concerns associated with these limitations, which further supported broad similarity in key efficacy and safety outcomes, aligning with UK clinical expert expectations for at least similar efficacy for acoramidis compared to tafamidis and similarity in safety profiles between treatments.(94)

B.3.9 Adverse reactions

Results of the safety analyses of the ATTRibute-CM study, demonstrate treatment with acoramidis to be safe and generally well tolerated in patients diagnosed with ATTR-CM.

The frequency, type, and severity of TEAEs were balanced between the acoramidis and placebo study arms, and a lower frequency of serious TEAEs was observed in acoramidis-treated patients. TEAEs were consistent with progression of cardiomyopathy and other comorbidities expected for this population.

No new safety issues have been identified in the ongoing OLE study AG10-304.

The safety profile of acoramidis appears similar to that of tafamidis, with diarrhoea found to be a common adverse event for both treatments.

B.3.9.1 Introduction to adverse event data

Data on the safety of acoramidis as a treatment for ATTR-CM is primarily drawn from ATTRibute-CM.(20) In addition, the primary objective of AG10-304, the ongoing OLE study of ATTRibute-CM is to evaluate long-term safety and tolerability of acoramidis, therefore any notable findings to date are reported under ‘Long-term safety’ heading within this section.

The population for safety analysis in ATTRibute-CM comprised all patients who received at least one dose of study drug (Acoramidis: n=421; Placebo: n=211).

Of the patients valid for safety analysis in ATTRibute-CM, the mean (SD) duration of exposure was [redacted] vs [redacted] months, respectively for acoramidis vs placebo, and the mean proportion of tablets taken of the expected number was high (0.97 overall and in each treatment group).(54)

B.3.9.2 Summary of adverse events

AEs in ATTRibute-CM were classified using MedDRA (Medical Dictionary for Regulatory Activities) Version 24.1.

The safety data from ATTRibute-CM indicate that acoramidis was generally well tolerated (see Table 33). The overall incidence of TEAEs was similar across acoramidis and placebo groups (98.1% vs 97.6%, respectively) and in most cases were of mild or moderate severity (acoramidis: 60.8%; placebo: 52.1%) (see Table 33). Serious adverse events (SAEs) occurred in 54.6% (n=230) of the patients in the acoramidis group and 64.9% (n=137) of those in the placebo group. Severe TEAEs (acoramidis: 37.3%; placebo: 45.5%), TEAEs with fatal outcome (acoramidis: 14.3%; placebo: 17.1%), and TEAEs leading to hospitalisation (acoramidis: 50.4%; placebo: 60.7%) were also lower in the acoramidis treatment group compared to the placebo group. Similar proportions of patients in the acoramidis and placebo groups discontinued study drug because of a TEAE (acoramidis: 9.3%; placebo: 8.5%), however, the incidence of treatment-emergent SAEs that led to treatment discontinuation was lower for acoramidis (5.0 vs 7.1%). The higher frequency of drug-related TEAEs in the acoramidis treatment group (11.9% versus 5.2% in the placebo group) was primarily driven by ‘gastrointestinal disorders’ (acoramidis: 4.8%; placebo: 0.5%; a 4.3% difference) and ‘investigations’ (acoramidis: 2.4%; placebo: 0.5%, a 1.9% difference). Overall, the pattern of TEAEs and SAEs was consistent with ATTR-CM, disease progression and comorbidities expected for this population.

Table 33. Overall summary of the number of patients with AEs in ATTRibute-CM to Month 30 (20)

	ATTRibute-CM (Safety population)	
Patients with one or more events	**Acoramidis N=421**	**Placebo N=211**
Any TEAE [1]	**413 (98.1%)**	**206 (97.6%)**
with fatal outcome [2]	60 (14.3%)	36 (17.1%)
leading to hospitalisation [3]	212 (50.4%)	128 (60.7%)
leading to study drug discontinuation [4]	39 (9.3%)	18 (8.5%)

	ATTRibute-CM (Safety population)	
Patients with one or more events	**Acoramidis N=421**	**Placebo N=211**
leading to dose reduction [5]	4 (1.0%)	0
Any Treatment-emergent SAE	**230 (54.6%)**	**137 (64.9%)**
leading to study drug discontinuation	21 (5.0%)	15 (7.1%)
leading to dose reduction	2 (0.5%)	0
Any study drug-related TEAE[6] drug-related treatment-emergent SAEs	50 (11.9%) 2 (0.5%)	11 (5.2%) 0
Severe TEAE[7]	157 (37.3%)	96 (45.5%)

AE = adverse event; eCRF = electronic clinical report form; FAS = full analysis set; OLE = open-label extension study; SAE = serious adverse event; TEAE = treatment-emergent adverse event
[1] **ATTRibute**: An AE with onset date on or after the first dose of study drug and up to 30 days after the last dose of study drug was counted as a TEAE.
[2] Outcome from the "Adverse Events" eCRF or "CV Hospitalisations and Events of Clinical Interest" eCRF.
[3] From serious criteria on the "Adverse Events" eCRF or "CV Hospitalisations and Events of Clinical Interest" eCRF. Adverse event results in initial or prolonged hospitalisation for the patient.
[4] Action Taken with Study Treatment on the "Adverse Events" eCRF or "CV Hospitalisations and Events of Clinical Interest" eCRF.
[5] Dose reduction not allowed for patients enrolled since protocol amendment 3.
[6] Relationship to study drug as assessed by the investigator.
[7] Severity as assessed by the investigator.

B.3.9.3 TEAEs

A summary of the most common TEAEs (occurring in ≥ 5% patients in either group) is presented in Table 34. AEs with a > 5% difference in incidence between treatment groups were cardiac failure (acoramidis: 24.0% vs. placebo: 39.3%), atrial fibrillation (acoramidis: 16.6% vs. placebo: 21.8%), and dyspnoea (acoramidis: 12.4% vs. placebo: 19.0%), which were reported at a lower incidence in the acoramidis treatment group compared to placebo. This is consistent with what would be expected in ATTR-CM and active treatment vs. placebo since cardiac failure, atrial fibrillation, and dyspnoea are associated with progression of the disease.

In the gastrointestinal disorders System organ class (SOC), the 6.1% higher incidence of TEAEs in the acoramidis treatment group compared to placebo was mainly driven by the events of diarrhoea (acoramidis: 11.6%; placebo: 7.6%); abdominal pain upper (acoramidis: 5.5%; placebo: 1.4%); and abdominal pain (acoramidis: 4.3%; placebo: 2.4%). Diarrhoea is labelled as a common adverse event for tafamidis,(95) also a TTR stabiliser, therefore it is possible that diarrhoea may be related to acoramidis treatment and is a potential class effect. Diarrhoea and/or constipation may also be symptoms of autonomic neuropathy and a common symptom of amyloidosis.(31)

'Fall' and 'constipation' were reported in >15% patients, albeit at a lower incidence in the acoramidis treatment group compared to placebo (fall: 15.9% vs. 18.5%; constipation: 12.4% versus 15.2%). Fall safety data were consistent with the ageing patient population under study and no clinically meaningful imbalance in TEAEs or SAEs was observed between the treatment groups and there was no evidence to establish a causal relationship between acoramidis and fall.

The TEAE of gout was also observed more frequently in patients on acoramidis compared with the placebo group (11.2% vs. 8.1%). Gout in the acoramidis treatment group was mostly mild and moderate and resolved (mild: n=20 [4.8%]; moderate: n=26 [6.2%]; severe: n=1 [0.2%]).

Table 34. TEAEs reported in ≥5% of patients in any treatment group in ATTRibute-CM (20)

	ATTRibute-CM (Safety population)	
System organ class Preferred Term	**Acoramidis N=421 n (%)**	**Placebo N=211 n (%)**
Any TEAE	**413 (98.1%)**	**206 (97.6%)**
Cardiac disorders	230 (54.6)	144 (68.2)
Cardiac failure	101 (24.0)	83 (39.3)
Atrial fibrillation	70 (16.6)	46 (21.8)
Cardiac failure acute	27 (6.4)	17 (8.1)
Bradycardia	23 (5.5)	9 (4.3)
Ventricular tachycardia	17 (4.0)	14 (6.6)
Atrial flutter	22 (5.2)	9 (4.3)
Cardiac failure chronic	17 (4.0)	11 (5.2)
Infections and infestations	**246 (58.4)**	**116 (55.0)**
COVID-19	89 (21.1)	30 (14.2)
Urinary tract infection	51 (12.1)	28 (13.3)
Upper respiratory tract infection	24 (5.7)	12 (5.7)
Nasopharyngitis	21 (5.0)	11 (5.2)
Pneumonia	16 (3.8)	14 (6.6)
Gastrointestinal disorders	221 (52.5)	98 (46.4)
Constipation	52 (12.4)	32 (15.2)
Diarrhoea	49 (11.6)	16 (7.6)
Nausea	24 (5.7)	11 (5.2)
Abdominal pain upper	23 (5.5)	3 (1.4)
Musculoskeletal and connective tissue disorders	**184 (43.7)**	**83 (39.3)**
Arthralgia	48 (11.4)	23 (10.9)
Back pain	39 (9.3)	14 (6.6)
Muscle spasms	34 (8.1)	15 (7.1)
Pain in extremity	30 (7.1)	11 (5.2)
Osteoarthritis	12 (2.9)	12 (5.7)
Nervous system disorders	**182 (43.2)**	**77 (36.5)**
Dizziness	46 (10.9)	23 (10.9)
Syncope	21 (5.0)	15 (7.1)
Metabolism and nutrition disorders	**149 (35.4)**	**85 (40.3)**
Gout	47 (11.2)	17 (8.1)
Hypervolaemia	23 (5.5)	18 (8.5)
Hypokalaemia	22 (5.2)	12 (5.7)
Decreased appetite	19 (4.5)	11 (5.2)
Respiratory, thoracic and mediastinal disorders	**146 (34.7)**	**86 (40.8)**
Dyspnoea	52 (12.4)	40 (19.0)
Cough	32 (7.6)	18 (8.5)

	ATTRibute-CM (Safety population)	
System organ class Preferred Term	**Acoramidis N=421 n (%)**	**Placebo N=211 n (%)**
Epistaxis	22 (5.2)	7 (3.3)
Pleural effusion	11 (2.6)	13 (6.2)
General disorders and administration site conditions	**144 (34.2)**	**79 (37.4)**
Fatigue	42 (10.0)	26 (12.3)
Oedema peripheral	33 (7.8)	25 (11.8)
Asthenia	22 (5.2)	9 (4.3)
Peripheral swelling	7 (1.7)	14 (6.6)
Injury, poisoning and procedural complications	**137 (32.5)**	**81 (38.4)**
Fall	67 (15.9)	39 (18.5)
Skin laceration	13 (3.1)	11 (5.2)
Renal and urinary disorders	**142 (33.7)**	**64 (30.3)**
Acute kidney injury	52 (12.4)	22 (10.4)
Renal impairment	37 (8.8)	17 (8.1)
Haematuria	18 (4.3)	16 (7.6)
Investigations	**127 (30.2)**	**68 (32.2)**
Blood creatinine increased	26 (6.2)	4 (1.9)
Weight decreased	16 (3.8)	13 (6.2)
Skin and subcutaneous disorders	**108 (25.7)**	**53 (25.1)**
Pruritis	25 (5.9)	8 (3.8)
Rash	21 (5.0)	11 (5.2)
Vascular disorders	**88 (20.9)**	**49 (23.2)**
Hypotension	33 (7.8)	14 (6.6)
Psychiatric disorders	**57 (13.5)**	**39 (18.5)**
Insomnia	20 (4.8)	16 (7.6)
Blood and lymphatic system disorders	**61 (14.5)**	**29 (13.7)**
Anaemia	37 (8.8)	17 (8.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**54 (12.8)**	**36 (17.1)**
Basal cell carcinoma	16 (3.8)	13 (6.2)
Eye disorders	**46 (10.9)**	**26 (12.3)**
Reproductive system and breast disorders	**28 (6.7)**	**23 (10.9)**
Ear and labyrinth disorders	**22 (5.2)**	**10 (4.7)**
Endocrine disorders	**22 (5.2)**	**9 (4.3)**

AE = adverse event; COVID-19 = coronavirus disease 2019; FAS = full analysis set; n = number of patients experiencing a TEAE (the patient was counted only once for each AE); N = number of patients in the study arm; TEAE = treatment-emergent adverse event

B.3.9.4 Treatment-related TEAEs

Drug-related TEAEs were higher in the acoramidis arm (11.9%) compared with the placebo arm (5.2%), [redacted]

([redacted]

Table 35).(54) Differences of >0.5% between treatment groups were reported for TEAEs, preferred terms (PTs) of [redacted]

[redacted]

Table 35. Treatment-related TEAEs reported in >0.5% of patients in any treatment group in ATTRibute-CM (20, 54)

	ATTRibute-CM (Safety population)	
System organ class Preferred Term	**Acoramidis N=421 n (%)**	**Placebo N=211 n (%)**
Any study drug-related TEAE	**50 (11.9%)**	**11 (5.2%)**
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Skin and Subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

AE = adverse event; COVID-19 = coronavirus disease 2019; FAS = full analysis set; n = number of patients experiencing a TEAE (the patient was counted only once for each AE); N = number of patients in the study arm; TEAE = treatment-emergent adverse event

B.3.9.5 Treatment-emergent serious adverse events (TESAEs)

A lower incidence of TESAEs was observed in the acoramidis arm compared with the placebo arm of the study (54.6 vs 64.9%). Most SAEs were attributable to the underlying disease or consistent with comorbidities expected for this population. The most frequent TESAEs in both treatment arms were cardiac failure (acoramidis: 10.7%; placebo: 18.5%); cardiac failure acute (acoramidis: 5.0%; placebo: 6.6%); atrial fibrillation (acoramidis: 4.5%; placebo: 7.1%); acute kidney injury (acoramidis: 5.0%; placebo: 3.8%); fall (acoramidis: 3.1%; placebo: 0.9%); and COVID-19 pneumonia (acoramidis: 0.5%; placebo: 3.8%).(57)

No SAEs were reported as treatment-related in the placebo group. In the acoramidis treatment group, three related SAEs were reported in two patients (cardiac failure acute in one patient, and syncope and hypotension in another patient). These cases were reviewed and determined not to be treatment-related by the study sponsor.(57)

B.3.9.6 Adverse events leading to premature permanent discontinuation of study drug

Similar proportions of patients in the acoramidis and placebo groups discontinued study drug because of a TEAE (acoramidis: 9.3%; placebo: 8.5%). The most common TEAEs that led to discontinuation of study drug were [redacted] in the acoramidis treatment and [redacted] in the placebo group.(54) Other than [redacted], there were no other TEAEs leading to discontinuation of study drug reported in >1% of patients in either treatment group.

B.3.9.7 Deaths

The incidence of TEAEs leading to a fatal outcome was lower in the acoramidis treatment group than in the placebo group (14.3% versus 17.1%). The most common TEAEs leading to fatal outcome in both groups were in the SOC of cardiac disorders, specifically the PT of cardiac failure (acoramidis: 4.3%; placebo: 3.8%).(57) All other SOCs with TEAEs leading to fatal outcome had a difference of < 1% between the treatment groups. None of the TEAEs leading to fatal outcome were considered related to study drug by the investigator. TEAEs leading to a fatal outcome were consistent with progression of ATTR-CM and other comorbidities expected for this population.

B.3.9.8 Laboratory values and vital signs

Findings from clinical laboratory investigations, vital signs, ECGs, and physical examination in ATTRibute-CM were generally consistent with the patient population under study. Mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate were similar in both treatment groups. The mean ECG intervals at baseline in both treatment groups were consistent and did not markedly change throughout the duration of the study.(54)

There was no clinically meaningful difference in laboratory parameters (haematology and clinical chemistry) between treatment groups except for a slight increase in creatinine (approximately 15%) and decrease in eGFR (acoramidis: -8.2 mL/min and placebo: -0.7 mL/min) which were most pronounced at Day 28. This change in eGFR and serum creatinine was non-progressive, reversible in those patients whose treatment was interrupted, and not associated with kidney injury consistent with a renal haemodynamic effect.(2) Nevertheless, the SmPC outlines a risk of eGFR change in the first month of treatment and warns treating clinicians that a renal haemodynamic effect has been identified.(57)

Due to its mechanism of action and its affinity for thyroxine binding sites, any safety issues with acoramidis treatment relating to thyroid function were of clinical interest. Modest reductions in serum free T4 levels were observed with acoramidis treatment, and these changes were not associated with clinical thyroid dysfunction, suggesting no safety concerns related to this effect. Lack of clinically meaningful treatment-related changes in thyroid function in either treatment group was also accompanied by no meaningful difference in the incidence of hypothyroidism.(57)

B.3.9.9 Long-term safety

Analysis of the first 12 months of study AG10-304, the ongoing OLE study to ATTRibute-CM provides longer-term safety information for acoramidis. AEs were consistent with those previously reported in ATTRibute-CM, disease severity, concurrent illness, and age. No new safety signals were identified.(48, 63) The most common classes of AEs reported in the continuous acoramidis group are presented in Table 36.

Table 36. Summary of treatment-emergent adverse event reporting in the continuous acoramidis group in AG10-304 (OLE FAS)(48, 63)

	Continuous Acoramidis n=263
Any TEAE in the OLE study (AG10-304)	**229 (87.1%)**
System organ classes where ≥10% of patients had an adverse event:	
Infections and infestations	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]
Cardiac disorders	[redacted]
Injury, poisoning and procedural complications	[redacted]
Metabolism and nutrition disorders	[redacted]
Gastrointestinal disorders	[redacted]
Renal and urinary disorders	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]
General disorders and administration site conditions	[redacted]
Investigations	[redacted]
Nervous system disorder	[redacted]
Any Treatment-emergent SAE	**88 (33.5%)**
Any study drug-related TEAE	**3 (1.1)**
Drug-related treatment-emergent SAEs	0

AE = adverse event; eCRF = electronic clinical report form; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; OLE = open-label extension study; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Notes:

A patient is counted only once within each preferred term or any primary SOC.

AEs are coded using MedDRA version 24.1

OLE (open-label extension) full analysis includes patients who were enrolled in the main study and received at least one dose of open-label acoramidis treatment. Data reflect TEAEs reported in the OLE from start of OLE (M12 of OLE / M42 since start of ATTRibute-CM).

AE is considered as open-label acoramidis TEAE if it is not present before the first dose of open-label acoramidis or if it is present but increases in severity during the open-label acoramidis treatment-emergent period. All AEs reported on the 'Adverse Events' or 'CV Hospitalisations and Events of Clinical Interest' eCRF are included in the analysis.

B.3.9.10 Comparative safety - acoramidis and tafamidis

Table 37 below summarises the adverse event reporting from both the acoramidis and tafamidis Phase 3 clinical trials and their OLE trials (by System organ classes [SOCs] where ≥30% of patients had an adverse event for any one treatment).

Comparing the phase 3 studies ATTRibute-CM and ATTR-ACT, generally the pattern of AE reporting across the SOCs is similar between acoramidis and tafamidis, if not a little higher in some SOCs for tafamidis. Differences in AE reporting between the trials are likely explained by acoramidis patients being more contemporary and recruited earlier in their disease process (discussed further in Section B.3.11). The current durations of the extension studies are vastly different meaning that no comparison or conclusions can be made.

Table 37. Comparative summary of treatment-emergent adverse event reporting for acoramidis in ATTRibute-CM (SAF) and AG10-304 (OLE FAS) trials and tafamidis in ATTR-ACT and ATTR-ACT LTE (20, 21, 48, 63, 88)

	Acoramidis		**Tafamidis**	
Trial	**ATTRibute-CM**	**OLE AG10-304 ongoing**	**ATTR-ACT**	**ATTR-ACT LTE Aug 2021 data cut**
System organ classes where ≥30% of patients had an adverse event for any one treatment:	**Acoramidis N=421**	**Continuous Acoramidis n = 263**	**Pooled Tafamidis N=264**	**Continuous tafamidis n=110**
Follow-up period	**30 months**	**12 months**	**30 months**	**~ 30 months**
Any TEAE	**413 (98.1%)**	**229 (87.1%)**	**260 (98.5%)**	**108 (98.2%)**
Cardiac disorders	230 (54.6%)	[redacted]	185 (70.1%)	79 (71.8%)
Gastrointestinal disorders	221 (52.5%)	[redacted]	135 (51.1%)	50 (45.5%)
General disorders and administration site conditions	144 (34.2%)	[redacted]	143 (54.2%)	54 (49.1%)
Infections and infestations	246 (58.4%)	[redacted]	165 (62.5%)	64 (58.2%)
Injury, poisoning and procedural complications	137 (32.5%)	[redacted]	107 (40.5%)	51 (51.8%)
Investigations	127 (30.2%)	[redacted]	104 (39.4%)	Not avail.
Metabolism and nutrition disorders	149 (35.4%)	[redacted]	119 (45.1%)	43 (39.1%)
Musculoskeletal and connective tissue disorders	184 (43.7%)	[redacted]	129 (48.9%)	49 (44.5%)
Nervous system disorder	182 (43.2%)	[redacted]	121 (45.8%)	51 (46.4%)
Renal and urinary disorders	142 (33.7%)	[redacted]	83 (31.4%)	35 (31.8%)
Respiratory, thoracic, and mediastinal disorders	146 (34.7%)	[redacted]	124 (47.0%)	55 (50.0%)
Skin and subcutaneous tissue disorders	108 (25.7%)	[redacted]	76 (28.8%)	42 (38.2%)

	Acoramidis		Tafamidis	
Trial	**ATTRibute-CM**	**OLE AG10-304 ongoing**	**ATTR-ACT**	**ATTR-ACT LTE Aug 2021 data cut**
Any Treatment-emergent SAE	**230 (54.6%)**	**88 (33.5%)**	**199 (75.4%)**	**Not reported**
Any study drug-related TEAE Drug-related treatment-emergent SAEs	**50 (11.9%)** 2 (0.5%)	**3 (1.1)** 0	**113 (42.8%)** 5 (1.9%)	**Not reported**

AE = adverse event; FAS = full analysis set; n = number of patients experiencing a TEAE (the patient was counted only once for each AE); N = number of patients in the study arm; OLE = open-label extension study; TEAE = treatment-emergent adverse event

In the phase 3 ATTR-ACT study, comparing tafamidis with placebo in ATTR-CM, the most commonly reported TEAEs (≥20% in either treatment group) *[Note tafamidis results only considered here]* were cardiac failure (tafamidis 28.8%), dyspnoea (tafamidis 18.9%), dizziness (15.9%), fall (26.5%), diarrhoea (tafamidis 12.1%) and nausea (tafamidis 11.0%).(96) This is similar to the safety profile of acoramidis in the ATTRibute-CM trial presented earlier in this section (see Table 34). Aside from the AEs consistent with the ATTR-CM and progression of disease and ageing population, diarrhoea is common to both treatments, and is a potential class effect and, correspondingly, is highlighted on both the acoramidis and tafamidis SmPC (see Appendix C for Acoramidis SmPC).(95)

The SmPC for tafamidis also lists rash and pruritius as common adverse reactions associated with tafamidis. In addition, the SmPC states that in patients receiving the 80 mg tafamidis formulation compared to placebo, flatulence (4.5% vs 1.7%) and liver function test increased (3.4% vs 1.1%) were reported more often in patients treated with tafamidis.(95)

For acoramidis, in ATTRibute-CM, the TEAE of gout was observed more frequently in patients compared with the placebo group (11.2% vs. 8.1%) and is listed on the acoramidis SmPC as a very common event (see Appendix C). In the ATTR-ACT trial, gout was reported in 10.6% of patients receiving tafamidis and in 16.4% of patients receiving placebo.

Supportive safety data from acoramidis phase 2 studies are presented in Appendix F, showing a consistent type and range of TEAEs and SAEs as those reported in ATTRibute-CM.

B.3.10 Conclusions about comparable health benefits and safety

Principal Findings from the Clinical Evidence Base on acoramidis

Evidence on the clinical benefit of acoramidis is derived from the phase 3 ATTRibute-CM trial and early results from its OLE study (AG10-304) (20, 48).

The primary endpoint was met (F-S test, p<0.0001) with a win ratio of 1.772 (96% CI: 1.402, 2.240) for the primary analysis, indicating that an acoramidis-treated patient had a 77.2% higher chance of deriving a treatment benefit than a placebo-treated patient. In addition, a pre-specified F-S analysis of ACM and frequency of CVH showed statistically significant treatment effect of acoramidis relative to placebo (nominal p=0.0182; win ratio: 1.464; 96% CI: 1.051, 2.040). There was a 14.6% ARR in Time to ACM or first CVH, HR=0.645; 95% CI: 0.500, 0.832; p=0.0008) and acoramidis treatment led to a 42% risk reduction in ACM and recurrent CVH events over 30 months compared with placebo (RRR: 0.58; 95% CI: 0.43-0.79; p=0.0005). In the OLE, early results (Month 42), confirm benefits of continuing acoramidis treatment for time to ACM or first CVH with a HR of 0.57 (0.46, 0.72) (p<0.0001)(Cox proportional model) and time to ACM or recurrent CVH (48% RRR; HR=0.52 [0.39, 0.68])

Acoramidis treatment was also associated with a clinically important point estimate of a 25% RRR in the key secondary endpoint of ACM (survival rate 81% vs 74% placebo) (p=0.1543); and a statistically significant (p<0.0001) and clinically meaningful 50% reduction in the annualised frequency of CVH. A separation in the survival curves for ACM between acoramidis and placebo was observed from 19 months. OLE results show that ACM risk continued to decrease with longer-term treatment of acoramidis (Month 42 RRR 33.7%) and was statistically significant at Month 42 compared with the cohort of patients who switched to acoramidis from placebo upon entry to the OLE (HR=0.64 95% CI [0.47, 0.88, P=0.006]). Analysis at Month 42 for first CVH alone also favoured continued acoramidis treatment (41% RRR; HR=0.53 95% CI [0.41, 0.69]; p<0.0001).

CV-related mortality - the most frequent cause of mortality events in ATTRibute-CM - was reported in 14.9% and 21.3% of patients in the acoramidis and placebo groups, respectively (6.4% ARR; 30% RRR)(59). Analysis of ATTRibute-CM results has also, for the first time in a clinical study, correlated the occurrence of CVH with increased risk of subsequent death in ATTR-CM (82). Patients experiencing a CVH during the study period had a significantly lower survival rate (~60%) than those patients who were not hospitalised for a CV-related event (~87%),(82) highlighting the importance of ATTR-CM treatments in reducing CVH.

Key secondary endpoints on measures of physical function and health status/QoL i.e. change from baseline in 6MWD and change from baseline in KCCQ-OS at Month 30, both statistically significantly favoured acoramidis relative to placebo (LS-mean difference: 39.6;

96% CI: 20.18, 59.10; p<0.0001; LS-mean difference: 9.94; 96% CI: 5.79, 14.10; p<0.0001, respectively), with effects continuing into the OLE.

Clinical efficacy results of acoramidis are further supported by favourable changes in prognostic cardiac biomarkers (NT-proBNP and TnI),(97) as well as in cardiac structure and function based on CMR imaging assessments.(98) Acoramidis attenuated the progressive increase in NT-proBNP, with the AGM change from baseline being 47% lower in patients receiving acoramidis (ratio of the AGM fold-change: 0.52; 95% CI: 0.463, 0.604; nominal p<0.0001). This effect continued into the OLE. Also, serum TTR was found to promptly and significantly increase with acoramidis compared with placebo (LS-mean difference: 7.10; 96% CI: [redacted]; p<0.001] and near-complete TTR stabilisation (≥ 90%) was achieved - effects which were sustained throughout the study.(5) Acoramidis-only treatment resulted in a 42% greater increase in the mean change from baseline in serum TTR levels than did the addition of tafamidis to placebo; and adding tafamidis to acoramidis had no incremental effect on TTR stabilisation. Upon initiation of open-label acoramidis in the placebo-to-acoramidis arm there was a prompt increase in serum TTR, including in the ATTRibute-CM placebo plus concomitant tafamidis patients.

Post-hoc analyses showed a correlation between TTR stabilisation and the clinical outcomes ACM, cardiovascular death and CVH.(70, 77, 78) For each 1 mg/dL increase in serum TTR at day 28, there was a 5.5% risk reduction in cardiovascular death observed through Month 30(70), and a 4.7% lower risk of a first CVH over 30 months.(78) For every 5mg/dL increase in serum TTR level at day 28 after treatment initiation, the risk of death through Month 30 was reduced by 30.9% (by the logistic model) and 26.1% (by the Cox proportional hazards model)(77), suggesting increasing serum TTR levels through stabilisation by acoramidis may be protective.

In other measures of morbidity, function, and QoL, separation between treatment arms was apparent earlier in the treatment period e.g., time to ACM or first CVH, NT-proBNP and KCCQ-OS were around 3 months.

Safety analyses also reveal acoramidis to be well tolerated, with a balanced frequency, type, and severity of TEAEs between the acoramidis and placebo study arms, and a lower frequency of serious TEAEs in acoramidis-treated patients. TEAEs were consistent with progression of cardiomyopathy and other comorbidities expected for this population.

These results demonstrate the effectiveness of acoramidis compared with placebo in adults with ATTR-CM and indicate that, in addition to improved CV outcomes and reduced mortality, acoramidis reduces disease progression as supported by improvements in functional capacity, QoL and measures of heart failure. The high degree of internal consistency of the beneficial effects of acoramidis observed in ATTRibute-CM across different endpoints and sensitivity analyses, with persistency of effect into the OLE, suggests broad applicability to UK clinical practice, and underscores the robustness of the efficacy results demonstrated with acoramidis.

Comparability to tafamidis

Tafamidis is the only approved treatment option for ATTR-CM in England.(16, 26) The pivotal phase 3 ATTR-ACT trial demonstrated a 30% and 32% RRR with tafamidis relative to placebo in ACM and CVH after 30 months, respectively, and a significant treatment effect favouring tafamidis in functional capacity (measured by 6MWD) and QoL (as measured by KCCQ-OS).(21) Preliminary survival rates after 5 years in patients taking continuous tafamidis treatment in the extension study, ATTR-ACT LTE are 53.2% versus 32.4% in the ATTR-ACT placebo patients who switched to receiving tafamidis.(19)

Compared with the clinical benefits of acoramidis presented above, it can be surmised that acoramidis and tafamidis exhibit similar positive treatment effects. Since direct clinical evidence for acoramidis vs. tafamidis is not available (tafamidis was not approved at the design stage of ATTRibute-CM), an anchored MAIC has been conducted to formally compare these two treatments.

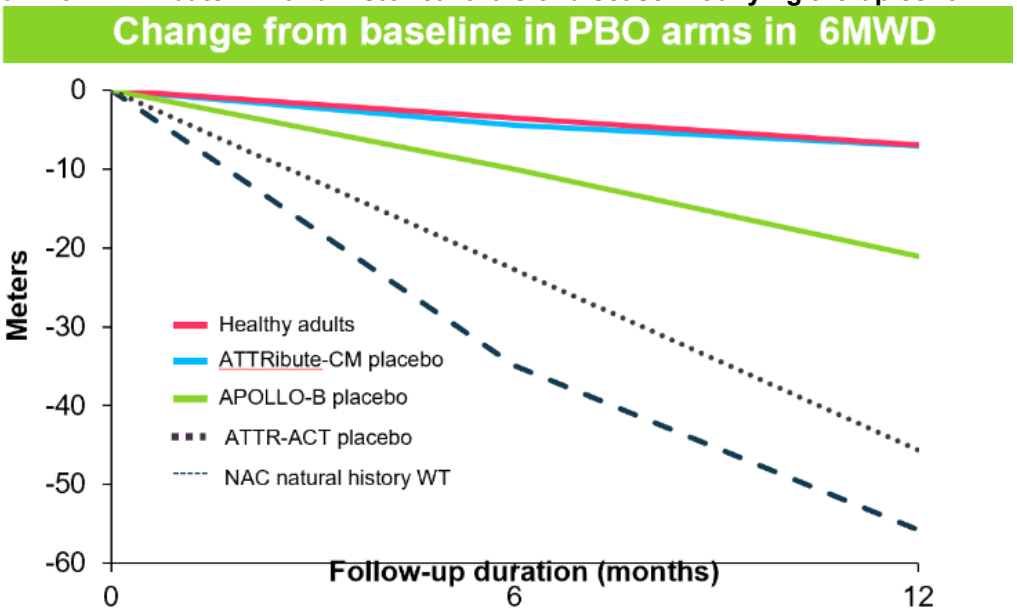
Prior to discussing MAIC outcomes, it is prudent to highlight a shift in the ATTR-CM patient population between the start of the tafamidis (ATTR-ACT) and acoramidis (ATTRibute-CM) clinical trials in ATTR-CM. During that time, the introduction of non-invasive diagnostic testing, increased disease awareness and improvements in disease management meant that the more recently diagnosed ATTR-CM patient (and hence, those enrolled into ATTRibute-CM [2019-2020]) is diagnosed earlier and lives longer even in the absence of targeted, disease-modifying therapy.(20, 25, 52) This shift is considered to reasonably explain different patterns of response in various outcomes between ATTR-ACT and ATTRibute-CM.

For example, the differences in mortality rates seen in ATTRibute-CM, when compared to experience with tafamidis in the ATTR-ACT study. The shift in patient populations between the two studies is demonstrated by the higher mortality rate observed with active treatment

(tafamidis) in the ATTR-ACT study than in the placebo arm in ATTRibute-CM (29.5% and 25.7%, respectively).(20, 21) Further context can be gained by examining estimated 30-month survival rates in an age-matched cohort of the general population, albeit from the US. Recent data from the US Social Security Administration estimates an 85% 30-month survival rate in an age-matched cohort, which compares well with survival of 80.7% shown in the acoramidis group in ATTRibute, whereas survival rates in patients treated with tafamidis in ATTR-ACT were 70.5% at 30 months.

The differences in 6MWD results between ATTR-ACT and ATTRibute-CM further illustrate the shift in ATTR-CM patient population. Considering ATTRibute-CM first. While significantly different between acoramidis and placebo by month 30, the change from baseline in 6MWD did not achieve statistical significance at 12 months (primary endpoint for Part A of ATTRibute-CM) as the curves between acoramidis and placebo-treated populations did not start to separate until 18 months (Figure 9). In ATTR-ACT however, differences in 6MWD between tafamidis and placebo were first observed at 6 months. Rather than any suggestion of superiority of tafamidis in improving functional capacity in patients with ATTR-CM, comparison of the 6MWD results in the placebo groups of trials for ATTR-CM disease-modifying therapies to 12 months (Figure 32), reveals the reason for the difference in response to treatments (at least initially) is more likely due to a shift in functional capacity, and disease status in the more contemporary patient.

Figure 32. Comparison of Changes from baseline of 6MWD to 12 months in placebo treatment arm of ATTRibute-CM and historical trials of disease-modifying therapies for ATTR-CM



6MWD = 6-minute walk distance; NAC = National Amyloidosis Centre; PBO = placebo; WT = wild-type.
Placebo arm comparisons (change from baseline in metres): Approximate decline at 12 months from baseline arms- Healthy adult (N=117):–5 m*; ATTRibute-CM placebo (n=211): mean change=-4.51m, Gillmore

2024 (54); APOLLO-B placebo (n=179) median change=–21.35m, Maurer 2023 (99); NAC natural history WT (n=289): change= –50 m†, Lane 2019 (12); ATTR-ACT placebo (n=177): change=–<60 m‡, Maurer 2018.(21) *Represents annual decline for a healthy elderly male, calculated using reference equations provided by Enright PL and Sherill DL (1998). †Actual 6MWD values not reported, but extrapolation from graph provided in source demonstrates that there was a less than 50 m decline at 1 year. ‡Actual 6MWD value not reported for 12 months, but extrapolation from graph provided in source demonstrates that there was a less than 60 m decline at 1 year for placebo.

Indirect treatment comparison

Results of the indirect treatment comparison indicated that acoramidis had a tendency for similar mortality and lower CV-related hospitalisation outcomes compared to tafamidis, with no statistically significant differences in mortality (with numerical improvements for all non-naïve comparisons), and numerical or statistically significant improvements in CV-related hospitalisation outcomes across all MAIC scenarios. Results of safety indirect treatment comparison analyses also suggested broadly similar safety profiles between treatments. Although some uncertainties and limitations were present with the MAIC, including differences in inclusion criteria and standards of care between the two trials, a variety of scenario analyses were also conducted to help address or mitigate some potential concerns associated with these limitations, which further supported broad similarity in key efficacy and safety outcomes.

In addition, efficacy results were also validated with two UK clinical experts, with both experts agreeing that survival outcomes and CV-related hospitalisations between tafamidis and acoramidis could be considered similar, with a lack of head-to-head data precluding definitive assertions of superiority for acoramidis over tafamidis despite most MAIC results indicating numerical or statistically significant improvements for acoramidis. Furthermore, both UK clinical experts also indicated that they expect no substantial differences between tafamidis and acoramidis in terms of AEs that would impact QoL, with both treatments generally expected to be safe and well tolerated.

Given the MAIC results and UK clinical expert feedback indicating comparable health benefits and safety profiles between treatments, with the same licensed indication and the similar mechanism of action for both treatments (TTR stabilisers), acoramidis was considered suitable for a cost-comparison analysis with tafamidis.

B.3.11 Ongoing studies

The OLE study (AG10-304) is an ongoing study for which further results will likely be released between the time of writing this submission and appraisal completion (dates unknown). This study has already been described in the clinical effectiveness section.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Acoramidis is not anticipated to require any changes to current service provision and management (Figure 1). Acoramidis is administered orally as two tablets twice daily and can be taken with water, with or without food. Tafamidis, the only active treatment comparator currently recommended by NICE, and understood to be the current standard of care for ATTR-CM in the UK based on clinical expert feedback,(94) is also administered orally as a capsule given once daily. Both treatments have the same mechanism of action (transthyretin stabilisers) and are used in conjunction with other therapies used for symptomatic management of ATTR-CM.

Although acoramidis is associated with an increased pill burden compared to tafamidis, this is not anticipated to have a substantial impact on efficacy and safety outcomes, as well as treatment compliance, which was supported by UK clinical experts.(94) Furthermore, UK clinical experts also indicated an expectation of no substantial treatment-related differences in healthcare resource use between acoramidis and tafamidis.(94)

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost-comparison analysis was conducted from an NHS and PSS perspective to evaluate the cost and resource use associated with acoramidis as a treatment for adult patients who have been clinically confirmed to have ATTR-CM in relation to tafamidis.

The time horizon was set to 25 years, which is considered as lifetime for the target population as the mean age of the patients in the mITT population in ATTRibute-CM trial was 77.2 years. Scenario analyses were also performed using 5- and 10-year time horizons.

The cost-comparison model was developed in Microsoft Excel®. The analysis considered relevant costs that were expected to differ between patients receiving acoramidis and tafamidis (both in combination with symptomatic management), namely drug acquisition and adverse event costs associated with treatment. Drug administration costs were excluded given all regimens included in the model are orally administered. Other costs, such as resource use for disease management, were generally expected to be equivalent among patients receiving acoramidis and tafamidis given the assumption of equivalence in efficacy. Feedback from clinical experts also indicated no expectation of treatment-specific

differences in resource use between acoramidis and tafamidis, and therefore these costs are not included in the analysis.(94)

Patients enter the model in either the acoramidis + symptomatic management (SM) or tafamidis + SM treatment arm and accrue associated drug acquisition and adverse event costs over time according to the proportion of patients remaining alive and on treatment. ACM data is used to determine the proportion of patients remaining alive over time, with TTD data used in combination with ACM to estimate a time to discontinuation or death (TTDD) curve. This TTDD curve is used to directly calculate the proportion of patients alive and on treatment over time. The proportion of patients alive and off treatment is then derived using the difference between the ACM and TTDD curves, with patients off treatment and alive assumed to incur treatment and AEs costs associated with SM treatment alone.

The model uses a monthly cycle length and includes half cycle correction, with cost outcomes discounted at 3.5% per year in line with the NICE reference case. A 1.5% discount rate was also explored in scenario analysis.

In line with the ATTRibute-CM trial mITT population, a baseline age of 77.2 years and proportion male of 90.8% were applied in the model to inform general population mortality estimates used to help prevent implausible ACM extrapolations.

B.4.2.2 Clinical effectiveness parameters used in the model

Clinical effectiveness parameters for the cost-comparison model were informed by the ATTRibute-CM trial OLE data, using the acoramidis mITT population (N=611). As described in section B.3.4, during discussions with regulatory authorities, an additional group of patients with severe renal impairment (eGFR between 15 and 30 mL/1.73m^2) were included in the ATTRibute-CM study to provide preliminary information on the safety and tolerability of acoramidis with this patient population, who are not typically enrolled in heart failure or ATTR-CM trials. As there was no intention to analyse efficacy outcomes in these patients, these patients were excluded from the primary efficacy analysis which was performed using the mITT population.

However, the acoramidis ITT population (N=632) was used for the MAIC to allow for better matching with the ATTR-ACT trial population, which also included patients with eGFR between 25 and 30 mL/1.73m^2. Although eGFR was identified as a potential treatment effect modifier, the results of the MAIC were assumed to be generalisable to the mITT population. This assumption was based on the similarity in comparative ACM and CVH outcomes between acoramidis and placebo observed in the ATTRibute-CM study for both populations

(see Table 11). The following clinical outcomes from the ATTRibute-CM OLE trial were used in the model:

- ACM
- TTD

The same ACM extrapolations based on the ATTRibute-CM trial OLE were used for both acoramidis and tafamidis in the cost-comparison model in line with the general assumption of equivalence in efficacy supported by MAIC analyses described in Section B.3.8, which indicated at least similar health benefits for acoramidis to tafamidis on ACM, and feedback from two UK clinical experts who both indicated an expectation of similar efficacy between the two treatments.(94)

Although median time on treatment data were available from the ATTR-ACT trial, TTD was also assumed to be equal for both treatments in the model base case given the differences in trial design between ATTRibute-CM and ATTR-ACT, and feedback from UK clinical experts that time on treatment would be anticipated to be similar between both treatments.(94) However, a TTD HR parameter was included for tafamidis versus acoramidis to allow exploration of differences in TTD, with exploratory scenario analyses conducted assuming 10% reductions and increases in the risk of discontinuation for tafamidis compared to acoramidis (i.e. HR values of 0.9 and 1.1, respectively).

Given the lifetime model time horizon, parametric survival analysis was undertaken to extrapolate ACM and TTD beyond the available follow-up for acoramidis from the OLE of the ATTRibute-CM trial. Following methods guidance from NICE DSU Technical Support Documents 14 (TSDs) (100) the rest of this section describes the methodology of parametric survival analyses performed on the ATTRibute-CM OLE data to extrapolate ACM and TTD over a lifetime horizon.

Parametric survival analysis assumes that times to an event follow a parametric distribution, with the following distributions considered in line with NICE DSU TSD14(100): exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma distribution. The properties of these distributions and approach to fitting them have been described by Ishak et al. (2013)(101) and can be found in standard textbooks on survival analysis (e.g., Collett 2003).(102)

To assess statistical fit of the different distributions, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used, with the lowest AIC and BIC indicating the best fitting distribution. In addition, statistical fit was categorised using modified

Burnham/Anderson (for AIC) and Kass/Raftery (for BIC) rules of thumb to check the appropriateness of the remaining distributions relative to the best fitting one.(103-107) While earlier Burnham/Anderson(103, 104) publications suggest use of a <2 difference rule for AIC differences, it is worth noting that Burnham/Anderson/Huyvaert 2011(105) found this to be arbitrary and implied that fits within 2-7 AIC points of the best one should still be considered. In addition, as the original Burnham/Anderson rules of thumb are not "complete" (with no explicit interpretations recommended for differences of 2-4 points or 7-10 points), slightly modified terminology were adopted for classification of statistical fit.

For BIC, while Kass/Raftery publications(106, 107) provide a more complete set of rules of thumb, the recommended interpretations of BIC differences are expressed in terms of evidence "against" the distribution instead of "for" the distribution (e.g., with differences of <2 BIC points noted as having weak evidence against the distribution). To provide a more consistent assessment framework with the rules of thumb applied for AIC, alternative terminology was adopted to categorise BIC differences in terms of evidence "for" the distributions based on reversing the interpretations provided by Kass/Raftery, with a 7-point cutoff also adopted in line with the adopted rules of thumb for AIC. The modified rules of thumb for assessing statistical goodness-of-fit are summarised in Table 38 below.

Table 38. AIC and BIC rules of thumb for statistical goodness-of-fit

Rule of thumb category	Difference from fit with lowest AIC	Difference from fit with lowest BIC
Reasonable	0-7 points	0-7 points
Inferior	7-10 points	7-10 points
Poor	>10 points	>10 points

AIC = Akaike information criterion; BIC = Bayesian information criterion

Following assessment of statistical fit, the fitted curves were visually inspected in relation to the observed KM data. Particular attention was given to visual fit at the tail, where larger differences are expected, but where sudden drops or long plateaus in the KM curves may be present and associated with low numbers of patients at risk and therefore may be interpreted with caution.

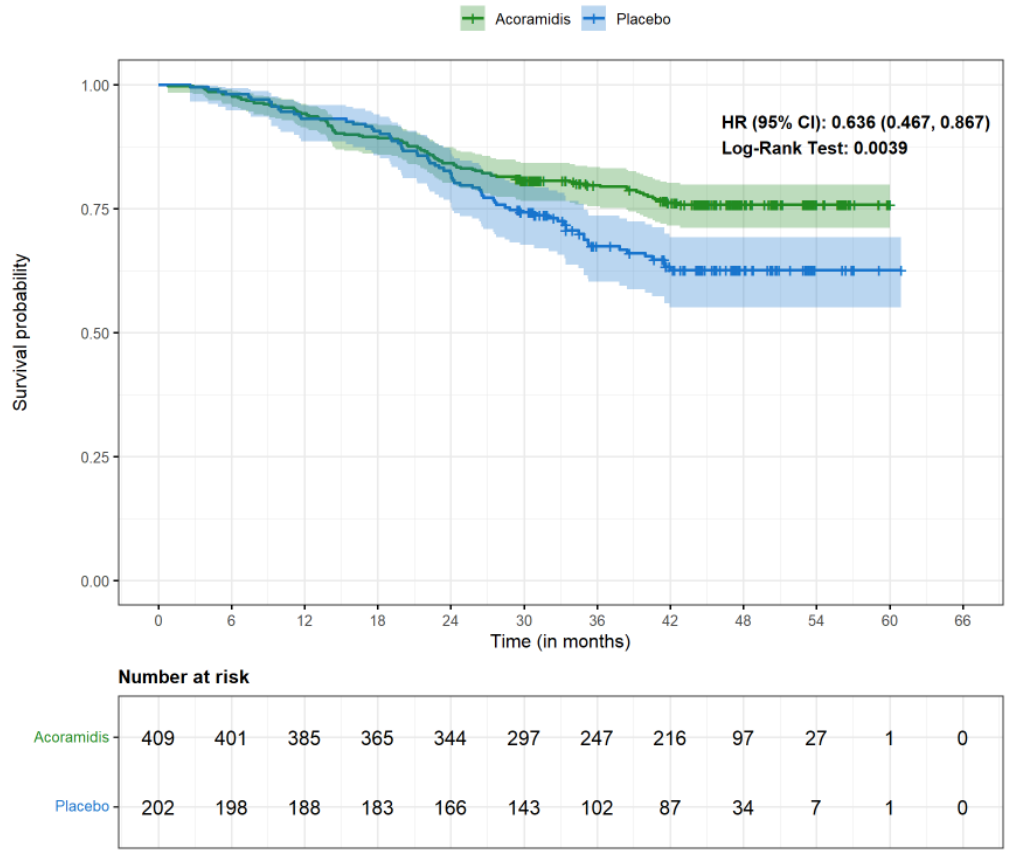
Smoothed hazard plots for the observed data were also compared to the hazard profiles produced for each of the distributions to determine which ones may provide more appropriate hazard profiles implied by the observed data.

Projections made with fitted distributions must also have face validity beyond the observed period. As such, long-term projections beyond the observed data were validated with UK clinical experts to help ensure plausibility of the selected extrapolations for the analysis.

B.4.2.2.1 ACM

The KM plot for acoramidis ACM is shown in Figure 33 based on the ATTRibute-CM OLE data for the mITT population. As noted in Section B.4.2.2, the same ACM curve was used for tafamidis in the model in line with the equal efficacy assumption for a cost-comparison analysis.

Figure 33. KM plot for ACM (mITT population)



ACM = all-cause mortality; CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; mITT = modified intent-to-treat

Statistical fit estimates for standard parametric extrapolations are summarised below in Table 39 with statistical fit classifications based on modified Burnham/Anderson and Kass/Raftery criteria for AIC and BIC, respectively, summarised in Table 40.

The log-normal distribution produced the best statistical fit with the lowest AIC and BIC. The exponential, log-logistic and generalised gamma distribution produced reasonable (0–7-point difference) relative fits to the log-normal distribution for both AIC and BIC, with all other distributions producing inferior statistical fits (7-10-point difference).

Table 39. AIC and BIC estimates for ACM standard parametric extrapolations

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

ACM = all-cause mortality; AIC = Akaike information criterion; BIC = Bayesian information criterion

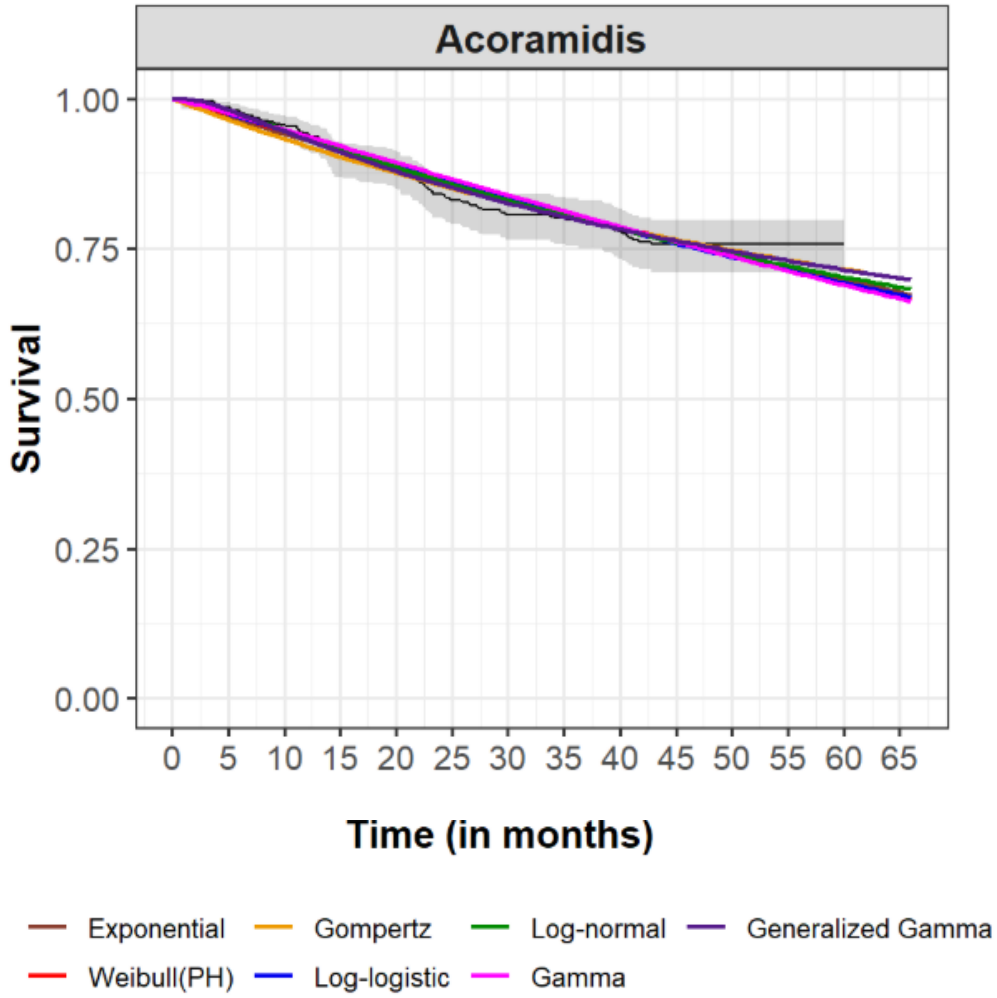
Table 40. AIC and BIC goodness-of-fit for each ACM distribution relative to the distribution with the lowest AIC and BIC

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Weibull	[redacted]	Inferior (7-10 difference)	[redacted]	Inferior (7-10 difference)
Gompertz	[redacted]	Inferior (7-10 difference)	[redacted]	Inferior (7-10 difference)
Log-logistic	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Log-normal	[redacted]	**Reference**	[redacted]	**Reference**
Gamma	[redacted]	Inferior (7-10 difference)	[redacted]	Inferior (7-10 difference)
Generalised Gamma	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)

ACM = all-cause mortality; AIC = Akaike information criterion; BIC = Bayesian information criterion

Figure 34 shows the fitted parametric survival curves overlaid on the KM curve for the observed trial period to help assess the visual fit. All distributions produced relatively similar visual fits to the observed data up to the tail of the KM curve, with the Gompertz distribution slightly underpredicting the KM curve between approximately 5-15 months and the gamma distribution overpredicting the KM curve slightly more than other distributions between approximately 20-35 months. The Gompertz and generalised gamma distributions appeared to produce the closest fit to the end of the KM curve with the log-normal distribution the next closest fit, although all parametric models generally underpredicted the long-flat tail of the KM curve. However, it is important to note that the observed differences in visual fit at the tail may not be particularly meaningful with the relatively flat extended tail of the KM curve produced as a result of a lack of events occurring within a fairly low number of patients at risk.

Figure 34. ACM standard parametric fits vs KM curve during observed trial period (mITT population)



ACM = all-cause mortality; KM = Kaplan-Meier; mITT = modified intent-to-treat

Smoothed hazard plots for the observed data are shown in Figure 35, which implied an increasing then decreasing hazard profile for acoramidis.

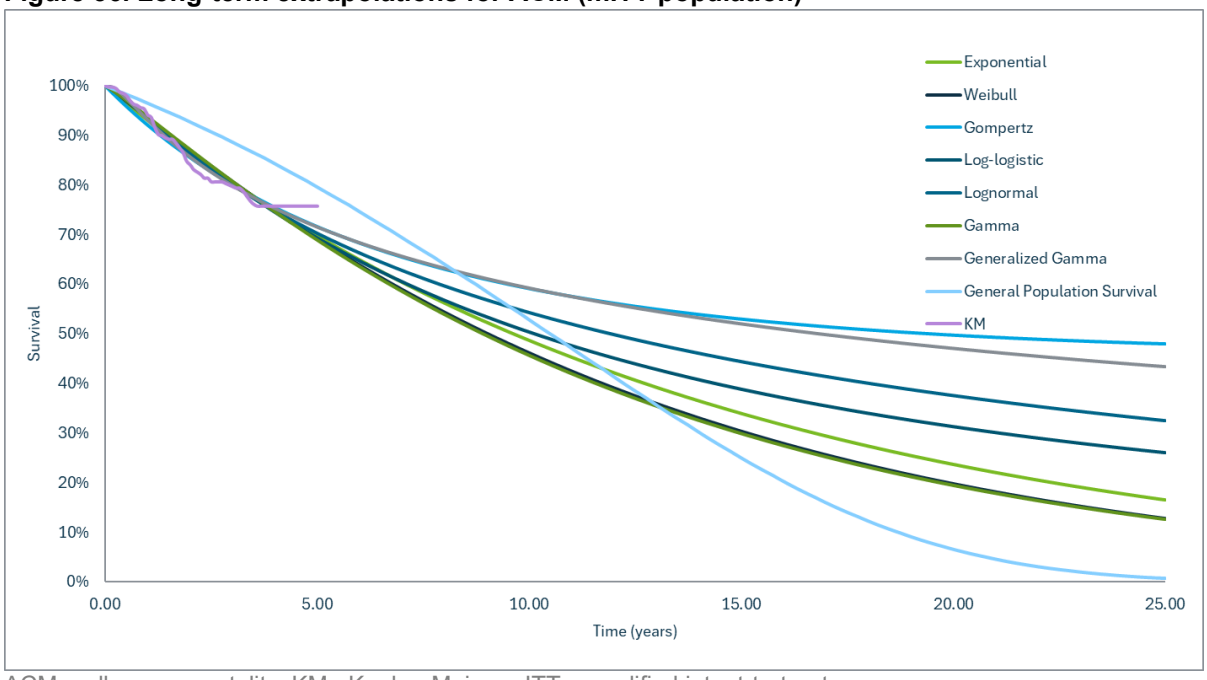
The log-normal, log-logistic and generalised gamma distributions produced the most similar types of broad hazard profile (increasing then decreasing) to that seen for the observed data. The exponential model (by definition) produced a constant hazard profile over time, while the Weibull and gamma distributions also produced relatively flat hazard profiles (albeit with a slight increase in hazards at the beginning), while the Gompertz distribution produced a continuously decreasing hazard profile, implying that these models may be less appropriate fits to the hazard profile suggested by the KM curve.

Figure 35. KM smoothed hazard function for ACM (mITT population)

ACM = all-cause mortality; mITT = modified intent-to-treat

Long-term extrapolations of the different standard parametric fits are shown in Figure 36, while milestone estimates are summarised in Table 41. All survival predictions are close at 5 years ranging from 68.9% (gamma) to 71.6% (Gompertz). Predictions at 10 years range from 30% (gamma) to 52.9% (Gompertz) while long-term extrapolations range from the most pessimistic gamma distribution with 12.7% to the most optimistic Gompertz distribution with 47.9%.

Figure 36. Long-term extrapolations for ACM (mITT population)



ACM = all-cause mortality; KM= Kaplan-Meier; mITT = modified intent-to-treat

Table 41. Milestone survival estimates (mITT population)

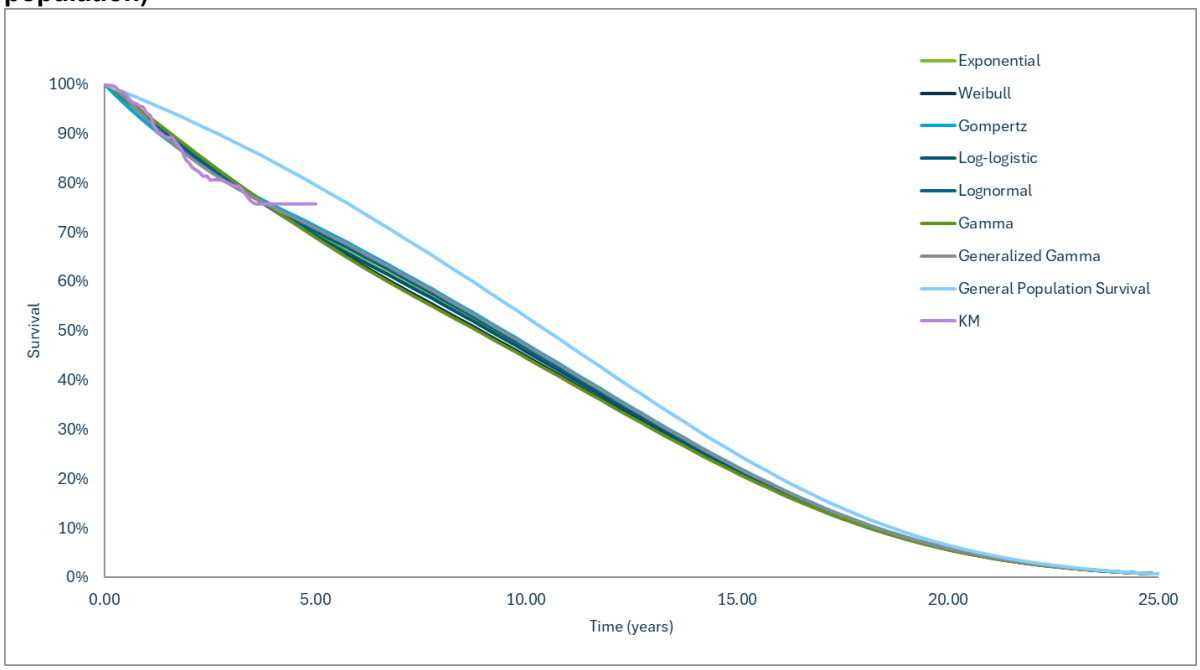
Distribution	5 years	10 years	15 years	20 years	25 years
Exponential	69.8%	48.7%	34.0%	23.7%	16.5%
Weibull	69.2%	46.2%	30.4%	19.8%	12.8%
Gompertz	71.6%	59.1%	52.9%	49.7%	47.9%
Log-logistic	69.3%	50.3%	38.8%	31.3%	26.0%
Log-normal	70.3%	54.3%	44.4%	37.6%	32.5%
Gamma	68.9%	45.7%	30.0%	19.5%	12.7%
Generalised Gamma	71.5%	59.2%	51.9%	47.0%	43.3%

mITT = modified intent-to-treat

However, as shown in Figure 36, all long-term survival extrapolations become higher than general population survival (based on the Office for National Statistics [ONS] national life tables for 2021-2023(108)) fairly shortly after the end of the observed data, given the fairly high baseline mean age of 77.2 years for the mITT population in the ATTRibute-CM trial. In the model, survival extrapolations are capped by general population mortality to prevent implausible long-term extrapolations where monthly survival probabilities from the parametric model exceed those from the general population, which produces a much narrower range of long-term extrapolation as shown in Figure 37 and Table 42. Clinical expert opinion supported that patients on disease-modifying treatment (acoramidis and tafamidis) would be expected to experience close to general population mortality longer-term.(94) However, one of the two clinical experts interviewed indicated that approaching general population mortality risk within 3-4 years may be too optimistic, suggesting that the Gompertz and

generalised gamma models, which both produce monthly survival probabilities lower than general population at around 4 years, may slightly overestimate ACM for patients on disease-modifying treatment.(94)

Figure 37. Long-term extrapolations for ACM capped by general population survival (mITT population)



ACM = all-cause mortality; KM = Kaplan-Meier; mITT = modified intent-to-treat

Table 42. Milestone survival estimates capped with general population mortality (mITT population)

Distribution	5 years	10 years	15 years	20 years	25 years	General population mortality capping time point (months)
Exponential	69.8%	45.9%	21.8%	5.7%	0.7%	82
Weibull	69.2%	44.8%	21.2%	5.6%	0.6%	94
Gompertz	71.2%	47.3%	22.4%	5.9%	0.7%	49
Log-logistic	69.3%	45.8%	21.7%	5.7%	0.7%	70
Log-normal	70.2%	46.6%	22.1%	5.8%	0.7%	58
Gamma	68.9%	44.5%	21.1%	5.6%	0.6%	94
Generalised Gamma	70.8%	47.0%	22.3%	5.9%	0.7%	48

mITT = modified intent-to-treat

Based on all these considerations, the log-normal distribution was selected as a model base case for ACM given it generated the best statistical fit with reasonable visual fit and a similar hazard function to that implied by the observed data (increasing then decreasing), while producing long-term estimates where patients reach general population mortality closer to 5 years (with clinical experts indicating 3-4 years may be too optimistic). Log-logistic and

generalised gamma distributions were also explored as more pessimistic and optimistic scenario analyses, respectively, with both models providing reasonable statistical and visual fits to the data, while also producing an increasing then decreasing hazard profile in line with the profile implied by the smoothed hazard plot for the KM curve.

B.4.2.2.2 TTD

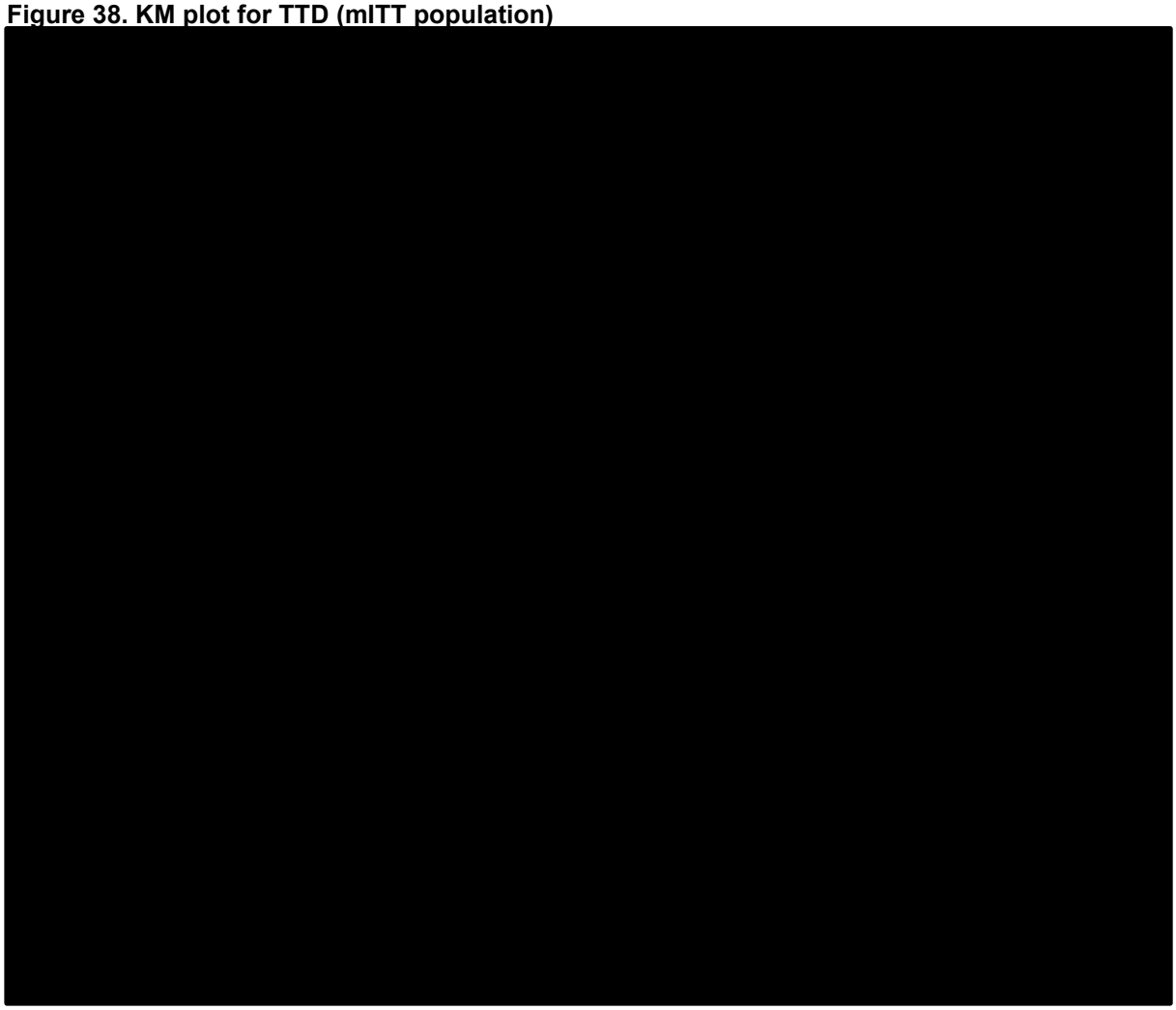
The KM plot for acoramidis TTD is shown in Figure 38 based on the ATTRibute-CM OLE data for the mITT population.

Although median time on treatment data is available from the ATTR-ACT trial, use of this to generate a TTDD curve was expected to substantially underestimate TTDD compared to acoramidis given differences in patient population compared to the ATTRibute-CM trial. Both UK clinical experts interviewed supported this assumption, with one of the experts highlighting that different patient composition in the ATTR-ACT trial, with more patients in an advanced disease stage, is likely to result in earlier and higher discontinuation rates compared to the acoramidis trial or compared to current UK clinical practice.(94)

Furthermore, although acoramidis is associated with an increased pill burden compared to tafamidis (four tablets daily compared to one), the first UK clinical expert interviewed stated that they did not anticipate this to affect compliance given that these patients are used to taking several pills per day. While the second UK expert interviewed suggested pill burden could be a differentiating factor, they also indicated that this may be balanced out by slight efficacy improvements of acoramidis.

Therefore, the same TTD curve was used for tafamidis as for acoramidis in the model to generate a TTDD curve in combination with the selected ACM curve, using data from the ATTRibute-CM trial.

Figure 38. KM plot for TTD (mITT population)



KM= Kaplan-Meier; mITT = modified intent-to-treat; TTD = time to treatment discontinuation

Statistical fit estimates for TTD standard parametric extrapolations are summarised in Table 43 with statistical fit classifications based on modified Burnham/Anderson and Kass/Raftery criteria for AIC and BIC, respectively, summarised in Table 44.

The Gompertz distribution produced the best statistical fit with the lowest AIC and BIC, with the log-normal, log-logistic, Weibull and gamma distributions all producing reasonable (0–7-point difference) relative fits for both AIC and BIC. The generalised gamma distribution produced a reasonable (0–7-point difference) relative fit for AIC but an inferior (7-10-pont difference) relative fit for BIC. Finally, the exponential distribution produced poor fits (>10-point difference) for both fit statistics.

Table 43. AIC and BIC estimates for TTD standard parametric extrapolations

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]

AIC = Akaike information criterion; BIC = Bayesian information criterion

Table 44. AIC and BIC goodness-of-fit for each TTD distribution relative to the distribution with the lowest AIC and BIC

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	[redacted]	Poor (>10 difference)	[redacted]	Poor (>10 difference)
Weibull	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Gompertz	**Lowest AIC**	**Reference**	**Lowest BIC**	**Reference**
Log-logistic	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Log-normal	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Gamma	[redacted]	Reasonable (0-7 difference)	[redacted]	Reasonable (0-7 difference)
Generalised Gamma	[redacted]	Reasonable (0-7 difference)	[redacted]	Inferior (7-10 difference)

AIC = Akaike information criterion; BIC = Bayesian information criterion

Figure 39 shows the fitted TTD parametric survival curves overlaid on the KM curve for the observed trial period. All distributions produced relatively similar visual fits to the observed data up to the tail of the KM curve, with the exception of the exponential model which appeared to overpredict the KM curve for most of the observed follow-up. The Gompertz distribution appeared to produce the closest fit to the end of the KM curve with the log-normal and generalised gamma distribution close behind. All other distributions slightly underpredict the tail; however, similar to ACM, the flat extended tail of the KM curve suggests that the observed differences in visual fit at the tail may not be meaningful due to a lack of events in a relatively low number of patients at risk.

Figure 39. TTD standard parametric fits vs KM curve during observed trial period (mITT population)

A smoothed hazard plot for the observed acoramidis TTD data is shown in Figure 40, which suggested a generally decreasing hazard profile. With the exception of the exponential distribution, all distributions provided a continuously decreasing hazard profile, suggesting that most provided a broadly reasonable hazard profile in relation to the observed data.

Figure 40. Smoothed and fitted hazard functions for TTD (mITT population)

Long-term extrapolations of the different TTD standard parametric fits are shown in Figure 41, while milestone estimates are summarised in

Table 45. The Gompertz distribution, which resulted in the best statistical fit, predicts a long-term plateau in treatment discontinuation at [redacted]% as a result of the estimated shape parameter being negative. All other distributions predict a substantially lower share of patients on treatment, with the most pessimistic (exponential) with [redacted]% and the next most optimistic (log-normal) with [redacted]% at 25 years, respectively.

Figure 41. Long-term extrapolations for TTD (mITT population)

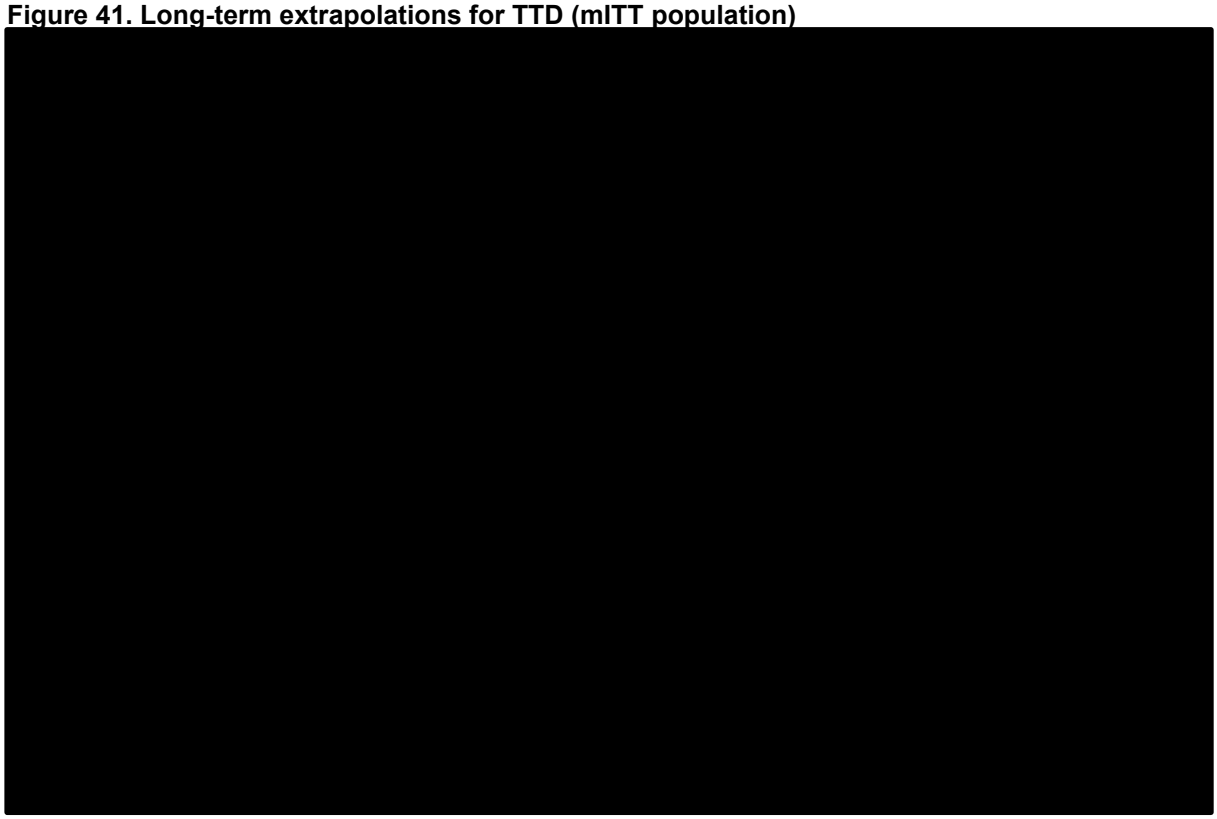


Table 45. Milestone TTD estimates (mITT population)

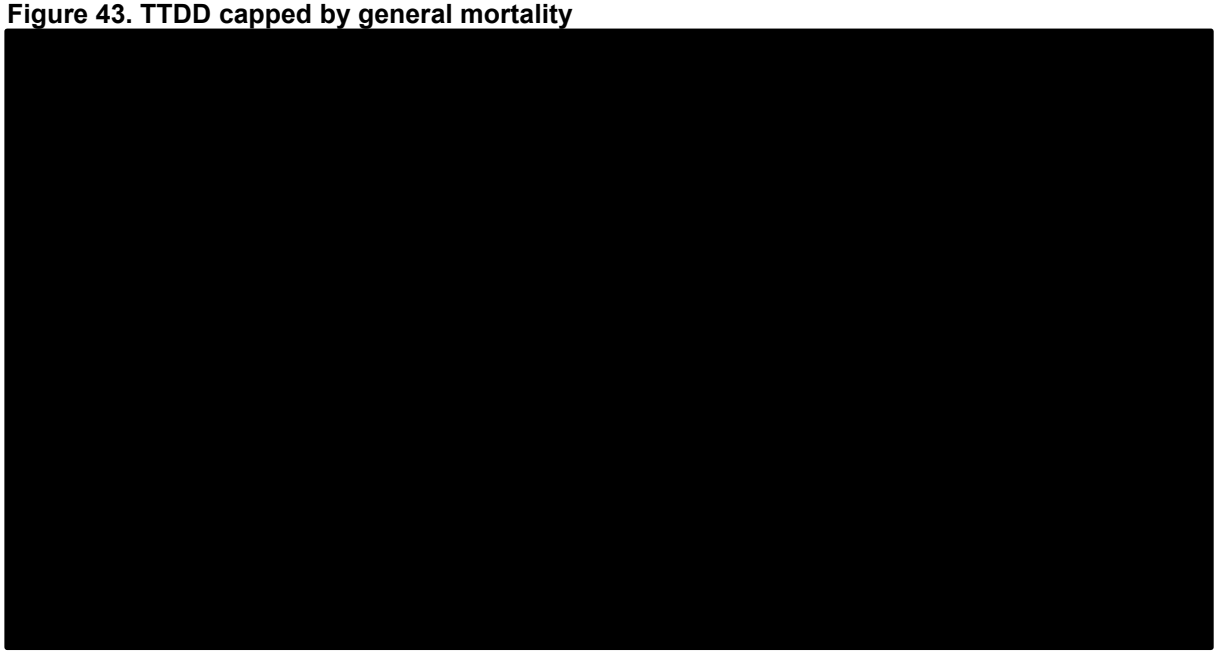
Distribution	5 years	10 years	15 years	20 years	25 years
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 42 and

Figure 43 show the TTDD curves produced by combining the base case ACM parametric curve (log-normal) with each of the different TTD parametric models, without and with general population mortality capping, respectively. General mortality capping results in more similar long-term extrapolations for all analysed distributions.

Figure 42. Time to treatment discontinuation or death (TTDD)

Figure 43. TTDD capped by general mortality



TTDD = Time to treatment discontinuation or death

Feedback from UK clinical experts suggested that clinicians would try to keep patients on treatment as long as possible until death, and so indicated a general expectation that the TTDD curve would fairly closely follow ACM.(94) However, given that the Gompertz model, which produced the best statistical fit and most optimistic TTD curve, resulted in what appeared to be an implausible plateau as a result of a negative shape parameter, the log-normal model, which produced the next best statistical fit and next most optimistic TTD extrapolation, was applied in the base case analysis, with Gompertz explored in a scenario analysis.

B.4.2.3 Intervention and comparators' acquisition costs

The list price for acoramidis is £8,547.60 per pack of 120 x 356 mg tablets. Based on the label dosing frequency of four tablets a day, the total drug acquisition cost for the intervention is estimated at £8,672 per month. For the submitted prospective patient access scheme (PAS) discounted price of [redacted] per pack, the estimated acquisition cost for acoramidis treatment is [redacted] per month.

The list price for tafamidis is £10,685.00 per pack of 30 x 61 mg capsules.(109) Based on the label dosing frequency of one capsule daily, the drug acquisition cost for tafamidis is estimated at £10,841 per month. Details are shown in Table 46.

Table 46. Acquisition costs of the intervention and comparator technologies

	Acoramidis	Tafamidis
Pharmaceutical formulation	Tablets (356 mg/ tablet)	Capsules (61 mg/capsule)
(Anticipated) care setting	Specialist centre	Specialist centre
Acquisition cost (excluding VAT) *	List price, per pack (120 tablets): £8,547.60 Proposed PAS price, per pack (120 tablets): [redacted]	List price, per pack (30 capsules): £10,685.00
Method of administration	Oral	Oral
Dose	356 mg	61 mg
Dosing frequency	2 tablets twice daily	1 capsule per day
Dose adjustments	N/A	N/A
Cost of treatment (per month)	List price based: £8,672 PAS price based: [redacted]	List price based: £10,841

N/A = not applicable; PAS = patient access scheme
Note: Each 356 mg tablet contains acoramidis equivalent to 400 mg acoramidis hydrochloride. Each 61 mg capsule contains tafamidis equivalent to 80 mg tafamidis meglumine.

Both acoramidis and tafamidis are given in addition to therapies used for SM. Details on the SM regimen and associated costs are presented in Section B.4.2.3.1.

Although wastage costs were considered in NICE TA696 and NICE TA984, wastage costs were not considered in the cost-comparison model as:

- The cost-comparison model will focus on comparing acoramidis with tafamidis, each in combination with SM, which are both orally administered treatments with pack sizes that provide doses for the same duration (30 days)
- UK clinical expert feedback indicated an expectation of similar time on treatment for both acoramidis and tafamidis, with minimal wastage and no differences in wastage costs expected for acoramidis and tafamidis (see Section B.4.2.7)

- Wastage applied in the tafamidis appraisals was based on assuming on average half a pack of wastage over the whole patient lifetime
- Bayer intend to offer acoramidis at a similar or lower cost to tafamidis

Bayer therefore do not anticipate substantial differences in wastage costs between treatment arms. Furthermore, RDI parameters are not included in the cost-comparison model based on number of capsules taken, which the Evidence Review Group in NICE TA696 stated as a key rationale for including wastage for tafamidis.

B.4.2.3.1 Symptomatic management acquisition costs

SM costs applied in the model consisted of a weighted average of multiple treatment groups comprising routinely administered treatments. Based on comments from UK clinical experts (see Section B.4.2.7), the distribution of SM therapies was based on the ATTRibute-CM trial, clinical expert feedback and a UK publication on conventional heart failure therapy in ATTR-CM (Table 47 and Table 48).(110, 111)

Table 47. Distribution of treatments in SM

Treatment	Proportion of patients	Source
Loop diuretics	76.8%	Ioannou et al 2023(111)
Antithrombotic agents	[redacted]%	ATTRibute-CM CSR PART B data, Table 14.1.8.3 (concomitant drug use)(54)
Beta blockers	55.4%	Ioannou et al 2023
Lipid modifying agents	[redacted]%	ATTRibute-CM CSR PART B data, Table 14.1.8.3 (concomitant drug use)(54)
ACEi/ARBs	57.4%	Ioannou et al 2023(111)
MRAs	39.0%	Ioannou et al 2023(111)
Calcium channel blockers	5.0%	Clinical expert feedback(110)
SGLT2i	80.0%	Clinical expert feedback(110)

ACEi = Angiotensin-converting-enzyme inhibitor; ARB = Angiotensin receptor blocker; MRA = Mineralocorticoid receptor antagonist; SGLT2i = Sodium-glucose cotransporter 2 (SGLT-2) inhibitor; SM= symptomatic management

SM acquisition costs (Table 48) are applied in addition to active treatment costs for patients on treatment, while patients who are off treatment and alive only incur SM related costs. With the exception of SGLT2 inhibitors, selection of representative treatments, as well as dosing, for each SM treatment group to estimate drug acquisition costs for SM was also based on external UK clinical expert feedback (110) and published real patient treatment data from the National Amyloidosis Centre.(111) While two SGLT2 inhibitors (dapagliflozin and empagliflozin) are currently recommended by NICE for heart failure, both treatments

have the same recommended dose (10 mg daily) with the same current list price on the BNF (£36.59 per 28 x 10 mg pack), and were broadly expected to have similar drug acquisition costs.(112, 113) Therefore, empagliflozin was used to represent costs for this component of SM. Weighting SM treatment acquisition costs (Table 48) and their usage (Table 47) resulted in a per cycle cost of £35.83.

Table 48. Acquisition costs of the SM technologies

	Loop diuretics (furosemide)	Antithrombotic agents (apixaban)	Beta blockers (bisoprolol)	Lipid modifying agents (atorvastatin)	ACEi/ARBs (ramipril)	MRAs (spironolactone)	Calcium Channel Blockers (amlodipine)	SGLT2i (empagliflozin)
Pharmaceutical formulation	Tablets (40 mg/ tablet)	Tablets (2.5 mg/ tablet)	Tablets (2.5 mg/ tablet)	Tablets (10 mg/ tablet)	Tablets (2.5 mg/ tablet)	Tablets (25 mg/ tablet)	Tablets (5 mg/ tablet)	Tablets (10 mg/ tablet)
(Anticipated) care setting	Primary care	Primary care	Primary care	Primary care	Primary care	Primary care	Primary care	Primary care
Acquisition cost (excluding VAT)	List price, per pack (28 tablets): £0.24(114)	List price, per pack (60 tablets): £2.97(115)	List price, per pack (28 tablets): £0.23(114)	List price, per pack (28 tablets): £0.32(114)	List price, per pack (28 tablets): £0.38(114)	List price, per pack (28 tablets): £0.97(114)	List price, per pack (28 tablets): £0.20(114)	List price, per pack (28 tablets): £36.59(112)
Method of administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Doses	40 mg/dose	2.5 mg/dose	2.5 mg/dose	10 mg/dose	2.5 mg/dose	25 mg/dose	5 mg/dose	10 mg/dose
Dosing frequency	1 dose per day	2 dose per day	1 dose per day	1 dose per day	1 dose per day	1 dose per day	1 dose per day	1 dose per day
Dose adjustments	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cost per monthly cycle	£0.27	£3.01	£0.25	£0.35	£0.41	£1.06	£0.21	£39.78

ACEi = Angiotensin-converting-enzyme inhibitor; ARB = Angiotensin receptor blocker; MRA = Mineralocorticoid receptor antagonist; N/A, not applicable; SGLT2i = Sodium-glucose cotransporter 2 (SGLT-2) inhibitor

B.4.2.4 Intervention and comparators' healthcare resource use and associated costs

As acoramidis and tafamidis are both orally administered medications, no administration costs are assumed for each treatment. Based on UK clinical expert feedback that no treatment-related differences were anticipated in terms of medical resource use, other healthcare resource use costs (such as those associated with monitoring and disease management) were also excluded from the analysis.(94)

B.4.2.5 Adverse reaction unit costs and resource use

Selection of AEs was based on NICE TA984 for tafamidis,(26) where the model included the following most common TEAEs: diarrhoea, nausea, urinary tract infection. The list of TEAEs included in the analysis was also validated with clinical experts, who highlighted the negligible impact anticipated from TEAEs given how safe the treatments were observed to be.(116) Other TEAEs were considered to be related to the age and condition of the target population, and hence were excluded from the analysis.

Data for TEAEs for acoramidis and SM was obtained from the ATTRibute-CM trial while the incidence for tafamidis arm was derived from ATTR-ACT trial data. AE related costs associated with SM were applied to all patients post-discontinuation of the index treatment, i.e., post acoramidis or tafamidis discontinuation. AE frequencies per cycle were estimated based on the incidence data reported for the trial follow-up period for all treatments (Table 49).

The cost of managing AEs considered in the model are presented in Table 50 and the resulting per cycle costs of AEs management are presented in Table 51. Exclusion of AE costs was explored in scenario analysis.

Table 49. Adverse event frequencies

Adverse event	Acoramidis + SM	Tafamidis + SM	SM
Observed frequency			
Diarrhoea	12%	12%	8%
Nausea	12%	9%	13%
Urinary tract infection	6%	11%	5%
Follow-up (months)	30	30	30
Estimated Monthly frequency			
Diarrhoea	0.39%	0.40%	0.25%
Nausea	0.19%	0.37%	0.17%

Adverse event	Acoramidis + SM	Tafamidis + SM	SM
Urinary tract infection	0.40%	0.32%	0.44%
Source reference for AE frequencies	Data on file, ATTRibute-CM CSR output, Table 14.3.1.11 Treatment-Emergent Serious Adverse Events by Preferred Term.	Maurer et al 2018(21)	Data on file, ATTRibute-CM CSR output, Table 14.3.1.11 Treatment-Emergent Serious Adverse Events by Preferred Term; These are applied for all treatment arms after treatment discontinuation.

AEs = Adverse Events; CSR = clinical study report; SM = symptomatic management

Table 50. Adverse event costs

Adverse event	Unit Cost	Source
Diarrhoea	£511.24	NHS Cost Collection 2023/2024 (FD10J-M, day case)(117)
Nausea	£511.24	NHS Cost Collection 2023/2024 (FD10J-M, day case)(117)
Urinary tract infection	£355.69	NHS Cost Collection 2023/2024 (LA04N-S, day case)(117)

NHS = National Health Service

Table 51. Monthly cost of AEs management of the intervention and comparator technologies

	Acoramidis + SM	Tafamidis + SM	SM
Monthly cost of AE management	£4.38	£5.05	£3.75

AEs = Adverse Events; SM = symptomatic management

B.4.2.6 Miscellaneous unit costs and resource use

No miscellaneous costs were included in the analysis.

B.4.2.7 Clinical expert validation

In preparation for the submission, a clinical expert validation exercise was conducted to gather feedback on key model settings, inputs, and assumptions for the cost-comparison model. Individual interviews with two clinical experts from the NAC were conducted to assess generalisability of the ATTRibute-CM trial population to UK clinical practice, comparative efficacy against tafamidis, resource use, and key modelling aspects (such as long-term ACM and TTD extrapolations). The interviews were conducted remotely on Microsoft Teams. Both clinicians were provided with pre-read materials containing the same information presented during the interviews.

The clinicians confirmed that the patient population characteristics in the ATTRibute-CM trial broadly reflect those in UK clinical practice, excluding very advanced multi-morbidity patients. They highlighted that in the UK most patients are treated with tafamidis + SM currently, with SM alone generally reserved for very severe, end-of-life cases. Both experts agreed that survival outcomes and CV-related hospitalisations between tafamidis and

acoramidis are generally similar, though the lack of head-to-head data precludes definitive assertions of superiority. Furthermore, both experts also indicated that they expect no substantial differences between tafamidis and acoramidis in terms of AEs that would impact QoL, with both treatments observed to be safe and well tolerated.

The experts indicated that though resource use increases with disease severity, no treatment-related differences in medical resource use were expected between tafamidis and acoramidis. The experts also highlighted that they would anticipate that treatment duration closely corresponds to ACM.

A follow-up joint interview was also conducted with the same two UK clinical experts to validate the SM treatment distributions and dosing applied, as well as to discuss generalisability of MAIC results and wastage assumptions:

- Clinical experts were initially presented with a distribution of SM therapies from the ATTRibute-CM trial using representative treatments for each drug category based on those utilised in NICE TA984, with the addition of SGLT2 inhibitors due to their expected wider use since the ATTR-ACT trial.
    - While clinical experts indicated that the proportion of patients on antithrombotic agents and lipid modifying agents in ATTRibute-CM was representative of clinical practice, they recommended using a recently published UK study (Ioannou et al 2023(111)) to help inform usage for other therapies.
    - Clinical experts suggested an alternative figure of 5% for calcium channel blockers with lower usage expected than in ATTRibute-CM (11.4%). Similarly, clinical experts suggested substantially higher usage of SGLT2i in current UK clinical practice (~80%) vs that observed in ATTRibute-CM (11.6%).
    - Representative treatments and associated dosing were also aligned with available data from Ioannou et al 2023(111) and clinical expert feedback.
- The clinical experts agreed that the results of the MAIC, based on a “restricted” ITT population of 621 patients, were generalisable to the mITT population used to inform key outcomes for the cost-comparison model, given the similarity in results observed between the ITT population and mITT populations in the ATTRibute-CM study (see Table 11)
- Both clinical experts indicated that very little drug wastage occur in UK clinical practice with tafamidis. Although clinical experts noted that the absolute number of

tablets of acoramidis wasted may be higher than tafamidis due to the larger number of tablets required per dose and the higher number of units per pack (120 vs 30), the experts agreed that this would not translate into differences in wastage costs given the pack sizes cover the same 30-day duration of treatment for both therapies, if assuming a similar pack price.

B.4.2.8 Uncertainties in the inputs and assumptions

Table 52 summarises the base case inputs and lower and upper bound values used to vary parameters in deterministic sensitivity analysis (DSA). All major model variables were tested in DSA to identify model drivers and examine key areas of uncertainty. Where possible, confidence intervals were used as alternative values. In the absence of confidence intervals being available, upper and lower bounds tested in the DSA were calculated as per the 95% confidence interval of the value given the distribution selected by type of the input. In the absence of available uncertainty data, we have assumed that the standard error is 20% of the mean value. This assumption allows for consistent evaluation and analysis of the data while accounting for a reasonable level of variability.

The beta distribution is confined by the interval 0 to 1 and is typically used for inputs such as proportions and utility values. The gamma distribution is confined by the interval 0 to infinity and is typically used for costs. The log-normal distribution is a normal distribution on the log scale, and is typically used for sampling relative risks, ORs, and HRs. The model also included Cholesky decomposition matrix calculation fields for modelling sets of input parameters for which the covariance structure between variables was known. For example, all survival curve function parameters (ACM and TTD) were varied using this method to account for the correlation between the estimated parameters of the survival functions.

Table 52. Base case and uncertainty estimates for model parameters varied in DSA

Variable	Base case Value	DSA Lower and Upper Bounds
Model Settings		
Age	77.20	76.68 to 77.72
Share of males	90.8%	88.39% to 92.96%
Clinical Inputs		
ACM: parameter 1	[redacted]	[redacted]
ACM: parameter 2	[redacted]	[redacted]
TTD: Acoramidis + SM – parameter 1	[redacted]	[redacted]
TTD: Acoramidis + SM – parameter 2	[redacted]	[redacted]

Variable	Base case Value	DSA Lower and Upper Bounds
Treatment Costs		
Distribution of SM Treatments: Loop diuretics	76.80%	75.08% to 78.48%
Distribution of SM Treatments: Antithrombotic agents	[redacted]	[redacted]
Distribution of SM Treatments: Beta blockers	55.40%	53.40% to 57.40%
Distribution of SM Treatments: Lipid modifying agents	[redacted]	[redacted]
Distribution of SM Treatments: ACEi/ARBs	57.40%	55.40% to 59.38%
Distribution of SM Treatments: MRAs	39.00%	37.05% to 40.97%
Distribution of SM Treatments: Calcium channel blockers	5.00%	3.74% to 6.43%
Distribution of SM Treatments: SGLT2i	80.00%	77.47% to 82.42%
Adverse Events		
Acoramidis + SM: Share of Patients Experiencing AEs per Cycle - Diarrhoea	0.39%	0.25% to 0.55%
Acoramidis + SM: Share of Patients Experiencing AEs per Cycle - Nausea	0.19%	0.12% to 0.27%
Acoramidis + SM: Share of Patients Experiencing AEs per Cycle - Urinary tract infection	0.40%	0.26% to 0.57%
Tafamidis + SM: Share of Patients Experiencing AEs per Cycle - Diarrhoea	0.40%	0.26% to 0.58%
Tafamidis + SM: Share of Patients Experiencing AEs per Cycle - Nausea	0.37%	0.24% to 0.52%
Tafamidis + SM: Share of Patients Experiencing AEs per Cycle - Urinary tract infection	0.32%	0.20% to 0.45%
Post-Discontinuation SM: Share of Patients Experiencing AEs per Cycle – Diarrhoea	0.25%	0.16% to 0.36%
Post-Discontinuation SM: Share of Patients Experiencing AEs per Cycle - Nausea	0.17%	0.11% to 0.25%
Post-Discontinuation SM: Share of Patients Experiencing AEs per Cycle - Urinary tract infection	0.44%	0.29% to 0.63%
AE costs: Diarrhoea	£511.24	£330.85 to £730.26
AE costs: Nausea	£511.24	£330.85 to £730.26
AE costs: Urinary tract infection	£355.69	£230.18 to £508.07

AE = adverse event; ACM = all-cause mortality; SM = symptomatic management; TTD = time to treatment discontinuation

The key assumptions of the economic analysis and their justifications are detailed in Table 53. The modelling approach makes the best use of available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of data, assumptions were designed to minimise potential bias in the analysis.

Table 53. Summary of key assumptions in the analysis

#	Assumption	Justification
1	The ATTRibute-CM trial population is assumed to be representative of patients receiving treatment for ATTR-CM in the UK.	UK clinical experts indicated that the population in ATTRibute-CM is broadly reflective of the population they would see in UK clinical practice.(118)
2	Results from the MAIC, conducted based on the ITT population, are generalisable to the mITT population used for informing the cost-comparison model.	A "restricted ITT" population was used for the MAIC, given eGFR-related inclusion criteria for the mITT population in ATTRibute-CM differed slightly from the ATTR-ACT population. Although eGFR was identified as a potential treatment effect modifier, MAIC results were assumed generalisable to the mITT population given similarity in comparative outcomes between both populations in ATTRibute-CM (Table 11), as well as small differences in the numbers of patients in each population. This assumption was also validated with UK clinical experts.
3	Tafamidis is assumed to have the same time on treatment as for acoramidis.	Differences in trial populations mean that use of available time on treatment data from the ATTR-ACT trial is likely to underestimate time on treatment for tafamidis. UK clinical experts supported an assumption of similar time on treatment using ATTRibute-CM trial data between acoramidis and tafamidis, which was anticipated to be more reflective of time on treatment in UK clinical practice.(118)
4	Wastage costs are not included in the cost-comparison model.	Analysis focuses on comparing acoramidis with tafamidis which are expected to have similar time on treatment and have the same pack duration (30 days). UK clinical experts also confirmed that no differences in wastage costs were anticipated between acoramidis and tafamidis.(118) Inclusion of half a pack of wastage over a patient lifetime was recommended by the ERG in the tafamidis NICE appraisal (44) due to use of RDI parameters based on number of capsules taken, which are not included in the cost-comparison model. Bayer also intend to offer acoramidis at a similar or lower cost to tafamidis.
5	Healthcare resource use costs (excluding adverse events) are assumed to be similar between acoramidis and tafamidis, and are therefore excluded from the analysis.	UK clinical experts indicated that no treatment-related differences in resource use were anticipated between acoramidis and tafamidis.(118)
6	Only adverse event costs associated with diarrhoea, nausea and urinary tract infections were included in the analysis.	Clinical expert feedback(116) and alignment with NICE TA984 for tafamidis.(26)

ERG = Evidence Review Group; MAIC = matching-adjusted indirect comparison

B.4.3 Base case results

Results of the base case analysis are shown in Table 54, including results based on the acoramidis list price and proposed PAS price. In both sets of analyses, the results indicate that acoramidis is cost saving in comparison to tafamidis (using the NHS list price) with total

cost savings of [redacted] for the list price analysis and [redacted] for the PAS price analysis, primarily driven by differences in drug acquisition costs between acoramidis and tafamidis.

Table 54. Base case results

Technologies	Acquisition costs (£)	Adverse event costs (£)	Total costs (£)
Acoramidis list price			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]
Acoramidis PAS price			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]

SM = symptomatic management, PAS = patient access schemes
Note: Values are rounded so total costs can be slightly different from the sum of the first two columns.

B.4.4 Sensitivity and scenario analyses

Results of scenario analyses are shown in Table 55. Across all scenarios, acoramidis remained cost saving in relation to tafamidis, with the time horizon, TTD HR and lower cost discount rate scenarios having the largest impact on the results.

Table 55. Scenario analysis results

Scenario	Overall cost for acoramidis + SM	Overall cost for tafamidis + SM	Difference in cost
List price			
Base Case	[redacted]	[redacted]	[redacted]
Time horizon: 5yrs	[redacted]	[redacted]	[redacted]
Time horizon: 10yrs	[redacted]	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]	[redacted]
ACM: Log-logistic	[redacted]	[redacted]	[redacted]
ACM: Generalised Gamma	[redacted]	[redacted]	[redacted]
TTD: Gompertz	[redacted]	[redacted]	[redacted]
AE costs excluded	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 0.9	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 1.1	[redacted]	[redacted]	[redacted]
Price inclusive of proposed PAS discount			
Base Case	[redacted]	[redacted]	[redacted]
Time horizon: 5yrs	[redacted]	[redacted]	[redacted]
Time horizon: 10yrs	[redacted]	[redacted]	[redacted]

Scenario	Overall cost for acoramidis + SM	Overall cost for tafamidis + SM	Difference in cost
List price			
Discount rate: 1.5%	[redacted]	[redacted]	[redacted]
ACM: Log-logistic	[redacted]	[redacted]	[redacted]
ACM: Generalised Gamma	[redacted]	[redacted]	[redacted]
TTD: Gompertz	[redacted]	[redacted]	[redacted]
AE costs excluded	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 0.9	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 1.1	[redacted]	[redacted]	[redacted]

ACM = all-cause mortality; AE = adverse event; HR = hazard ratio; SM = symptomatic management; TTD = time to treatment discontinuation

DSA results (Figure 44) show that the main drivers of the analysis results were the TTD HR for tafamidis compared to acoramidis, TTD and ACM parametric distribution parameters in the acoramidis arm and ACM distribution parameters, with some slight sensitivity in results also observed with variation in baseline age. Variation in other parameters (such as adverse event probabilities) appeared to have a negligible impact on the results.

Similar to the scenario analyses, no parameter variations resulted in overall cost increases for acoramidis for either the list price or PAS price results.

Figure 44. DSA results – list price

ACM = all-cause mortality; AE = adverse event; HR = hazard radio; SM = symptomatic management; TTD = time to treatment discontinuation

Figure 45. DSA results – PAS price

ACM = all-cause mortality; AE = adverse event; HR = hazard radio; PAS = patient access scheme; SM = symptomatic management; TTD = time to treatment discontinuation

B.4.5 Subgroup analysis

Not applicable. Acoramidis provides similar or greater health benefits at a similar or lower cost to the comparator in the full population for whom the comparator has been recommended by NICE. Therefore, no subgroup analyses were conducted as part of the cost-comparison analysis.

B.4.6 Interpretation and conclusions of economic evidence

For both list price and PAS price based analyses, acoramidis resulted in cost savings compared to tafamidis for the base case as well as all scenario analyses and DSA parameter variations, driven by reductions in drug acquisition costs with both list price and PAS price producing lower monthly drug acquisition costs for acoramidis compared to tafamidis, applying an assumption of equal ACM and TTD between treatment arms in the base case. An assumption of 10% lower time on treatment for tafamidis was explored in a scenario analysis, although this variation did not sufficiently reduce acquisition costs for tafamidis to offset the lower monthly costs for acoramidis when using either the list price or PAS price. However, it is important to note that the analyses were performed using the tafamidis list price, with the PAS price not publicly available. Bayer are committed to offering acoramidis at a similar or lower price to tafamidis to help enable timely access for patients to an effective alternative treatment option for clinicians to use in patients diagnosed with ATTR-CM. A key strength of the cost-comparison analysis is the detailed consideration of parametric survival curve extrapolations, as well as the exploration of uncertainty in key

parameters through DSA and scenario analyses, and the use of extensive UK clinical expert feedback to help validate important assumptions adopted in the model.

The primary limitation of the cost-comparison analysis is the lack of comparable time on treatment data for acoramidis and tafamidis, with available time on treatment data from the ATTR-ACT trial for tafamidis considered inappropriate to be compared directly with time on treatment data from ATTRibute-CM given differences in patient populations between trials. However, feedback from UK clinical experts indicated an expectation of similar time on treatment for both therapies, with acoramidis and tafamidis having similar mechanisms of action and safety profiles as well as efficacy outcomes.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Summary of Information for Patients (SIP)

August 2025

File name	Version	Contains confidential information	Date
ID6354_acoramidis v. NICE_SIP_050825	FINAL	NO	5th August 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

UK approved name: Acoramidis **Brand name:** Beyonttra®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being considered by NICE in this appraisal is adult patients with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Acoramidis received a marketing authorisation in the UK on 24th April 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

- Co-creation of patient booklet
  - Amyloidosis UK. Two patients were paid for three hours of work each and these payments were in line with Fair Market Value

- Primary Market research to gain patient insights in relation to ATTR-CM
  - Amyloidosis UK & Cardiomyopathy UK: Referral fees paid to the organisations to aid recruitment of patients into the market research. The project aims to understand the experience of individuals living with this condition, from symptoms onset to the initiation of a management strategy (honoraria also paid to patients for their time within the Fair Market Value rates). This project is ongoing.

- Review of plain language summary
  - Pumping Marvellous. Bayer engaged the services of the patient organisation to review a plain English summary of a document. Payments for this were in line with Fair Market Value for this work, which was expected to take 5 hours. The organisation also drafted a letter on current unmet need for another treatment area but this was not a paid for activity.

Bayer has supported the British Heart Foundation's (BHF) 'Hearts Needs More' policy campaign, endorsing the BHF consensus statement on CVD. The statement calls on the Government to deliver a dedicated National Cardiovascular Disease Plan that sits beneath the 10-Year Health Plan. The statement mentions heart failure and was also signed by the Alliance for Heart Failure, Cardiomyopathy UK and the British Society for Heart Failure.

All details of Bayer's relevant partnerships and transfers of value to patient organisations are listed on the Bayer website, https://www.bayer.co.uk/en/patient-group-donations

Please note, the collaborations listed are from January 2024 and only collaborations relevant to the therapy area are listed.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

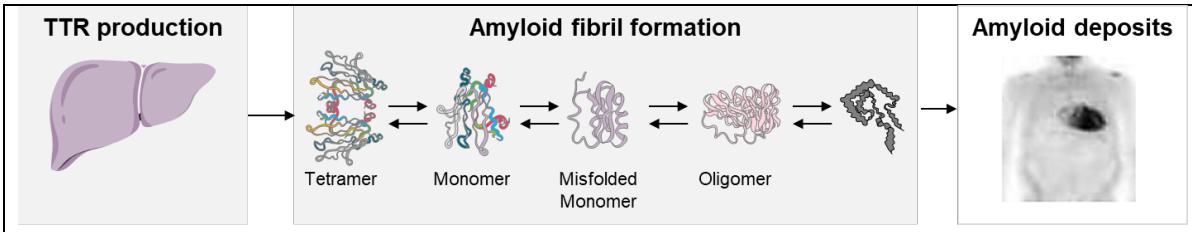
Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Please note – when reading this document, there is a glossary at the end of the document.

Transthyretin (TTR) is produced by the liver and exists in the body normally as a tetrameric protein that transports both thyroxine and retinol-binding protein in the bloodstream (1).

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease arising from the breaking up of TTR tetramers into monomer components that can misfold and aggregate into amyloid fibrils which deposit in cardiac tissues. When amyloid fibrils form in the heart, the heart muscle stiffens, and the heart can no longer work normally. This ultimately leads to heart failure (HF) and early death (2, 3, 4, 5).



Adapted from Ruberg 2019(4)

There are two forms of ATTR-CM: variant ATTR-CM (vATTR-CM, also known as "mutant" or "hereditary" ATTR-CM, which arises from pathogenic variants in the TTR gene) and wild-type ATTR-CM (wtATTR-CM, in which the TTR misfolding is not related to a pathogenic variant, but instead caused by factors such as aging); vATTR-CM typically has an earlier age of onset compared to wtATTR-CM (2).

The disease course is characterised by years of relatively stable clinical status, followed by substantial increase in severity of HF that becomes refractory to conventional treatment (4, 6). As ATTR-CM generally progresses slowly with minimal and non-specific symptoms until advanced stages, diagnosis is often delayed or incorrectly given another cause. This can result in patients having short life expectancy due to being in more advanced states of disease at diagnosis (2, 3, 4).

The clinical presentation of ATTR-CM is typically associated with chronic HF and often includes non-specific cardiovascular (CV)-related symptoms though non-CV symptoms have also been observed (2, 7, 8, 9, 10, 11, 12) – see table below.

Common symptoms	
Cardiovascular	Non-cardiovascular
HF	Neurologic disorders
Arrhythmias	Autonomic disorders
Aortic stenosis	Gastrointestinal disorders
Syncope or pre-syncope	Musculoskeletal disorders
Angina	Visual disorders
Atrial fibrillation	Auditory disorders
Shortness of breath	Renopathy
Conduction system disease	
Cough	
Palpitations	

Alongside progressive heart failure and conduction abnormalities, patients with ATTR-CM typically experience frequent hospitalisations, irreversible loss of physical function, significantly impaired quality of life (QoL) and high mortality / premature death (11, 13, 14, 15, 16, 17).

The significant effect on the cardiovascular (CV) system means that ATTR-CM is associated with substantial healthcare resource and therefore costs, which are driven by CV-related hospitalisation (15).

ATTR-CM is distinct from HF alone and, when left untreated, is associated with a shorter duration of survival (2.5 to 3.6 years) that is less than half of that of patients diagnosed with HF (6 years)(18, 19).

Substantial caregiver burden has also been reported, including a negative impact on mental health (17).

True United Kingdom (UK) prevalence of ATTR and ATTR-CM is unknown. There are thought to be around 1500 people with ATTR-CM in England(20). An increase in disease awareness and the availability of more conclusive non-invasive diagnostic testing and new disease-modifying therapies means that prognosis is improving as more patients can now receive an earlier diagnosis and treatments which delay disease progression(4, 14, 21, 22, 23). Prevalence and incidence of ATTR-CM is expected to increase as a consequence of improvements in diagnostic techniques, earlier diagnoses and patients surviving longer with new treatments.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

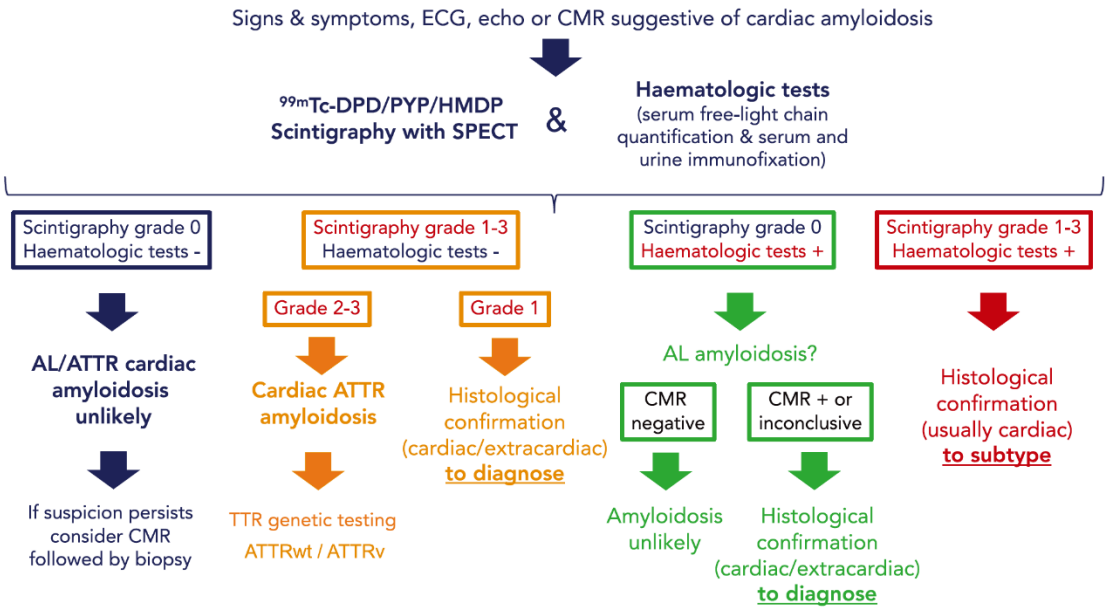
Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Many symptoms of ATTR-CM are non-specific and can also be linked to other more common conditions such as heart failure (HF) or hypertrophic cardiomyopathy, often leading to missed or delayed diagnosis (11, 12, 15, 23, 24).

With the introduction of disease-modifying treatments for ATTR-CM, a rapid diagnosis is therefore important since early initiation of treatment can prevent further amyloid deposition and irreversible damage to the heart and have a favourable impact on survival (4, 21, 22, 23, 25).

With symptoms suggestive of ATTR-CM, investigations are performed according to a diagnostic algorithm (3, 12, 26, 27, 28, 29), with the figure below taken from ESC guidelines, Garcia-Pavia 2021 (26).

Diagnostic testing algorithm for Cardiac Amyloidosis (ATTR-CM)



99Tc—DPD/PYP/HMDP=Technetium labelled 3-diphosphono-1,2-propanodicarboxylic acid / pyrophosphate / hydroxymethylene diphosphonate; ATTR=transthyretin amyloidosis; ATTRv=hereditary transthyretin amyloidosis; ATTRwt=wild-type transthyretin amyloidosis; AL=light-chain amyloidosis; CMR=cardiac magnetic resonance; ECG=electrocardiogram; ESC=European Society of Cardiology; SPECT=single photon emission computed tomography; TTR=transthyretin.

Both echocardiography and cardiac magnetic resonance (CMR) imaging have important roles in raising the suspicion of cardiac amyloidosis although a diagnosis cannot be made without further confirmatory tests (3, 4, 30).

Previously, definitive diagnosis of ATTR-CM could only be made by endomyocardial biopsy (EMB) and demonstration of amyloid fibril deposits on Congo red staining (4), however this is invasive and carries procedural risks such as myocardial perforation and tamponade (31). Non-invasive imaging with technetium-labelled bone scintigraphy has largely replaced biopsy for identification of ATTR-CM (4, 31).

Prior to performing scintigraphy, a monoclonal protein screen is conducted to exclude amyloid light chain (AL) amyloidosis. Once AL is ruled out, the specificity of bone scintigraphy for ATTR-CM approaches 100% (4). After radiotracer injection, imaging is performed to compare uptake of the radiotracer in the myocardium (heart muscle) to the bone (rib) structures. If uptake in the myocardium is equal to or greater than uptake in bone, the scan is considered consistent with ATTR-CM (4).

Upon diagnosis of ATTR-CM, genetic testing differentiates between the hereditary and wild-type forms of the disease and identifies the exact mutation (27, 32).

The diagnosis to identify patients suitable for treatment with acoramidis will follow standard diagnostic pathways.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Management of ATTR-CM was, until recently, symptomatic, focusing on management of heart failure and arrhythmias including diuretics, careful regulation of fluid balance and supportive care (33).

Treatment of ATTR-CM now focuses on 3 main approaches: management of heart failure, management of arrhythmias and conduction disorders, and initiation of disease-modifying therapies to reduce the formation of amyloid fibrils / regress existing amyloid fibril deposition.

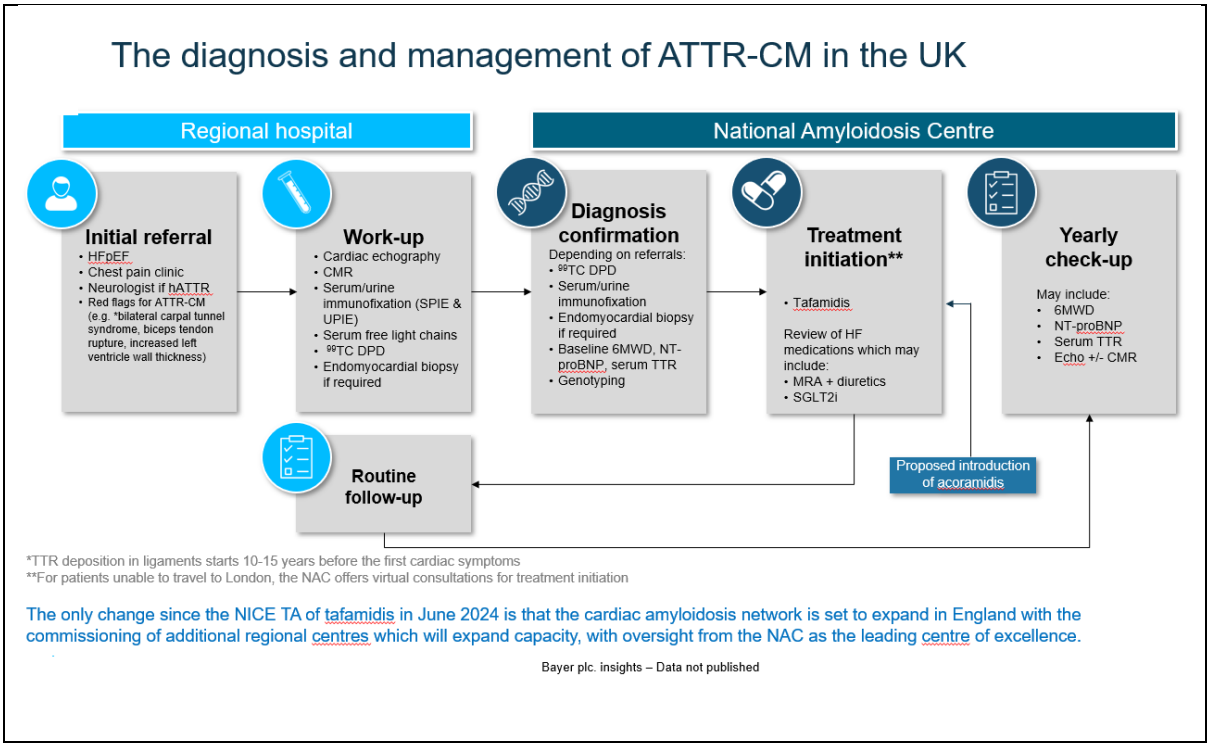
Management of heart failure can be challenging in patients with ATTR-CM since many of the usual heart failure treatments such as beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and digoxin can be poorly tolerated in these patients (3, 32, 34, 35). ATTR-CM patients are therefore more typically managed with dietary sodium restriction, fluid control and the use of diuretics (3, 32). UK clinical experts have also reported usage of sodium-glucose co-transporter 2 inhibitors (SGLT2i) in these patients.

Amiodarone is the anti-arrhythmic treatment of choice in patients with ATTR-CM (3, 32, 34, 35). A pacemaker may be considered for bradycardia (32). ATTR-CM patients are also at high risk of thromboembolism and those with atrial fibrillation (AF) should receive an anti-coagulant (3, 32, 34, 35).

Recently, NICE recommended tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA984) (36). Tafamidis is a TTR stabiliser (37).

Tafamidis is therefore the key comparator in the appraisal of acoramidis. As well as being recommended by NICE for the same population and in the same position in the treatment pathway, tafamidis is from the same drug class as acoramidis and has a similar mechanism of action. Both treatments are administered orally. Tafamidis is delivered to patients via a "homecare service" for the whole country. Acoramidis will also be delivered to patients at home via a homecare service.

The NAC in London provides a highly specialised service for people with amyloidosis and related disorders and UK patients have generally been referred here for assessment, diagnosis, monitoring and treatment. To cope with the increase in patient referrals and continue to provide a timely diagnosis, new hubs are being established around the UK, receiving remote multidisciplinary expertise from the NAC. Please see the diagram below which presents the treatment pathway.



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

After a review of the literature, several publications were found to have reported on the negative quality of life (QoL) impact of ATTR-CM on both patients and families/carers (11, 13, 14, 16, 17).

Rintell et al (11) report on the results of two focus groups designed to describe the patient and family experience of living with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN). Topics discussed at the focus groups included (1) the patient's experience of seeking and establishing a correct diagnosis, (2) physical or psychological symptoms experienced and (3) impact on the QoL of the patient and family. Participants were also asked to list the symptoms of ATTR that affected their physical health and quality of life and to choose the top three that had the greatest effects on their lives.

(1) Diagnosis - the diagnostic process for ATTR-CM was reported as often long and difficult. Patients reported that they were misdiagnosed and given inappropriate treatments, sometimes multiple times
(2) Symptoms - participants in the ATTR-CM focus group reported several features directly related to the disease's effect on the heart including shortness of breath, atrial fibrillation, and arrhythmias. Patients experienced dramatic loss of strength and stamina. Several patients suffered from carpal tunnel syndrome. Mood changes and depression were widely mentioned as patients and family members faced an uncertain future and a

reduced life expectancy. Several patients experienced insomnia. The group identified intolerance to activity and inability to exercise as well as insomnia and fatigue as the most troubling symptoms they experienced.

(3) The family - The illness was very stressful for both patients and their families. Spouses experienced considerable stress associated with the illness but also played a major role in coping with it. When patients had hereditary or variant disease, they experienced stress from the effects of the illness but also from watching family members cope with the illness. Patients and their spouses reported that they were sometimes overcome emotionally as they came to terms with the effect of the disease on their lives. Participants talked about the fear and anxiety spouses felt.

Eldhagen et al (13), reports on a study in the Nordics to investigate the health-related quality of life (HRQoL) in 169 ATTR-CM patients. Patients completed health related quality of life (HRQoL) questionnaires in the form of the Kansas City Cardiomyopathy Questionnaire (KCCQ), the EQ-5D-5L index with Visual Analog Scale (VAS), and the Major Depression Inventory (MDI). The paper concluded that KCCQ scores were lower than reported for patients with other heart diseases of non-ATTR CM origin (lower score indicates poorer health status and HRQoL). The paper also reports that patients with higher New York Heart Association (NYHA) classes had a poorer quality of life as reflected in lower KCCQ and EQ-5D-5L scores and higher MDI scores. The same was the case when disease severity was assessed by use of National Amyloidosis Centre (NAC) stages.

There are also patient experiences described in the appraisal committee papers for the NICE evaluation of tafamidis from Cardiomyopathy UK and the UK ATTR Amyloidosis Patient Association (36). Impact of the disease include descriptions of breathlessness, fatigue, exercise intolerance, dizziness, abnormal heart rhythms, pain, emotional impact, psychological burden, loss of independence and financial burden. The impact on caregivers is also described, with reference to stress, fatigue, financial burden, isolation and a negative impact on mood.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

As described in section 2 a) above, transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease arising from the breaking up of TTR tetramers into monomer components that can misfold and aggregate into amyloid fibrils which deposit in cardiac tissues. When amyloids form in the heart, the heart muscle stiffens, and the heart can no longer work normally. This ultimately leads to heart failure (HF) and early death (2, 3, 4, 5).

Acoramidis binds to the TTR tetramer and prevents it breaking down into monomers and forming amyloid fibrils. It is classified as a TTR stabiliser and by binding to the TTR tetramer, it slows down the progression of disease (5, 38).

Acoramidis was specifically designed to mimic the stabilising effects of the disease protective genetic variant known as "T119M" (38, 39). As assessed in vitro, acoramidis has a higher binding affinity for TTR than other known TTR stabilisers, including diflunisal and tafamidis (40), achieving a near-complete (≥ 90%) and sustained TTR stabilisation (39, 41).

In the main clinical study, ATTRibute-CM, described in sections below, in patients (wild-type and variant ATTR) treated with acoramidis, near-complete (≥ 90%) TTR stabilisation was observed at the first post-dose initiation assessment (Day 28) and sustained through to Month 30 (38, 39).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

When the ATTRibute-CM trial was designed, tafamidis was not approved for treating ATTR-CM. To provide optimal care, participants were allowed to start tafamidis therapy once it became commercially available for ATTR-CM. Participants could use tafamidis as a concomitant medication, at the discretion of the treating physician, provided they had completed at least 12 months of blinded study treatment. **It is important to note that the treatments would not be used together in clinical practice.**

Acoramidis would be prescribed in addition to the standard of care treatments that the patient is receiving for the management of heart failure, arrhythmias and conduction disorders, and other co-morbidities.

The patient's doctor and pharmacist should be made aware if the patient is taking, have recently taken or might take any other medicines (5).

Acoramidis may change patient's thyroid blood tests, but these changes should not be harmful to their thyroid function (5).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Each tablet contains acoramidis hydrochloride equivalent to 356 mg acoramidis (38).

The recommended dose is two tablets (712 mg) taken by mouth twice a day. The total daily dose is 1,424 mg acoramidis (5).

The tablets should be swallowed whole. They can be taken with water, with or without food. The patient should take 2 tablets in the morning (sun symbol on the blister) and 2 tablets in the evening (moon symbol on the blister) (5).

Treatment will be lifelong until the physician and patient decide to stop.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The key trial relating to the efficacy and safety of acoramidis in patients with symptomatic transthyretin amyloid cardiomyopathy is the phase 3 clinical study, ATTRibute-CM (22). This study was a prospective, randomised, double-blind, placebo-controlled, parallel-group, international multicentre phase 3 study. Patients included in the study had a diagnosis of ATTR-CM (either wild-type TTR or a variant TTR genotype). The number randomised was 421 to acoramidis and 211 to placebo. The primary objective of ATTRibute-CM was to determine the efficacy of acoramidis compared with placebo, on a background of stable heart failure therapy, in patients with symptomatic ATTR-CM using the combined endpoint of all-cause mortality (ACM), the cumulative frequency of cardiovascular hospitalisations (CVH), change from baseline in NT-proBNP, and change from baseline in six-minute walking distance (6MWD). This endpoint combined key cardiac outcomes as well as a means of assessing the effect of acoramidis on a key biomarker of heart failure (NT-proBNP) and physical function (6MWD), associated with prognosis and disease progression in ATTR-CM. The study has been published in full(22).

In addition, there is an ongoing open-label extension study for patients who were still on treatment at the end of the ATTRibute-CM trial (25).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy of acoramidis was demonstrated in the ATTRibute-CM study and continues to be explored in an open-label extension study.

ATTRibute-CM was a multicentre, international, randomised, double-blind, placebo-controlled clinical study conducted in 632 adult participants with wild-type or variant ATTR-CM and heart failure NYHA Class I-III, with current or prior symptoms of heart failure. Participants were randomised in a 2:1 ratio to receive acoramidis 712 mg (n = 421), or matching placebo (n = 211) twice daily for 30 months. Treatment assignment was stratified by whether participants had variant ATTR-CM (ATTRv-CM) or wild-type ATTR-CM (ATTRwt-CM) and baseline disease severity, i.e., NT-proBNP level and renal function as defined by eGFR. Patients with eGFR < 15 mL/min/1.73 m^2 were excluded from participation in the study (38).

The four-step primary hierarchical analysis included death from any cause, cumulative frequency of cardiovascular-related hospitalisation, the change from baseline in the NT-proBNP level, and the change from baseline in the 6-minute walk distance (22). This endpoint includes endpoints which are relevant to patients i.e mortality/survival, hospitalisations, as well as physical function and mobility and a measure of heart failure severity.

ATTRibute-CM met its primary endpoint (Finkelstein-Schoenfeld test, p < 0.001) of the four-step hierarchical analysis (22). The "Win Ratio" was 1.8 (95% confidence interval (CI) 1.4 to 2.2). This means that patients who received acoramidis were 1.8 times more likely to have a better outcome than those who received the standard treatment or placebo. This difference was statistically significant, meaning it's very unlikely to be due to chance.

In addition, a pre-specified secondary Finkelstein-Schoenfeld analysis of the two-component hierarchy of death from any cause and cardiovascular-related hospitalisation (CVH) was carried out. The result of this analysis was statistically significant (38).

All-cause mortality (ACM) was reported in 19.3% and 25.7% of participants in the acoramidis and placebo groups, respectively. The majority (79%) of deaths were cardiovascular (CV)-related with acoramidis demonstrating a 30% relative risk reduction in CV-related mortality compared with placebo. CV-related mortality was reported in 14.9% and 21.3% of participants in the acoramidis and placebo groups, respectively; hazard ratio: 0.709 (95% CI: 0.476, 1.054, p = 0.0889, Cox proportional hazards model) (38).

A Cox regression analysis indicated a 35.5% decrease in the risk of the composite of ACM or first CV hospitalisation (hazard ratio: 0.645 [95% CI: 0.500, 0.832; p = 0.0008]). Separation in the Kaplan-Meier curves was observed at Month 3 and steadily diverged through Month 30 (38, 42).

Compared with placebo, acoramidis reduced the occurrence of first CVH (acoramidis, 26.7%; placebo, 42.6%; HR: 0.60; 95% CI: 0.45-0.80; P = 0.0005), with Kaplan-Meier curves separating at month 3 and continuing to diverge through month 30 (42).

Annualised frequency of CVH was reduced with acoramidis compared with placebo (acoramidis, 0.22; placebo, 0.45; relative risk ratio: 50%; 95% CI: 0.36-0.70; P < 0.0001) (42). The Number Needed to Treat (NNT) was 5 patients to prevent 1 CVH per year over 30 months of treatment. The open-label extension (OLE) study, with initial results reported at Month 42, further confirms the benefits of continuing acoramidis treatment for ACM or first CVH, with a hazard ratio (HR) and 95% CI of 0.57 (0.46, 0.72) (P-value < 0.0001). Similar analyses were performed on ACM alone and first CVH alone, with hazard ratios of 0.64 (95% CI, 0.47–0.88; P = 0.006) and 0.53 (95% CI, 0.41–0.69; P<0.0001), respectively, at month 42 (25).

In the acoramidis group of the ATTRibute-CM study, at month 30, the decrease from baseline in the 6-minute walking distance (6MWD) was less than that in the placebo group, with a LS mean

difference of 39.6m in favour of acoramidis (95% CI, 21.1 to 58.2; P<0.001) (22). Post-hoc analysis with imputation (that accounted for missing observations), at Month 30, found a net increase in 6MWD relative to baseline, an indication of clinical improvement, in 26.2% of acoramidis-treated patients versus 13.4% in the placebo group (nominal p = 0.0002)(43).

An indirect comparison to tafamidis is described in section "Value and economic considerations" below.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The EQ-5D is a preference based generic instrument for the assessment of Health-Related Quality of Life (HRQoL). Change from baseline in the EQ-5D-5L questionnaire was recorded in the study. Acoramidis significantly reduced the decline in EQ-5D-5L compared to placebo(44).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a heart failure-specific patient reported outcome (PRO) instrument.

Patients treated with acoramidis showed significantly improved preservation of quality of life from baseline to Month 30 compared to placebo (22). A statistically significant ($p < 0.0001$) treatment benefit on the KCCQ-OS (Overall Summary Score), was observed favouring acoramidis, with a 10-point increase from baseline LS mean difference observed between the two treatment groups (95% CI, 5.97 to 13.91; P<0.001). The curves started to separate at month 3, indicating an early effect of acoramidis on preserving quality of life.

In patients with chronic heart failure, a KCCQ-OS change of five or more points has been shown to be a clinically significant and independent predictor of reduced mortality and reduced CVH (45, 46).

In a post-hoc analysis a net increase in KCCQ-OS relative to baseline, an indication of clinical improvement in health status, was observed in 43.8% of patients in the acoramidis treatment group, compared to 26.5% in the placebo group. With imputation (that accounted for missing observations), at Month 30, a net increase in KCCQ-OS score relative to baseline was observed in 30.8% of acoramidis-treated patients compared to 17.8% in the placebo group (stratified CMH; nominal p value=0.0005)(47).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The possible side effects are:

Very common (may affect more than 1 in 10 people)
- diarrhoea
- painful inflammation in the joints (gout)(5)

The majority of events of diarrhoea and gout were non-serious and resolved(38).

The Medicines and Healthcare products Regulatory Agency (MHRA) decided that the benefits of acoramidis are greater than the risks and recommended that it could be approved for use(48).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Acoramidis is a potent, highly selective TTR stabiliser designed to mimic the protective T119M mutation, which hyper-stabilises TTR, preventing it splitting into monomers and development of amyloid (39).

Summarising the information above, studies in patients with ATTR-CM have shown that acoramidis in comparison to placebo (22, 25, 42):

- Reduces all-cause mortality (ACM)
- Reduces cardiovascular-related mortality (CVM)
- Reduces the occurrence of first cardiovascular-related hospitalisation (CVH)
- Reduces the annualised frequency of CVH
- Reduces the decline in 6-minute walking distance (6MWD)
- Reduces the decline in quality of life

In addition, the majority of the very common side effects that occurred in studies were non-serious and resolved.

Bayer (the company) believe that at least similar clinical effectiveness to tafamidis can be demonstrated with acoramidis.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Acoramidis has to be taken as two tablets twice per day, which some may consider increases the "pill burden" for patients.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

As noted in sections above, the only NICE recommended treatment for patients with ATTR-CM is tafamidis (36). As such, acoramidis will be evaluated by NICE in comparison to tafamidis.

Bayer (the company) believe that at least similar clinical effectiveness to tafamidis can be demonstrated with acoramidis. There is no head-to-head data, but an anchored matching-adjusted indirect comparison (MAIC) of tafamidis and acoramidis has been conducted using data from the ATTR-ACT (49) and ATTRibute-CM (22) studies respectively.

The MAIC indicates at least similar health benefits for acoramidis to tafamidis on key clinical outcomes (all-cause mortality (ACM) and cardiovascular hospitalisation (CVH) as well as safety). An expectation for similarity of health benefits and safety endpoints likely to substantially impact health outcomes has also been supported by two clinical experts based at the National Amyloidosis Centre (NAC) in London.

Bayer do not expect there to be a difference in medical resource use between acoramidis and tafamidis. This has also been supported by two clinical experts based at the NAC in London.

By assuming no difference in efficacy and safety, a cost-comparison analysis has been conducted.

The cost-comparison analysis only considers the costs associated with treatment.

The outcome of the cost-comparison analysis showed that acoramidis generates cost savings compared with tafamidis, when the NHS list prices of the treatments are considered. NICE will be able to undertake an analysis using the confidential discounted prices offered by the manufacturers of tafamidis and acoramidis.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Acoramidis is a potent, highly selective TTR stabiliser specifically designed to mimic the protective T119M mutation, which hyper-stabilises TTR, preventing it splitting into monomers and development of amyloid fibrils (36).

With its unique mode of binding to the TTR binding site, the rationale for drug-design of acoramidis is based on the hypothesis that near-complete, sustained TTR stabilisation will slow or stop ongoing amyloid formation, reduce and/or stabilise the rate of disease progression and improve clinical outcomes.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Patients affected by ATTR-CM are typically over 70 years of age, which could bring issues for accessibility and attendance at the National Amyloidosis Centre (NAC) in London for diagnosis, treatment and review. It is envisaged that a UK amyloidosis network with regional amyloid services across the England / UK will ensure older patients have equal access to recommended treatments.

Additionally, one of the most prevalent variants of ATTRv in the UK is V142I, which has a primarily cardiac phenotype and is most common in men of Afro-Caribbean origin (50, 51, 52). Patients with V142I ATTRv-CM have the worst prognosis of all forms of ATTR-CM, including ATTRwt-CM and non-Val142I ATTRv-CM (median survival from diagnosis: 31, 57 and 69 months, respectively, $p<0.0001$)(14). While it is understood that any NICE treatment recommendations apply equally, irrespective of ethnicity, the susceptibility of this patient group could be highlighted to facilitate

earlier identification and treatment of V142I ATTR-CM mediated heart failure versus other forms of heart failure in patients of Afro-Caribbean origin.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

6-minute walk test (distance): A test to measure how far a person can walk in six minutes, used to assess their physical fitness.

AL type amyloidosis: Amyloidosis caused by light chain proteins, often associated with blood disorders.

Amyloid (fibrils): Protein deposition in organs like the heart which can cause severe damage

Amyloidosis: A group of diseases where abnormal proteins, called amyloids, build up in the body.

Arrhythmia: An arrhythmia, or abnormal heart rhythm, usually means your heart is beating too fast, too slow or irregularly

ATTR-CM: A rare disease where abnormal proteins build up in the body, causing damage to the heart (stiffening).

ATTR-PN: A rare disease where abnormal proteins build up in the body, causing damage to the nerves.

ATTRv-CM: Variant version of ATTR-CM, caused by specific mutations

ATTRwt-CM: Wild type version of ATTR-CM, caused by aging

Binding affinity: describes the strength of the interaction between two molecules, such as a drug and its target protein

Bradycardia: heart beats very slowly

Cardiac: related to the heart

Cardiac Magnetic Resonance scan: A CMR scan uses a strong magnetic field and radio waves to create detailed images of the heart. It gives information on the structure of the heart and blood vessels and how well they are working.

Cardiomyopathy: A disease of the heart muscle that makes it harder for the heart to pump blood to the rest of the body.

Cardiovascular (CV)-related: anything related to the heart and blood vessels

Cardiovascular-related hospitalisation: Hospital admission due to heart-related problems.

Carpal Tunnel Syndrome: Carpal tunnel syndrome (CTS) is pressure on a nerve in the wrist. It causes tingling, numbness and pain in hand and fingers.

Co-morbidity: the presence of two or more health conditions occurring in the same person at the same time

Congo red staining: a diagnostic method to identify amyloid

Cox regression analysis: a statistical method used to analyse clinical trial data

eGFR: A test to check how well the kidneys are working.

endomyocardial biopsy (EMB): invasive diagnostic procedure to obtain small samples of heart muscle for testing

EuroQOL 5-Dimension Instrument: A tool to measure a person's health status and quality of life.

Finkelstein-Schoenfeld test: a statistical method used to analyse clinical trial data

Hazard ratio: A way of comparing the chance of an event happening in one group with the chance of it happening in another group over time.

Heart failure (HF): Inability of the heart to circulate blood effectively enough to meet the body’s needs

Hierarchical analysis: A method of analysing data by ranking outcomes in order of importance.

Homecare service: In the NHS, a homecare medicines service delivers hospital-prescribed medications directly to a patient's home, rather than requiring collection from the hospital pharmacy.

Hypertrophic cardiomyopathy: A disease where the heart muscle becomes abnormally thick, making it harder for the heart to pump blood.

in vitro: (of a process) performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.

Kansas City Cardiomyopathy Questionnaire: A survey used by doctors to understand how a heart disease affects a person's life.

Kaplan-Meier (curve): a statistical method used to analyse clinical trial data

LS mean difference: a statistical method used to analyse clinical trial data

MAIC: A Matching Adjusted Indirect Comparison (MAIC) is a statistical technique used in healthcare research to compare the effect measures of different treatments or interventions, enabling a comparative analysis between treatments despite the absence of direct comparative data

MHRA: Medicines & Healthcare products Regulatory Agency. The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK.

Monomer: a chemical substance whose basic molecules can join together to form polymers

National Amyloidosis Centre (NAC) stages: A staging system for prognosis of cardiac transthyretin amyloidosis based on NT-proBNP and eGFR

New York Heart Association (NYHA) classes: A classification system for heart failure based on physical activity limitations

NT-proBNP: A substance released into the blood when the heart is under stress. Measurement of which is used as an aid in the diagnosis and assessment of the severity of heart failure

Number needed to treat: The Number Needed to Treat (NNT) is the number of patients you need to treat to prevent one additional bad outcome (death, stroke, etc.).

Pathogenic: anything that causes disease

Refractory: not affected by a treatment

Retinol: Vitamin A

Scintigraphy: A diagnostic procedure performed in a nuclear medicine department where a radioactive tracer is injected prior to the diagnostic scan.

SPECT: Single Photon Emission Computed Tomography is a type of scan

Tamponade: In relation to the heart “cardiac tamponade” is pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle and the outer covering sac (pericardium) of the heart

Tetrameric protein (tetramer): Structure such as a molecule or a polymer made of four structural subunits

Thromboembolism: Thromboembolism refers to a condition where a blood clot (thrombus) forms in a blood vessel and then breaks loose, traveling through the bloodstream to lodge in another blood vessel, obstructing blood flow

Transthyretin (TTR): Key transport protein for retinol binding protein (vitamin A) and thyroxine (thyroid hormone) in the blood; TTR is primarily produced in the liver.

Win ratio: A measure used in clinical trials to compare the effectiveness of treatments.

4c) References

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Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Response to clarification questions

September 2025

File name	Version	Contains confidential information	Date
[ID6354] Acoramidis EAG clarification responses [CON]_02092025_redacted.docx	1	Yes	02/09/2025

Section A: Clarification on effectiveness data

Outcome measures

A1. Please provide further justification for the choice of primary endpoint in ATTRibute-CM. While composite endpoints are not rare, the EAG considers composite endpoints including a biomarker to be unusual.

Initially, the primary endpoint for Part B of the study was a two-component hierarchical analysis using the Finkelstein-Schoenfeld (F-S) test, combining all-cause mortality (ACM) and cardiovascular-related hospitalisation (CVH). This was later expanded to include three components by adding change from baseline (CFB) in 6-minute walk distance (6MWD), and subsequently to a four-step hierarchical analysis incorporating ACM, CVH, CFB in NT-proBNP, and CFB in 6MWD. This endpoint combined cardiac outcomes as well as a means of assessing the effect of acoramidis on a key biomarker of heart failure (NT-proBNP) and physical function (6MWD), both of which have been associated with prognosis and disease progression in ATTR-CM.(1-3)

Rationale for Primary Endpoint Modification

In March 2021, the study protocol was amended to add 6MWD to the primary endpoint to maintain statistical power after allowing participants to start concomitant tafamidis treatment – in countries where they had access to it - following 12 months of blinded study drug. The change anticipated increasing concomitant tafamidis use due to its expanding approval for ATTR-CM and was proposed based on the potential for more ties after comparison of the CVH component than originally expected at the time of study design. For the win ratio analysis in particular, ties remaining at the end of the hierarchical process of examining pairwise comparisons do not contribute to the final result. Using 6MWD information, which is captured on a near continuous scale, minimises the number of ties left at the end of the hierarchical analysis and consequently boosts power.(4)

NT-proBNP was added in June 2022 after blinded reviews showed lower than anticipated mortality and CVH event rates, which again threatened study power with an elevated risk of Type II error. During study design in late 2018, original

assumptions on estimated rates of mortality and CVH had been based on the results of the ATTR-ACT study conducted in patients with ATTR-CM from 2013 to 2018.(3)

[redacted] Therefore, incorporating NT-proBNP as a clinically relevant biomarker was used to maintain statistical power.

The hierarchical order of components in the primary endpoint corresponds to clinical impact, with ACM and CVH as the first and second components due to their importance in clinical benefit-risk assessment, followed by NT-proBNP and 6MWD as morbidity and functional measures, respectively.

The initial power calculations, based on data from the ATTR-ACT study, estimated over 90% power for the two-component F-S test with approximately 510 participants. Simulations to assess power for the four-component hierarchical endpoint were conducted under various scenarios taking into consideration potential tafamidis use

and potentially missing data. The estimated power across the various scenarios remained above 80%.

The lower event rate for CVH appeared to be primarily driven by two factors:

1. A shift in the ATTR-CM patient population characterised by earlier diagnosis, increased disease awareness, and better disease management, as reported in the literature.(5) Changes in the management of ATTR-CM patients since ATTRibute-CM was initiated in March 2019 led to improved patient outcomes.(6-9) These factors contributed to increased survival, even in the absence of tafamidis. A more cautious use of traditional heart failure drugs like beta blockers, ACE inhibitors, and ARBs and increased reliance on diuretics had evolved.(8) This change reflected the unique cardiac pathophysiology of ATTR-CM, characterised by amyloid infiltration that stiffens the myocardium and reduces stroke volume, making patients sensitive to hypotension and intolerant to conventional therapies.(7, 8) Diuretics, along with dietary sodium restriction and careful dose adjustments, had become central to managing volume overload, while the use of calcium channel blockers and digoxin had declined due to associated risks in this population;(9-11) and

2. the shift toward remote assessments during the COVID-19 pandemic.(6, 12, 13) The COVID-19 pandemic led to a significant shift in healthcare utilisation, characterised by up to a 50% decrease in inpatient services due to patients' and providers' fears of virus exposure. This situation prompted increased reliance on outpatient resources, such as oral diuretic therapy, and a substantial rise in telehealth and remote assessments to manage patient care while minimising hospital admissions.

Appropriateness of Additional Components of the Hierarchical Primary Endpoint

CFB in NT-proBNP - NT-proBNP is a peptide biomarker released by the heart in response to ventricular wall stress and stretching, which is a common feature of heart failure and cardiomyopathy. Its levels rise as ATTR-CM progresses, making it a clinically relevant marker of disease progression and morbidity. It is recommended

by Cardiac Societies (e.g., the American Heart Association, American College of Cardiology, European Society of Cardiology, and the Heart Failure Society of America) for the diagnosis and clinical management of heart failure and cardiomyopathy.(14-16)

A clinically meaningful difference in NT-proBNP change from baseline (≥500 pg/mL) was added to primary analyses as a marker of disease progression after CV outcome assessments. While NT-proBNP is not considered a surrogate for clinical outcomes in the general HF population, the choice of NT-proBNP as a component in the hierarchical endpoint reflected current best practice of outpatient heart failure management and prognostic staging in ATTR-CM and was based on the following evidence:

- Its role as an intrinsic marker of disease activity in ATTR-CM with its progressive rise over time, as observed in the placebo arm of ATTR-ACT (3), reflecting the underlying disease pathophysiology with continued deposition of amyloid fibrils in the myocardium leading to progressively worsening heart failure leading to death.

- NT-proBNP plays a critical prognostic role in the clinical management of patients with ATTR-CM. Its role as a strong independent predictor of survival in ATTR-CM, has led to it being the cornerstone of all current well-established staging systems for ATTR-CM;(2, 17-19) in addition, the change in NT-proBNP at 1 year correlated with mortality (2) – a finding more recently validated in a multicentre study with a large cohort of patients with ATTR-CM (variant and wild type), including some patients prescribed disease-modifying therapy.(20) Between baseline and 1-year visits, 551 (34.5%) National Amyloidosis Centre (NAC) patients and 204 (30.1%) patients in the external validation cohort experienced NT-proBNP progression (NT-proBNP increase >700 ng/L and >30%), which was associated with mortality (NAC cohort: hazard ratio [HR]: 1.82; 95% CI: 1.57-2.10; p<0.001; validation cohort: HR: 1.75; 95% CI: 1.32-2.33; p<0.001).

- Its use in clinical practice guidelines to determine early cardiac disease (with its marked elevation disproportionate to the degree of heart failure, serving as

a “red flag”) and disease progression (21, 22) e.g., Changes in NT-proBNP, specifically relative increases greater than 30% and absolute increases over 300 pg/mL, are recommended by the European Society of Cardiology (ESC) expert consensus panel as indicators of disease progression in ATTR-CM patients.(23)

- NT-proBNP reduction following tafamidis treatment correlates with clinical improvement in ATTR-CM,(24, 25) paralleling findings in SGLT-2 inhibitor heart failure trials where NT-proBNP decreases aligned with better cardiovascular outcomes.(26, 27) Across randomised controlled trials of ATTR-CM specific therapies, treated patients typically show stabilisation or smaller NT-proBNP increases compared to placebo, with these differences emerging within months, underscoring NT-proBNP's value in monitoring disease progression and potentially guiding early intervention to alter high-risk patient trajectories.

- Data reported from studies of patients with AL amyloidosis (another cause of a similarly infiltrative, restrictive cardiomyopathy due to deposition of immunoglobulin light chain-derived amyloid in the heart) have established NT-proBNP as a reliable biomarker of clinical improvement in contemporary clinical studies.

Results from ATTRibute-CM and the open-label extension (OLE) support the above assertions of the clinical relevance of NT-proBNP as a biomarker of disease progression in ATTR-CM (and inversely a measure of treatment efficacy). Acoramidis treatment sharply attenuated the progressive increase in NT-proBNP. At Month 30, compared to baseline: AGM (adjusted geometric mean) fold-change in NT-proBNP was 47% lower with acoramidis relative to placebo (ratio of the AGM fold-change: 0.529; 95% CI: 0.463, 0.604; nominal p<0.0001).(4) This effect continued into the OLE.(28)

A recent abstract presentation at the European Society of Cardiology Congress (August 2025), further confirmed correlations between NT-proBNP and disease progression. In ATTRibute-CM, acoramidis treatment resulted in improved or stable NT-proBNP at Month 30 in about 50% of study participants compared with fewer

than 20% with placebo, indicating a clinically meaningful improvement in NT-proBNP and better stabilisation of their disease.(29)

CFB in 6MWD - 6MWD, assessed via the 6-minute walk test (6MWT) was conducted based on the guidelines of the American Thoracic Society guidelines (30). 6MWD measures submaximal exercise tolerance and serves as a clinically relevant endpoint recognised by regulatory agencies such as the US FDA and EMA in heart failure studies.(31, 32)

The 6MWD is a predictor of survival,(33) and is used as an index to evaluate functional exercise capacity, and risk of hospital readmission in patients with cardiopulmonary diseases including ATTR-CM, where a decline in 6MWD reflects worsening functional capacity and heart failure severity.(3, 30, 34, 35) Short-term improvements in 6MWD post-treatment are significant predictors of survival in chronic heart failure patients,(36) underscoring its importance in evaluating treatment efficacy in ATTR-CM.

In a recent analysis of ATTRibute-CM results - presented at the ESC Congress (August 2025) – showed acoramidis achieved clinically meaningful improvements from baseline in NT-proBNP and/or six-minute walk distance test across 30 months in >25% of patients.(37) A total of 106 (25.9%) participants in the acoramidis group showed improvement in at least one parameter compared with 19 (9.4%) in the placebo group (Odds ration [OR] 3.4, 95% CI 2.0–5.7, p<0.0001). Among those meeting both improvement criteria, 12 (2.9%) were in the acoramidis group compared with two (1.0%) in the placebo group (OR 3.0, 95% CI 0.7–13.6, p<0.1502).

Clinical Efficacy Outcomes

Despite changes to the primary endpoint, efficacy analyses consistently favoured acoramidis across multiple endpoint definitions and populations. Consistently positive findings were observed for the win ratios and F-S analyses across all the hierarchical component analyses as specified by the previous and current versions of the statistical analysis plan (SAP) (two-, three- or four-component F-S primary analysis), indicating the robustness of the observed efficacy of acoramidis regardless of the changes.(4) Statistically significant results were observed in both the modified intention-to-treat (mITT) and intention-to-treat (ITT) populations.

A2. Please confirm whether you searched for any relevant minimally clinically important differences (MCIDs) that could inform a formally specified non-inferiority margin.

No formal searches were conducted to identify MCIDs; however, based on ad-hoc searches of the literature, no studies were identified with MCIDs that could inform formally specified non-inferiority margins for key outcomes most relevant to informing the appropriateness of a cost comparison analysis between acoramidis and tafamidis (i.e., ACM and cardiovascular hospitalisation [CVH]).

It is important to highlight that the preferred setting for assessing equivalence between acoramidis and other treatments would have been a non-inferiority trial; however, no manufacturer of therapies indicated for ATTR-CM has yet conducted a head-to-head clinical trial. Phase III trials assessing non-inferiority typically require around four times the sample size than that of a similar superiority trial,(38) and therefore recruitment of sufficiently large samples sizes for a robust non-inferiority study in rare diseases (such as ATTR-CM) would be challenging. Therefore, it is not possible to undertake robust formal non-inferiority testing of these treatments.

To explore the concept of formal equivalence testing, some additional post-hoc analysis ("fixed margin analysis") was performed as outlined in Kaul and Diamond 2007.(39) However, it is critical to note that these types of post-hoc analyses typically suffer from a lack of statistical power and should only be interpreted as exploratory. Given that the MAIC results showed a statistically significantly lower rate of CVH for acoramidis compared to tafamidis, conducting non-inferiority testing is not required for this outcome. The primary purpose of non-inferiority testing is to establish that a new treatment is not worse than an existing treatment by a specified margin. However, since the MAIC indicates acoramidis to have superior efficacy in reducing CVH events compared to tafamidis, further non-inferiority testing would be redundant and would not provide any additional meaningful information, and therefore non-inferiority testing was performed for ACM only.

Fixed margin analyses seek to determine whether a new treatment (i.e., acoramidis) is inferior to the standard treatment (i.e., tafamidis) by no more than a predefined margin, and are applicable when the comparator study has demonstrated that the standard treatment (tafamidis) is superior to placebo. According to the "fixed margin

analysis", the maximum non-inferiority margin, d_{max}, is derived as the 95% lower confidence limit (LCL) of the HR for placebo versus the standard treatment. Non-inferiority of the new treatment versus the standard treatment is then declared when the 2-sided 95% CI of the MAIC results comparing the new treatment vs the standard treatment is entirely below this margin.

For example, when investigating non-inferiority of acoramidis vs tafamidis for ACM, the reported HR and 95% CI for tafamidis vs placebo in ATTR-ACT ($HR_{TAFA\ vs\ PBO}$=0.690 [95% CI: 0.487 – 0.979]) are inverted to obtain a HR and 95% CI for placebo vs tafamidis ($HR_{PBO\ vs\ TAFA}$ = 1.449 [95% CI: 1.021 – 2.053]). In this example, $d_{max} = 1.021$ and [redacted]

To further explore equivalence testing, Monte-Carlo simulation was used to estimate the probability that the MAIC-weighted HR for acoramidis vs placebo, is lower than the observed HR for tafamidis vs placebo. This simulation was conducted by drawing 1,000,000 values from two independent normal distributions, parameterised to match the reported HRs and their corresponding 95% confidence intervals.

- A probability of $HR_{ACO\ vs\ PBO} < HR_{TAFA\ vs\ PBO}$ that is close to 50%, supports the hypothesis of non-inferiority as it reflects that the distributions of the reported HRs are indistinguishable.

- A probability of $HR_{ACO\ vs\ PBO} < HR_{TAFA\ vs\ PBO}$ that is higher than 50% may indicate that the assumption of non-inferiority is conservative.

- The probability of $HR_{ACO\ vs\ PBO} < HR_{TAFA\ vs\ PBO}$ will typically be lower than 50% when the MAIC-weighted HR in ATTRibute-CM is higher than the reported HR

from ATTR-ACT. However, acoramidis could still be non-inferior to tafamidis if both treatments are efficacious compared to placebo and a fixed margin analysis supports non-inferiority.

The table below shows the results and conclusions from the fixed margin analyses and Monte-Carlo simulation probability calculations conducted to investigate the non-inferiority of acoramidis vs tafamidis based on the MAIC. Monte-Carlo simulation probabilities presented are those for the company-preferred base case MAIC analyses (MAIC scenarios 3 and 6, with hypothetical strategy).

Table 1. Results and conclusions from fixed margin analyses and probability calculations conducted to investigate the non-inferiority of acoramidis vs tafamidis

Outcome	Study	Comparison	HR (95% CI)	d_{max}	Probability that $HR_{ACO\ vs\ PBO} < HR_{TAFA\ vs\ PBO}$	Non-inferiority assessment
ACM	ATTRibute-CM	ACO vs PBO (naïve comparison)	[redacted]	1.021	MAIC Scenario 3: [redacted] MAIC Scenario 6: [redacted]	[redacted]
		ACO vs PBO (MAIC-weighted)	MAIC Scenario 3: [redacted] MAIC Scenario 6: [redacted]*			
	ATTR-ACT	TAFA vs PBO	0.690 (0.487 – 0.979)			
	MAIC	ACO vs TAFA	MAIC Scenario 3: 0.719 (0.409, 1.264)* MAIC Scenario 6: [redacted]*			

ACM = all-cause mortality; ACO = acoramidis; CI = confidence interval; HR = hazard ratio; MAIC = matching adjusting indirect comparison; PBO = placebo; TAFA = tafamidis.
*With hypothetical strategy results.

Indirect treatment comparison

A3. Priority question: The CS states that network meta-analysis (NMA) was considered inappropriate due to heterogeneity. However, random-effects NMA models can be used to allow for a between-study variance component to take heterogeneity into account and typically produce more reliable estimates and involve fewer assumptions around effect modifiers than MAIC analyses.

a) Could the company please provide further justification for the choice of anchored MAIC over NMA?

As only one study each were available comparing acoramidis vs. placebo (i.e., ATTRibute-CM) and comparing tafamidis vs. placebo (ATTR-ACT), it was not possible to estimate a random-effects variance component in any ITC. Thus, only Bucher analyses were conducted and results provided in Table 26 and Table 28 in the original company submission (CS). We would also like to note that the NMA model as well as Bucher ITCs have a strong assumption of no effect modification; the anchored MAIC model does not have this assumption. If the variables adjusted for in the MAIC model are not in fact effect modifiers, they will have little impact on the point estimates but may increase uncertainty. Therefore, we believe that the anchored MAIC analyses presented provide a more robust comparison of acoramidis versus tafamidis than an NMA model or Bucher ITC.

b) NMA results would be useful for validation of the MAIC

The effect of acoramidis vs. tafamidis for ACM and CVH from the Bucher ITC are reproduced below in Table 2.

Table 2. Bucher ITC: ITT population

Comparison	ACM		CVH (excl. EOCI)	
	Without HS HR (95% CI)	**HS HR (95% CI)**	**Without HS RRR (95% CI)**	**HS RRR (95% CI)**
Acoramidis vs. Tafamidis 80 mg	1.105 (0.678, 1.799)	1.268 (0.765, 2.103)	0.725 (0.540, 0.975)	0.744 (0.550, 1.008)

ACM = all-cause mortality; CI = confidence interval; CVH = cardiovascular-related hospitalisation; EOCI = events of clinical interest; HR = hazard ratio; HS = hypothetical scenario; ITC = indirect treatment comparison; ITT = intent to treat; RRR = relative risk reduction

For more detailed results please see Table 26 and Table 28 of the original CS where detailed results from the Bucher ITC and MAIC analyses were provided.

c) Given that the control arm (usual care) has changed between the tafamidis and acoramidis trials and is unlikely to be of the same efficacy, please justify why an anchored MAIC is considered appropriate, instead of an unanchored MAIC

In the ATTRibute-CM study, the change in the standard of care (SOC) impacted not only patients who were randomised to the placebo arm, but also those in the acoramidis arm, i.e., both placebo and acoramidis were administered on top of the SOC. Therefore, it can be assumed that the added benefit of the improved SOC impacts outcomes for both the placebo and acoramidis arms similarly. In other words, standard of care is a prognostic factor but not an effect modifier, which was also confirmed by clinical experts. Thus, the added SOC effect is expected to cancel out when deriving the relative effect of acoramidis vs. placebo within the ATTRibute-CM from anchored MAIC analyses.

Similarly, in the ATTR-ACT study, both tafamidis and placebo treatments were given in addition to the older SOC. Thus, the estimated relative effect of tafamidis vs. placebo from ATTR-ACT should also be unaffected by background SOC. Nevertheless, sensitivity analyses were performed for the MAIC analyses adjusting for differences in SOC by including beta blockers, agents acting on renin-angiotensin system, diuretics, antithrombotic agents and permanent pacemaker as additional covariates in the adjustment. Results and conclusions were the same as for Scenario 3 or 6, which confirms the hypothesis that SOC is likely a prognostic factor and not an effect modifier (see Table 27 and Table 29 of the original CS).

In contrast, in unanchored MAIC analyses, the derived estimand will be the relative effect of tafamidis combined with the old SOC versus acoramidis with the new SOC. It would be impossible to isolate the effect of tafamidis compared to acoramidis in this scenario and assess the impact of the new versus old SOC on the estimated treatment effect. Additionally, unanchored MAIC requires much stronger assumptions and is subject to significant limitations, as described in the NICE TSD 18.

d) It appears (Document B, p.83 onwards) that the company MAIC adjusted for prognostic factors as well as treatment effect modifiers. Please justify this, given TSD guidance that all MAICs should adjust for treatment effect modifiers, but only unanchored MAICs should adjust for prognostic factors.

Six different matching scenarios were conducted to address differences in clinical expert opinion on potential effect modifiers or to allow for more granular adjustment for some effect modifiers (i.e., age). The selection of potential treatment effect modifiers for matching was informed by published evidence from each trial (i.e., forest plots) and interviews with UK clinical experts.(40) As a result, NYHA class, eGFR, NT-proBNP, TTR genotype, and age were selected as potential treatment effect modifiers which are also considered strong prognostic factors. Table 2 shown below in response to clarification question A3e summarises the details of the matching scenarios that were considered in the MAIC analyses.

To address the concerns regarding the differences in the SOC between the ATTRibute-CM and ATTR-ACT studies, which are evident from the large imbalance in medications and the use of permanent pacemakers at baseline (See Table 23 and Table 24 in the original CS), additional exploratory MAIC analyses were conducted. These analyses adjusted for the following factors:

- Beta blockers
- Agents acting on renin-angiotensin system
- Diuretics
- Antithrombotic agents
- Permanent pacemaker

Results from these analyses were similar and consistent to results from MAIC Scenario 3 and Scenario 6 but with additional reduction in ESS (see Table 27 and Table 29 of the original CS), which suggest that these factors are indeed only prognostic and not effect modifiers. Clinical experts also agreed that these medications and devices are likely only prognostic factors. Thus, these additional analyses were considered as exploratory and confirmatory.

e) Please provide a table clearly stating what each of the MAIC scenarios adjusts for and which is the company's preferred analysis.

Table 3 shown below was presented as Table 13 in Appendix D of the original CS, and summarises the details of the matching scenarios that were considered in the MAIC analyses. Results from Scenario 3 and Scenario 6 analyses were considered as the primary analyses since in these scenarios, all selected EMs were matched and adjusted for. After applying the hypothetical strategy, the results suggested a statistically significantly lower cumulative frequency of CVH (RRR: 0.663 [95% CI: 0.463, 0.948] in Scenario 3 and RRR: [redacted] in Scenario 6) for acoramidis vs. tafamidis and a tendency for lower ACM (HR: 0.719, [95%CI: 0.409, 1.264] in Scenario 3 and HR: [redacted] in Scenario 6).

Table 3. MAIC matching scenarios for efficacy

Matching scenarios	Effect modifiers adjusted through matching by exclusion of patients in the ITT population of ATTRIBUTE to match inclusion criteria of ATTR-ACT	Effect modifiers selected for adjusting through weights	Description
Scenario 1	• Patients with eGFR <25mL/min/1.73m^2 or missing at screening • Patients with NT-proBNP <0.600 ng/mL or missing at screening	• TTR genotype (proportions mutant vs. wild type) • NYHA class (proportions I vs. II vs. III) • NT-proBNP (pg/mL) (median, min, max, mean)	This scenario was designed excluding age because clinical experts were not sure if age is an effect modifier or prognostic factor. One clinical expert felt that age can be an effect modifier at the extremities of age (e.g. age ≥75).
Scenario 2	• Patients with eGFR <25mL/min/1.73m^2 or missing at screening • Patients with NT-proBNP <0.600 ng/mL or missing at screening	• NYHA class (proportions I vs. II vs. III) • NT-proBNP (pg/mL) (median, min, max, mean)	This scenario was designed excluding TTR genotype in addition to age because one of the clinical experts wasn't sure if genotype and age are effect modifiers or merely prognostic factors.
Scenario 3	• **Patients with eGFR <25mL/min/1.73m^2 or missing at screening** • **Patients with NT-proBNP <0.600 ng/mL or missing at screening**	• **TTR genotype (proportions mutant vs. wild type)** • **NYHA class (proportions I vs. II vs. III)** • **NT-proBNP (pg/mL) (median, min, max, mean)** • **Age (median, min, max, proportion <65 vs. ≥65)**	**This scenario was designed to evaluate the impact of matching on all potential effect modifiers.**
Scenario 4	• Patients with NT-proBNP <0.600 ng/mL or missing at screening	• TTR genotype (proportions mutant vs. wild type) • NYHA class (proportions I vs. II vs. III)	This scenario was designed without excluding patients with eGFR <25mL/min/1.73m^2 per clinical experts request to offset the fact that ATTR-ACT may have included some

Matching scenarios	Effect modifiers adjusted through matching by exclusion of patients in the ITT population of ATTRIBUTE to match inclusion criteria of ATTR-ACT	Effect modifiers selected for adjusting through weights	Description
		• NT-proBNP (pg/mL) (median, min, max, mean) • Age (median, min, max, proportion <65 vs. ≥65)	patients with NT-proBNP ≥8,500 pg/ml.
Scenario 5	• Patients with eGFR <25mL/min/1.73m^2 or missing at screening • Patients with NT-proBNP <0.600 ng/mL or missing at screening	• NYHA class (proportions I vs. II vs. III) • NT-proBNP (pg/mL) (median, min, max, mean) • Age (median, min, max, proportion <65 vs. ≥65, proportion <80 vs. ≥80)	This scenario was designed to assess impact of adjusting for age but not TTR genotype as two factors are correlated.
Scenario 6	• **Patients with eGFR <25mL/min/1.73m^2 or missing at screening** • **Patients with NT-proBNP <0.600 ng/mL or missing at screening**	• **TTR genotype (proportions mutant vs. wild type)** • **NYHA class (proportions I vs. II vs. III)** • **NT-proBNP (pg/mL) (median, min, max, mean)** • **Age (mean, median, min, max, proportion <65 vs. ≥65, proportion <80 vs. ≥80)**	**This scenario was designed to evaluate the impact of matching on more moments of the distribution of age than were matched in scenario 3.**

eGFR = estimated glomerular filtration rate; ITT= intention-to-treat; MAIC = matching-adjusted indirect comparison; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; TTR = transthyretin

Adverse events

A4. No information in ATTRibute-CM was provided specifically on Grade 3 Adverse Events or Grade 3 Treatment-Emergent Adverse Events. Is such information available?

Adverse events (AEs) were not classified as per the CTCAE scale using Grade1-5. *(Common Toxicity Criteria version 5.0 Grade 3 definition: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL).* Instead, the protocol for

ATTRibute-CM specified that the investigator provide an assessment of the severity of each AE according to the following scale:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

TEAEs in ATTRibute-CM include any AE occurring from the time that the participant signed an ICF:

(1) Until 30 days after the last dose of study drug, if the participant did not rollover to the OLE Study AG10-304, or rolled over in Study AG10-304 (received first dose in Study AG10-304) 30 days or more after the last dose in Study AG10-301 or

(2) until the day of rollover in Study AG10-304 (day of first dose in Study AG10-304) if the participant rolled over in Study AG10-304 less than 30 days after the last dose in Study AG10-301.

All AEs reported in the acoramidis submission are treatment-emergent adverse events (TEAEs) in line with the above definition.

A summary of the most common TEAEs (occurring in ≥ 5% patients in either group) by System Organ Class, Preferred Term and Worst Severity is presented in Table 4. Where an investigator deemed an AE was related to study drug, this is noted in the table.

Table 4. Severity and relationship of TEAEs reported in ≥5% of patients in any treatment group in ATTRibute-CM (Safety population) (4, 41)

	Acoramidis N=421				Placebo N=211			
System organ class Preferred Term	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Any TEAE *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	**157 (37.3%)**	**413 (98.1%)**	[redacted]	[redacted]	**96 (45.5%)**	**206 (97.6%)**
Cardiac disorders	[redacted]	[redacted]	[redacted]	230 (54.6)	[redacted]	[redacted]	[redacted]	144 (68.2)
Cardiac failure	[redacted]	[redacted]	[redacted]	101 (24.0)	[redacted]	[redacted]	[redacted]	83 (39.3)
Atrial fibrillation	[redacted]	[redacted]	[redacted]	70 (16.6)	[redacted]	[redacted]	[redacted]	46 (21.8)
Cardiac failure acute *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	[redacted]	27 (6.4)	[redacted]	[redacted]	[redacted]	17 (8.1)
Bradycardia	[redacted]	[redacted]	[redacted]	23 (5.5)	[redacted]	[redacted]	[redacted]	9 (4.3)
Ventricular tachycardia	[redacted]	[redacted]	[redacted]	17 (4.0)	[redacted]	[redacted]	[redacted]	14 (6.6)
Atrial flutter	[redacted]	[redacted]	[redacted]	22 (5.2)	[redacted]	[redacted]	[redacted]	9 (4.3)
Cardiac failure chronic	[redacted]	[redacted]	[redacted]	17 (4.0)	[redacted]	[redacted]	[redacted]	11 (5.2)
Infections and infestations	[redacted]	[redacted]	[redacted]	**246 (58.4)**	[redacted]	[redacted]	[redacted]	**116 (55.0)**
COVID-19	[redacted]	[redacted]	[redacted]	89 (21.1)	[redacted]	[redacted]	[redacted]	30 (14.2)
Urinary tract infection	[redacted]	[redacted]	[redacted]	51 (12.1)	[redacted]	[redacted]	[redacted]	28 (13.3)
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	24 (5.7)	[redacted]	[redacted]	[redacted]	12 (5.7)
Nasopharyngitis	[redacted]	[redacted]	[redacted]	21 (5.0)	[redacted]	[redacted]	[redacted]	11 (5.2)
Pneumonia	[redacted]	[redacted]	[redacted]	16 (3.8)	[redacted]	[redacted]	[redacted]	14 (6.6)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	**221 (52.5)**	[redacted]	[redacted]	[redacted]	**98 (46.4)**
Constipation *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	[redacted]	52 (12.4)	[redacted]	[redacted]	[redacted]	32 (15.2)
Diarrhoea *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	[redacted]	49 (11.6)	[redacted]	[redacted]	[redacted]	16 (7.6)
Nausea *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	[redacted]	24 (5.7)	[redacted]	[redacted]	[redacted]	11 (5.2)
Abdominal pain upper *[deemed Drug-Related by investigator]*	[redacted]	[redacted]	[redacted]	23 (5.5)	[redacted]	[redacted]	[redacted]	3 (1.4)
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	**184 (43.7)**	**44 (20.9)**	**33 (15.6)**	**6 (2.8)**	**83 (39.3)**
Arthralgia	[redacted]	[redacted]	[redacted]	48 (11.4)	[redacted]	[redacted]	[redacted]	23 (10.9)
Back pain	[redacted]	[redacted]	[redacted]	39 (9.3)	[redacted]	[redacted]	[redacted]	14 (6.6)
Muscle spasms	[redacted]	[redacted]	[redacted]	34 (8.1)	[redacted]	[redacted]	[redacted]	15 (7.1)
Pain in extremity	[redacted]	[redacted]	[redacted]	30 (7.1)	[redacted]	[redacted]	[redacted]	11 (5.2)
Osteoarthritis	[redacted]	[redacted]	[redacted]	12 (2.9)	[redacted]	[redacted]	[redacted]	12 (5.7)
Nervous system disorders	[redacted]	[redacted]	[redacted]	**182 (43.2)**	[redacted]	[redacted]	[redacted]	**77 (36.5)**

	Acoramidis N=421				Placebo N=211			
System organ class **Preferred Term**	**Mild** **n (%)**	**Moderate** **n (%)**	**Severe** **n (%)**	**Total** **n (%)**	**Mild** **n (%)**	**Moderate** **n (%)**	**Severe** **n (%)**	**Total** **n (%)**
Dizziness *[deemed Drug-Related by investigator]*				46 (10.9)				23 (10.9)
Syncope				21 (5.0)				15 (7.1)
Metabolism and nutrition disorders				**149 (35.4)**				**85 (40.3)**
Gout				47 (11.2)				17 (8.1)
Hypervolaemia				23 (5.5)				18 (8.5)
Hypokalaemia				22 (5.2)				12 (5.7)
Decreased appetite *[deemed Drug-Related by investigator]*				19 (4.5)				11 (5.2)
Respiratory, thoracic and mediastinal disorders				**146 (34.7)**				**86 (40.8)**
Dyspnoea *[deemed Drug-Related by investigator]*				52 (12.4)				40 (19.0)
Cough				32 (7.6)				18 (8.5)
Epistaxis *[deemed Drug-Related by investigator]*				22 (5.2)				7 (3.3)
Pleural effusion				11 (2.6)				13 (6.2)
General disorders and administration site conditions				**144 (34.2)**				**79 (37.4)**
Fatigue *[deemed Drug-Related by investigator]*				42 (10.0)				26 (12.3)
Oedema peripheral *[deemed Drug-Related by investigator]*				33 (7.8)				25 (11.8)
Asthenia				22 (5.2)				9 (4.3)
Peripheral swelling				7 (1.7)				14 (6.6)
Injury, poisoning and procedural complications				**137 (32.5)**				**81 (38.4)**
Fall				67 (15.9)				39 (18.5)
Skin laceration				13 (3.1)				11 (5.2)
Renal and urinary disorders				**142 (33.7)**				**64 (30.3)**
Acute kidney injury				52 (12.4)				22 (10.4)
Renal impairment				37 (8.8)				17 (8.1)
[deemed Drug-Related by investigator]								
Haematuria				18 (4.3)				16 (7.6)
Investigations				**127 (30.2)**				**68 (32.2)**
Blood creatinine increased *[deemed Drug-Related by investigator]*				26 (6.2)				4 (1.9)
Weight decreased *[deemed Drug-Related by investigator]*				16 (3.8)				13 (6.2)

	Acoramidis N=421				Placebo N=211			
System organ class Preferred Term	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Skin and subcutaneous disorders				**108 (25.7)**				**53 (25.1)**
Pruritis *[deemed Drug-Related by investigator]*				25 (5.9)				8 (3.8)
Rash *[deemed Drug-Related by investigator]*				21 (5.0)				11 (5.2)
Vascular disorders				**88 (20.9)**				**49 (23.2)**
Hypotension *[deemed Drug-Related by investigator]*				33 (7.8)				14 (6.6)
Psychiatric disorders				**57 (13.5)**				**39 (18.5)**
Insomnia				20 (4.8)				16 (7.6)
Blood and lymphatic system disorders				**61 (14.5)**				**29 (13.7)**
Anaemia				37 (8.8)				17 (8.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)				**54 (12.8)**				**36 (17.1)**
Basal cell carcinoma				16 (3.8)				13 (6.2)
Eye disorders				**46 (10.9)**				**26 (12.3)**
Reproductive system and breast disorders *[deemed Drug-Related by investigator]*				**28 (6.7)**				**23 (10.9)**
Ear and labyrinth disorders				**22 (5.2)**				**10 (4.7)**
Endocrine disorders *[deemed Drug-Related by investigator]*				**22 (5.2)**				**9 (4.3)**

AE = adverse event; COVID-19 = coronavirus disease 2019; n = number of patients experiencing a TEAE (the patient was counted only once for each AE); N = number of patients in the study arm; TEAE = treatment-emergent adverse event

Section B: Clarification on cost-effectiveness data

Symptomatic management acquisition costs

B1. Please clarify why symptomatic management acquisition costs are included in the company's analysis. Section B.4.2.3.1 states that "*SM acquisition costs (Table 48) are applied in addition to active treatment costs for patients on treatment, while patients who are off treatment and alive only incur SM related costs*".
This suggests that patients who are on treatment, off treatment, and alive all incur SM treatment costs. Are those costs allocated consistently across acoramidis and tafamidis? If so, please explain the rationale for including symptomatic management acquisition costs in the analysis or confirm that they can be ignored in the incremental analysis.

Symptomatic management (SM) costs are included for patients on both acoramidis and tafamidis, as well as for those discontinuing active treatment, with the same distribution of SM therapies applied in each case. Although inclusion of these costs does not impact the incremental analysis results, SM costs were included to more accurately represent the total expected drug acquisition costs for each comparator, as well as the overall cost of patients alive and off treatment after discontinuation of acoramidis or tafamidis (when combined with SM only adverse event costs).

Adverse events

B2. Please clarify the rationale for selecting nausea, diarrhoea, and urinary tract infection as the adverse events included in the company's base case analysis. [redacted]? In addition, section B.3.9.10 notes that gout occurred more frequently with acoramidis than placebo (11.2% vs 8.1%) and is

listed in the acoramidis SmPC as a very common event; why was gout not included as an adverse event in the analysis?

As described in Section B.4.2.5 of the original CS, the selection of AEs was based on NICE TA984 for tafamidis, due to the similar mechanism of action between tafamidis and acoramidis. The list of TEAEs included in the analysis was also validated with clinical experts,(40) who emphasized the negligible impact anticipated from TEAEs given the observed safety of the treatments, with both treatments considered safe and well-tolerated. Other TEAEs were deemed to be related to the age and condition of the target population and were thus excluded from the analysis.

Although a higher incidence of gout events (11.2% vs 8.1%) was observed for the acoramidis arm than the placebo arm in ATTRibute-CM, a similar total proportion of patients on tafamidis in the ATTR-ACT trial (10.6%) experienced gout compared to acoramidis in ATTRibute-CM, and therefore inclusion of these events in addition to those included in the model based on NICE TA984 were not expected to have a substantial impact on the results. Abdominal discomfort and upper abdominal pain events were not reported for tafamidis from the ATTR-ACT study making it challenging to present a fair comparison to acoramidis. However, given that lower overall TEAE incidence was observed in ATTRibute-CM for acoramidis and placebo arms for abdominal discomfort and upper abdominal pain than other TEAEs included in the cost comparison model (diarrhoea, nausea and urinary tract infection), inclusion or exclusion of these events was also not anticipated to have a substantial impact on the results.

It is important to note that the costs associated with AEs generally have a negligible impact on results, accounting for <1% of the total costs in either comparator arm and <0.1% of total incremental costs in both list and PAS prices analyses, despite a relatively conservative approach to costing where day case hospitalisation costs are applied to all AEs in the analysis regardless of severity. Furthermore, the cost comparison model also conservatively uses TEAEs rather than treatment-related adverse events (TRAEs) which may include a number of events relating to other factors (such as age) rather than events directly relating to the treatments themselves.

However, an additional scenario analysis has been conducted to assess the impact of including abdominal discomfort, upper abdominal pain and gout as adverse events in the cost comparison model.

The frequencies applied for these adverse events, along with those utilised in the original company cost comparison analysis, are presented in Table 5. Abdominal discomfort and upper abdominal pain adverse event frequencies were not identified from the ATTR-ACT trial and therefore were conservatively assumed to be 0%. Please note that figures utilised for abdominal discomfort and upper abdominal pain differ from those presented in Section B.3.9.4 of the original CS, as TEAE frequencies are utilised rather than TRAEs for consistency with other AE probabilities included in the model.

Table 5. Adverse event frequencies

Adverse event	Acoramidis + SM	Tafamidis + SM	SM
Observed frequency			
Diarrhoea	11.6%	12.1%	7.6%
Nausea	12.1%	9.5%	13.3%
Urinary tract infection	5.7%	11.0%	5.2%
Gout	11.2%	10.6%	8.1%
Abdominal discomfort	[redacted]	NR	[redacted]
Upper abdominal pain upper	5.5%	NR	1.4%
Follow-up (months)	30	30	30
Estimated Monthly frequency			
Diarrhoea	0.39%	0.40%	0.25%
Nausea	0.19%	0.37%	0.17%
Urinary tract infection	0.40%	0.32%	0.44%
Gout	0.37%	0.35%	0.27%
Abdominal discomfort	[redacted]	0%*	[redacted]
Abdominal pain upper	0.18%	0%*	0.05%
Source reference for AE frequencies	Data on file, ATTRibute-CM CSR output, Table 14.3.1.11 Treatment-Emergent Serious Adverse Events by Preferred Term.	Maurer et al 2018(3)	Data on file, ATTRibute-CM CSR output, Table 14.3.1.11 Treatment-Emergent Serious Adverse Events by Preferred Term; These are applied for all treatment arms after treatment discontinuation.

AEs = Adverse Events; CSR = clinical study report; SM = symptomatic management
*Assumed equal to 0% in the absence of events identified from the ATTR-ACT trial.

Cost inputs for each event, including AEs included in the original company model, are shown in Table 6, with the resulting total monthly costs of AE management displayed in Table 7. A weighted average of abdominal pain-related day case hospitalisation costs (FD05A and FD05B) also applied for abdominal discomfort adverse events in the absence of other appropriate NHS reference cost codes. For gout, day case hospitalisation costs were applied based on a weighted average of codes for inflammatory, spine, joint or connective tissue disorders (HD23D-J).

Table 6. Adverse event costs

Adverse event	Unit Cost	Source
Diarrhoea	£511.24	NHS Cost Collection 2023/2024 (FD10J-M, day case)(42)
Nausea	£511.24	NHS Cost Collection 2023/2024 (FD10J-M, day case)(42)
Urinary tract infection	£355.69	NHS Cost Collection 2023/2024 (LA04N-S, day case)(42)
Gout	£558.97	NHS Cost Collection 2023/2024 (HD23D-J, day case)(42)
Abdominal discomfort	£421.88	NHS Cost Collection 2023/2024 (FD05A-B, daycase)
Upper abdominal pain	£421.88	NHS Cost Collection 2023/2024 (FD05A-B, daycase)

AEs = Adverse Events; SM = symptomatic management

Table 7. Monthly cost of AEs management of the intervention and comparator technologies (Additional AEs scenario analysis)

	Acoramidis + SM	Tafamidis + SM	SM
Monthly cost of AE management	[redacted]	£7.01	[redacted]

AEs = Adverse Events; SM = symptomatic management

Cost comparison analysis results for the base case analysis, compared with a scenario analysis including gout, abdominal discomfort and upper abdominal pain adverse event costs, are presented in Table 8. Including these additional AEs in the analysis results in an additional total cost of [redacted] in the acoramidis + SM treatment arm and [redacted] in the tafamidis + SM treatment arm. Consequently, the total incremental cost differences between acoramidis and tafamidis changes from [redacted] to [redacted] for the acoramidis list price analysis, and from [redacted] to [redacted] when considering the acoramidis price inclusive of the proposed PAS discount, indicating a marginal change in the total incremental costs.

Table 8. Results comparison

Technologies	Acquisition costs (£)	Adverse event costs (£)	Total costs (£)
Acoramidis list price – base case			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]
Acoramidis list price – additional AEs scenario analysis			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]
Acoramidis PAS price – base case			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]
Acoramidis PAS price – additional AEs scenario analysis			
Acoramidis + SM	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]

AE = adverse event; PAS = patient access scheme; SM = symptomatic management

Systematic cost and resource use review

B3. Appendix G contains a systematic review to identify published studies reporting costs and healthcare resource use in patients with wild type or hereditary transthyretin amyloid cardiomyopathy. Was the information gathered from this review used in the company's submission? If so, please indicate where and how it was incorporated; if not, please explain why.

Although some ATTR-CM cost and healthcare resource use studies were identified from the systematic literature review (such as Asher 2022 and Lane 2019),(34, 43) no studies identified were determined to be relevant to the cost comparison analysis in terms of indicating differences in drug wastage and medical resource use (or other non-drug acquisition and adverse event costs) between acoramidis and tafamidis. As

noted in Section 4.2.7 of the original CS, drug wastage and other medical resource use costs were anticipated to be similar between both treatments, under the assumption of equivalent efficacy based on results of the MAIC and feedback from two UK clinical experts.(44)

In addition, no suitable alternative values for other relevant inputs included in the cost comparison analysis (such as time on treatment or adverse events) were identified from the systematic literature review. Therefore, use of ATTRibute-CM and ATTR-ACT trial data in combination with standard UK sources for drug acquisition and adverse event costs was determined to be the most appropriate approach.

Section C: Textual clarification and additional points

C1. Please state the source of the study type search filters used for the systematic review searches – are they validated filters or developed in house?

The SLR used the SIGN filters for randomised controlled trials:
Scottish Intercollegiate Guidelines Network. Randomised Controlled Trials. [undated]. https://www.sign.ac.uk/what-we-do/methodology/search-filters/.

Additional queries

Can acoramidis be managed via remote consultation like tafamidis (for patients who do not live within the catchment area of a specialist centre)?

Yes, acoramidis treatment will be managed in the same way as tafamidis. The NAC in London provides a highly specialised service for people with amyloidosis and related disorders and UK patients have generally been referred here for assessment, diagnosis, monitoring and treatment. To cope with the increase in patient referrals and continue to provide a timely diagnosis, new hubs are being established around the UK, receiving remote multidisciplinary expertise from the NAC. It is envisaged that, upon introduction within the NHS, acoramidis will provide an effective alternative treatment option to tafamidis for clinicians to use in patients diagnosed with ATTR-CM. Use of acoramidis does not require any additional tests or investigations beyond those already used in standard clinical practice.

Can the company describe the package of care for acoramidis and how this differs (if at all) from that supplied for tafamidis?

Bayer are currently in consultation with a homecare provider to put in place arrangements to deliver prescribed acoramidis to patients in their own home. The intention is that this Bayer funded service will mirror that provided by Pfizer for tafamidis. In addition, Bayer are in the process of exploring the development of a patient support programme in collaboration with the NAC.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Patient Organisation Submission

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 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. [Please note that declarations of interests relevant to this topic are compulsory].

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	Amyloidosis UK (formerly UK ATTR Amyloidosis Patients Association or UKATPA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a small national charity who aim to improve the lives of anyone affected by amyloidosis in the UK by providing information, support and access to a community of other living with the disease. To the best of our knowledge, we are the only charity in the UK dedicated solely to supporting patients living with amyloidosis. Our board of trustees consists entirely of individuals living with amyloidosis, ensuring patient-led insight in all our work. We are funded through a combination of donations and industry grants. While we are not a membership organisation, we currently maintain a mailing list of approximately 400 individuals.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Yes – Amyloidosis UK received a grant of £7500 from BridgeBio/Eidos to help us support the Amyloidosis Ireland Conference in June 2025.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information about the experiences of patients and caregivers in the following ways: • Our board of trustees comprises only amyloidosis patients, including two ATTR-CM patients, therefor the patient experience is always at the heart of our work. • Speaking directly to patients about their lived experience of cardiac ATTR amyloidosis. • Observing the common problems & questions people seek our support with, observation of discussion during patient support groups. • Engaging with healthcare professionals who have a wealth of experience in caring for patients with ATTR amyloidosis including staff from the National Amyloidosis Centre, and members of our advisory group. • Attending conferences and events that bring the amyloidosis community together.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Cardiac ATTR amyloidosis (ATTR-CM) progressive, debilitating and ultimately fatal disease that affects every aspect of a patient's life. It causes loss of mobility and independence, leading to a poor quality of life for both sufferers and their carers. Patients with ATTR-CM can experience a wide range of multisystemic symptoms and severely delayed or misdiagnoses are common, meaning patients often live with these symptoms for years without appropriate treatment. Below is a description of some of the impacts of living with ATTR-CM **as expressed by patients:** **Severely reduced exercise/exertion tolerance** Many patients struggle to walk up the stairs in their homes. One patient said he needs to rest after climbing every 2 to 3 steps, so it can take a long time, sometimes resorting to using his hands and knees to 'crawl' up the stairs. Many patients have to simply avoid walking up even small inclines. This can affect every aspect of life from work, shopping, visiting family and friends, to holidays. Another patient described the feeling of not being able to join in with the dancing at a family party, saying how this made him feel frustrated and upset. *[Patients with ATTR-CM] reported low energy, malaise, and "heaviness" in their limbs, 'twitching, clumsiness, buckling knees, and trouble maintaining their balance*.[1] 1. Rintell, D., Heath, D., Braga Mendendez, F., Cross, E., Cross, T., Knobel, V., Gagnon, B., Turtle, C., Cohen, A., Kalmykov, E. and Fox, J. (2021). Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: results of two focus groups. *Orphanet Journal of Rare Diseases*, 16(1). doi:https://doi.org/10.1186/s13023-021-01706-7. **Fatigue** Fatigue is very common among ATTR-CM patients. One patient described how he struggles to walk 300 to 400 yards from his car to his desk at work and is fatigued by the time he gets to his desk. Fatigue has a substantial impact on every aspect of life, including work, social and family life. It frequently interferes with the patient's ability to take part in everyday tasks or activities that previously brought enjoyment. Many ATTR-CM patients are forced to retire early due to fatigue. **Breathlessness** Breathlessness is another symptom common symptom that contributes to reduced mobility and can be very distressing. Almost all patients with cardiac ATTR amyloidosis, even those at earlier stages of the disease, find that the breathlessness is extremely limiting in their usual daily activities, and for some can be the cause of anxiety or panic.

	'I used to walk the dog all the time, every day, morning and at night. Now, when I physically start to walk, I get really tired, my legs ache, get out of breath, that is the thing that really bugs me, is getting out of breath.' – Patient **Dizziness, falling and fainting.** Many patients have unstable blood pressure so if they stand up too quickly it can cause them to feel very dizzy such that they have to sit down again, or they fall over or faint. This can happen anywhere, is dangerous, and can result in serious injury and hospitalisation. The fear of fainting or falling is very common among patients with some restricting their activities for fear of fainting when out in public or alone. 'I*f I get up too quick, I might faint or when I am walking and out of breath or if I bend over try to do my shoelaces or whatever and I find I get a little bit lightheaded'.* - Patient **Abnormal heart rhythms** One of the effects of ATTR-CM is that the heart develops abnormal rhythms- beating too slow, too fast or skipping beats. These can be distressing when they happen and can also be dangerous, causing people to faint or the heart can even stop beating which can result in death. To manage these arrhythmias patients often need to have pacemakers and/or other medical devices fitted. Sometimes, even that does not work, patients, therefore, must live with the constant spectre of a potential heart attack. **Pain** People with cardiac amyloidosis can experience severe chest pain, as well as pain in the limbs. Water retention in the legs can make them swell and become uncomfortable or painful further restricting mobility. ATTR-CM can cause gastric symptoms, so stomach pain and cramps are also common among patients. **Loss of independence** Being less mobile and breathless after even minor tasks means that patients must depend on their caregivers more and more as the disease advances. Male and female patients alike find this difficult as they are less and less able to care for themselves independently or to carry out household tasks. Frequently patients' partners and sometimes their children become carers. Patients often struggle with the loss of independence coupled with feeling like a burden on their loved ones. **Financial burden** Having to reduce working hours or retire earlier than expected can place a huge financial strain on patients and their families. **Caregivers** often also retire or reduce working hours due to the burden of care. Traveling (sometimes very long distances) to hospital appointments can cost significant amounts of time and money. Purchasing mobility

	aids (e.g., wheelchair, mobility scooter, stair lift etc) and modifying the home to aid mobility can lead to further expense. With NHS social care services under strain, many families must foot the bill for care themselves. This coupled with family members' reduced ability to work further compounds the financial burden carried by ATTR-CM patients and their loved ones. **Psychological burden** Living with ATTR cardiomyopathy (ATTR-CM) can place a significant psychological burden on patients, affecting their mental health, emotional well-being, and quality of life. It is not uncommon for patients to experience low mood or depression as a result. Some key aspects of this burden: *Emotional Distress & Anxiety* • Uncertainty about the future: ATTR-CM is a progressive disease, and the unpredictability of symptoms (such as worsening heart function and mobility issues) can cause anxiety and stress. • Fear of complications: Patients often worry about heart failure, arrhythmias, and other serious complications, leading to constant worry about their health. *Depression & Low Mood* • Loss of independence: As physical limitations increase, patients may struggle with activities they once found easy, leading to feelings of helplessness and frustration. • Social withdrawal: Fatigue and mobility issues can lead to reduced participation in social activities, which may result in isolation and loneliness. • Guilt & burden on family: Many patients feel guilty about depending on caregivers and family members for support, adding to their emotional distress. *Cognitive & Mental Fatigue* • Brain fog & concentration issues: Some patients report difficulty with memory and focus, which can make daily tasks and decision-making more challenging. • Medication side effects: Treatments like Tafamidis can help slow disease progression, but managing medications and medical appointments can feel overwhelming. *Coping with Diagnosis & Adjustment*

	• Shock & denial: Many patients have trouble accepting their diagnosis, particularly if they were previously active and healthy. • Adjustment challenges: Adapting to lifestyle changes, dietary restrictions, and new routines can be mentally exhausting. *Impact on Relationships* • Strained relationships: Partners, family, and friends may struggle to understand the emotional toll of the disease, sometimes leading to misunderstandings or frustration. • Fear of being a burden: Patients may hesitate to express their struggles, further increasing their sense of loneliness. *Impact on Family* • Some forms of ATTR-CM are hereditary, meaning that multiple members of the same family may be affected. This brings a huge psychological burden to the patient and their family members. Many have watched their grandparents, parents or even siblings succumb painfully to the disease; they therefore worry for themselves and for their children and grandchildren who may inherit the disease. **Caregivers** The burden on caregivers is significant. Most caregivers are partners or spouses, sometimes children. Watching the health of someone you love deteriorate is inherently stressful. In addition to the financial burden mentioned above caregivers often experience chronic fatigue; apart from caring for their spouse they also gradually assume more and more of the household duties as their spouse/parent becomes less and less able to help. Caregivers also experience isolation as they are either afraid or unable to leave their spouses alone or simply spend so much of their time caring that they have limited opportunity to get out of the house and socialise. Caregivers often suffer from low mood, depression, or anxiety because of the impact of the disease on them and their families.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Tafamidis is only disease altering treatment available in the UK at present, it has only been available in the UK for a few months but has been widely available internationally for over a decade. Tafamidis is seen by patients and carers as a lifeline, giving hope where previously there was none. It slows the progression of the disease, giving patients a better quality of life, for longer. It is generally well tolerated and as an oral medication patients find it simple to administer. However not all patients can tolerate or respond to tafamidis. While tafamidis slows the progression of the disease it does not stop or reverse the disease progression.
8. Is there an unmet need for patients with this condition?	While the approval of tafamidis has been welcomed by both patients and caregivers, it only slows the progression of ATTR-CM. This condition remains progressive and ultimately fatal, and not all patients will respond to or tolerate tafamidis. Beyond the need for more effective treatments, there is a significant gap in holistic care that addresses the wide range of challenges faced by ATTR-CM patients. For most patients, this need for comprehensive support remains unmet.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	If acoramidis were to be approved, it would become the second disease-modifying treatment available for ATTR-CM patients in the UK. Since not all treatments are suitable for every patient, having an additional option is seen as a significant advantage by the patient community. Patients also feel that the availability of additional treatment options could open the door to combination therapies, which may further slow disease progression and improve outcomes. This brings more hope to the community. Acoramidis is an oral medication so it is simple to self-administer.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Groups of patients whose amyloidosis presents as predominantly cardiac rather then neurological will benefit the most. These groups include wild type ATTR patients and V122i patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As noted, ATTR-CM disproportionately affects two protected characteristic groups due to the nature of the disease. First, wild-type ATTR-CM primarily impacts older individuals, with most patients presenting at age 60 or older. Second, the most common hereditary ATTR mutation, V122I, is found almost exclusively in individuals of West African ancestry. Therefor both these groups will be disproportionately impacted by the approval or rejection of this treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	Diagnosis is a major challenge for amyloidosis patients. The majority of clinicians remain unaware of amyloidosis resulting in many ATTR-CM patients going undiagnosed or misdiagnosed for years. **Accurate** diagnosis down to the exact type of amyloidosis is crucial for patients to get the appropriate treatment. As awareness and treatment options increase there is a corresponding increase in the risk that patients will be misdiagnosed and started on an inappropriate treatment. This needs to be managed carefully to ensure the best outcomes for patients.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• ATTR-CM is a progressive, debilitating and ultimately fatal condition that impacts every aspect (physical, financial, social, emotional, psychological) of a patient's life. • ATTR-CM has a major impact on patients' family and friends, with partners or other loved ones often adjusting their own life so they can take on caring responsibilities as the patient deteriorates. • Not all treatments are suitable for all patients. The approval of acoramidis would give patients a second option and open the possibility of combined treatments. • Delayed/inaccurate diagnosis is a major challenge, accurate diagnosis is critical to ensure patients receive the correct treatment. • Patients would welcome the approval of acoramidis and do not see any disadvantages of having this treatment available.

Thank you for your time.

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Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Cardiomyopathy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cardiomyopathy UK is the national charity for people affected by all forms of cardiomyopathy. The charity provides a range of support and information services, provides clinical education opportunities, raises awareness of the condition among the general public, supports research and advocates for improved access to quality treatment. The charity's database contains 22,000 individuals and there are around 100 active volunteers who facilitate support groups, provide peers support, advocate for improvements in health services, undertake fundraising activities and take on a range of other roles. The charity's trustees, the majority of whom have personal experience of the condition are ultimately responsible for the charity and are supported by a professional team of 19 staff. The charity is funded by community fundraising, donations and legacies (78%) charitable trusts and foundations (8%) the pharmaceutical industry (14%) Total income from the year January - December 2024 was £1,054,678
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12	Total income received from the pharmaceutical industry in 2024 (the most recent audited accounts) was £145,455. This comprises: Cytokinetics £35,000: Towards national survey project Cytokinetics £15,255: Towards case study content creation AstraZeneca £15,000: Towards online medical education work

months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Tenaya £20,100: Towards national conference and helpline costs Tenaya £20,100: Towards online medical education work Alnylam £10,000: Towards online medical education work Pfizer £30,000: Towards regional advocacy work In addition to this £6,500 was raised as commercial income from the pharmaceutical industry for the provision of exhibition stand space at medical education events. Of this amount £2,000 was from Alnylam and £1,500 was from Pfizer. The remaining amounts were from BMS and Medtronic. A further £4,200 was raised through services on advisory boards and steering groups. Companies contributing towards this were BMS, Alnylam and Iqvia.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Cardiomyopathy UK conducted a national survey of the cardiomyopathy community, called the MyInsight survey, in summer 2024. Cardiomyopathy UK commissioned the Picker Institute to provide expertise on the survey development and design. Picker is a leading international health and social care charity, which carries out research to understand individuals' needs and their experiences of care. A total of 1323 people responded to the survey. Of those respondents, 22 reported having amyloidosis cardiomyopathy. Cardiomyopathy UK also ran a focus group with 5 people who reported having amyloidosis cardiomyopathy in December 2024. Cardiomyopathy UK ran a follow up focus group in January 2025 with 4 people who reported having amyloidosis cardiomyopathy, in which participants provided feedback on this Cardiomyopathy UK submission to ensure it reflects their views and experiences. We also gathered intel from our nurse-run helpline.

Living with the condition 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The MyInsight survey of the cardiomyopathy community in 2024 found the following: • 62% of all people with cardiomyopathy reported that their exercise had been negatively impacted in the last two years. • This is in comparison to 80% of people with amyloidosis cardiomyopathy stated that exercise had been negatively impacted by amyloidosis cardiomyopathy. • 34% of all people with cardiomyopathy reported that their mobility had been negatively impacted in the last wo years. • By contrast, 55% of people with amyloidosis cardiomyopathy stated that their mobility had been negatively impacted by amyloidosis cardiomyopathy. • 51% of all people with cardiomyopathy reported that their self-confidence had been negatively impacted in the last two years. • 50% of people with amyloidosis cardiomyopathy stated that their self-confidence had been negatively impacted by amyloidosis cardiomyopathy. • 49% of all people with cardiomyopathy reported that their mental health had been negatively impacted in the last two years. • 40% of people with amyloidosis cardiomyopathy stated that their mental health had been negatively impacted by amyloidosis cardiomyopathy. Therefore, the MyInsight survey highlights that amyloidosis cardiomyopathy has a very significant impact on individuals' ability to exercise (which our wider work shows has impacts for people's social lives), as well as significantly constraining individuals' mobility. Amyloidosis cardiomyopathy changes how people feel, with a detrimental impact on many people's confidence. A significant minority of people with amylodisis cardiomyopathy have had negative mental health impacts from living the condition. These survey results are reinforced and brought to life by what participants in the focus group discussed. They described a feeling that their body was wearing away, or losing a little bit of life every day. Most reported that they cannot do as much as they used to. This was often due to an enforced reduction in physical activity: Several of the participants had previously been very active, but now this was not possible due to breathlessness and neuropathy, which are symptoms of amyloidosis cardiomyopathy. As one person explained, even as a 70-year-old, he used to play golf and walk, run and go to the gym four times a week, until he experienced severe

	breathlessness – as well as a decrease in physical activity, he has also stopped doing a hobby that he really enjoyed. Participants in the focus group also reported a negative impact on their mobility and self-confidence. As one person described, he experiences neuropathy in his feet (a symptom of amyloidosis) and recently fell as he couldn't feel his feet. He now is feeling less confident to go outside or walk too far in case he falls again. One participant in the focus group explained that the amyloidosis has affected his mobility, the ability to swallow, his bowels and circulation. Participants did also report that, given their age (amyloidosis cardiomyopathy is more prevalent in older people), they are living with comorbidities. This means that the symptoms of amyloidosis cardiomyopathy can worsen other conditions and vice versa. It is important to note that all the focus group participants had been referred to the National Amyloidosis Centre (NAC). A lack of awareness of amyloidosis was a barrier in getting a diagnosis and accessing treatment, as reported by the participants, but the NAC has been a much more positive experience. As a result of being under the NAC, all participants had been offered the opportunity to take part in clinical trials. Nevertheless, the focus group participants all reported feeling isolated, given that amyloidosis is a rare condition. The psychological impact of amyloidosis cannot be ignored.

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	Broadly, patients are grateful for treatment being available for their condition – given this was not the case for so long. They are grateful for the potential increase in treatment options. The focus group participants reported mixed views of current drug treatment for amyloidosis. Most had a positive experience with no side effects from tafamadis. One person reported that he had diarrhoea and needed to take pro-biotics now alongside tafamadis. Whilst patients are grateful for the care and the level of expertise available at the NAC, there is inevitably some reluctance about the travel involved – especially amongst those that have to travel the furthest, and/or more often. There is a need to further expand capacity for amyloidosis care and treatment beyond the existing specialist centre hub and two spokes, so that more people with the condition can access quality care near to where they live. Whilst we want to ensure patients receive the highest level of care, this must also be balanced against both what is important to patients, and the ongoing increase in the numbers of ATTR-cardiomyopathy patents in need of care and treatment. A future where treatment can be initiated at any one of a number of centres around the country, with less travel needed to the NAC (whilst retaining strong links and expertise) would be preferable. Whilst NHS care is heading in the right direction, in terms of opening up the geographical spread of care and treatment options, from a patient perspective we would want to see this work going further and faster.

8. Is there an unmet need for patients with this condition?	Whilst acoramidis isn't the first dedicated drug for this population, we still think it has the capacity meet some unmet need. Firstly, there are inevitably some patients for whom tafamidis will not work, or will not work well enough to make the difference needed. Having another treatment option bodes very well for the population of people with ATTR-CM, as their clinicians will be able to choose the best drug for them – tailoring their decision to the individual far more than they can with just one drug. The earlier patients get on to treatment – and the better suited the treatment is to them, the less resultant damage there will be in those patients' hearts – with all the personal, NHS and societal costs this entails. We believe acoramidis could be significant in further reducing symptom burden, in more patients. More broadly, the cardiomyopathy population in general, and the ATTR-cardiomyopathy population in particular, still have a number of unmet needs. In the MyInsight survey (2024), people with cardiomyopathy overall reported the following: • 76% do not have a care or treatment plan which details their care and support. • 32% do not have mood or emotional support, but wanted or needed this. • 32% do not have support from a dietician of nutritionist, but wanted or needed this. • 39% have had no support around physical activity, but wanted or needed this. Among people with amyloidosis cardiomyopathy, these data are as follows: • 62% have no care plan. • 39% do not have but wanted emotional support. • 38% do not have but would like support from a dietician or nutritionist. • 37% do not have but wanted support around physical activity. A lack of care plan was also reflected in feedback from the focus group participants. As a result, they reported feeling in the dark about their care a disease management. The participants also described the challenges of presenting at the Emergency Department without a care plan as emergency doctors are not familiar with amyloidosis cardiomyopathy to understand what are 'normal' test results for the individual. One participant explained he now has a personal information sheet which requests the emergency doctors contact his consultant for more information on amyloidosis cardiomyopathy.

	Several of the participants reported a lack of cardiac rehabilitation and were unsure how much exercise they could do to build muscle mass and improve their fitness without causing a shortness of breath or aggravating other symptoms of amyloidosis cardiomyopathy. Whilst it is unlikely to feature amongst the criteria that NICE takes into account during technology appraisals, we note that the addition of another drug treatment option bodes well for the community in terms of the profile of the condition, and therefore the level of interest and engagement amongst healthcare professionals. As NICE noted in the draft scope for the appraisal of tafamidis in 2023 [ID6327], there is under-diagnosis and under-reporting of ATTR-CM, though thankfully the number of new diagnoses made each year is rapidly increasing. More literature, and more treatment options, can only serve to help drive up HCP interest and awareness in this area, potentially further driving up diagnosis rates.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We do not have data relating to acoramidis specifically. However, we know that patients are hugely grateful for drugs, especially when drugs are specifically tailored for their particular condition – and that these can have a transformative effect on patients' lives. We also know that a wider variety of drugs available means that clinicians can better tailor their treatment choices to the individual – especially in giving alternatives where a drug is not well tolerated. However, we also know that, beyond a positive technology appraisal recommendation, the real test for patients would be whether they can get on to the medication; from our perspective, the measure of success in relation to new medicines is uptake, not just access. There are ongoing issues for patients in relation to the delays in securing the full network of amyloidosis centres. Given the stats presented above on the extent to which people's mobility is impaired by having ATTR-CM, the concern is whether some people will not end up on acoramidis even if it is approved unless and until more care and treatment is available closer to their home. Conversely, should the technology appraisal recommend the use of acoramidis, the need for the network is arguably further accentuated. We would hope that a recommendation for use could help push this work along.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We suspect that patients who live in the South East, close to the NAC, are the most likely to benefit. Beyond that group, people living in the Midlands, or near Liverpool, stand the next most likely chance of benefitting – due to the current spread of the network. We suspect that patients living in the North East, or in the South West, stand the least chance of benefitting from the new technology, in the event of a positive recommendation. This is most especially the case for patients with more advanced ATTR-CM who therefore have the poorest mobility.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The disease burden amongst people living with ATTR-CM is high. Acoramidis could be significant in further reducing symptom burden, in more patients. • Having an additional treatment option stands to benefit patients with ATTR-CM – enabling choice between treatment options and more personalised treatment decisions. • The benefit of an additional treatment option is only realised in relation to patient uptake. This is likely to be improved by the work on the network of amyloidosis centres – especially if the delays to opening up the two additional amyloidosis spoke centres are addressed. A successful drug appraisal may somewhat help accentuate the need/push this along. • Another drug treatment option bodes well for the community in terms of the profile of the condition, and therefore the level of interest and engagement amongst healthcare professionals, potentially helping to drive up diagnosis rates. •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES if they relate to ATTR/Cardiomyopathy, or heart failure.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Patient Organisation Submission

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 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. [Please note that declarations of interests relevant to this topic are compulsory].

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	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We are dedicated to funding and promoting research that will lead to better treatments and ultimately a cure for kidney disease. Our vision is the day when everyone lives free from kidney disease.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Kidney Research UK has not received any funding from Bayer during the past 12 months.
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have extensive experience of consulting with CKD patients living with a wide range of long-term conditions involving the kidney. Our patients want to know the impact that treatments for related conditions will have on pre-existing disease.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Not applicable.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	
8. Is there an unmet need for patients with this condition?	Currently patients with ATTR-CM have one treatment option that has been shown to improve mortality and CVD end points (3 Committee discussion | Tafamidis for treating transthyretin amyloidosis with cardiomyopathy | Guidance | NICE). Having another treatment option that is more efficacious would improve patients' outcomes and prevent development of other CVRM conditions, such as heart failure and kidney disease both of which can be a cause or consequence of the other. All conditions reduce patients' quality of life; ESRD is also expensive for the NHS to manage.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Not applicable.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Not applicable.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The working age population of patients with this condition would benefit from earlier diagnosis and management of their disease which has a profound impact of quality of life, mental health and financial earnings at this stage in their lives, as well as preventing or delaying the onset of multiple long-term conditions. Compared to the other drugs currently being tested for treatment of ATTR-CM (as mentioned in Transthyretin amyloid cardiomyopathy: a paradigm for advancing precision medicine | European Heart Journal | Oxford Academic) acoramidis has the benefit of lacking the nephrotoxicity associated with the other treatments requiring extensive kidney monitoring and putting patients at risk of developing AKI and potentially CKD. This means acoramidis provides more benefit to this patient population who might be at elevated risk of kidney damage, more head-to-head trials to compare the available and potential drugs are needed, however, to truly understand the benefits on the development of CVRM conditions and CKD specifically.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	Cost-analysis should include the longer-term benefits of the different treatments, looking at patients in a holistic way. While one study showed that 24.0% of patients experienced a decline in their kidney function (Kidney Outcomes in Transthyretin Amyloid Cardiomyopathy - PMC), it is important to consider the other related conditions a patient may develop without access to treatments to manage their disease.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Please consider the potential beneficial impact of this treatment on the kidney in comparison to other treatments with the potential to be nephrotoxic. • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Professional organisation submission

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.

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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	[redacted]
2. Name of organisation	The British Association for the Study of the Liver (BASL)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Association for the Study of the Liver is the National Association for hepatology. BASL is dedicated to advancing knowledge and understanding of the biology and pathology of the liver for the optimal care of patients. BASL is composed of interested individuals from clinical medicine, clinical and basic research and allied professions. BASL is a not for profit Association whose income is derived from membership fees, donations and its various activities, such as the revenue of scientific meetings. Monies derived from such activities are used to support further educational events and the attendance thereto of its members.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Transthyretin amyloid cardiomyopathy (ATTR-CM) is an inexorably progressive disease due to either variant or wild-type transthyretin amyloid deposition in the heart , is associated with significant morbidity and is fatal if left untreated. ATTR Cardiac amyloidosis is characterized by the deposition of misfolded monomeric transthyretin (TTR) in the heart and disease progression depends on continuing supply of amyloid fibrils. Medical therapies are needed to address the underlying pathology, improve cardiac outcomes and morbidity and prolong survival. Acoramidis is a high-affinity TTR stabilizer that acts to inhibit dissociation of tetrameric TTR and leads to more than 90% stabilization. The main aim of treatment with Acoramidis is to slow down the continuing production of amyloid fibrils and delay/prevent progression of cardiac amyloid deposition . This result, along with ongoing supportive care to address symptoms and signs of cardiac impairment as a continuing key aspect in the overall management of ATTR-CM, is very plausibly expected to bring about significant benefit in outcomes in morbidity, hospital admissions, disability features and improvements in cardiac function and overall survival.
7. 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.)	Clinically significant treatment response measures would involve improvement or stabilisation in cardiac function, improvement in performance status and quality of life, and reduced cardiac hospital admissions and reduced mortality. Acoramidis has been robustly tested in a double- blind placebo controlled trial, published in NEJM , January 2024. It has been shown to consistently meet all Primary end points of all cause mortality, cardiac hospital admissions and improvement from baseline in cardiac markers NT-proBNP and 6 min walk test, with good safety profile.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The introduction of the TTR stabiliser Tafamidis in the treatment of ATTR-CM has provided significant benefits in the management of the cardiac amyloidosis, however there are still largely unmet needs in the treatment of patients with amyloid cardiomyopathy and more potent treatments are required. ATTR -CM remains a debilitated disease which affect the patients and significantly impacts their families and carers, in addition to the associated pressures on the Health system. Improved and more effective treatments are needed to help make a difference in patients outlook and quality of life. The results of the double blind Acoramidis trial hold much promise and have been welcomed as a landmark breakthrough by the Amyloid patients and families support groups in Europe, UK and the US, as well as, the Medical community and health professionals.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	TTR-CM treatment at present focuses on 1.supportive care and 2. use of disease modifiers such as the TTR stabiliser Tafamidis , while other treatments such as SiRNA (Patisiran and Vutrisiran) and antisense oligonucleotide (Inotersen and Eplontersen) which have shown clinical benefit in the hereditary forms of ATTR familial amyloid polyneuropathy remain under consideration for treatment of cardiac amyloidosis. Solid organ transplantation has a limited role and can be utilised in a very small number of patients with very strict indications for heart transplant, while liver transplantation which has been widely utilised as the only treatment available for FAP with neuropathy before the availability of anti-TTR medication, offers almost no benefit in genetic ATTR-CM with advanced cardiac amyloidosis and has no role in wt ATTR-CM (wild -type).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The guidelines used in the treatment of ATTR-CM broadly suggest 1. Management of heart failure and arrhythmias according to standards of care and 2. Therapies targeting Transthyretin. Tafamidis, a TTR stabilizer is approved for the treatment of TTR-CM in the UK
9b. 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.)	With increased awareness regarding cardiac amyloidosis in the past decade in the medical community, a more structured diagnostic pathway has evolved, leading to the condition being more readily suspected and hopefully diagnosed at an earlier stage. The diagnostic pathway for cases where ATTR-CM is suspected utilizes non-invasive investigations, widely available in routine practice and imaging modalities including Cardiac DPD scintigraphy and Cardiac MRI, while cardiac histology may be required in a small number of cases. Lastly, gene sequencing to distinguish between wild type or variant ATTR CM is available in specialist centres of excellence. Disease staging for assessment of disease severity is well defined, based on biochemical parameters (NT-proBNP and eGFR or Cardiac DPD grading) to categorise according to disease severity and predict prognosis. The UK National Amyloidosis Centre in London has a central role in providing diagnostic advice and support and subsequently guidance on treatment. With the evolution in awareness and diagnosis of ATTR-CM, as well as, advances in treatment options, a number of regional ATTR amyloid MDT and amyloid NHS services have been developed in UK cities (opening up 'amyloid treatment services' outside London). The regional amyloid MDT groups are hospital based, in secondary care, in collaboration with the NAC, for formal presentation and discussion of diagnosed ATTR-CM cases and subsequent treatment plans. This is a major advance in the care of all UK patients with ATTR-CM, enabling timely review for prompt diagnosis and equality in accessing appropriate anti-TTR treatments, at present limited to Tafamidis.

9c. What impact would the technology have on the current pathway of care?	I believe any new treatments, and in particular Acoramidis which is an orally administer agent, would fit very well in the current pathway of care, initially as an alternative to Tafamidis, without posing any additional stress, pressures or additional requirements to the current pathway. It is very likely that Acoramidid as perhaps the first near complete TTR stabiliser may become the front line medication for the treatment of TTR-CM.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, this is an easily administered medication in tablet form twice daily, with good safety profile. The indications for use of the medication and follow up care during treatment will be along the same lines currently employed for the use of Tafamidis.
10a. How does healthcare resource use differ between the technology and current care?	I am not aware of pricing and whether the new medication may increase funding requirements, however any additional cost will be offset against likely reduced requirements of cardiac-related hospital care and admissions.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Acoramidis should more appropriately be prescribed in secondary care with routine follow-up in secondary care (not in primary care) at least in the beginning; with the possibility of prescribing the medication in primary care under supervision and routine follow up in secondary care in the long term.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I do not foresee any needs for additional investment in facilities and equipment over and above what is already established or ought to be established as routine services. As an example, Cardiac DPD imaging and Cardiac MRI, blood testing of NT-proBNP, troponins, eGFR, and Free light chains are (or ought to be) part of routine investigations in a hospital setting. Indeed they are already available in secondary care and more specifically in all of the regional amyloid services and MDTs in collaboration with the NAC. I can however envisage ongoing evolution and increase in number of cases diagnosed and being referred for treatments, which will create further needs in staffing, as well as, training of junior doctors and health professionals; Cardiac amyloid training however, will most likely become part of the curriculum and core Cardiology training in the long term , as ATTR amyloidosis and in particular ATTR-CM appears to be graduating from Rare Diseases to ‘mainstream ‘ relatively common, increasingly widely diagnosed cardiac conditions
11. Do you expect the technology to provide clinically meaningful	Yes, I believe it may well do. The benefit of efficient reduction of the associated amyloidogenic protein in terms of slowing down and even causing regression of amyloid disease and protecting organ function, has been well described in many of the other types of systemic amyloidosis such as AL amyloidosis, AA amyloidosis and many of the hereditary amyloidosis.

benefits compared with current care?	Acoramidis is a near complete (> 90%) ATTR stabiliser that inhibits dissociation of tetrameric TTR, thereby halting or slowing down further amyloid deposition. It is plausible that it may well prove to be superior to Tafamidis in achieving improved clinical results and health-related quality of life as well.
11a. Do you expect the technology to increase length of life more than current care?	I do hope it may do. It will be very appropriate and very interesting to assess the long term benefits of Acoramidis and learn more about durability of its benefits that have bene documented in the clinical trial.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes it is plausible that it may well prove to be superior to Tafamidis in achieving improved clinical results and health-related quality of life as well. It has been shown to consistently meet all Primary end points in the clinical trial, achieved improvements in clinical manifestations and outcomes as well as, quality of life. It is another potent medication in the treatment of amyloidosis and very valuable treatment option for ATTR-CM. It will be very interesting and appropriate to assess and confirm this in long term clinical trials.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The recent Acoramidis trial excluded patients with stage IV chronic renal disease. I am not aware of any other differences in demographics. It may be possible that patients with earlier cardiac disease may derive greater benefit . I would like to propose 2 groups of patients , namely those with Familial amyloid polyneuropathy and the group of acquired de novo ATTR-CM following Domino Liver Transplantation using liver grafts from patients with familial transthyretin amyloid polyneuropathy (FAP) as potentially favourable groups for treatment. The potential development of ATTR-CM in FAP and the de novo ATTR-CM after Domino Liver Transplant is well described, and patients undergo regular evaluation and assessments for early diagnosis of such developments. These groups can potentially be diagnosed at the earliest disease stage compared to the general population and may conceivably be favourable groups in response to timely onset of treatment

The use of the technology

13. 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	I would not anticipate any differences in use of Acoramidis compared to current care. There is no need for concomitant treatments such as for example those required with SiRNAs, and no additional clinical requirements, over and above pretreatment tests and routine follow up tests and investigations in

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	treatment with Tafamidis. It is an easily administered medication in tablet form with excellent safety profile.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Renal function, cardiac markers and routine blood tests will be required as part of follow up, similar to those in current care.
15. 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?	I cannot comment on possible additional substantial benefits unlikely to be included in the QALY calculation
16. 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?	The science and anti-TTR approach of Acoramidis through TTR stabilisation comes largely from a similar angle to Tafamidis. Both agents are TTR stabilizers, however, Acoramidis is a novel TTR stabilizer that is designed to mimic the action of the T119M variant with better stabilization of the tetramer and achieving near complete stabilisation. Outcomes of the initial trial indicate this is a very promising agent which may well have a substantial impact on health related benefits..

16a. Is the technology a 'step-change' in the management of the condition?	Acoramidis may well prove to be the long awaited breakthrough in management of ATTR-CM, however long term observations will be needed to assess its impact on survival , morbidity and quality of life in comparison to current treatment, as well as establishing the appropriate duration of treatment. It will also be appropriate and very intriguing to potentially evaluate Acoramidis in future combined treatments with other effective agents in the treatment of TTR amyloidosis generally, such as gene silencers ie Vitrusiran. This approach would very plausibly offer additional and sustained effectiveness through reducing the hepatic production of TTR (through Vitrusiran) as well as, stabilising any circulating plasma TTR (through Acoramidis)
16b. Does the use of the technology address any particular unmet need of the patient population?	The new agent provides for the first time near complete TTR stabilization in a tablet form, and has been shown to be effective and achieve all end points in a very robust evaluation.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The reported side effects relate mainly to gastrointestinal disturbances with diarrhoea. These are easily addressed in either primary or secondary care, and did not appear to be severe or affect the patients quality of life, however patient awareness and follow up will be recommended to ensure adequate fluid intake and avoid dehydration and renal impairment.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the clinical trials reflect current UK practice and routine markers follow up.

18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes include survival and cardiovascular-related hospitalization and were included in the trials, primary end points being death from any cause, cardiovascular-related hospitalization, the change from baseline in the NT-proBNP level, and the change from baseline in the 6-minute walk distance. Outcome in the acoramidis group were better than in the placebo group.The outcomes listed are appropriate, crucially addressing the unmet needs in TTR-CR.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, NT-proBNP is a very accurate marker.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any additional side effects at this stage
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology	Not aware

appraisal guidance TA984 (tafamidis)?	
21. How do data on real-world experience compare with the trial data?	From my experience and to the best of my knowledge the results of the trial suggest superior outcomes compared to current treatment for ATTR-CM

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No concerns regarding equality issues
22b. Consider whether these issues are different from issues with current care and why.	No difference

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Amyloid cardiomyopathy (ATTR-CM) due to transthyretin amyloidosis either wild type or due to genetic mutations in the gene for the transthyretin protein, is a progressive, debilitating disease with no specific curative treatment available at present. • There has been significant progress in recent years with the emergence of treatment options such as Tafamidis, Diflunisal, SiRNA and ASO agents, aiming to reduce further transthyretin amyloid production and to slow down/ prevent progression of the disease, but there are still significant unmet needs to be addressed • Acoramidis is a high-affinity TTR stabilizer that acts to inhibit dissociation of tetrameric TTR and leads to more than 90% stabilization of the protein. The results of the recent Acoramidis double-blind placebo control trial are very encouraging, showing the agent met all the Primary end points, including Primary end points of all cause mortality, cardiac hospital admissions and improvement from baseline in cardiac markers NT-proBNP and 6 min walk test, with good safety profile and easy administration as oral tablet twice daily. • Acoramidis merits consideration as a treatment option for the treatment of Transthyretin Amyloid Cardiomyopathy; indeed based on the trial results have been welcomed by patients and carers support groups, as well as the medical society , as a landmark breakthrough medication that holds much promise to address the unmet needs in the care of ATTR-CM. It has been approved by the FDA and EMA • •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

Professional organisation submission

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Ophthalmologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes if ocular complications occur A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The organisation is a membership organisation that looks after the Ophthalmology profession in the UK and wider jurisdictions. We are a registered charity. The organisation is mainly funded by membership subscriptions, Exams and Seminar courses fees and Income from the sale of our professional journal.
5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	We have not received any non-commercial income or funding from either Bayer or Pfizer in the past 12 months.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	No response
7. 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.)	No response
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	No response

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	No response
9a. Are any clinical guidelines used in the	No response

treatment of the condition, and if so, which?	
9b. 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 response
9c. What impact would the technology have on the current pathway of care?	Longer survival times may allow time for ocular complications to develop, affecting vision in rare cases or requiring intervention. Long term surveillance for ocular complications may therefore need to be considered. Although it is noted that the 30 month trial did not show a difference in ocular adverse events between the treatment group and the placebo.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No response
10a. How does healthcare resource use differ between the technology and current care?	No response
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	No response
10c. What investment is needed to introduce the technology? (For example,	Surveillance for ocular complications could occur within existing NHS pathways for referral to specialist clinics.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No response
11a. Do you expect the technology to increase length of life more than current care?	No response
11b. Do you expect the technology to increase health-related quality of life more than current care?	No response
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No response

The use of the technology

13. 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	Long term surveillance for ocular complications may be required or should be reviewed for a requirement after implementation if approved.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No response
15. 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?	No response
16. 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?	No response
16a. Is the technology a 'step-change' in the	No response

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	No response
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Unknown long term ocular side effects or effects on complications. This would not be a barrier to implementation, but should be considered in the clinical pathways after approval. It is noted that the trial (duration 30 months) did not show a difference in the rate of ocular adverse events between the treatment and the placebo groups. **N Engl J Med 2024;390:132-142 DOI: 10.1056/NEJMoa2305434**

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No response.
18a. If not, how could the results be extrapolated to the UK setting?	No response
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	No response
18c. If surrogate outcome measures were used, do	

they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA984 (tafamidis)?	Long term vision-threatening complications of TTR may progress despite effective systemic therapy. Therefore, screening for ocular side effects would be recommended post-marketing authorisation. Clin Ophthalmol . 2022 Jul 9;16:2227–2233. doi: 10.2147/OPTH.S359312 . However, it is noted that the trial (duration 30 months) did not show a difference between treatment and placebo groups for ocular adverse events. N Engl J Med 2024;390:132-142 DOI: 10.1056/NEJMoa2305434
21. How do data on real-world experience compare with the trial data?	No response

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No response
22b. Consider whether these issues are different from issues with current care and why.	No response

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Ocular side effects and complications of TTR are rare, but have the potential to affect quality of life. • Ocular side effects have been described to continue to progress despite effective systemic therapy, so surveillance post-marketing would be advised. These could include questions about symptoms, visual acuity tests and retinal imaging.

Thank you for your time.

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Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

A Cost Comparison Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

Maxwell S. Barnish	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report.
Saul Stevens	Critical appraisal of the company's economic evidence and analysis, conducted additional economic analyses, and drafted sections of the report.
Frank Grimsey Jones	Conducted additional economic analyses and drafted sections of the report.
Alan Lovell	Project manager. Critical appraisal of the company's literature search strategies, drafted sections of the report, and editorial input.
Dawn Lee	Drafted sections of the report and reviewed report.
Edward C. F. Wilson	Project director. Drafted sections of the report and reviewed report.

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Abbreviations

6MWD	six-minute walking distance
6MWT	six-minute walk test
ACM	all-cause mortality
AE	adverse event
AGM	adjusted geometric mean
ARR	absolute risk reduction
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin-related amyloidosis cardiomyopathy
ATTRv	hereditary transthyretin amyloidosis
ATTRwt	wild-type transthyretin amyloidosis
BMI	Body Mass Index
CEAC	cost-effectiveness acceptability curve
CEC	Clinical Events Committee
CFB	change from baseline
CI	confidence interval
CMH	Cochrane-Mantel-Haenszel
CMR	Cardiac Magnetic Resonance
CQ	Clarification question
CS	company submission
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVH	CV-related hospitalisation
eGFR	estimated glomerular filtration rate
EOCI	event of clinical interest
EQ-5D	EuroQol five dimension
ERG	Evidence Review Group
ESS	effective sample size
FAS	full analysis set
F-S	Finkelstein-Schoenfeld
HF	heart failure
HR	Hazard ratio
HRQoL	health-related quality of life
HS	hypothetical strategy

HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICER	Institute for Clinical and Economic Review
IQR	interquartile range
ITCRP	International Clinical Trials Registry Platform
ITT	intention-to-treat
IXRS	Interactive Voice/Web Response System
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire overall summary;
KM	Kaplan-Meier
LS	Least squares
MAIC	Matching Adjusted Indirect Comparison
MCID	minimally clinically important difference
mITT	modified intention-to-treat
NA	not applicable
NAC	National Amyloidosis Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
NT-proBNP	N-terminal pro-brain-type natriuretic peptide
NYHA	New York Heart Association
OLE	open-label extension
OR	Odds ratio
OWSA	one-way sensitivity analysis
PAS	Patient access scheme
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QA	quality assessment
QALY	quality adjusted life year
RBP	vitamin A)-binding protein
RCT	randomised controlled trial
RD	risk difference
RRR	relative risk reduction
SC	subcutaneous
SD	standard deviation

SAE	serious adverse event
SLR	systematic literature review
SM	Symptomatic management
SPIE	serum protein electrophoresis with immunofixation
STC	simulated treatment comparison
T4	thyroxine
TA	Technology Appraisal
TC DPD	Tc-radio-labelled diphosphono-1,2-propanodicarboxylic acid
TEAE	treatment-emergent adverse events
TIA	transient ischaemic attack
TTR	transthyretin
TTD	time to treatment discontinuation
UK	United Kingdom
UPIE	urine protein electrophoresis with immunofixation
US	United States (of America)
VAT	Value added tax
vs	versus
WTP	willingness to pay

1. SUMMARY OF THE EAG'S VIEW OF THE COMPANY'S COST COMPARISON CASE

1.1. Similarity of effectiveness relative to scoped comparators

A matching-adjusted anchored indirect comparison (MAIC) was conducted to compare the effectiveness of acoramidis and tafamidis. This was considered broadly appropriate based on the clinical appropriateness of effect modifiers and given the changing standard of care between the time when the tafamidis and acoramidis trials were conducted.

For all-cause mortality (ACM) (Figure 1), all but the naïve analysis numerically favoured acoramidis over tafamidis. For cardiovascular-related hospitalisation (CVH) (Figure 2), all analyses statistically or numerically favoured acoramidis over tafamidis. Therefore, the EAG was satisfied that acoramidis can be considered at least as effective as tafamidis. However, one area of concern was that subgroups were not included in the company decision problem. Bayer considered that there was insufficient data for the subgroups proposed in the final scope which could lead to conclusions based on underpowered analysis. The EAG noted the [redacted] in those with severe heart failure (NHYA Class III) and that European guidelines do not recommend tafamidis in people assessed at NYHA Class III (although tafamidis was recommended in TA984 for ATTR CM without any reference to subgroups).

Figure 1. All-cause mortality for the ITT population

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HS, hypothetical strategy; ITT, intention-to-treat

Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis

Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class

Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Source: CS Document B, Figure 29, p.94.

Figure 2. Cumulative frequency of CVH excluding EOCIs, ITT population

Abbreviations: CI, confidence interval; CV,cardiovascular; CVH, CV-related hospitalisation; eGFR, estimated glomerular filtration rate; EOCI, event of clinical interest; HS, hypothetical strategy; ITT, intention-to-treat; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis

Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class

Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Source: CS Document B, Figure 30, p.97.

1.2. Safety of the treatment

Comparative safety data for acoramidis and tafamidis are presented below (Table 1). The EAG agreed that – from the available information – it appears that the population-level safety of acoramidis is at least comparable to that of tafamidis. It should be noted that this is a naïve comparison of safety results from two different trials, rather than a population-adjusted indirect comparison.

Table 1. Comparative safety profiles for acoramidis and tafamidis

	Acoramidis		Tafamidis	
Trial	**ATTRibute-CM**	**OLE AG10-304 ongoing**	**ATTR-ACT**	**ATTR-ACT LTE Aug 2021 data cut**
System organ classes where ≥30% of patients had an adverse event for any one treatment:	**Acoramidis n=421**	**Continuous Acoramidis n = 263**	**Pooled Tafamidis n=264**	**Continuous tafamidis n=110**
Follow-up period	**30 months**	**12 months**	**30 months**	**~ 30 months**
Any TEAE	**413 (98.1%)**	**229 (87.1%)**	**260 (98.5%)**	**108 (98.2%)**
Cardiac disorders	230 (54.6%)	[redacted]	185 (70.1%)	79 (71.8%)
Gastrointestinal disorders	221 (52.5%)	[redacted]	135 (51.1%)	50 (45.5%)
General disorders and administration site conditions	144 (34.2%)	[redacted]	143 (54.2%)	54 (49.1%)
Infections and infestations	246 (58.4%)	[redacted]	165 (62.5%)	64 (58.2%)
Injury, poisoning and procedural complications	137 (32.5%)	[redacted]	107 (40.5%)	51 (51.8%)
Investigations	127 (30.2%)	[redacted]	104 (39.4%)	Not avail.
Metabolism and nutrition disorders	149 (35.4%)	[redacted]	119 (45.1%)	43 (39.1%)
Musculoskeletal and connective tissue disorders	184 (43.7%)	[redacted]	129 (48.9%)	49 (44.5%)
Nervous system disorder	182 (43.2%)	[redacted]	121 (45.8%)	51 (46.4%)
Renal and urinary disorders	142 (33.7%)	[redacted]	83 (31.4%)	35 (31.8%)
Respiratory, thoracic, and mediastinal disorders	146 (34.7%)	[redacted]	124 (47.0%)	55 (50.0%)
Skin and subcutaneous tissue disorders	108 (25.7%)	[redacted]	76 (28.8%)	42 (38.2%)
Any Treatment-emergent SAE	**230 (54.6%)**	**88 (33.5%)**	**199 (75.4%)**	**Not reported**
Any study drug-related TEAE	**50 (11.9%)**	**3 (1.1)**	**113 (42.8%)**	**Not reported**
Drug-related treatment-emergent SAEs	2 (0.5%)	0	5 (1.9%)	

Abbreviations: OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: CS Table 37, p.117.

1.3. Similarity of costs across interventions

The EAG considered only acquisition costs, given that symptom management costs, resource use costs, administration costs and adverse event costs were consistent across treatments. The

list price per pack of 120 tablets of acoramidis is £8,547.60, the list price per pack of 30 capsules of tafamidis is £10,685.00. Both packs are a one-month course of treatment, four tablets per day for acoramidis and one capsule per day for tafamidis. Acoramidis is the lower cost treatment option at the list price, with a cost difference of £2,137.40 between acoramidis and tafamidis. The confidential appendix contains the cost analysis using confidential pricing.

1.4. Areas of uncertainty

The EAG noted uncertainty regarding the effectiveness of acoramidis in those assessed as having severe heart failure (NYHA Class III). Data were not available to compare acoramidis to tafamidis in relation to the NT-pro-BNP biomarker.

2. CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

2.1. Summary of the decision problem

The decision problem assessed acoramidis for transthyretin-related amyloidosis cardiomyopathy (ATTR-CM). The company's decision problem broadly met the final NICE scope. The EAG's considerations in respect of population, intervention, comparators, and outcomes assessed are provided in Table 2 below. The key point of difference between the NICE scope and the company decision problem was whether to include subgroups. The EAG was concerned that subgroups by severity of heart failure were not included in the company decision problem. Bayer considered that there was insufficient data for subgroups based on severity of heart failure which could lead to conclusions based on underpowered analysis. The EAG noted a [redacted] in those with severe heart failure (NHYA Class III) and that European guidelines do not recommend tafamidis in people assessed at NYHA Class III (although tafamidis was recommended in TA984 for ATTR-CM without any reference to subgroups).

Table 2: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)	Adult patients with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM)	Slightly amended wording to reflect the marketing authorisation	The EAG was satisfied that the population in the ATTRibute-CM trial was aligned to the company's decision problem and that the slightly amended wording versus the NICE scope was to reflect the marketing authorisation. The CS stated that the UK prevalence of ATTR-CM was unknown but was likely around 1,500 people in England. Clinical expert advice to the EAG was that the population in England was likely at least 2,000 based on current tafamidis prescriptions, but that underdiagnosis is an issue, especially in women.
Intervention	Acoramidis	Acoramidis	NA	The EAG was satisfied that the intervention was appropriate.
Comparator(s)	Tafamidis	Tafamidis	NA	The EAG was satisfied that the comparator was appropriate. Clinical advice to the EAG was that tafamidis is currently the standard of care in ATTR-CM and is a safe and effective treatment. In the absence of direct head-to-head evidence for acoramidis versus tafamidis,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				an indirect treatment comparison was used.
Outcomes	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as global longitudinal strain or brain natriuretic peptide [BNP] level) • outpatient diuretic intensification • serum transthyretin and transthyretin stabilisation • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients and carers)	The outcome measures to be considered include: • overall survival • cardiovascular-related mortality • cardiac function (such as brain natriuretic peptide [BNP] level) • serum transthyretin and transthyretin stabilisation • cardiovascular-related hospitalisation • functional exercise capacity • signs and symptoms of heart failure (such as breathlessness) • adverse effects of treatment • health-related quality of life (of patients)	The following outcomes are not addressed as these are not reported within the study data: • outpatient diuretic intensification • global longitudinal strain (although there was an exploratory Cardiac Magnetic Resonance [CMR] Imaging sub-study of ATTRibute-CM, which is briefly reported in the submission) The following additional measure is reported: • Troponin I	The EAG was satisfied that the outcomes in the ATTRibute-CM trial and company decision problem were broadly aligned to the NICE scope. Clinical expert advice to the EAG was that the included outcome measures were appropriate and that the excluded outcomes (outpatient diuretic intensification and global longitudinal strain) were not of particular importance, as they are newer measures and would not be available for the tafamidis trial.
Economic analysis	As the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same	As the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same	NA	The EAG considered the case for cost comparison to be *prima facie* reasonable.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	indication, a cost-comparison may be carried out	indication, a cost-comparison has been conducted		
Subgroups	If the evidence allows, the following subgroups will be considered: • severity of heart failure (such as by New York Heart Classification class or National Amyloidosis Centre staging) • wild-type or hereditary ATTR-CM	Bayer do not believe that any subgroups should be considered in this appraisal.	Bayer consider that the subgroups suggested would not be relevant for this appraisal due to insufficient trial data which could lead to conclusions based on underpowered analysis. Specifically: • only 9.7% of the ATTRibute-CM study population had a variant transthyretin genotype, with the remainder wild-type • when considering NYHA classification, the majority of patients in the ATTRibute-CM study had NYHA Class II at baseline (72%), with fewer in Class III and even fewer in Class I. Tafamidis was recommended as a treatment option by NICE in accordance with the marketing authorisation without any reference to subgroups.	The EAG noted that the company decision problem was not aligned with the NICE scope in terms of the inclusion of subgroups. Clinical expert advice to the EAG was that subgroups by severity of heart failure may be salient, as poorer response may be experienced by those with more severe heart failure. The EAG noted that forest plot for NYHA Class III i.e. severe heart failure (CS Appendix D Figure 4) shows the [redacted] However, Bayer considered that there was insufficient data for subgroups based on severity of heart failure which could lead to conclusions based on underpowered analysis. The same issue with lack of efficacy for those with severe heart failure was also found in the ATTR-ACT trial for tafamidis. An ICER report[1] indicated that while US

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				guidelines recommend tafamidis for those with NYHA Class III symptoms, European guidelines do not. Therefore, it may be important to consider subgroups by severity of heart failure (although tafamidis was recommended in TA984 for ATTR CM without any reference to subgroups)
Special considerations including issues related to equity or equality	No specific equality considerations were listed on the scope for this appraisal, besides the standard NICE policy.	The CS states that people with ATTR-CM are typically aged over 70, which could result in issues for accessibility and attendance at the National Amyloidosis Centre (NAC) in London for diagnosis, treatment and review. Furthermore, it states that one of the most prevalent variants of ATTRv in the UK is V142I, which has a primarily cardiac phenotype and is most common in men of Afro-Caribbean origin. This variant also has the worst prognosis.[2]	The company identified these as relevant equity and equality considerations.	Clinical expert advice to the EAG was that these equity considerations were generally appropriate. The EAG was advised that all prescriptions are issued by the NAC in London, regardless of where the consultation takes place. However, a national network of centres is being established (the West Midlands centre in Birmingham is currently operational) to reduce the need for long-distance travel. Furthermore, the EAG was advised that when patients do not live within the catchment area of a local centre and do not wish to (or are unable to) travel to London, patients may receive treatment by a local general

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				cardiologist supplemented by remote consultation from specialist staff at the NAC in London. Clinical advice to the EAG was that the approach to consultations would be identical regardless of whether tafamidis or acoramidis is being prescribed. In response to CQ additional question, the company confirmed that acoramidis treatment would be managed in the same way as tafamidis. It is anticipated that the package of care, including home delivery of acoramidis, would mirror that for tafamidis, but it has not yet been confirmed.

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; EAG, External Assessment Group; ICER, Institute for Clinical and Economic Review; NA, not applicable; UK, United Kingdom; US, United States.

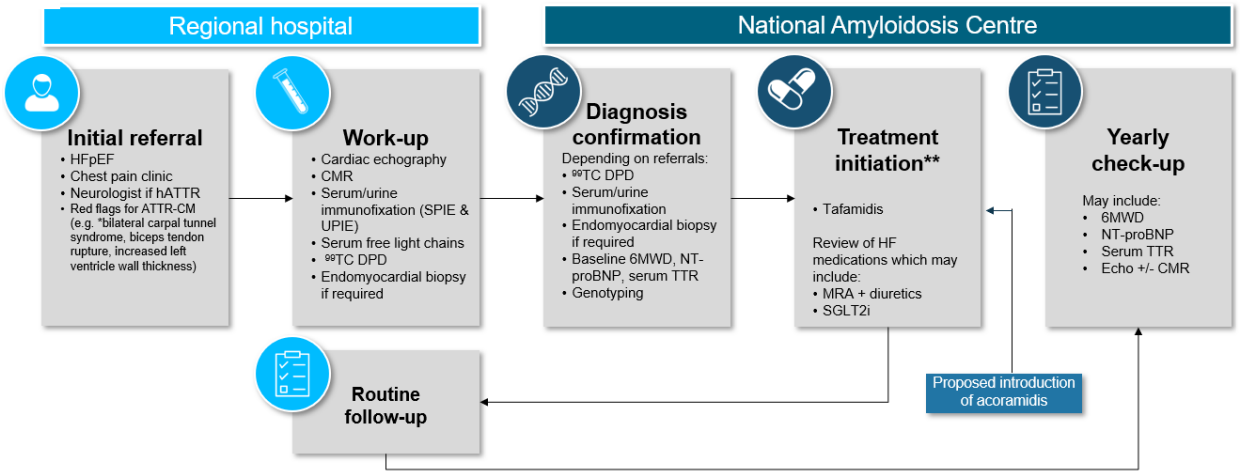
2.2. Place of the technology in the current treatment pathway

The rationale presented in the CS for the appraisal of acoramidis being considered as a cost-comparison is that acoramidis is likely to provide similar or greater health benefits compared to tafamidis at similar or lower cost. Tafamidis likely has most of the market share for ATTR-CM currently. NICE stated that the routing decision was because acoramidis and tafamidis are both TTR stabilisers, are indicated for the same population, and are expected to have the same resource use.

The EAG considered the company's description of the disease area and treatment pathway to be appropriate. Clinical expert advice to the EAG was that the treatment pathway (Figure 3) appeared appropriate. Acoramidis is positioned as an alternative to tafamidis, which is the only disease-modifying treatment for the full population of ATTR-CM currently available in the NHS. Tafamidis is the standard of care for ATTR-CM, whilst SC vutrisiran would currently be used for a small proportion (estimated at about 3% by a clinical expert) of people with hereditary ATTR-CM but is not presently used for wild-type ATTR-CM in routine practice. A NICE appraisal of vutrisiran in a broader ATTR-CM population broadly equivalent to the population of the current appraisal is ongoing (ID11598).

Table 3 below compares the features of acoramidis and tafamidis. Clinical advice to the EAG noted that twice daily administration, combined with larger tablet size, may affect tolerability for a minority of patients.

Figure 3. Overview of current treatment pathway showing intended positioning of acoramidis



Abbreviations: 6MWD, six-minute walking distance; ^{99}TC DPD, ^{99}Tc-radio-labelled diphosphono-1,2-propanodicarboxylic acid; ATTR-CM, Transthyretin amyloid cardiomyopathy; CMR, Cardiac Magnetic Resonance; HF, heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SPIE, serum protein electrophoresis with immunofixation; TTR, Transthyretin; UPIE, urine protein electrophoresis with immunofixation

Note: *TTR deposition in ligaments starts 10-15 years before the first cardiac symptoms

**For patients unable to travel to London, the NAC offers virtual consultations for treatment initiation

Source: CS, Figure 1, p.20.

Table 3: Comparability of intervention with current comparators

Comparison	Proposed medicine	Comparator
International non-proprietary name (Brand)	Acoramidis (Bayer)	Tafamidis (Pfizer)
Available formulation(s), strength(s)	2 tablets (356mg) twice daily	1 capsule (61mg) once daily
Principle pharmacological action and therapeutic class	The mechanism of action of acoramidis is an oral, selective, second-generation stabiliser of transthyretin (TTR) which inhibits the dissociation of tetrameric TTR. This is produced by the liver and transports both thyroxine (T4) and retinol (vitamin A)-binding protein (RBP) in the bloodstream.[3]	The mechanism of action of acoramidis and tafamidis is considered similar because both are TTR stabilisers.
Line of treatment	First-line	First-line
Concomitant or subsequent medicines that are included in the submission	The CS stated that it was not intended that acoramidis and tafamidis would be used together in clinical practice, although concomitant tafamidis was permitted in the trial from month 12. Subsequent treatments were not discussed in the CS, potentially reflecting the lack of alternative licensed targeted therapies for ATTR-CM.	The CS stated that it was not intended that acoramidis and tafamidis would be used together in clinical practice. When tafamidis was licensed, no other disease-modifying treatments were available.
Proposed/approved indications	The approved indication is adults with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM). Acoramidis is not currently licensed for any other indications in the UK.	The licensed population in the UK for tafamidis is ATTR-CM. This comprises wild-type or variant (i.e. hereditary) types. The intended populations for acoramidis and tafamidis are equivalent.
Any differences that may result in different populations using the medicine	Oral, 2 tablets twice a day, TTR stabilizer.	Oral, one capsule per day, TTR stabilizer.
Any differences that may result in growth in the market	The overall available market is unlikely to change because of the potential introduction of acoramidis. Therefore, if acoramidis were to be introduced, it is likely to result in partial displacement of tafamidis.	N/A

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; RBP, vitamin A)-binding protein; T4, thyroxine; TTR, transthyretin.

3. SUMMARY OF THE EAG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1. Systematic literature review conducted by the company

The company undertook a systematic literature review (SLR) to identify evidence for the clinical efficacy and safety of available treatments for people with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). The SLR was originally conducted on 23 November 2023 in Embase, MEDLINE and Cochrane Central, with subsequent updates on 1 November 2024 and 31 March 2025. In response to CQ C1, the company reported that SIGN RCT filters were used. The EAG noted that simple text word terms were added to the SIGN filters with a view to identifying pooled analyses or open-label extensions. While not ideal, the EAG considered these additions to the SIGN filter adequate, given the needs of the search. The EAG considered that the strategies used were suitable for the scope.

In addition to the bibliographic database searches, the company also searched ClinicalTrials.gov and the International Clinical Trials Registry Platform (ITCRP) for ongoing clinical trials, the proceedings of seven relevant conferences, and hand-searched the bibliographies of up to five relevant SLRs. The details of how these sources were searched was not provided.

An overview of the SLR methods used by the company and the EAG appraisal of these is shown in Table 4. The EAG considered the SLR methods to be broadly appropriate.

Table 4: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D.1.1	The EAG considered the searches to be appropriate and suitably aligned to the scope. Modifications to the study type search filter used were not gold standard but were adequate given the needs of the search.
Inclusion criteria	Appendix D.1.1, Table 1	The EAG considered the inclusion criteria for the SLR to be appropriate though broader than the decision problem. It was noted, however, that observational studies were excluded, while single arm trials were included.
Screening	Appendix D.1.2.	Screening was conducted independently by 2 reviewers with any disagreements resolved by a third reviewer. The EAG considered this appropriate.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Data extraction	Appendix D.1.2.1	Data extraction was conducted by one reviewer and checked for consistency by a second reviewer. A third reviewer was consulted to resolve disagreements. While the EAG did not consider this approach gold standard, as the initial two reviewers did not work independently, it was considered to be acceptable.
Tool for quality assessment of included study or studies	Appendix D.3	Risk of bias assessment was conducted for included RCTs only using the Cochrane Risk of Bias 2 (RoB 2 tool). This was considered acceptable, although it would have been preferable to also assess non-RCT studies, for example using ROBINS. It was, however, not stated how many reviewers assessed risk of bias.
Evidence synthesis	Appendix D.1.3.1	No pairwise meta-analysis was conducted as there was only one RCT available for acoramidis. The EAG considered this to be appropriate. Given the absence of head-to-head evidence comparing acoramidis and tafamidis, the company conducted an indirect treatment comparison. This is critiqued in Section 3.4.4

Abbreviations: CS, Company submission; EAG, External Assessment Group; RCT, randomised controlled trial; SLR, systematic literature review.

3.2. Overview of clinical evidence submitted by the company

One Phase 3 clinical study (ATTRibute-CM) was identified relating to the efficacy and safety of acoramidis in adult patients with symptomatic ATTR-CM.[2] Initial results were also available from the ongoing open label extension (OLE) study (AG10-304) for patients still on treatment at the end of the ATTRibute-CM trial. See Table 5 for an overview. Furthermore, two Phase 2 studies (AG10-201; AG10-202) were available that focused primarily on the safety and tolerability of acoramidis. The results of these studies were not included in the evidence synthesis nor used for economic modelling. The EAG considered this appropriate given the availability of RCT and OLE evidence.

Table 5: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
ATTRibute-CM[2,4]: Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy	Prospective, international, randomised, double-blind, placebo-controlled, parallel-group,	Patients with a diagnosis of symptomatic (NYHA Class I-III) ATTR-CM (either wild-type TTR or a variant TTR genotype).	Acoramidis hydrochloride (+/- stable heart failure therapy*) 800 mg† BID (administered	Placebo (+/- stable heart failure therapy*) N=211 patients randomised	RCT

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
	multicentre phase 3 study		as two 400 mg tablets) N=421 patients randomised		
AG10-304: Open-label extension study for patients completing ATTRibute-CM[5,6]	Open-label extension study from the ATTRibute-CM double-blind study	Patients with symptomatic (NYHA Class I-III) ATTR-CM who have completed 30 months of blinded study treatment and the Month 30 assessments of the double-blind treatment period of the phase 3 ATTRibute-CM trial and who met OLE eligibility criteria	Acoramidis hydrochloride (+/- stable heart failure therapy*): 800 mg† BID (administered as two 400 mg tablets) N=389 (263 continuous acoramidis, 126 placebo to acoramidis).	Not applicable	Open label single arm extension study

Abbreviations: ATTR-CM, transthyretin amyloidosis with cardiomyopathy; NYHA, New York Heart Association; OLE, open-label extension; RCT, randomised controlled trial; TTR, transthyretin.

*Patients taking cardiovascular medical therapy, except for diuretic dosing, must have been on stable doses for at least 2 weeks prior to screening.

†The dose of acoramidis was 356mg per tablet (712mg across the two tablets) – this was equivalent to 400mg acoramidis hydrochloride per table (800mg across the two tablets)

Source: Adapted from CS Document B, Table 4, p.24.

3.3. Methodology of the included studies submitted by the company

A comparative overview of the methods used in the studies included is provided in Table 6.

Table 6: Comparative summary of trial methodology

Study	ATTRibute-CM[2,4,7]	AG10-304[5-7]
Location	International ([redacted] recruited from the UK)	International (recruited from those who completed ATTRibute-CM)
Trial design	RCT Part A: 0-12 months Part B: 12-30 months (with concomitant tafamidis allowed)	OLE (ongoing, interim data available)
Key eligibility criteria	Age 18-90. Established diagnosis of wild-type or variant ATTR-CM. Clinical heart failure with at least one previous hospitalisation for heart failure, or signs and symptoms of volume overload, or heart failure that resulted in diuretic treatment. NYHA Class I-III symptoms due to ATTR-CM. Left ventricular wall thickness of ≥12 mm on a previous imaging study. Stable doses of any cardiovascular medication, except for diuretics.	Completed 30 months of the blinded study treatment in ATTRibute-CM and that study's Month 30 visit including assessments and procedures.
Interventions evaluated	Acoramidis (vs placebo)	Acoramidis
Concomitant medication	Tafamidis was not permitted during the initial 12 months of the trial, although could be taken thereafter (during Part B).	Patients who received concomitant tafamidis in ATTRibute-CM were required to discontinue to be eligible for the OLE.
Primary outcomes*	Part A: CFB in 6MWD to month 12. Part B: The hierarchical combination of ACM, cumulative frequency of CVH*, clinically meaningful difference (≥ 500pg/mL) in CFB in NT-proBNP, and CFB in 6MWD over a 30-month time period.	Long-term safety and tolerability.
Key secondary outcomes*	Part A: CFB in KCCQ-OS, TTR level, TTR stabilisation to month 12. Part B:	Time to ACM Time to ACM or first CVH Time to CVH

Study	ATTRibute-CM[2,4,7]	AG10-304[5-7]
	CFB in 6MWD, KCCQ-OS, TTR level, TTR stabilisation to month 30.	ACM or recurrent CVH events CFB in 6MWD CFB in KCCQ-OS / EQ-5D-5L CFB in NT-proBNP CFB in serum TTR
Other secondary endpoints relevant to decision problem	A hierarchical combination of ACM and cumulative frequency of CVH over a 30-month fixed treatment duration. A hierarchical combination of ACM, cumulative frequency of CVH, and CFB in 6MWD over a 30-month fixed treatment duration. CV-mortality by Month 30. Cumulative frequency of CVH by Month 30. TTR stabilisation measured in established ex vivo assays (FPE and WB) CFB to Month 30 in NT-proBNP CFB in EQ-5D-5L questionnaire Safety	Shifts in NYHA class from baseline.
Pre-planned subgroups	Subgroup analyses were conducted for the primary endpoint, components of the primary endpoint, and key secondary endpoints using randomisation stratification factors. No subgroup analysis was included in the submission in alignment with the company decision problem.	Not stated.

Abbreviations: 6MWD, six-minute walking distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CFB, change from baseline; CV, cardiovascular; CVH, cardiovascular-related hospitalization; EQ-5D, EuroQoL Five Dimensions; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; RCT, randomised controlled trial; TTR, transthyretin.

*Gillmore et al[2] reports on Part B of ATTRibute-CM, detailed information on Parts A and B can be found in CS Document B, Appendix D, Table 8.

3.4. Clinical effectiveness of acoramidis

3.4.1. Risk of bias assessment

Risk of bias assessment of the ATTRibute-CM trial was conducted using the University of York Centre for Reviews and Dissemination (CRD) tool. While not the gold standard Cochrane Risk of Bias 2 (RoB 2), the EAG considered this to be appropriate. Only specific relevant aspects of risk of bias (e.g. recruitment / cohort composition, treatments, confounding factors) were considered for AG10-304, as this is an ongoing OLE study. The risk of bias assessment table for ATTRibute-CM is shown below in Table 7.

Table 7. ATTRibute-CM risk of bias assessment

ATTRibute-CM	Company assessment	EAG assessment
Was randomisation carried out appropriately?	Yes	Yes – an Interactive Voice/Web Response System (IXRS) portal was used
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes – there were no substantial imbalances in prognostic factors
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis was a modified intention-to-treat (mITT) analysis. Analyses were also performed in the ITT population, which included patients with eGFR<30mL/min/1.73m2 in order to gather safety data on this small group of patients. Appropriate methods were used to account for missing data.	Yes Imputation for missing data was conducted (Gillmore et al[2] – Supplementary methods) although not for all outcomes and causes of missing data. The EAG considered the analysis appropriate.

ATTRibute-CM	Company assessment	EAG assessment
Did the authors declare any conflicts of interest?	Yes	Yes – employment, consultancy and funding related to the manufacturer

Abbreviations: EAG, External assessment group; IXRS, Interactive Voice/Web Response System; mITT, modified intention-to-treat.

Source: Adapted from CS Document B, Table 10, p.45.

The EAG agreed with the company's assessment of risk of bias in the OLE study. In particular, enrolment into the OLE was by choice, so the final cohort for the OLE was determined in a non-randomised manner. Enrolment was 62.5% for those who had been treated with acoramidis and 59.7% for those who had been treated with placebo. This ensured that the treatment groups remained balanced. Although attrition (i.e. the fact that just 62.5% of those treated with acoramidis in ATTRibute-CM enrolled in the OLE study) may have reduced the power of treatment effects.

The EAG noted that exposure to tafamidis in ATTRibute-CM may have been a confounding factor, given co-administration of acoramidis and tafamidis in clinical practice is not anticipated. In the RCT, n=61 (14.9%) of those in the acoramidis arm and n=46 (22.8%) of those in the placebo arm received concomitant tafamidis. In the OLE study, n=29 (11.0%) of those in the continuous acoramidis group and n=23 (18.3%) of those in the placebo to acoramidis group had prior exposure to tafamidis. This is slightly lower than in the full ATTRibute-CM population.

The unblinded nature of the OLE carries uncertainty regarding the interpretation of efficacy analyses and long-term safety data. Furthermore, baseline characteristics of patients in the two arms of the OLE were not balanced. This was because patients who received acoramidis for 30 months in ATTRibute-CM derived a treatment benefit, while those who received placebo experienced a greater degree of disease progression.

3.4.2. Baseline characteristics

The baseline characteristics for ATTRibute-CM[2] are shown in Table 8. The primary trial analysis population is modified intention-to-treat (mITT), although the indirect treatment comparisons (ITC) use the intention-to-treat (ITT) population for comparability with the tafamidis evidence. The mITT population was defined as all participants who had been randomised, received at least one dose of acoramidis or placebo, and had at least one efficacy evaluation after baseline;[2] participants with stage 4 chronic kidney disease (eGFR <30ml per 1.73m^2) were excluded.

Table 8. Baseline demographic and disease characteristics for the mITT and ITT ATTRibute-CM study populations

	mITT		**ITT**	
	Acoramidis (N=409)	Placebo (N=202)	Acoramidis (N=421)	Placebo (N=211)
Age (yr) (mean±SD)	77±6.5	77±6.7	77.4±6.5	77.1±6.8
n (%):				
<65	12 (2.9)	9 (4.5)	[redacted]	[redacted]
≥65 to <78	186 (45.5)	92 (45.5)	[redacted]	[redacted]
≥78	211 (51.6)	101 (50.0)	[redacted]	[redacted]
Male, n (%)	374 (91.4)	181 (89.6)	384 (91.2)	186 (88.2)
Race, n (%)				
White	358 (87.5)	179 (88.6)	368 (87.4)	187 (88.6)
Black	19 (4.6)	10 (5.0)	20 (4.8)	10 (4.7)
Asian	10 (2.4)	3 (1.5)	10 (2.4)	3 (1.4)
Other	[redacted]	[redacted]	23 (5.5)	11 (5.2)
Not reported	[redacted]	[redacted]	-	-
Transthyretin genotype, n (%)				
Wild-type	370 (90.5)	182 (90.1)	380 (90.3)	191 (90.5)
Variant	39 (9.5)	20 (9.9)	41 (9.7)	20 (9.5)
Transthyretin variant. n (%)				
V30M	[redacted]	[redacted]	1/39 (2.6)	0
V122I (=V142I)	23/37 (62.2)	12/19 (63.2)	24/39 (61.5)	12/19 (63.2)
T60A (=T80A)	3/37 (8.1)	2/19 (10.5)	3/39 (7.7)	2/19 (10.5)
E89Q	0	1/19 (5.3)	0	1/19 (5.3)
Other	11/37 (29.7)	4/19 (21.1)	11/39 (28.2)	4/19 (21.1)
Duration of ATTR-CM (years)	[redacted]	[redacted]	[redacted]	[redacted]
NT-proBNP (ng/L)				
Mean (±SD)	2865±2150	2650±1899	2946±2226	2725±1971
Median (IQR)	2273 (1315- 3872)	2274 (1128-3599)	2326 (1332-4019)	2306 (1128-3754)
eGFR (ml/min/1.73m^2)				
Mean	62±17.4	63±17.5	61±18	61±19
< 45 ml/min/1.73 m^2, n (%)	65 (15.9)	29 (14.4)	[redacted]	[redacted]
≥ 45 mL/min/1.73 m^2, n (%)	344 (84.1)	173 (85.6)	[redacted]	[redacted]

	mITT		**ITT**	
	Acoramidis (N=409)	Placebo (N=202)	Acoramidis (N=421)	Placebo (N=211)
NAC stage, n (%)				
I	241 (58.9)	120 (59.4)	241 (57.2)	120 (56.9)
II	130 (31.8)	66 (32.7)	134 (31.8)	69 (32.7)
III	38 (9.3)	16 (7.9)	46 (10.9)	22 (10.4)
Mean serum TTR* (mg/dl) (±SD)	n=406 23.0±5.6	n=199 23.6±6.1	 23±6	 24±6
NYHA functional class, n (%)				
I	51 (12.5)	17 (8.4)	51 (12.1)	17 (8.1)
II	288 (70.4)	156 (77.2)	293 (69.6)	162 (76.8)
III	70 (17.1)	29 (14.4)	77 (18.3)	32 (15.2)
6MWD (metres)	[redacted] [redacted]	[redacted] [redacted]	n=419 361.2±103.7	n=211 348.4±93.6
KCCQ-OS	N=408 71.7 (19.37)	N=202 70.5 (20.65)	n=420 71.5±19.4	n=211 70.3±20.5
Atrial Fibrillation, n (%)	236 (57.7)	117 (57.9)	[redacted]	[redacted]
History of Thromboembolic Event or Stroke/TIA / Reversible Ischaemic Neurological Defect, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Thromboembolic event	[redacted]	[redacted]	[redacted]	[redacted]
TIA	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Permanent pacemaker placed	77 (18.8)	38 (18.8)	[redacted]	[redacted]
Implantable cardioverter-defibrillator placed	[redacted]	[redacted]	[redacted]	[redacted]
Prior carpal tunnel release surgery	[redacted]	[redacted]	[redacted]	[redacted]
Patients initiating tafamidis, n (%)	61 (14.9)	46 (22.8)	61 (14.5)	46 (21.8)
Months to initiation	[redacted]	[redacted]	Not available	Not available
Months of exposure	[redacted]	[redacted]	“	“

Abbreviations: 6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; dl, decilitre; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire, Overall Summary Score; mg, milligram; ml, millilitre; mITT, modified intention-to-treat; NAC, National Amyloidosis Centre; ng, nanogram; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin; n, number; TIA, transient ischaemic attack

*Normal serum TTR range is 18 to 45 mg/dL.

Source: CS Document B, Table 6, pp.34-35.

Gillmore et al. (2024)[2] stated that the baseline characteristics in ATTRibute-CM were reflective of a contemporary ATTR-CM population. They aligned closely with a UK retrospective observational study (n=1,967, data from referrals to the NAC in 2002-2021).[8] In total, [redacted] in ATTRibute-CM were recruited from the UK.

Clinical advice to the EAG was that the trial baseline characteristics reflected the demographics and clinical characteristics of patients encountered in clinical practice in England. Baseline characteristics at time of enrolment into the OLE are shown below in Table 9. As noted in Section 3.4.1, the baseline characteristics in the OLE were imbalanced between those on continuous acoramidis and those switching from placebo to acoramidis because of disease progression in the placebo group of ATTRibute-CM.

Table 9. Patient baseline characteristics at entry to the OLE (OLE FAS)

Patient characteristics [a,b]	**Continuous acoramidis n=263**	**Placebo to acoramidis n=126**
Age, years, mean (SD) [c]	78.8 (6.50)	79.7 (6.33)
Male sex, n (%)	244 (92.8)	115 (91.3)
ATTR-CM duration at time of randomisation in ATTRibute-CM [d,e] years,		
n	262	126
Mean (SD)	1.2 (1.10)	1.1 (1.29)
Transthyretin genotype, n (%) [f]		
Wild-type	242 (92.0)	120 (95.2)
Variant	21 (8.0)	6 (4.8)
NYHA class, n (%) [g]		
I or II	216 (82.1)	79 (62.7)
III	44 (16.7)	45 (35.7)
IV	3 (1.1)	1 (0.8)
NT-proBNP, pg/ml,		
n	252	121
Median (IQR)	2064.0 (1240.5-3442.5)	2905.0 (1624.0-5087.0)
eGFR (ml/min/1.73m^2)		
< 45 ml/min/1.73 m^2, n (%)	[redacted]	[redacted]
≥ 45 mL/min/1.73 m^2, n (%)	[redacted]	[redacted]

Patient characteristics [a,b]	Continuous acoramidis n=263	Placebo to acoramidis n=126
NAC stage, n (%) [h]		
I	136 (51.7)	52 (41.3)
II	66 (25.1)	46 (36.5)
III	53 (20.2)	26 (20.6)
Missing	8 (3.0)	2 (1.6)
6MWD (metres)	[redacted]	[redacted]
KCCQ-OS	[redacted]	[redacted]
Serum TTR, mg/dL,		
n	253	120
Mean (SD)	32.8 (6.27)	25.6 (6.61)
Patients who received tafamidis in the ATTRibute-CM study, n (%)	29 (11.0)	23 (18.3)

Abbreviations: ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRwt-CM, transthyretin amyloidosis wild-type cardiomyopathy; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IQR, interquartile range; NAC, National Amyloidosis Centre; ng, nanogram; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension study; SD, standard deviation; TTR, transthyretin; n, number

[a] Data are for all patients who enrolled in the OLE and received at least one dose of open label acoramidis.

[b] Baseline values are the last non-missing assessment values completed before the first OLE acoramidis treatment.

[c] Age calculated from the first OLE treatment date and date of birth/age.

[d] Data at the time of randomisation in ATTRibute-CM (not at OLE entry).

[e] Calculated as (randomisation date – date of ATTR-CM diagnosis)/365.25.

[f] Genotype based on ATTRibute-CM stratification factors at the time of randomisation (not at OLE entry).

[g] Data missing for one patient in the placebo to acoramidis group.

[h] NAC ATTR Stage: NAC ATTR Stage I, defined as NT-proBNP≤3000ng/L and eGFR≥45 mL/1.73 m^2; Stage III defined as NT-proBNP > 3000 ng/L and eGFR < 45 mL/1.73 m^2; the remainder categorised as Stage II when both NT-proBNP and eGFR are not missing.

Source: CS Table 7, pp.35-36.

3.4.3. Clinical effectiveness results

Following cost-comparison guidance notes, the narrative in this section focuses on outcomes considered most important by clinical advisors to the EAG. These are all-cause mortality, cardiovascular-related hospitalisation and health-related quality of life. It is noted that the primary endpoint in the ATTRibute-CM trial was a composite endpoint including clinical and biomarker components, but this was not used in the MAIC because it was not available in the evidence for tafamidis. An overview of efficacy results across the ATTRibute-CM RCT and AG10-304 OLE is provided in the Appendix (Table 17).

There was a statistically significant benefit for acoramidis over placebo in time to all-cause mortality or cardiovascular-related hospitalization in the ATTRibute-CM ITT population (hazard ratio 0.661, 95% CI 0.516, 0.848, p=0.0011) and for continuous acoramidis over placebo to acoramidis in the AG10-304 OLE (HR 0.57, 95% CI 0.46, 0.72, p<0.0001). There was a numerical benefit for acoramidis over placebo in all-cause mortality in the ATTRibute-CM ITT population (HR 0.762, 95% CI .542, 1.072, p=0.1184) and a statistically significant benefit for continuous acoramidis over placebo to acoramidis in the AG10-304 OLE (HR 0.64, 95% CI 0.47, 0.88). There was a statistically significant benefit for acoramidis over placebo in time to first cardiovascular-related hospitalization in the ATTRibute-CM ITT population (HR 0.611, 95% CI 0.461, 0.809, p=0.0006) and for continuous acoramidis over placebo to acoramidis in the AG10-304 OLE (HR 0.53, 95% CI 0.41, 0.69, p<0.0001). Mean difference at Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS) disease-specific health-related quality of life scale in the ATTRibute-CM ITT population was [redacted], in favour of acoramidis. Mean (SD) change from baseline in the AG10-304 OLE was -4.0 ([redacted]) in the continuous acoramidis group and [redacted] in the placebo to acoramidis group. However, while there was clear evidence that acoramidis is more effective than placebo, the most relevant comparison for this appraisal is versus tafamidis, which is covered in Section 3.4.4.

The company assumed equal time on treatment between acoramidis and tafamidis and considered that comparing time on treatment between these treatments based on trial data would be inappropriate due to differences in trial design. Clinical expert advice both to the company and the EAG was that time on treatment would be expected to be similar for acoramidis and tafamidis. A KM plot of time to treatment discontinuation (TTD) for acoramidis from the OLE study is shown below as Figure 4. No median TTD was presented for acoramidis in the CS or in Gillmore et al. (2024).[2] From Figure 4, it appears that median TTD was not reached in the OLE study, as the survival probability did not fall to 0.5. This may reflect the fact that the OLE study is ongoing, and only interim data were available.

The CS did not state a value for median TTD for tafamidis but said that using these data would be inappropriate due to differences in study design between ATTRibute-CM and ATTR-ACT. The CS stated that median time on treatment data were available from ATTR-ACT but did not cite a source. The EAG searched the trial publications for ATTR-ACT[9] and ATTR-ACT-LTE (the long-term extension study)[10] but could not find this information. Further, the TTD graphs are redacted in TA984 for tafamidis. Finally, the EAG searched the FDA label,[11] CADTH Clinical

Review Report,[12] and EMA EPAR product information[13] and none provided public information on time-to-treatment or TTD for tafamidis. Therefore, the EAG could not identify the source from which the CS had stated TTD was available for tafamidis. As such, it was not possible to assess the extent to which the assumption of equivalence made by the company appears reasonable.

Figure 4. KM plot for TTD for acoramidis from ATTRibute-CM OLE (mITT population)

Abbreviations: KM, Kaplan-Meier; mITT, modified intent-to-treat; TTD, time to treatment discontinuation
Source: CS Document B Figure 38, p.135.

3.4.4. Indirect treatment comparison

Direct comparisons are only available between acoramidis and placebo and between tafamidis and placebo. Therefore, an indirect treatment comparison (ITC) was used for the comparison between acoramidis and tafamidis. The company used an anchored Matching Adjusted Indirect Comparison (MAIC). This was performed based on the 1 November 2024 SLR update. No further relevant data were identified in the 31 March 2025 SLR update.

In response to CQ A2, the company confirmed that no formal searches were conducted to identify minimally clinically important differences (MCIDs) in outcomes included in the ITC. Based on ad-hoc searches, the company considered that there were no available MCIDs that could inform formally specified non-inferiority margins. The EAG and company agreed that the preferred setting for assessing non-inferiority would have been a non-inferiority trial. However, no head-to-head trials have been conducted – non-inferiority trials are challenging to conduct in rare conditions due to the much larger sample size required.[14] In response to CQ A2, the company provided post-hoc 'fixed margin analysis',[15] although the EAG agreed with the company that these analyses can only be seen as exploratory due to lack of statistical power.

The company preferred an anchored MAIC over a network meta-analysis (NMA) based on clinical expert advice that systems and standards of care changed substantially between the ATTR-ACT trial for tafamidis (2013-2018) and the ATTRibute-CM trial for acoramidis (2019-2023). Clinical advice to the EAG agreed that standard of care had changed considerably over this period, as the introduction of tafamidis had made a targeted treatment for ATTR-CM available. The EAG was advised that the availability of this tafamidis had changed treatment pathways and led to earlier diagnosis. The EAG therefore agreed that the resultant change in baseline characteristics between the tafamidis and acoramidis trials was likely to bias the relative effect versus placebo against acoramidis. This is because the standard of care with earlier diagnosis and a targeted treatment is now better than it was when the tafamidis trial was conducted. As trials are compared to placebo plus standard of care, this meant that participants in the control arm of the acoramidis trial were likely to do better than participants in the control arm of the tafamidis trial, biasing the effect estimate against acoramidis. It should also be noted that patients with eGFR <15 mL/min/1.73 m^2 at screening were excluded to align the inclusion criteria from ATTRibute-CM to the inclusion criteria in ATTR-ACT.

The company further explained in CQ A3 that, as there was only one study comparing acoramidis and placebo and one study comparing tafamidis and placebo, it would not be possible to calculate a random effects variance. Therefore, a random-effects NMA could not be conducted. Given the changing standard of care between the ATTR-ACT and ATTRibute-CM trials, the EAG agreed that a fixed effects NMA would be inappropriate. An alternative to a MAIC, according to TSD 18[16] is a simulated treatment comparison (STC). The EAG considered MAIC to be a more frequently encountered method than STC. Both methods are appropriate to settings where IPD are available for one treatment but not another treatment, and can be used

to conduct anchored analyses. The EAG considered MAIC to be appropriate but thought that the company could have presented an STC as a scenario.

The MAIC analysis used IPD from ATTRibute-CM[2] for acoramidis (data cutoff: 06 July 2023) and aggregate data published on effect modifiers from the phase III trial ATTR-ACT[9] for 80 mg tafamidis. Efficacy analyses were all based on the ITT population. The selection of potential treatment effect modifiers for matching was informed by the trial papers[2,4-6,9] and interviews with UK clinical experts. NYHA class, eGFR, NT-proBNP, TTR genotype, and age were selected as potential treatment effect modifiers. The EAG considered the evidence assessed to be appropriate. Six matching scenarios were conducted to address differences in clinical expert opinion on potential effect modifiers or to allow for more granular adjustment on certain effect modifiers. The effect modifiers considered in each scenario are profiled below in Table 10.

Table 10. MAIC matching scenarios for efficacy

Matching scenarios	Effect modifiers adjusted through matching by exclusion of patients in the ITT population of ATTRIBUTE to match inclusion criteria of ATTR-ACT	Effect modifiers selected for adjusting through weights	Description
Scenario 1	Patients with eGFR <25mL/min/1.73m^2 or missing at screening Patients with NT-proBNP <0.600 ng/mL or missing at screening	TTR genotype (proportions mutant vs. wild type) NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean)	This scenario was designed excluding age because clinical experts were not sure if age is an effect modifier or prognostic factor. One clinical expert felt that age can be an effect modifier at the extremities of age (e.g. age ≥75).
Scenario 2	Patients with eGFR <25mL/min/1.73m^2 or missing at screening Patients with NT-proBNP <0.600 ng/mL or missing at screening	NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean)	This scenario was designed excluding TTR genotype in addition to age because one of the clinical experts wasn't sure if genotype and age are effect modifiers or merely prognostic factors.
Scenario 3	Patients with eGFR <25mL/min/1.73m^2 or missing at screening Patients with NT-proBNP <0.600 ng/mL or missing at screening	TTR genotype (proportions mutant vs. wild type) NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean) Age (median, min, max, proportion <65 vs. ≥65)	This scenario was designed to evaluate the impact of matching on all potential effect modifiers.
Scenario 4	Patients with NT-proBNP <0.600 ng/mL or missing at screening	TTR genotype (proportions mutant vs. wild type)	This scenario was designed without excluding patients with eGFR <25mL/min/1.73m^2 per

Matching scenarios	Effect modifiers adjusted through matching by exclusion of patients in the ITT population of ATTRIBUTE to match inclusion criteria of ATTR-ACT	Effect modifiers selected for adjusting through weights	Description
		NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean) Age (median, min, max, proportion <65 vs. ≥65)	clinical experts request to offset the fact that ATTR-ACT may have included some patients with NT-proBNP ≥8,500 pg/ml.
Scenario 5	Patients with eGFR <25mL/min/1.73m^2 or missing at screening Patients with NT-proBNP <0.600 ng/mL or missing at screening	NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean) Age (median, min, max, proportion <65 vs. ≥65, proportion <80 vs. ≥80)	This scenario was designed to assess impact of adjusting for age but not TTR genotype as two factors are correlated.
Scenario 6	Patients with eGFR <25mL/min/1.73m^2 or missing at screening Patients with NT-proBNP <0.600 ng/mL or missing at screening	TTR genotype (proportions mutant vs. wild type) NYHA class (proportions I vs. II vs. III) NT-proBNP (pg/mL) (median, min, max, mean) Age (mean, median, min, max, proportion <65 vs. ≥65, proportion <80 vs. ≥80)	This scenario was designed to evaluate the impact of matching on more moments of the distribution of age than were matched in scenario 3.

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

Source: CQ response A3.

Additional exploratory analyses, matching on baseline characteristics that were assumed by the company to be prognostic factors only and were imbalanced between the studies (e.g. baseline medications and permanent pacemaker), were also performed. TSD 18[16] states that only effect modifiers and not prognostic factors should be included in an anchored MAIC. However, clinical advice to the EAG was that one issue in this clinical setting is that the variables that act as prognostic factors and effect modifiers are largely similar. For example, the EAG was advised that baseline medications, which the company considered solely a prognostic factor, are also a treatment effect modifier. Therefore, it was not possible to be sure that only effect modifiers and not prognostic factors are included. However, clinical expert advice to the EAG was that the effect modifiers included were appropriate. CQ response A3 stated that the company conducted

sensitivity analyses, including on diuretics, and the results were consistent with scenarios 3 and 6, indicating that diuretics are unlikely to be an important issue. Key baseline characteristics for the company preferred scenario 3 are shown below as Table 11.

Although the company noted that were there some differences in outcome definitions, CQ response A1 confirmed that in the ATTRibute-CM trial the clinical efficacy outcomes in favour of acoramidis were robust across multiple different endpoint definitions, so this was not considered likely to be a major issue. The EAG agreed that matching was largely successful but also noted that the variance was notably lower for NT-proBNP in the matched data than in ATTR-ACT. Furthermore, the EAG noted a reduction in ESS, linked to the presence of some high weights. These may reflect limitations in the reliability of the data, including the possibility that the imbalance was too great to fully overcome by matching and weighting.

Table 11 Key baseline characteristics before and after matching ATTRibute-CM to ATTR-ACT (Scenario 3), ITT Population

	Acoramidis Matched Scenario 3	Placebo Matched Scenario 3	Tafamidis	Placebo
TTR Genotype, n (%)				
ATTRv	23.9	24.3	42 (23.9)	43 (24.3)
ATTRwt	76.1	75.7	134 (76.1)	134 (75.7)
NYHA Class, n (%)				
I	9.1	7.3	16 (9.1)	13 (7.3)
II	59.7	57.1	105 (59.7)	101 (57.1)
III	31.2	35.6	55 (31.3)	63 (35.6)
NT-proBNP (ng/ml), Mean (SD)	3.9 (2.1)	3.8 (1.6)	3.9 (3.1)	3.8 (3.0)
Age (years, Mean (SD))	75.5 (5.4)	75.0 (5.1)	75.2 (7.2)	74.1 (6.7)

Source: Adapted from CS, Document B, Table 23, p.p.86-89.

Abbreviations: 6MWT, six-minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type; BMI, body mass index; ESS, effective sample size; ITT, intention-to-treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

Figure 5. All-cause mortality for the ITT population

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HS, hypothetical strategy; ITT, intention-to-treat

Note: In the HS, participants' observations censored at the initiation of concomitant tafamidis

Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class

Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Source: Adapted from CS document B, Figure 29, p.94.

Figure 6. Cumulative frequency of CVH excluding EOCIs, ITT population

Abbreviations: CI, confidence interval; CV, cardiovascular; CVH, CV-related hospitalisation; eGFR, estimated glomerular filtration rate; EOCI, event of clinical interest; HS, hypothetical strategy; ITT, intention-to-treat; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin

Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis

Scenario 1 matched on eGFR, NT-proBNP, NYHA Class, and TTR genotype

Scenario 2 matched on eGFR, NT-proBNP, and NYHA Class

Scenario 3 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age (proportion ≥65, median, min, max)

Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age (mean, proportion ≥80, proportion ≥65, median, min, max)

Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max)
Source: CS Document B, Figure 30, p.97.

For all-cause mortality, all but the naïve analysis numerically favoured acoramidis over tafamidis. The naïve analysis used the Bucher method, which the company argued was inappropriate, given changes in baseline characteristics reflecting improvements in standard of care between the time when the tafamidis and acoramidis trials were conducted. It was noted that the naïve analysis with the hypothetical strategy (HS) – i.e. seeking to be more reflective of clinical practice by excluding concomitant tafamidis – still numerically favoured tafamidis. However, as tafamidis initiation was not randomised, a possible selection bias remained in the naïve analysis with HS which would be attenuated through matching in the MAIC. Therefore, the EAG agreed that the MAIC results, which numerically favour acoramidis, are more likely to be reflective of observations in clinical practice than the naïve Bucher analyses. Since clinical advice to the company was that changes in standard of care were a prognostic factor, the EAG

considered it inappropriate to discount the use of the Bucher method purely on these grounds, although there are additional reasons why a MAIC would be preferred, for example imbalance in effect modifiers. For cardiovascular-related hospitalization, all analyses statistically or numerically favoured acoramidis over tafamidis.

3.5. Safety of acoramidis

The primary source of safety information on acoramidis was the RCT ATTRibute-CM.[2] No new safety issues have been identified in the interim results available from the OLE study of AG10-304. ATTRibute-CM showed that treatment-emergent adverse events (TEAEs) were very common, but the frequency was similar across acoramidis and placebo groups (98.1% vs 97.6%). Most TEAEs were classified as mild or moderate (acoramidis: 60.8%; placebo: 52.1%). Both serious adverse events (SAEs, 54.6% vs 64.9%) and severe TEAEs (37.3% vs 45.5%) were less common in the acoramidis group than the placebo group. No information was provided specifically on Grade 3 AEs. In response to CQ A4, the company stated that AEs were not classified as per the CTCAE scale using Grade 1-5.

Drug-related TEAEs were higher in the acoramidis group than the placebo group (11.9% vs 5.2%), primarily driven by '[redacted]' (acoramidis: [redacted]; placebo: [redacted] and '[redacted]' (acoramidis: [redacted] placebo: [redacted]). The effect of gastrointestinal disorders was mainly related to diarrhoea (acoramidis: 11.6%; placebo: 7.6%); abdominal pain upper (acoramidis: 5.5%; placebo: 1.4%); and abdominal pain (acoramidis: 4.3%; placebo: 2.4%). Diarrhoea was also noted as a common AE for tafamidis,[17] suggesting a potential class effect for TTR stabilisers. TEAEs with a > 5% difference in incidence between treatment groups were cardiac failure (acoramidis: 24.0% vs. placebo: 39.3%), atrial fibrillation (acoramidis: 16.6% vs. placebo: 21.8%), and dyspnoea (acoramidis: 12.4% vs. placebo: 19.0%), all of which favoured acoramidis.

The CS stated that "The safety profile of acoramidis appears similar to that of tafamidis, with diarrhoea found to be a common adverse event for both treatments." Section B.3.9.10 compared the safety of acoramidis and tafamidis (see Table 12). The EAG agreed that from the available information, it appeared that the population-level safety of acoramidis is at least comparable to that of tafamidis. It should be noted, however, that this was a naïve comparison of safety results from two different trials, rather than a population-adjusted indirect comparison. The company's rationale for this was that no baseline characteristic represented an effect modifier.

Table 12. Comparative safety profiles for acoramidis and tafamidis

	Acoramidis		Tafamidis	
Trial	**ATTRibute-CM**	**OLE AG10-304 ongoing**	**ATTR-ACT**	**ATTR-ACT LTE Aug 2021 data cut**
System organ classes where ≥30% of patients had an adverse event for any one treatment:	Acoramidis n=421	Continuous Acoramidis n = 263	Pooled Tafamidis n=264	Continuous tafamidis n=110
Follow-up period	30 months	12 months	30 months	~ 30 months
Any TEAE	413 (98.1%)	229 (87.1%)	260 (98.5%)	108 (98.2%)
Cardiac disorders	230 (54.6%)	[redacted]	185 (70.1%)	79 (71.8%)
Gastrointestinal disorders	221 (52.5%)	[redacted]	135 (51.1%)	50 (45.5%)
General disorders and administration site conditions	144 (34.2%)	[redacted]	143 (54.2%)	54 (49.1%)
Infections and infestations	246 (58.4%)	[redacted]	165 (62.5%)	64 (58.2%)
Injury, poisoning and procedural complications	137 (32.5%)	[redacted]	107 (40.5%)	51 (51.8%)
Investigations	127 (30.2%)	[redacted]	104 (39.4%)	Not avail.
Metabolism and nutrition disorders	149 (35.4%)	[redacted]	119 (45.1%)	43 (39.1%)
Musculoskeletal and connective tissue disorders	184 (43.7%)	[redacted]	129 (48.9%)	49 (44.5%)
Nervous system disorder	182 (43.2%)	[redacted]	121 (45.8%)	51 (46.4%)
Renal and urinary disorders	142 (33.7%)	[redacted]	83 (31.4%)	35 (31.8%)
Respiratory, thoracic, and mediastinal disorders	146 (34.7%)	[redacted]	124 (47.0%)	55 (50.0%)
Skin and subcutaneous tissue disorders	108 (25.7%)	[redacted]	76 (28.8%)	42 (38.2%)
Any Treatment-emergent SAE	230 (54.6%)	88 (33.5%)	199 (75.4%)	Not reported
Any study drug-related TEAE	50 (11.9%)	3 (1.1)	113 (42.8%)	Not reported
Drug-related treatment-emergent SAEs	2 (0.5%)	0	5 (1.9%)	

Abbreviations: OLE, open label extension; SAE, serious adverse event, TEAE, treatment-emergent adverse event.
Source: CS Table 37, p.117.

The company's naïve Bucher ITC analyses for safety typically favoured acoramidis or showed no significant difference between acoramidis and tafamidis. There was [redacted] of a significant difference, for example in cardiac failure (OR using hypothetical strategy (HS) [redacted] 95% CI [redacted], dyspnoea [redacted] and atrial fibrillation ([redacted]. However, for [redacted], the results with HS applied suggested [redacted] of experiencing a [redacted] with acoramidis vs. tafamidis (odds ratios [OR]: [redacted], [95% CI: [redacted]]). [redacted] without the HS applied ([redacted]. The EAG considered this finding to be a potential concern regarding safety.

3.6. EAG conclusions on the clinical effectiveness of acoramidis

The EAG considered the clinical effectiveness evidence submitted in support of acoramidis in adults with symptomatic ATTR-CM to be appropriate. Evidence was presented from an international RCT (ATTRibute-CM) as well as its ongoing open label extension (OLE) study (AG10-304). Baseline characteristics were generally well matched between arms and were considered reflective of the UK clinical practice population. The EAG agreed that the trial was generally high-quality, though risk of bias in the OLE could not be fully assessed.

The evidence presented showed that acoramidis was more effective than, and at least as safe as, placebo. An anchored MAIC was conducted to make the comparison with tafamidis. Some limitations were identified, particularly around changing standards of care over time, but the EAG considered the analysis to be broadly appropriate. In the MAIC versus tafamidis, for all-cause mortality, all but the naïve analysis numerically favoured acoramidis over tafamidis. Meanwhile, for cardiovascular-related hospitalization, all analyses statistically or numerically favoured acoramidis over tafamidis. From the available information, the EAG agreed that the population-level efficacy of acoramidis appeared to have at least similar health benefits as tafamidis. Furthermore, it appeared that the population-level safety of acoramidis was at least comparable to that of tafamidis. However, one area of concern was that subgroups were not included in the company decision problem. Bayer considered that there was insufficient data for the subgroups proposed in the final scope which could lead to conclusions based on underpowered analysis. The EAG noted the [redacted] in those with severe heart failure (NHYA Class III) and that European guidelines do not recommend tafamidis in people assessed at NYHA Class III (although tafamidis was recommended in TA984 for ATTR CM without any reference to subgroups).

4. SUMMARY OF THE EAG'S CRITIQUE OF THE COST-EFFECTIVENESS EVIDENCE SUBMITTED

4.1. Company's cost comparison analysis

4.1.1. Overview of cost comparison

The company conducted a cost-comparison analysis of acoramidis and tafamidis with symptom management from an NHS and Personal Social Services (PSS) perspective. The analysis had a 25-year time horizon and a mean patient age of 77.2 years, based on the patient population in the ATTRibute-CM trial. The model had a 1-month cycle length and a discount rate of 3.5%. The EAG noted that NICE cost-comparison guidance[18] states that discounting is not generally required in these analyses and, if it is implemented, a rationale should be provided. The company did not provide a rationale for including a discount rate of 3.5%, but the EAG did not believe this will materially impact the results.

The company analysis considered only costs that were expected to differ between acoramidis and tafamidis, which were drug acquisition and adverse event costs. There were no administration costs, as both treatments are orally administered. Resource use for disease management was not included in the company submission as the treatments are assumed to have equivalent efficacy and background medication. Wastage costs were not included in the cost comparison model. The EAG believed this was appropriate as the pack sizes cover the same number of days of treatment.

The EAG considered the company's decision to exclude resource use costs, administration costs and wastage costs to be appropriate, given the justifications provided by the company and the conclusions of the EAG clinical effectiveness review.

4.1.2. Technology acquisition costs

Table 13 presents the technology acquisition costs provided in the company submission.

[redacted] The PAS prices for acoramadis and tafamidis are included in the cPAS appendix. The acquisition costs and proportions of patients receiving the symptom management technologies were reported in Table 47 and Table 48 of the company submission. The proportion of patients receiving each type of symptom management medication was derived from clinical expert feedback, the ATTribute-CM trial and Ioannou et al (2023).[19]

Given the proportions of patients receiving symptom management technologies was consistent between acoramidis and tafamidis, the EAG considered it appropriate for this cost to be excluded from the analysis.

Table 13: Technology acquisition costs

	Acoramidis	**Tafamidis**
Pharmaceutical formulation	Tablets (356 mg/ tablet)	Capsules (61 mg/capsule)
(Anticipated) care setting	Specialist centre	Specialist centre
Acquisition cost (excluding VAT)	List price, per pack (120 tablets): £8,547.60 Proposed PAS price, per pack (120 tablets): [redacted]	List price, per pack (30 capsules): £10,685.00
Method of administration	Oral	Oral
Dose	356 mg	61 mg
Dosing frequency	2 tablets twice daily	1 capsule per day
Dose adjustments	N/A	N/A
Cost of treatment (per month)	List price based: £8,672 PAS price based: [redacted]	List price based: £10,841

Abbreviations: mg, milligram; PAS, patient access scheme; VAT, value added tax.

Source: CS Table 46

4.1.3. Adverse event costs

The decision to include diarrhoea, nausea and urinary tract infections in the cost comparison analysis was based on their inclusion in TA984[20] and validated by clinical experts. Other events observed in the trials – considered to be related to the age and condition of the target population – were excluded.

Adverse event frequencies for acoramidis were informed by ATTRibute-CM data. Tafamidis adverse event frequencies were taken from Maurer et al. (2018),[9] presented in Table 49 of the company submission. The unit costs of adverse events used in the cost comparison are presented in Table 50 of the company submission.

The EAG considered it appropriate to exclude adverse event costs from the cost comparison, on the assumption that they are equivalent across treatments. This was supported by the similar safety profile seen in the EAG clinical evidence review, as well as comments from clinical experts that it is unlikely that adverse events differ between acoramidis and tafamidis.

4.1.4. Survival analysis

The company conducted a parametric survival analysis of the ATTRibute-CM OLE data to extrapolate all-cause mortality and time-to discontinuation over a lifetime horizon. Given that time-to-discontinuation and all-cause mortality are consistent between acoramidis and tafamidis, this analysis was not necessary for the cost comparison.

4.1.5. Company results

The company base case results are presented in Table 14. Based on the list price, acoramidis represents a reduction in cost compared to the tafamidis list price of [redacted] over a 25-year time horizon. When acoramidis PAS discount is applied, the reduction in cost compared to the tafamidis list price is [redacted].

Table 14: Company base case results

Technology	Acquisition cost	AE cost	Monthly cost*	Lifetime cost
	Acoramidis list price			
Acoramidis + SM	[redacted]	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]	[redacted]
	Acoramidis PAS price			
Acoramidis + SM	[redacted]	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis + SM	[redacted]	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment (SM)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SM, symptomatic management; PAS, patient access schemes

Notes: *Monthly costs were calculated by dividing the total lifetime costs by the model time horizon in months (300), and account for the proportion of patients remaining alive and on treatment over time".

4.1.6. Company scenario and sensitivity analysis

Results of the company scenario analysis are presented in Table 55 of the CS. [redacted] The time

horizon, time-to-discontinuation hazard ratio and discount rate had the largest impact on the results (see Table 15).

Table 15: Company scenario analysis

Scenario	Overall cost for acoramidis + SM (List price)	Overall cost for acoramidis + SM (PAS price)	Overall cost for tafamidis + SM (List price)	Incremental cost (Acoramidis List price)	Incremental cost (Acoramidis PAS price)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 0.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tafamidis TTD HR: 1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD, time to discontinuation; HR, hazard ratio; SM, symptomatic management

Deterministic sensitivity analysis results are presented in Figure 44 and Figure 45 of the CS. There were no instances in which varying the parameters resulted in the costs of acoramidis being higher than the costs of tafamidis. The parameter that the results were most sensitive to was the TTD hazard ratio for tafamidis.

4.1.7. EAG preferred base case results

In the EAG base case, the acquisition costs of both treatments were compared, with all other costs excluded. Table 16 shows that acoramidis costs [redacted] per month, whereas at the list price tafamidis costs £10,841 per month, when only including the acquisition cost. A further set of results incorporating the acoramidis and tafamidis PAS discounts are available in the confidential appendix.

Table 16: EAG base case results

Technology	Pack cost	Pack size	Recommended dose	Cost per month*
Acoramidis	[redacted]	120 tablets	1424mg per day (4x356mg tablets)[21]	[redacted]

Technology	Pack cost	Pack size	Recommended dose	Cost per month*
Tafamidis	£10,685	30 capsules	61mg per day (1x61mg capsule)[17]	£10,841

Notes: *Cost per month calculated using 30.44 days per month, consistent with the company submission

4.2. EAG conclusion on the company's cost comparison

The company's cost-comparison analysis assessed acoramidis versus tafamidis over a 25-year time horizon from an NHS and PSS perspective, applying a 1-month cycle length and a 3.5% discount rate. The analysis restricted costs to those expected to differ between treatments, which were drug acquisition and adverse event costs. Resource use, administration, and wastage were excluded on the assumption of equivalent clinical effectiveness and mode of administration. The EAG considered these exclusions justified. The EAG noted that the guidance states a 0% discount rate should be applied, unless there is a rationale provided to include a discount rate. No rationale was provided by the company.

Adverse events included in the analysis were limited to diarrhoea, nausea, and urinary tract infection, consistent with TA984 and validated by clinical experts. However, given the comparable safety profiles of acoramidis and tafamidis, the EAG considered it reasonable to exclude adverse event costs from the comparison. Similarly, the modelling of discontinuation was judged methodologically appropriate but unnecessary, as time to discontinuation was consistent across treatments. The costs of symptom management were consistent across treatments. Therefore, the EAG preferred to exclude symptom management costs from the analysis.

In the company's base case, acoramidis was associated with lower total costs relative to tafamidis over the modelled 25-year horizon at list price. [redacted] The cPAS Appendix compares the costs of acoramidis and tafamidis using the PAS prices for both.

An alternative cost comparison is presented in Table 16. In this comparison, the EAG has excluded everything except acquisition cost, as this is the only important difference between the two treatments. In the EAG base case acoramidis has a [redacted] lower cost per month than tafamidis.

5. EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

5.1. Strengths

5.1.1. Clinical evidence

The primary source of clinical effectiveness evidence for acoramidis was an international double-blind placebo-controlled RCT (ATTRibute-CM). [redacted] of participants in the trial were recruited from UK sites. Baseline characteristics were considered to match well to the clinical practice population in England. Outcomes were considered to be relevant and clinically appropriate. An anchored MAIC was used to compare acoramidis and tafamidis. This was considered an appropriate method in the absence of head-to-head trial evidence.

5.1.2. Economic evidence

The evidence was clear and consistent, suggesting that all costs, except acquisition costs, were the same for both treatments.

5.2. Weaknesses and areas of uncertainty

5.2.1. Clinical evidence

Safety evidence relied on a naïve comparison of the acoramidis and tafamidis trials without adjustment for population characteristics. Data were not available to compare acoramidis to tafamidis in relation to the NT-pro-BNP biomarker. Changing standard of care over time between the tafamidis and acoramidis trials was a limitation of the ITC. However, one area of concern was that subgroups were not included in the company decision problem. Bayer considered that there was insufficient data for the subgroups proposed in the final scope which could lead to conclusions based on underpowered analysis. The EAG noted the [redacted] in those with severe heart failure (NHYA Class III) and that European guidelines do not recommend tafamidis in people assessed at NYHA Class III (although tafamidis was recommended in TA984 for ATTR CM without any reference to subgroups).

5.2.2. Economic evidence

No important areas of uncertainty were identified.

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Appendix

Table 17. Summary of Efficacy results for ATTRibute-CM and AG10-304 OLE

	ATTRibute-CM		**OLE at Month 42 (FAS)** **(OLE Month 12 data cut)**	
	mITT	**ITT**	**Continuous acoramidis (i.e., Acoramidis in ATTRibute-CM)**	**Placebo to acoramidis** **(i.e., Placebo in ATTRibute-CM)**
	N=611	**N=632**	**N=409**	**N=202**
4-step hierarchical analysis of ACM, CVH, CFB in NT-proBNP and CFB in 6MWD over a 30-month period	Win Ratio 1.772 95% CI: (1.417, 2.217) p-value from F-S Method: <0.0001	Win Ratio 1.763 95% CI: [redacted] p-value from F-S Method: <0.0001	-	-
2-step hierarchical analysis of ACM and CVH over a 30-month period	Win Ratio 1.464 95% CI: (1.067, 2.009) p-value from F-S Method: 0.0182	Win Ratio 1.459 (95% CI): [redacted] p-value from F-S Method: 0.0168	-	-
Time to ACM or First CVH Hazard Ratio (95% CI)[a]	0.645 (0.500, 0.832) p-value: 0.0008	0.661 (0.516, 0.848) p-value: 0.0011	0.57 (0.46, 0.72) p<0.0001	
ACM Hazard Ratio[a] (96% / 95% CI) p-value ARR, RRR (%)	0.772 95% CI: (0.54, 1.1) p-value: 0.1543 6.4%, 25% (p=0.0569)[c]	0.762 95% CI: (0.542, 1.072) p-value: 0.1184 7%, 26% (p=0.0390)[c]	0.64 95% CI: (0.47, 0.88) p=0.006	

	ATTRibute-CM		**OLE at Month 42 (FAS)** **(OLE Month 12 data cut)**	
	mITT	**ITT**	**Continuous acoramidis (i.e., Acoramidis in ATTRibute-CM)**	**Placebo to acoramidis** **(i.e., Placebo in ATTRibute-CM)**
	N=611	**N=632**	**N=409**	**N=202**
Time to first CVH Hazard Ratio (95% CI) [a]	0.601 (0.451, 0.800) p-value: 0.0005	0.611 (0.461, 0.809) p-value: 0.0006	0.53 (0.41, 0.69) p<0.0001	
Annualised frequency of CVH Relative risk ratio (95% CI) [b]	0.496 (0.355, 0.695) p-value: <0.0001	0.510 (0.368, 0.708) p-value: <0.0001	NA	NA
CV-related Mortality Hazard Ratio (95% CI) [a] ARR, RRR (%)	0.709 (0.476, 1.054) p-value: 0.0889) 6.4%, 30% (p=0.037)[c]	[redacted]	NA	NA
	LS-Mean Difference at Month 30 (95% CI)		Mean change from baseline (SD)	
6MWD (m) LS-Mean Difference at Month 30: (96% / 95% CI) p-value	39.64 95% CI: (21.1, 58.2) p<0.001	[redacted] 95% CI: [redacted] [redacted]	[redacted] -24.5m ([redacted])	[redacted] [redacted]
KCCQ-OS LS-Mean Difference at Month 30: (96% / 95% CI) p-value	9.94 95% CI: (5.97, 13.91) p<0.001	[redacted] 95% CI: [redacted] [redacted]	[redacted] -4.0 ([redacted])	[redacted] [redacted]
Serum TTR (mg/dL)	LS-Mean Difference at Month 30 (96% / 95% CI): Acoramidis-Placebo		Mean change from baseline (SE) to month 31	
	7.10 95% CI: (5.79, 8.40)	[redacted]	8.9 (0.38)	7.4 (0.55)

	ATTRibute-CM		**OLE at Month 42 (FAS)** **(OLE Month 12 data cut)**	
	mITT	**ITT**	**Continuous acoramidis (i.e., Acoramidis in ATTRibute-CM)**	**Placebo to acoramidis** **(i.e., Placebo in ATTRibute-CM)**
	N=611	**N=632**	**N=409**	**N=202**
	p<0.001	95% CI: [redacted]		
NT-proBNP (pg/mL)	Ratio of AGM Fold-change (95% CI)		Geometric mean (Geometric SD) of fold-change	
	0.529 (95% CI: 0.463, 0.604) Nominal p<0.0001	[redacted]	1.10 (1.93)	2.29 (2.19)

Abbreviations: 6MWD, 6-minute walk distance / distance achieved in a standardised 6MWT; 6MWT, 6-minute walk test; ACM, all-cause mortality; AGM, Adjusted geometric mean; ARR, absolute risk reduction; CEC, Clinical Events Committee; CFB, change from baseline; CI, confidence interval; CMH, Cochrane-Mantel-Haenszel; CV, cardiovascular; CVH, cardiovascular-related hospitalisation; eGFR, estimated glomerular filtration rate; F-S, Finkelstein-Schoenfeld; FAS, full analysis set; ITT, intent-to-treat; IXRS, Interactive Voice/Web Response System; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Score; LS, Least squares; mITT, modified intent-to-treat; NA, not available; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RRR, relative risk reduction; SD, standard deviation; TTR, transthyretin.

Full Analysis Set relating to OLE results includes all patients in ATTRibute-CM mITT population.

[a] Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWT as a covariate, and is stratified by randomisation stratification factors of genotype, NT-proBNP level and eGFR level as recorded in IXRS.

[b] Negative binomial regression model with treatment group, randomisation stratification factors of genotype, NT-proBNP level and eGFR level from IXRS, and the offset term is used to analyse the cumulative frequency of CEC adjudicated CVH. c calculated via CMH test.

Source: CS Document B, Table 11, p.p.48-49.

Cost Comparison Appraisal

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 29 September** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Subgroups were not included in the company decision problem (specifically comments about severity of heart failure)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On **page 10** of the EAG report is the following text: "*However, one area of concern was that subgroups were not included in the company decision problem. The EAG noted the* [redacted] *in those with severe heart failure (NHYA Class III)…..."* On **page 46** of the EAG report is the following text: *"However, one area of concern was that subgroups were not included in the company decision problem. The EAG noted that the* [redacted]	On **page 10** of the EAG report (and **pages 46 and 52**) Bayer propose the following amended text: *"However, one area of concern was that subgroups were not included in the company decision problem. Bayer considered that there was insufficient data for the subgroups proposed in the final scope which could lead to conclusions based on underpowered analysis. The EAG noted the* [redacted] *in those with severe heart failure (NHYA Class III)."* On **page 15** of the EAG report, Bayer propose the following amended text: *"The EAG was concerned that subgroups by severity of heart failure were not included in the*	To accurately reflect that Bayer did consider the subgroups proposed in the final scope but concluded that the evidence did not allow for meaningful analysis. To provide more information on the NYHA Class III HR value and associated uncertainty data.	Thank you for your comments. The EAG agree that these are not factual inaccuracies. However, for additional clarity, the EAG has made the requested revisions.

[redacted] *in those with severe heart failure (NHYA Class III)….."* On **page 52** of the EAG report is the following text: *"One area of concern was that subgroups were not included in the company decision problem. The EAG noted that the* [redacted] *in those with severe heart failure (NHYA Class III)….."* On **page 15** of the EAG report is the following text: *"The EAG was concerned that subgroups by severity of heart failure were not included in the company decision problem. The EAG also noted a* [redacted] *in those with severe heart failure (NHYA Class III)….."*	*company decision problem. Bayer considered that there was insufficient data for subgroups based on severity of heart failure which could lead to conclusions based on underpowered analysis The EAG ~~also~~ noted a* [redacted] *in those with severe heart failure (NHYA Class III).."* In Table 2, **page 18** of the EAG report, Bayer propose the following amended text: *"The EAG noted that forest plot for NYHA Class III i.e. severe heart failure (CS Appendix D Figure 4) shows the* [redacted] *However, Bayer considered that there was insufficient data for subgroups based on severity of heart failure*		

In **Table 2, page 18** of the EAG report is the following text: "*The EAG noted that forest plot for NYHA Class III i.e. severe heart failure (CS Appendix D Figure 4) shows the* [redacted] Whilst not a factual inaccuracy, Bayer did consider presenting subgroups as suggested in the final scope: ***"if the evidence allows"***. The conclusion was that there was insufficient trial data for the proposed subgroups which could lead to conclusions based on underpowered analysis (Table 1, Bayer submission). Bayer believes that if the result in NYHA class III is presented in the EAG report, it is important to clarify that	*which could lead to conclusions based on underpowered analysis."*		

the HR estimate was fairly close to 1 and show the degree of uncertainty around the result.			

Issue 2 Recommendations from European Guidelines

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On **page 10** of the EAG report (and **pages 15, 46 and 52**) is the following text: *"European guidelines do not recommend tafamidis in people assessed at NYHA Class III".* Whilst not a factual inaccuracy, the European guidelines which Bayer believe the EAG are referring to pre-date the NICE technology appraisal for tafamidis.	Bayer propose deleting the following text: *"…and that European guidelines do not recommend tafamidis in people assessed at NYHA Class III."*	Bayer believe the EAG may be referring to the following guidelines which pre-date the NICE technology appraisal for tafamidis (TA984 June 2024). Tafamidis was recommended as a treatment option by NICE in this TA in accordance with the marketing authorisation without any reference to subgroups. McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart	The EMA approval of tafamidis for ATTR-CM came on 18 February 2020 and therefore tafamidis could be considered in the European guidelines, which recommend this treatment for NYHA Class I and II but not Class III. The later date of the NICE approval does not affect the relevance of the European guidelines. As such, there is no factual inaccuracy. Nevertheless, we agree that adding contextual

		failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021;42(36):3599-3726. And/ or: Arbelo E et al. 2023 ESC Guidelines for the management of cardiomyopathies: Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC). European Heart Journal (2023) 44, 3503–3626.	information regarding the recommendation made in TA984 would be useful for the reader. We have therefore added the following text after each of the statements listed in the issue description: "(although Tafamidis was recommended in TA984 for ATTR-CM without any reference to subgroups)"
On **page 18** of the EAG report is the following text: *"An ICER report indicated that while US guidelines recommend tafamidis for those with NYHA Class III symptoms, European guidelines do not."*	Bayer propose deleting the following text: *"An ICER report indicated that while US guidelines recommend tafamidis for those with NYHA Class III symptoms, European guidelines do not."*	Bayer believe the EAG may be referring to the following guidelines which pre-date the NICE technology appraisal for tafamidis (TA984 June 2024). Tafamidis was recommended as a treatment option by NICE in this TA in accordance with the marketing authorisation	We agree that this is not a factual inaccuracy, but we have added contextual text as above.

Whilst not a factual inaccuracy, the European guidelines which Bayer believe the EAG are referring to pre-date the NICE technology appraisal for tafamidis.		without any reference to subgroups. McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021;42(36):3599-3726. And/ or: Arbelo E et al. 2023 ESC Guidelines for the management of cardiomyopathies: Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC). European	

		Heart Journal (2023) 44, 3503–3626W.	

Issue 3 Proposed/ approved indications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23 of the EAG report refers to the *"proposed indication"* for acoramidis. This is the approved indication for acoramidis.	Please amend the text as follows: *"The ~~proposed~~ approved indication is adults with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM)".*	Please amend for accuracy.	Our original text referred to the proposed indication regarding NICE approval. However, we agree that it could be misconstrued as referring to regulatory approval. Therefore, we have amended as requested.

Issue 4 Clarity that values are percentages

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 11 on **page 41** of the EAG report, there are numbers within the columns *"Acoramidis Matched Scenario 3"* and *"Placebo Matched Scenario 3"* which are percentages. This is not clear within the table. The specific values in these columns relate to TTR genotype and NYHA Class.	Please ensure it is clear these values are percentages.	Please amend for clarity.	Thank you for your comment. This table states in the left-hand column that the values for TTR genotype and NYHA class are n (%). Therefore, no edits are required.

Issue 5 Categorisation of adverse events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On **page 44** of the EAG report, there is reference to *"serious"* TEAEs but this should refer to *"severe"* TEAEs	Please amend the text as follows: *"….and ~~serious~~ severe TEAEs (37.3% vs 45.5%)"*	Please amend for accuracy.	Thank you for your comment. Amended as requested.

Issue 6 EAG results clarification and potential calculation error

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 14 of **page 49** of the EAG report, the EAG has included a "monthly cost" column with figures that appear to be calculated by dividing the total lifetime cost by the model time horizon in months (i.e. 25*12 = 300). However, it may not be clear to the reader how these are generated given that they were not included in the company results presented in the submission dossier or clarification questions, they account for the proportion of patients alive and on treatment over time in the cost comparison model, and the EAG reports separate monthly treatment	Please add footnote to Table 14 as follows: *"Monthly costs were calculated by dividing the total lifetime costs by the model time horizon in months (300), and account for the expected proportion of patients remaining alive and on treatment over time".*	Please amend for clarity.	Thank you for your comment. Whilst this is not a factual inaccuracy, we believe this change would add clarity, so have added the suggested text as a footnote to Table 14.

costs in Table 16 which are calculated as more simple monthly acquisition costs without accounting for discontinuation or mortality.			
In Table 14 of **page 49** of the EAG report, some values reported in the monthly costs column appear incorrect, assuming that they are calculated by dividing the total lifetime costs by the model time horizon in months.	For list price results, correct monthly acoramidis + SM on treatment costs from [redacted] to [redacted]. For PAS price results, correct total monthly acoramidis + SM costs from [redacted] to [redacted] and monthly acoramidis + SM on treatment costs from [redacted] to [redacted].	Please amend for accuracy.	Thank you for these corrections which appear to be typos and have now been implemented.

Issue 7 Table headers are not descriptive

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Table 15 on **page 50** of the EAG report would benefit from clearer column headings (columns 2-4)	The headings for the following columns should be amended: *"~~Acoramidis (List price)~~ Overall cost for acoramidis +SM (List price)"* *"~~Acoramidis (PAS price)~~ Overall cost for acoramidis +SM (PAS price)*	Please amend for clarity.	We agree that the suggested amendment to the column titles would improve clarity. Titles amended

	"~~Tafamidis (List price)~~ Overall cost for tafamidis +SM (List price)"		

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21 of the EAG report refers to "*TTF stabilisers"*	Bayer believe the EAG are referring to "*TTR stabilisers".*	Please amend for accuracy.	Thank you for bringing to our attention these typographical errors. They have all been corrected
Page 26 of the EAG report, in a footnote to Table 5 refers to *"acoramidis hydrochroloride per table*	Please amend the text as follows: *"acoramidis ~~hydrochroloride~~ hydrochloride per tablet"*	Please amend for accuracy.	
Page 29 of the EAG report refers to a publication by *"Gilmore et al."*	Please amend the text to *"Gillmore et al."*	Please amend for accuracy.	
On **page 46** of the EAG report, two sentences refer to *"population-level safety"* but Bayer considers the EAG may have intended one of these to refer to *"population-level efficacy".*	Is the following text what the EAG intended?: *"From the available information, the EAG agreed that the population-level ~~safety~~ efficacy of acoramidis appeared to have at least similar health benefits as tafamidis. Furthermore, it appeared that the population-level safety of*	Please amend for clarity.	

	acoramidis was at least comparable to that of tafamidis."		
At the bottom of **page 49** of the EAG report, the EAG incorrectly refers to *"time to death"* instead of *"time to discontinuation"*	Please amend the text as follows: *"The time horizon, ~~time-to-death~~ time-to-discontinuation hazard ratio and discount rate had the largest impact on the results."*	Please amend for accuracy.	

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
EAG report, **Page 44**	There is text and numbers which is currently unmarked as confidential in the EAG report which is marked as confidential in the Bayer submission.	Drug-related TEAEs were higher in the acoramidis group than the placebo group (11.9% vs 5.2%), primarily driven by '[redacted]' (acoramidis: [redacted]%; placebo: [redacted]%) and '[redacted]' (acoramidis: [redacted]%; placebo: [redacted]%).	Amended as requested.
EAG report, **Page 49**, Table 14 and number in the text above this table	There are numbers in Table 14 which are currently unmarked as confidential in the EAG report which are marked as confidential in the Bayer submission.	Please mark all £ values in Table 14 as [redacted].	Thank you for your comment, this has now been amended.

	There is a number in the text above this table which is currently unmarked as confidential in the EAG report which is marked as confidential in the Bayer submission	Please mark the following number above Table 14 as confidential: [redacted]	
EAG report, **Page 50**, Table 15	There are numbers in Table 15 which are currently unmarked as confidential in the EAG report which are marked as confidential in the Bayer submission.	Please mark all £ values in Table 15 as [redacted].	Thank you for your comment, this has now been amended.