National Institute for Health and Care Excellence

Health Technology Evaluation

Acoramidis for treating transthyretin-related amyloidosis cardiomyopathy [ID6354]

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

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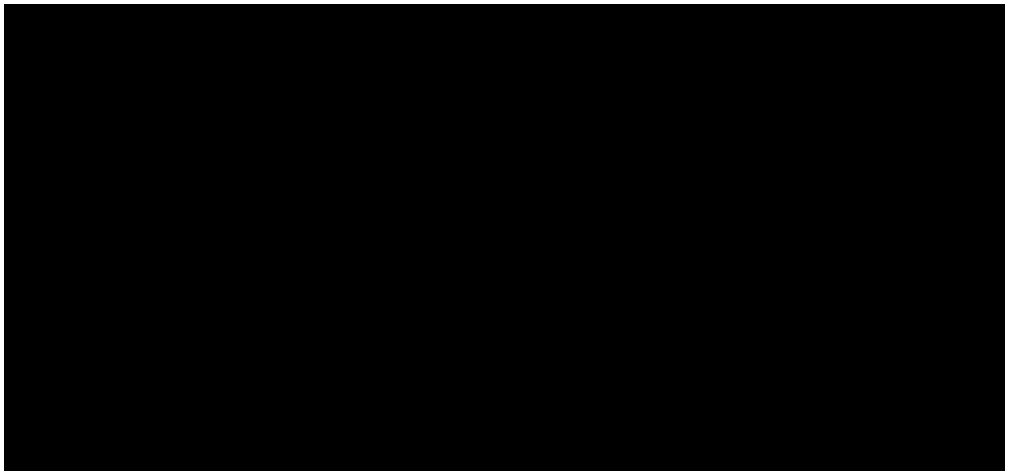
Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Alnylam	Alnylam regards the proposed evaluation of acoramidis to be appropriate.	Thank you for your comment.
	Amyloidosis UK	We would welcome evaluation through the cost comparison route as this will potentially result in faster treatments access for patients.	Thank you for your comment. Acoramidis will be appraised via the cost comparison route.
	British Association for the Study of the Liver	Transthyretin amyloid cardiomyopathy is a progressive and fatal disease if left untreated. Medical therapies are needed to address the underlying pathology, improve cardiac outcomes and morbidity, and prolong survival. Acoramidis is a new agent that has been shown to hold much promise and deserves evaluation	Thank you for your comment.
	Bayer	Bayer is proposing a cost-comparison approach for the appraisal of acoramidis.	Thank you for your comment. Acoramidis

Section	Stakeholder	Comments [sic]	Action
		According to the NICE process and methods manual (1) (4.2.13) *"a cost-comparison analysis is for technologies that are likely to provide similar or greater health benefits at similar or lower cost than the relevant comparator(s)".* For these appraisals, *"relevant comparators are those recommended in published NICE guidance for the same population".* Bayer consider the appropriate comparator for acoramidis to be tafamidis, which was positively appraised by NICE in 2024 for the same patient population i.e. for treating adults with wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) (2). Acoramidis and tafamidis are both oral drugs within the same therapeutic class and share a similar mechanism of action in the treatment of ATTR-CM as disease modifying transthyretin (TTR) stabilisers. They also share the same indication. Tafamidis is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (3). Acoramidis is indicated in the EU for the treatment of wild-type or variant transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (4). It is anticipated that the UK marketing authorisation will reflect the EU indication. Bayer believe that at least similar clinical effectiveness to tafamidis can be demonstrated. There is no head-to-head data, but after undergoing a feasibility assessment, an anchored matching-adjusted indirect comparison (MAIC) of tafamidis and acoramidis has been conducted using data from the ATTR-ACT(5) and ATTRibute-CM studies (6), respectively.	will be appraised via the cost comparison route.

Section	Stakeholder	Comments [sic]	Action
		The MAIC indicates [redacted] health benefits for acoramidis to tafamidis on key clinical outcomes (all-cause mortality (ACM) and cardiovascular hospitalisation (CVH) as well as safety). A very brief outline is set out below. Individual patient data from ATTRibute-CM was available and weighted to match aggregate published data on effect modifiers from ATTR-ACT. The selection of potential treatment effect modifiers for matching was informed by published evidence from each trial and interviews with clinical experts. 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 in the ATTRibute-CM study, the hypothetical strategy (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. The following endpoints were compared: all-cause mortality (ACM), cumulative frequency of cardiovascular (CV) hospitalisation (CVH) and safety outcomes. Results across most matching scenarios suggest [redacted] of acoramidis versus tafamidis in reducing CVH and [redacted] all-cause mortality. Matching Scenario 3 and Scenario 6 which adjust for all potential effect modifiers and applying HS were considered primary analyses (see Appendix 1 for description of scenarios).	

Section	Stakeholder	Comments [sic]	Action
		After matching, the effective sample sizes of acoramidis and placebo were [redacted] ([redacted]% reduction) and [redacted] ([redacted]% reduction), respectively for Scenario 3 and [redacted] ([redacted]% reduction) and [redacted] ([redacted]% reduction), respectively for Scenario 6. After applying the HS, the results suggested [redacted] cumulative frequency of CVH (RRR: [redacted] [95% CI: [redacted], [redacted]] in Scenario 3 and RRR: [redacted] [95% CI: [redacted], [redacted]] in Scenario 6) for acoramidis vs. tafamidis and [redacted] all-cause mortality (HR: [redacted], [95%CI: [redacted], [redacted]] in Scenario 3 and HR: [redacted], [95%CI: [redacted], [redacted]] in Scenario 6). Forest plots for ACM and CV hospitalisation across different MAIC scenarios are presented in Appendix 1. **Appendix 1 – MAIC Results** **Figure 1. ACM in the ITT population** 	

Section	Stakeholder	Comments [sic]	Action
		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) (base-case) Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max) **Figure 2. Cumulative Frequency of CV-related Hospitalization Excluding EOCIs, ITT Population**  **Abbreviations:** CI = confidence interval; CV = cardiovascular; EOCIs = events of clinical interest; HS = hypothetical strategy; ITT = intention-to-treat	

Section	Stakeholder	Comments [sic]	Action
		Note: In the HS, observations following the initiation of tafamidis were excluded for subjects who received concomitant tafamidis **Note:** In these scenarios, Events of Clinical Interest (EOCIs) were excluded from the CVH outcome definition to match the definition in ATTR-ACT. 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) (base-case) Scenario 4 matched on NT-proBNP, NYHA Class, TTR genotype, and age Scenario 5 matched on eGFR, NT-proBNP, NYHA Class, and age Scenario 6 matched on eGFR, NT-proBNP, NYHA Class, TTR genotype, and age (mean, proportion ≥80, proportion ≥65, median, min, max) The safety profiles of acoramidis and tafamidis were found to be comparable. Whilst data from MAIC are subject to certain limitations, Bayer believe the detailed results of this MAIC will demonstrate at least similar clinical effectiveness of acoramidis to tafamidis for the EAG and NICE committee. 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 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 National Amyloidosis Centre in London. Whilst the confidential net price of tafamidis is not known to Bayer, it will be Bayer’s intention to offer acoramidis at a similar or lower cost to tafamidis. Answering the specific questions in Appendix B:	

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		Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators? Yes, Bayer expect acoramidis to be at least similar in its clinical effectiveness, safety outcomes and resource use to tafamidis. This has also been supported by two clinical experts based at the National Amyloidosis Centre in London. *Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe* Yes, Bayer expect acoramidis to be used in the same place in the treatment pathway as tafamidis. Bayer are not aware of any major changes to the treatment pathway recently. *Will the intervention be used to treat the same population as the comparator(s)?* Yes, Bayer expects that acoramidis will be used to treat the same population as tafamidis. *Overall is the technology likely to offer similar or improved health benefits compared with the comparators?* Yes, Bayer expects that acoramidis will offer similar or improved health benefits compared with tafamidis, as well as offer no substantial differences in safety endpoints that might impact health benefits compared with tafamidis. This has been supported by the results of a MAIC conducted by Bayer, as	

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		well as by feedback from two clinical experts based at the National Amyloidosis Centre in London. *Would it be appropriate to use the cost-comparison methodology for this topic?* Yes, Bayer believe that based on all of the information provided above that it would be appropriate to use the cost-comparison methodology for the appraisal of acoramidis. 1. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE process and methods. PMG362023. Available from: https://www.nice.org.uk/process/pmg36. 2. National Institute for Health and Care Excellence (NICE). TA984: Tafamidis for treating transthyretin amyloidosis with cardiomyopathy2024 27th October 2024. Available from: http://www.nice.org.uk/guidance/ta984. 3. Pfizer Limited. Vyndaqel (tafamidis) 61 mg soft capsules: Summary of product characteristics (SmPC). Electronic Medicines Compendium [Internet]. 2023 23/01/2025. Available from: http://www.medicines.org.uk/emc/product/11141/smpc. 4. BridgeBio Europe. Beyonttra Summary of Product Characteristics (SmPC).2025. 5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with	

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		Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. 6. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024;390(2):132-42.	
	British Cardiovascular Society	Appropriate.	Thank you for your comment.
	British Society for Heart Failure	This is appropriate as a treatment for ATTR cardiomyopathy. There is one treatment at present available but this treatment may be more efficacious and would provide patients with an alternative if there are side effects from the current treatment	Thank you for your comment.
	Cardiomyopathy UK	We welcome the prospect of another medicine to treat ATTR cardiomyopathy and have no reason to question the appropriateness of evaluating on this topic. We would question the decision to take acoramidis through the STA rout on the basis of the rarity of the disease e.g. Delgado, D., Dabbous, F., Shivappa, N. *et al.* Epidemiology of transthyretin (ATTR) amyloidosis: a systematic literature review. *Orphanet J Rare Dis* 20, 29 (2025). https://doi.org/10.1186/s13023-025-03547-0	Thank you for your comment. Acoramidis will be appraised via the cost comparison route.
	Genetic Alliance UK	In preparation for this submission, Genetic Alliance UK spoke with representatives from Myeloma UK, Cardiomyopathy UK and Consultants with the National Amyloidosis Centre at the Royal Free London. We also reached out to representatives from Amyloidosis UK. Based on these conversations, we understand that hereditary transthyretin amyloidosis (ATTR-CM) is a rare	Thank you for your comment. Acoramidis will be appraised via the cost comparison route.

Section	Stakeholder	Comments [sic]	Action
		condition that can have a significant impact on quality of life. However, as this technology has been routed through an STA rather than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers. Given the challenges of making decisions on a treatment for rare conditions like ATTR-CM using the HST pathway, we therefore suggest that NICE instead considers passing this to the HST committee to review by applying the STA protocol, an approach previously taken for other rare conditions (e.g. treatments for ataxia).	
	Pfizer	Overall, we do not believe it would be appropriate to use the cost comparison methodology for this topic, due to the following reasons: • Acoramidis is not likely to demonstrate similar or improved reduction in all-cause mortality versus placebo when compared to tafamidis ○ All-cause mortality is a key endpoint for determining cost-effectiveness of treatments in ATTR-CM • There was concomitant use of tafamidis in the treatment and placebo arms of ATTRibute, which may have biased results • The concomitant use of tafamidis in ATTRibute and the fact that tafamidis has become standard of care for ATTR-CM in the UK warrants the committee to consider whether it may be more appropriate to consider acoramidis in combination with tafamidis rather than an alternative treatment option. We have provided further detail in the 'Questions' section of the draft scope comment.	Thank you for your comment. Acoramidis will be appraised via the cost comparison route. Acoramidis will be appraised in line with its UK marketing authorisation.
Wording	Alnylam	Alnylam regards the wording of the remit to be appropriate.	Thank you for your comment.
	Amyloidosis UK	No comments	N/A

Section	Stakeholder	Comments [sic]	Action
	British Association for the Study of the Liver	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
	Bayer	Bayer agree that the wording of the remit is appropriate i.e. *"To appraise the clinical and cost effectiveness of acoramidis within its marketing authorisation for treating transthyretin-related amyloidosis cardiomyopathy."*	Thank you for your comment.
	British Cardiovascular Society	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
	British Society for Heart Failure	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
	Cardiomyopathy UK	No comment	N/A
	Genetic Alliance UK	No comments.	N/A
	Pfizer	N/A	N/A
Timing issues	Alnylam	Alnylam notes that patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in the UK currently have access to tafamidis (a transthyretin [TTR] stabiliser, which employs the same mechanism of action as acoramidis). Additionally, vutrisiran, an RNA interference therapy, is currently under NICE appraisal for ATTR-CM.	Thank you for your comment.

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	Amyloidosis UK	No comments	N/A
	British Association for the Study of the Liver	There are two types of effective, approved medical treatments in ATTR amyloidosis. These include the gene silencing RNA approach for reduction of the hepatic production of Transthyretin (2 agents, NICE and FDA approved) for treatment of neuropathy in ATTR amyloidosis, and the TTR stabiliser approach medication (Tafamidis) for treatment of neuropathy and cardiomyopathy in ATTR Amyloidosis. Acoramidis, a small molecule, near complete (> 90%) ATTR stabiliser that inhibits dissociation of tetrameric TTR, thereby halting or slowing down further amyloid deposition, 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, improvement from baseline in cardiac markers NT-proBNP and 6 min walk test, with good safety profile, and has been approved by the FDA for the treatment of TTR-CM. This new orally administered agent, which provides near complete stabilisation of TTR and achieved improvements in clinical manifestations and outcomes as well as, quality of life, represents a landmark breakthrough and valuable treatment option for TTR-CM.	Thank you for your comment.
	Bayer	Effective disease modifying treatment can lessen both the patient and economic burden of ATTR-CM, in particular by reducing the number of costly CV complications and hospitalisations, improving quality of life, functionality and prolonging independent living (5, 6, 7, 8, 9). Whilst tafamidis has been recommended as a treatment option for the population of patients with ATTR-CM, it is important that an alternative effective treatment option is available for prescribers and patients.	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
		5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. 6. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024;390(2):132-42. 7. Fontana M, Sperry B, Kastritis E, Krejci J, Lam K, Patel J, et al., editors. Improved health-related quality of life in acoramidis-treated patients with ATTR-CM, demonstrated by improvements in KCCQ scores. ESC World Congress on Acute Heart Failure 2024, 11-14 May; 2024; Lisbon, Portugal. 8. Hanna M, Arad M, Coelho T, editors. Health-Related Quality of Life in Patients With Symptomatic Transthyretin Amyloid Cardiomyopathy Treated With Acoramidis: an Analysis From the ATTRibute-CM Study. ESC World Congress on Acute Heart Failure 2024, 11-14 May; 2024; Lisbon, Portugal. 9. Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, et al. Impact of Tafamidis on Health-Related Quality of Life in Patients With Transthyretin Amyloid Cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Am J Cardiol. 2021;141:98-105.	
	British Cardiovascular Society	N/A	N/A
	British Society for Heart Failure	Urgent to have alternatives and increasing prevalence of ATTR cardiomyopathy	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
	Cardiomyopathy UK	No comment	N/A
	Genetic Alliance UK	It is to our understanding that while tafamidis is effective for some people with ATTR-CM, a sizable number of patients might still experience progression of symptoms. Given the significant impact on quality of life of ATTR-CM - indicated by the previous approval of compassionate usage schemes for tafamadis in the EU and US - underscores that the need for additional treatment options for this population is urgent. Further, the trial data and real-world evidence gathered thus far suggests that acoramadis may be very slightly superior in terms of efficacy than tafamadis, although they have not been compared head to head. Effect of Timely Availability of TTR-Stabilizing Therapy on Diagnosis, Therapy, and Clinical Outcomes in ATTR-CM - PMC	Thank you for your comment.
	Pfizer	N/A	N/A
Additional comments on the draft remit	Alnylam	Alnylam does not have further comments on the draft remit.	N/A
	Amyloidosis UK	N/A	N/A
	British Association for the Study of the Liver	N/A	N/A
	Bayer	Bayer have no additional comments on the draft remit.	N/A

Section	Stakeholder	Comments [sic]	Action
	British Cardiovascular Society	N/A	N/A
	British Society for Heart Failure	N/A	N/A
	Cardiomyopathy UK	N/A	N/A
	Genetic Alliance UK	N/A	N/A
	Pfizer	N/A	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alnylam	Alnylam regards the background information to be appropriate.	Thank you for your comment.
	Amyloidosis UK	• This statement would be more complete if it acknowledged that while TTR amyloidosis has traditionally been associated with either cardiac or neurological manifestations, growing evidence suggests that many patients present with a mixed phenotype, experiencing both cardiac and neurological symptoms[1]. • It is stated that Wild-type ATTR-CM is more common in men than women. To state that it is diagnosed more in men would be more	Thank you for your comment – the background section of the scope has been updated to reflect all of these points.

Section	Consultee/ Commentator	Comments [sic]	Action
		accurate, as the true prevalence in men and women is unknown and the true picture is that women are underdiagnosed at present. • It is noted that individuals with African, Caribbean and Hispanic family backgrounds are disproportionately impacted by ATTR-CM. The information that these patients also have worse outcomes is missing. 1) González-Moreno J, Dispenzieri A, Grogan M, Coelho T, Tournev I, Waddington-Cruz M, Wixner J, Diemberger I, Garcia-Pavia P, Chapman D, Gupta P, Glass O, Amass L; THAOS investigators. Clinical and Genotype Characteristics and Symptom Migration in Patients With Mixed Phenotype Transthyretin Amyloidosis from the Transthyretin Amyloidosis Outcomes Survey. Cardiol Ther. 2024 Mar;13(1):117-135. doi: 10.1007/s40119-023-00344-3. Epub 2023 Dec 20. PMID: 38117424; PMCID: PMC10899146.	
	British Association for the Study of the Liver	There are broadly 2 types of transthyretin cardiac amyloidosis, namely the wild type ATTR wt-CM and the hereditary, variant cardiac amyloidosis ATTRv-CM. The commonest variants of ATTRv-CM hereditary amyloidosis are the ATTRVal122Ile in the Afro-Caribbean population and the ATTR Val30Met amongst Hispanics. The most commonly diagnosed variants in the UK and Ireland include ATTR Thr60Ala, Val122Ile and Val30Met (and in particular late onset Val30Met with onset at >50 years old)	Thank you for your comment, the background section of scope has been updated – we have focussed on the variants that are most commonly identified in the UK, based on Pocari et al. Specifically, Var122Ile.
	Bayer	Bayer would suggest that the following sentence is reworded as follows: Transthyretin amyloidosis (ATTR) is caused by abnormal transthyretin (TTR) proteins being produced by the liver, which accumulate as ~~deposits~~ amyloid fibrils in the tissues of the body. These amyloid ~~deposits~~ fibrils can disrupt the structure and damage the function of the affected tissues.	Thank you for your comments, the scope has been updated with the following wording: “which accumulate as

Section	Consultee/ Commentator	Comments [sic]	Action
		Please note that the brand name reported under “The Technology” is incorrect. The brand name quoted is that which is used in the US and marketed by Bridge Bio. Please replace with the Bayer EU brand name which is Beyonttra.	amyloid deposits (fibrils) in the tissues of the body”.
	British Cardiovascular Society	The wording set out below in the background section is misleading and needs to be re-written. *“Hereditary ATTR-CM (also known as familial or variant amyloid cardiomyopathy) affects people born with inherited mutations in the TTR gene. The most prevalent TTR variants in the UK are Val112Ile and Thr60Ala. People with African or Caribbean and Hispanic family backgrounds are more likely to have hereditary ATTR-CM because of the increased prevalence of variants (such as the Val112Ile variant) in these groups. People in these groups are also more likely to develop cardiomyopathy, without neuropathy.”* The founder population for T60A is based in the Northwest of Ireland. The wording should reflect that as Hispanic background is associated with the V30M variant and is more prevalent in Scandinavia, Portugal and Spain but relatively rarely seen in the UK. People with V122I are likely to develop a predominant cardiomyopathy but T60A patients typically develop a mixed polyneuropathy and cardiomyopathy.	Thank you for your comment, this section has now been re-written to focus on the variants that are most commonly identified in the UK, based on Pocari et al. Specifically, Var122Ile. The background section of the scope focuses on the specific indication, ATTR-CM.
	British Society for Heart Failure	Agree	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	Cardiomyopathy UK	No comments	N/A
	Genetic Alliance UK	No specific comments.	N/A
	Pfizer	N/A	N/A
Population	Alnylam	Alnylam regards the population definition to be appropriate.	N/A
	Amyloidosis UK	No comment	N/A
	British Association for the Study of the Liver	There is a separate, distinct subtype of variant transthyretin ATTR-CM which is the acquired variant transthyretin amyloidosis with neurological manifestations and TTR cardiomyopathy, following Domino Liver Transplant using liver grafts from patients with familial transthyretin amyloid polyneuropathy (FAP).	Thank you for your comments. The population currently specified in the scope covers all people with ATTR-CM.
	Bayer	The relevant population of patients for this appraisal are adult patients with wild-type or variant transthyretin amyloidosis with cardiomyopathy (ATTR-CM).	Thank you for your comments. The wording has been amended to “adults”. The scope does not specify the type of ATTR-CM, this is discussed under “subgroups”. Acoramidis will be

Section	Consultee/ Commentator	Comments [sic]	Action
			appraised in line with its marketing authorisation.
	British Cardiovascular Society	See above.	N/A
	British Society for Heart Failure	*Is the population defined appropriately?* yes	N/A
	Cardiomyopathy UK	No comments	N/A
	Genetic Alliance UK	There is more recent evidence from August 2024 suggesting that the prevalence of ATTR-CM might be higher than the previously reported: Prevalence, Cardiac Phenotype, and Outcomes of Transthyretin Variants in the UK Biobank Population | Genetics and Genomics | JAMA Cardiology | JAMA Network	Thank you for your comment. No updates needed.
	Pfizer	N/A	N/A
Subgroups	Alnylam	Alnylam regards it reasonable that subgroups defined by level of heart failure severity (via New York Heart Association [NYHA] classification) and disease type (hereditary transthyretin amyloidosis with cardiomyopathy [hATTR-CM] versus wild-type transthyretin amyloidosis with cardiomyopathy [wtATTR-CM]) may be of potential interest to assess clinical effectiveness and cost effectiveness.	Thank you for your comment. No updates needed.
	Amyloidosis UK	No comments	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	British Association for the Study of the Liver	The subgroup of acquired, de novo systemic transthyretin amyloidosis (cardiac or neuropathic or both), should be considered as a candidate cohort of patients who could potentially benefit from treatment with Acoramidis.	Thank you for your comment. This subgroup has not been added as it is likely to be extremely small therefore data availability would be challenging. However, this subgroup is included in the population covered by the scope.
	Bayer	Bayer do not believe that any subgroups should be considered in this appraisal. Bayer consider that the subgroups suggested in the scope 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.	Thank you for your comment. Subgroups are included when the clinical effectiveness or value for money of the technology might differ in a specific group compared with the overall population. Subgroups are not defined based on the trial data.

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	British Cardiovascular Society	I would suggest incorporation of NAC staging as well as NYHA Class. Ref: Gillmore JD, Damy T, Fontana M et al (2018) A new staging system for cardiac transthyretin amyloidosis. European Heart Journal 7;39(30):2799-806.	Thank you for your comment. NAC staging has been added as an additional measure of severity.
	British Society for Heart Failure	N/A	N/A
	Cardiomyopathy UK	No comments	N/A
	Genetic Alliance UK	No comments.	N/A
	Pfizer	We agree that the subgroups already identified in the draft scope are relevant. NICE may also want to also consider: • severity of heart failure by NAC staging (I-III) Severity of heart failure by NAC staging was captured in the ATTRibute trial.[1] 1. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. Jan 11 2024;390(2):132-142. doi:10.1056/NEJMoa2305434	Thank you for your comment. NAC staging has been added as an additional measure of severity.
Comparators	Alnylam	Alnylam understands that all patients eligible for treatment with acoramidis would, if not treated with acoramidis, otherwise be treated with another therapy specifically approved for ATTR-CM. Therefore, established clinical management (i.e., without another therapy specifically approved for ATTR-CM) is not a relevant comparator.	Thank you for your comment. Acoramidis will be appraised via the cost comparison route. As such, the

Section	Consultee/ Commentator	Comments [sic]	Action
		Alnylam notes that tafamidis is currently the only Medicines and Healthcare products Regulatory Agency (MHRA)-approved[1] NICE-recommended[2] therapy for patients with ATTR-CM. 1. Medicines and Healthcare products Regulatory Agency (MHRA). VYNDAQEL (tafamidis) Summary of Product Characteristics. Kent, United Kingdom: Pfizer Limited B.V.; Date 25 May 2023. 2. National Institute for Health and Care Excellence (NICE). Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA984). 2024.	comparators have been updated to include tafamidis only.
	Amyloidosis UK	No comments	N/A
	British Association for the Study of the Liver	Yes, Tafamidis, Vutrisiran (potentially-subject to NICE evalution) and standards of care clinical management are the only treatment options to-date for these otherwise progressive and fatal diseases. Efficient treatment options or combination therapies are crucially needed to improve symptoms, survival and quality of life.	Thank you for your comment. Acoramidis will be appraised via the cost comparison route. As such, the comparators have been updated to include tafamidis only.
	Bayer	According to the NICE process and methods guide(1), section 2.2.12 states *"The scope identifies all potentially relevant comparators that are **established practice** in the NHS."* Also, section 2.6.1 in relation to cost-comparison appraisals: *"The chosen comparator must be **established in practice**…."*. Lastly, section 4.2.13 states: *"For technologies evaluated using a cost-comparison analysis in the technology appraisal programme, relevant*	Thank you for your comment. Acoramidis will be appraised via the cost comparison route. As such, the comparators have been

Section	Consultee/ Commentator	Comments [sic]	Action
		comparators are those ***recommended in published NICE guidance for the same population****."* Tafamidis is the only treatment currently recommended by NICE for ATTR-CM (2) and represents established practice in the NHS. Bayer considers that tafamidis is the only relevant comparator in this appraisal. 1. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE process and methods. PMG362023. Available from: https://www.nice.org.uk/process/pmg36. 2. National Institute for Health and Care Excellence (NICE). TA984: Tafamidis for treating transthyretin amyloidosis with cardiomyopathy2024 27th October 2024. Available from: http://www.nice.org.uk/guidance/ta984.	updated to include tafamidis only.
	British Cardiovascular Society	Yes, this is appropriate - the other therapies being evaluated in phase 3 trials (ASO, antibody, gene editing therapies) are too far away from reporting to be considered in the current appraisal.	Thank you for your comment.
	British Society for Heart Failure	*Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?* yes	Thank you for your comment.
	Cardiomyopathy UK	*Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?* Yes, as far as we are aware	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance UK	No comments.	N/A
	Pfizer	N/A	N/A
Outcomes	Alnylam	Alnylam regards the outcomes to be appropriate; however, given the role of loop diuretics for symptomatic management of worsening heart failure, loop diuretic dose has also emerged as a useful indicator of disease severity predicting mortality risk in ATTR-CM.[3] Specifically, longitudinal changes in daily loop diuretic dose have shown prognostic value in patients with ATTR-CM, as patients seen at the National Amyloidosis Centre (NAC; n=1,598) experiencing outpatient diuretic intensification (ODI; defined as new initiation of oral loop diuretics or any increase in loop diuretic dose [furosemide equivalent]) from diagnosis to 1 year post-diagnosis, had a 1.9-fold increase (vs. patients without ODI) in mortality risk from 1 year post-diagnosis onward.[4] Therefore, Alnylam considers that ODI and/or composite outcomes incorporating ODI should be added to the list of outcomes. 3. Slama M, Charron P, Algalarrondo V, et al. Development of an algorithm using the dispensed daily doses of loop diuretics to assess survival of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) according to the disease severity [Presented at ISPOR Europe, virtual, Nov 19–Dec 20, 2020]. Value Health. 2020;23:S487. 4. Ioannou A, Cappelli F, Emdin M, et al. Stratifying disease progression in patients with cardiac ATTR amyloidosis. J Am Coll Cardiol. 2024;83(14):1276-1291.	Thank you for your comment. Outpatient diuretic intensification has been added as an outcome.

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	Amyloidosis UK	No comments	N/A
	British Association for the Study of the Liver	The outcomes listed are appropriate, crucially addressing the unmet needs in TTR-CR. These outcomes essentially represent the components of the primary end-points assessed on hierarchical analysis in the large double blind Acoramidis vs placebo study, published in NEJM January 2024.	Thank you for your comment.
	Bayer	The following outcomes listed in the scope will be considered within the submission: • overall survival (all-cause mortality) • cardiovascular-related mortality • cardiac function (NT-proBNP and Troponin I) • cardiovascular-related hospitalisation • functional exercise capacity (6MWD) • signs and symptoms of heart failure (KCCQ) • safety i.e. adverse effects of treatment • health-related quality of life (EQ-5D). In addition, the following will be reported: • serum TTR and stabilisation Bayer believe these outcome measures will capture the most important health related benefits and harms of acoramidis.	Thank you for your comment. Serum TTR and TTR stabilisation have been added as outcomes.
	British Cardiovascular Society	It was reassuring to see that health-related quality of life of patients and their carers is being included. Quality of life rather than survival is often more important to older patients with ATTRwt-CA.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Heart Failure	*Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?* yes	Thank you for your comment.
	Cardiomyopathy UK	No comments	N/A
	Genetic Alliance UK	No comments.	N/A
	Pfizer	N/A	N/A
Equality	Alnylam	Alnylam does not consider that the draft remit and scope need to be modified to meet equality goals.	Thank you for your comment.
	Amyloidosis UK	While we do not have any specific equality concerns, as previously noted, less women are currently diagnosed with ATTR-CM than men. Further evidence on prevalence, presentation and diagnosis in women is needed. ATTR-CM is most common in older people and individuals with African, Caribbean or Hispanic heritage. Therefor any of these three protected characteristics (gender, race, age) groups could be disproportionately impacted by this decision.	Thank you for your comment. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	British Association for the Study of the Liver	No concerns	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	Bayer	Bayer do not consider that the draft remit and scope need to be changed in order to address any potential equality issues.	Thank you for your comment.
	British Cardiovascular Society	No concern.	Thank you for your comment.
	British Society for Heart Failure	No	N/A
	Cardiomyopathy UK	We feel that it is important to recognise the average age of patients likely to be suitable for this treatment (60-70+ depending on type) and the increased prevalence of hereditary ATTR-CM in some communities. These factors should be considered when discussing ability to detect and reach potential patients and where the treatment sits in the care pathway.	Thank you for your comment. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	Genetic Alliance UK	As noted in the draft scope, there appears to be a significantly increased prevalence of pathogenic variants for ATTR-CM in some communities and this is an important area to consider more, as outlined in Aung *et al* 2024. Prevalence, Cardiac Phenotype, and Outcomes of Transthyretin Variants in the UK Biobank Population | Genetics and Genomics | JAMA Cardiology | JAMA Network	Thank you for your comment. The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the

Section	Consultee/ Commentator	Comments [sic]	Action
			committee during the evaluation.
	Pfizer	N/A	N/A
Other considerations	Alnylam	Alnylam has no suggestions for additional issues to be covered.	N/A
	Amyloidosis UK	We would welcome any consideration of the impact of ATTR-CM on the patients' family and friends, not just the patient. Family members often act as unpaid carers, reduce working hours etc. This disease has a significant impact that extends far beyond the patient.	Thank you for your comment. NICE considers quality of life for patients and carers – this has been reflected in the outcomes section of the scope.
	British Association for the Study of the Liver	Acoramidis could potentially be evaluated in due course for 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 (Vitrusiran) as well as, stabilising the circulating TTR (Acoramidis)	Thank you for your comment. Acoramidis will be evaluated in line with its current marketing authorisation.
	Bayer	Bayer have no other suggestions for consideration.	N/A
	British Cardiovascular Society	Not applicable	N/A

Section	Consultee/ Commentator	Comments [sic]	Action
	British Society for Heart Failure	N/A	N/A
	Cardiomyopathy UK	N/A	N/A
	Genetic Alliance UK	No comments.	N/A
	Pfizer	N/A	N/A
Questions for consultation	Alnylam	**Where do you consider acoramidis will fit into the existing care pathway for transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)?** Acoramidis, like tafamidis, is a TTR stabiliser, acting downstream of hepatic TTR production in the ATTR-CM disease pathway. Thus, Alnylam anticipates that acoramidis will be positioned as an alternative to tafamidis in the UK. Further support for this position is provided by the shared limitations of tafamidis and acoramidis, in that neither therapy has demonstrated a mortality benefit in a contemporary ATTR-CM population (i.e., current real-world patients who more often are diagnosed earlier in the disease course and have access to improved supportive care). As ATTR-ACT (pivotal trial of tafamidis) took place between 2013–2018,[5] the trial population therefore no longer represents the contemporary ATTR-CM population, which questions whether the observed mortality benefit versus placebo would be reflected in current real-world practice. Acoramidis, on the other hand, was studied in a contemporary ATTR-CM population in the ATTRibute-CM pivotal trial (2019–2023[6]), but did not show a	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		statistically significant survival benefit versus placebo (secondary endpoint analysis of all-cause mortality [ACM]) in this population.[7] In its recently concluded review of treatments for ATTR-CM, the Institute for Clinical and Economic Review (ICER) noted the mortality benefit limitations of TTR stabilisers. Specifically, ICER expressed uncertainty over how results observed with tafamidis in ATTR-ACT would translate to the contemporary, real-world ATTR-CM population.[8] In addition, ICER noted that although ATTRibute-CM was conducted in a contemporary population, acoramidis did not show a statistically significant survival benefit in the secondary endpoint analysis of ACM in this trial.[8] On the basis of this finding, ICER concluded that:[8] *"The lack of a statistically significant mortality benefit with acoramidis affects our judgment of both acoramidis and tafamidis in a contemporary population."* **What treatment will most people with ATTR-CM have in NHS clinical practice currently?** Tafamidis is currently the only MHRA-approved[1] NICE-recommended[2] therapy for patients with ATTR-CM, and all patients with ATTR-CM who are eligible to receive a treatment specifically approved for ATTR-CM will receive tafamidis. **Is there any evidence available directly comparing tafamidis and acoramidis? Are the populations included in the clinical trial for tafamidis in ATTR-CM (ATTR-ACT) and the clinical trial for acoramidis (ATTRibute-CM) comparable?** The ATTR-ACT and ATTRibute-CM trials took place over different periods of time (ATTR-ACT: 2013–2018[5]; ATTRibute-CM: 2019–2023[6]). This makes a methodologically robust indirect treatment comparison (ITC) across the two	

Section	Consultee/ Commentator	Comments [sic]	Action
		trials infeasible, considering recent developments in the ATTR-CM management landscape. Of particular note is due to the increased awareness of ATTR-CM within the clinician community, patients with ATTR-CM have increasingly been diagnosed earlier in the disease course, with less severe disease. This has been aided by improved diagnostic techniques (e.g., more widespread availability of technetium scintigraphy as a non-invasive alternative to cardiac biopsy).[9,10] For these reasons, baseline disease characteristics were broadly different between patients in ATTR-ACT and ATTRibute-CM.[11] Further, recent advancements in general management of heart failure have improved the baseline prognosis of patients with ATTR-CM (including placebo-treated patients in clinical trials) in a way that may modify the magnitude of effect of an active disease-modifying treatment. In contrast to patients in ATTR-ACT, patients in ATTRibute-CM would have been exposed to these advancements in background heart failure management, which could have confounded the comparison of observed treatment effects between the two trials.[12] For these reasons, a methodologically robust indirect treatment comparison of acoramidis in ATTRibute-CM and tafamidis in ATTR-ACT is likely unfeasible. This remains the case even with the use of matching-adjusted indirect comparison (MAIC) methods, as certain differences between the two trial populations (e.g., due to general improvements in heart failure management over time) may not be well captured in a way that allows quantitative adjustment for these differences. The above stated differences between the two trials (ATTR-ACT and ATTRibute-CM) was also what prevented ICER from conducting an indirect treatment comparison tafamidis and acoramidis in its review of ATTR-CM treatments, in which ICER stated:[8]	

Section	Consultee/ Commentator	Comments [sic]	Action
		"Given the changing population of patients studied over time [in ATTR-ACT and ATTRibute-CM], we do not feel we have adequate evidence to compare the net health benefits of tafamidis and acoramidis." **Please select from the following, will acoramidis be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** It is anticipated that the proposed routes for prescription and routine follow-up care align with option "C". For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. The setting for prescribing and routine follow-up does not differ for the comparator or subsequent treatments. **NICE is considering evaluating this technology through its cost comparison evaluation process.** **Please provide comments on the appropriateness of appraising this topic through this process.** • **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.** • **Will the intervention be used to treat the same population as the comparator(s)?** • **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** • **Would it be appropriate to use the cost-comparison methodology for this topic?** There are substantial barriers that make it difficult to establish comparable clinical efficacy between acoramidis and tafamidis in patients with ATTR-CM. The failure of acoramidis to demonstrate benefit versus placebo on ACM[7] and on the co-primary endpoint of 6-MWT change from baseline to Month 12 in ATTRibute-CM[13] contrasts with the demonstration of benefit with tafamidis versus placebo on ACM and on the primary endpoint (composite of ACM and CV hospitalisations) in ATTR-ACT.[14] The extent to which this is influenced by differences in patient characteristics and supportive care interventions in the ATTRibute-CM and ATTR-ACT populations is unclear, but nonetheless, it is possible that these findings reflect fundamental differences in efficacy between acoramidis and tafamidis. Thus, given the infeasibility of a methodologically robust ITC comparing the two treatments, and given the uncertainty raised by negative findings from ATTRibute-CM regarding ACM and the co-primary endpoint of 6-MWT change from baseline at Month 12, it is challenging to establish comparability between acoramidis and tafamidis in terms clinical efficacy, and the potential for cost comparison may be impacted as a result.	

Section	Consultee/ Commentator	Comments [sic]	Action
		1. Medicines and Healthcare products Regulatory Agency (MHRA). VYNDAQEL (tafamidis) Summary of Product Characteristics. Kent, United Kingdom: Pfizer Limited B.V.; Date 25 May 2023. 2. National Institute for Health and Care Excellence (NICE). Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA984). 2024. 3. Slama M, Charron P, Algalarrondo V, et al. Development of an algorithm using the dispensed daily doses of loop diuretics to assess survival of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) according to the disease severity [Presented at ISPOR Europe, virtual, Nov 19–Dec 20, 2020]. Value Health. 2020;23:S487. 4. Ioannou A, Cappelli F, Emdin M, et al. Stratifying disease progression in patients with cardiac ATTR amyloidosis. J Am Coll Cardiol. 2024;83(14):1276-1291. 5. ClinicalTrials.gov. Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT) (NCT01994889). https://clinicaltrials.gov/study/NCT01994889. Accessed 31 October 2023. 6. ClinicalTrials.gov. Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy (ATTRibute-CM; NCT03860935). https://classic.clinicaltrials.gov/ct2/show/NCT03860935.	

Section	Consultee/ Commentator	Comments [sic]	Action
		7. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. N Engl J Med. 2024;390(2):132-142. 8. Institute for Clinical and Economic Review (ICER). Disease Modifying therapies for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) 2024. 9. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol. 2023;81(11):1076-1126. 10. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075. 11. Girard AA, Sperry BW. Contextualizing the results of HELIOS-B in the broader landscape of clinical trials for the treatment of transthyretin cardiac amyloidosis. Heart Fail Rev. 2024. 12. Porcari A, Cappelli F, Nitsche C, et al. SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2024;83(24):2411-2422.	

Section	Consultee/ Commentator	Comments [sic]	Action
		13. BridgeBio. BridgeBio Pharma Reports Month 12 Topline Results from Phase 3 ATTRibute-CM Study. 2021. 14. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379(11):1007-1016.	
	Amyloidosis UK	**Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** Not all patients respond to or tolerate treatments in the same way. Currently, there is only one treatment available in the UK for wild-type ATTR-CM and two for hereditary ATTR-CM. The introduction of an additional treatment would significantly expand patient options, potentially leading to better outcomes. Beyond clinical benefits, increased treatment choices can also provide psychological reassurance for patients, knowing they have alternative options if needed.	Thank you for your comment.
	British Association for the Study of the Liver	**Questions for consultation** **Where do you consider acoramidis will fit into the existing care pathway for transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)?** I believe Acoramidis as perhaps the first near complete TTR stabiliser would be a front line medication for the treatment of TTR-CM. It is crucial to be able to provide improved and promising treatment options for these progressive diseases.	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		What treatment will most people with ATTR-CM have in NHS clinical practice currently? Treatment options are very limited at present including Tafamidis or established conservative medical care 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 prescription in primary care and routine follow up in secondary care in the long term.	
	Bayer	**Where do you consider acoramidis will fit into the existing care pathway for transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)?** Bayer expect acoramidis to be used in the same place in the care and treatment pathway for ATTR-CM as tafamidis. **What treatment will most people with ATTR-CM have in NHS clinical practice currently?** Bayer understands that diagnosed patients are being offered tafamidis in line with its marketing authorisation further to the publication of the NICE guidance in June 2024 (2). **Is there any evidence available directly comparing tafamidis and acoramidis?**	Thank you for your comments.

Section	Consultee/ Commentator	Comments [sic]	Action
		There is no head-to-head randomised controlled data comparing tafamidis and acoramidis. However, after undergoing a feasibility assessment, an anchored matching-adjusted indirect comparison (MAIC) of tafamidis and acoramidis has been conducted using data from the ATTR-ACT (5) and ATTRibute-CM studies (6), respectively. **Are the populations included in the clinical trial for tafamidis in ATTR-CM (ATTR-ACT) and the clinical trial for acoramidis (ATTRibute-CM) comparable?** When considering whether an indirect comparison could be conducted, study eligibility criteria, baseline characteristics and outcomes definition were carefully compared between ATTRibute-CM and ATTR-ACT. The comparison revealed that the trials differed in several eligibility criteria, baseline characteristics, and outcome definitions, thus traditional methods for anchored ITCs, such as Bucher's ITC (10) and network meta-analysis (NMA) (11), may produce biased results due to heterogeneity between trials. To adjust for imbalances between trial populations, when individual patient data (IPD) from an index trial and aggregate summary data from comparator studies are available, indirect comparisons can be conducted by using population-adjusted ITC methods (12), such as matching-adjusted indirect treatment comparison (MAIC) (13).	

Section	Consultee/ Commentator	Comments [sic]	Action
		A MAIC has been conducted and Bayer believe the detailed results of this MAIC will demonstrate at least similar clinical effectiveness of acoramidis to tafamidis for the EAG and NICE committee. **Please select from the following, will acoramidis be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** Bayer understands that acoramidis will be prescribed by a specialist in ATTR-CM in a named specialist hospital centre with routine follow-up in a specialist hospital centre. Management and prescribing for patients with ATTR-CM is currently led by the National Amyloidosis Centre (NAC) in London. It is planned that four regional specialist centres in amyloidosis management will be commissioned but with oversight from the NAC. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** The setting for prescribing and routine follow-up for comparators and subsequent treatments would be the same as for acoramidis. **Would acoramidis be a candidate for managed access?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Bayer do not believe acoramidis would meet the criteria for managed access. **Do you consider that the use of acoramidis can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** No. **NICE is considering evaluating this technology through its cost comparison evaluation process.** **Please provide comments on the appropriateness of appraising this topic through this process.** Bayer believe that it would be appropriate for acoramidis to be appraised through the cost comparison evaluation process. Please see a detailed consideration of this point in our response to *"Appropriateness of an evaluation and proposed evaluation route"* on pages 1-5 above. 1. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE process and methods. PMG362023. Available from: https://www.nice.org.uk/process/pmg36. 2. National Institute for Health and Care Excellence (NICE). TA984: Tafamidis for treating transthyretin amyloidosis with cardiomyopathy2024 27th October 2024. Available from: http://www.nice.org.uk/guidance/ta984. 3. Pfizer Limited. Vyndaqel (tafamidis) 61 mg soft capsules: Summary of product characteristics (SmPC). Electronic Medicines Compendium [Internet].	

		2023 23/01/2025. Available from: http://www.medicines.org.uk/emc/product/11141/smpc. 4. BridgeBio Europe. Beyonttra Summary of Product Characteristics (SmPC).2025. 5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-16. 6. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024;390(2):132-42. 7. Fontana M, Sperry B, Kastritis E, Krejci J, Lam K, Patel J, et al., editors. Improved health-related quality of life in acoramidis-treated patients with ATTR-CM, demonstrated by improvements in KCCQ scores. ESC World Congress on Acute Heart Failure 2024, 11-14 May; 2024; Lisbon, Portugal. 8. Hanna M, Arad M, Coelho T, editors. Health-Related Quality of Life in Patients With Symptomatic Transthyretin Amyloid Cardiomyopathy Treated With Acoramidis: an Analysis From the ATTRibute-CM Study. ESC World Congress on Acute Heart Failure 2024, 11-14 May; 2024; Lisbon, Portugal. 9. Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, et al. Impact of Tafamidis on Health-Related Quality of Life in Patients With Transthyretin Amyloid Cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Am J Cardiol. 2021;141:98-105. 10. Bucher HC, Guyatt GH, Griffith LE, SD. W. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. . J Clin Epidemiol. 1997;50(6):683-91. 11. Dias S, AJ S, AE A, NJ. W. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-	

Section	Consultee/ Commentator	Comments [sic]	Action
		analysis of randomized controlled trials. . Med Decis Making. 2013;33(5):607-17. 12. KJ I, I P, A. B. Simulation and matching-based approaches for indirect comparison of treatments. . Pharmacoeconomics. 2015;33(6):537-49. 13. Signorovitch JE, Sikirica V, Erder MH ea. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. . Value Health 2012;15(6):940-7.	
	British Cardiovascular Society	**Where do you consider acoramidis will fit into the existing care pathway for transthyretin-related amyloidosis cardiomyopathy (ATTR-CM)?** It could be used either as first-line disease modifying therapy or in combination with siRNA therapy (pending approval of vutrisiran). A shared care decision between the physician and patient including a discussion around the different routes of drug administration and the home care package on offer in association with novel treatments will be needed. The newly appointed National Amyloidosis Network centres Liverpool and Birmingham (due to start formally in May 2025 following highly specialised commissioning award from NHSE) will likely have prescribing rights with continued oversight from the National Amyloidosis Centre, Royal Free London. **What treatment will most people with ATTR-CM have in NHS clinical practice currently?** Other than supportive / conventional heart failure treatments, the only available disease modifying TTR directed treatment for patients diagnosed with ATTR-CA currently available on the NHS is tafamidis. To-date, suitable patients have been offered and prescribed this therapy via the Royal Free London, except in a minority of cases where there is deemed to be futility following MDT discussion.	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
		Is there any evidence available directly comparing tafamidis and acoramidis? Are the populations included in the clinical trial for tafamidis in ATTR-CM (ATTR-ACT) and the clinical trial for acoramidis (ATTRibute-CM) comparable? Attempts to compare the outcomes from these two trials have been made but these are inherently flawed because the trial populations were very different at baseline. **Please select from the following, will acoramidis be:** **D. Other (please give details):** If approved for use, prescribing of acoramidis is likely to be authorised only from NHSE highly specialised commissioned amyloidosis network centres with follow up shared between local centres and network centres. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Requirements for follow-up are still being discussed at a network level and have not yet been finalised. It is likely that local centres will be expected to provide ongoing local care with reference centres providing a bare minimum of annual review. This is likely to include history, blood work, ECG, 6MWD, echo as a minimum dataset requirement. **Would acoramidis be a candidate for managed access?** **Do you consider that the use of acoramidis can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** As commented on previously – the importance of effects on functional status, psychosocial health and quality of life should not be underestimated and be incuded in the outcomes analysis. Furthermore, the effects on carers and	

Section	Consultee/ Commentator	Comments [sic]	Action
		minimising work days lost would arguably lead to wider economic benefit for the country and lesser requirement for an overburdened social healthcare system. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Data available from the open-label extension as well as post-hoc analyses of the ATTRibute-CM trial: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.124.072771 https://investor.bridgebio.com/static-files/e0c1b57d-78b7-4667-a9bc-aa0486880475 https://investor.bridgebio.com/static-files/20f168d6-c43a-4b37-b2c0-7ae80a460cba **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which acoramidis will be licensed;** **• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**	

Section	Consultee/ Commentator	Comments [sic]	Action
		• **could have any adverse impact on people with a particular disability or disabilities.** Not applicable **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Not applicable **NICE is considering evaluating this technology through its cost comparison evaluation process.** **Please provide comments on the appropriateness of appraising this topic through this process.** Reasonable approach. We do not have definitive data yet to confirm the likelihood that combination TTR directed therapies provide additive or synergistic positive effects on outcomes in these patients but we do need more than one available treatment option on the NHS for these patients. It would make most sense to cost compare with tafamidis given their same mode of action (TTR stabiliser). *(Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).*	
	British Society for Heart Failure	N/A	N/A
	Cardiomyopathy UK	**1) Where do you consider acoramidis will fit into the existing care pathway for ATTR-CM?**	Thank you for your comment.

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		We expect that the treatment would be prescribed in secondary care with primary care follow up. The committee would need to consider planed changes to the provision of care and treatment of amyloidosis from 2025, particularly relating to the establishment of a network of regional centres connected to the National Amyloidosis Centre in London. **2) Do you consider that the use of acoramidis can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, it is important to recognise that there is a collective health benefit to the wider amyloidosis and cardiomyopathy communities with the introduction of new treatments. A new drug leads to greater clinical interest and awareness that would lead to overall improvement in the recognition of and detection of all forms of cardiomyopathy and amyloidosis. **3)Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Cardiomyopathy UK will be able to provide evidence from our national survey 2024 (completed but as yet unpublished) and focus group/s on the impact of ATTR-CM and the experience of people with ATTR-CM of their care and treatment. The national survey was done according to a rigorous methodology by Picker Institute, and received 20 responses from people with amyloidosis cardiomyopathy. We would be happy to provide data on the experiences of people with amyloidosis cardiomyopathy, should that be helpful at all.	
	Genetic Alliance UK	No comments.	N/A

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	Pfizer	We have provided answers to specific questions requested by NICE to help determine whether it is appropriate to assess acoramidis via cost-comparison methodology, please see below: **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?** All cause-mortality is a key endpoint across all landmark Phase III ATTR-CM trials including, ATTRibute-CM (acoramidis)[1], ATTR-ACT (tafamidis)[2], and HELIOS-B (vutrisiran)[3], and in turn an important endpoint for assessing cost-effectiveness. In ATTR-ACT, tafamidis was associated with a with lower all-cause mortality than placebo (hazard ratio, 0.70; 95% confidence interval [CI], 0.51 to 0.96).[2] Cumulative survival benefit has also continued to increase with longer-term follow-up: with nearly 5 years of follow-up in the ATTR-ACT long-term extension study, statistically significant improvement in all-cause mortality have been observed for all NYHA classes.[4,5] In ATTRibute, among the four key secondary outcomes that were included in the hierarchical plan to control for multiple testing, the between-group difference was significant for the 6-minute walk distance, KCCQ-OS score, and TTR serum level but not for death from any cause.[1] Results from a Matching Adjusted Indirect Comparison (MAIC) conducted by Pfizer showed tafamidis had a numerically favourable hazard ratio for all-cause mortality versus placebo compared to acoramidis, both pre- and post-	Thank you for your comment.

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		MAIC adjustment, with strengthened results after accounting for treatment effect modifier imbalances.[6] Despite results from the MAIC not reaching statistical significance due to large confidence intervals. Lack of statistical equivalence cannot be relied upon to conclude clinical equivalence for all-cause mortality. The concomitant use of tafamidis in the placebo arm of ATTRibute (described in more detail in the response to the next question) may have biased the relative effectiveness of acoramidis versus placebo, thereby skewing results from the MAIC. **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** As per our response to the previous question, we do not believe acoramidis is likely to offer similar or improved health benefits associated with reduction of all-cause mortality versus placebo – a key endpoint for determining cost-effectiveness of treatment in ATTR-CM – when compared to tafamidis. ***Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe*** ***Will the intervention be used to treat the same population as the comparator(s)?*** In ATTRibute, there was concomitant tafamidis use in both the treatment and placebo arms. After 12 months, 14.9% of patients in the acoramidis arm and 22.8% of patients in the placebo arm received tafamidis.[1]	

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		Considering the concomitant use of tafamidis in ATTRibute and that tafamidis has now become standard of care for treating ATTR-CM in the UK, it may be more appropriate to consider acoramidis as a combination therapy to be administered with tafamidis rather than an alternative treatment option to tafamidis. **Would it be appropriate to use the cost-comparison methodology for this topic?** Overall, we do not believe it would be appropriate to use the cost comparison methodology for this topic, due to the abovementioned reasons: • Acoramidis is not likely to demonstrate similar or improved reduction in all-cause mortality versus placebo when compared to tafamidis ○ All-cause mortality is a key endpoint for determining cost-effectiveness of treatments in ATTR-CM • There was concomitant use of tafamidis in both treatment arms of ATTRibute, which may have biased results The concomitant use of tafamidis in ATTRibute and the fact that tafamidis has become standard of care for ATTR-CM in the UK warrants the committee to consider whether it may be more appropriate to consider acoramidis in combination with tafamidis rather than an alternative treatment option.	

Section	Consultee/ Commentator	Comments [sic]	Action
		1. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. Jan 11 2024;390(2):132-142. doi:10.1056/NEJMoa2305434 2. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. Sep 13 2018;379(11):1007-1016. doi:10.1056/NEJMoa1805689 3. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. Jan 2 2025;392(1):33-44. doi:10.1056/NEJMoa2409134 4. Elliott P, Drachman BM, Gottlieb SS, et al. Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy. Circ Heart Fail. Jan 2022;15(1):e008193. doi:10.1161/circheartfailure.120.008193 5. Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. Eur J Heart Fail. Nov 2023;25(11):2060-2064. doi:10.1002/ejhf.2974 6. Pfizer. MAIC of Vyndaqel versus Acoramidis in transthyretin cardiomyopathy	
Additional comments on the draft scope	Alnylam	N/A	N/A
	Amyloidosis UK	N/A	N/A
	British Association for the Study of the Liver	N/A	N/A

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	Bayer	None	N/A
	British Cardiovascular Society	None	N/A
	British Society for Heart Failure	N/A	N/A
	Cardiomyopathy UK	N/A	N/A
	Genetic Alliance UK	We also just wanted to note that Cardiomyopathy UK shared with us that they anticipate publishing survey data on the experience of ATTR patients in the near future and this might support the consultation process at a later stage.	Thank you for your comment. The committee will consider all evidence submitted as part of the appraisal process.
	Pfizer	N/A	N/A

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

N/A