National Institute for Health and Care Excellence

Health Technology Evaluation

Vutrisiran for treating transthyretin-related amyloidosis cardiomyopathy [ID6470]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Alnylam Pharmaceuticals	Alnylam regards the proposed evaluation of vutrisiran to be appropriate.	Thank you for your comment. No action required.
	British Cardiovascular Society	STA is suitable.	Thank you for your comment. No action required.
Wording	Alnylam Pharmaceuticals	Alnylam regards the wording of the remit to be appropriate.	Thank you for your comment. No action required.
Timing Issues	Alnylam Pharmaceuticals	Alnylam considers this evaluation to be highly urgent for the NHS, for several reasons. Transthyretin amyloidosis with cardiomyopathy (ATTR-CM), is a burdensome, rapidly progressive, and fatal disease. Patients with ATTR-CM experience a range of debilitating symptoms associated with heart failure and conduction	Thank you for your comment. This topic is currently scheduled into the NICE work programme. For further

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		disorders,[1-5] with progressive cardiomyopathy leading to ongoing, irreversible worsening of physical functioning and the ability to perform everyday activities.[6-9] The loss of physical functioning results in substantial and irreversible declines in health-related quality of life (HRQoL) and other detrimental humanistic impacts.[6-8,10] ATTR-CM substantially shortens patient lifespan, with median survival from diagnosis ranging from 2.1 to 5.8 years.[2,5,11-19] Tafamidis is the only therapy available for patients with ATTR-CM in the UK.[20] Tafamidis is a transthyretin (TTR) stabiliser, which acts downstream of liver-mediated TTR protein production in the ATTR-CM disease pathway. TTR protein is the causative agent that drives the disease process in ATTR-CM.[21] Several efficacy limitations associated with tafamidis have been identified. In particular, patients receiving tafamidis continue to experience excess mortality and morbidity and show ongoing worsening in functional exercise capacity, HRQoL, and cardiac injury relative to their pre-treatment baseline.[6] In addition, the therapeutic benefit of tafamidis appears to be limited in some patient types.[6] In patients with ATTR-CM, AMVUTTRA (vutrisiran), an RNA interference (RNAi) therapeutic, administered subcutaneously every 3 months (Q3M), delivers: • Silencing of TTR protein production at its source in the liver, leading to rapid and sustained knockdown of circulating TTR levels.[22] • Significant reduction in morbidity and mortality.[8] • Halting or significant reduction in declines in functional exercise capacity, HRQoL, and cardiac injury.[8] • Consistent efficacy across all patient types.[8] • The ability to address extra-cardiac clinical manifestations that may be seen in ATTR-CM (e.g., peripheral and autonomic neuropathy). Vutrisiran has	details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta11598 No action required.

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		shown clinical benefit in treating polyneuropathy in patients with hereditary transthyretin amyloidosis (hATTR-PN),[23] and is Medicines and Healthcare products Regulatory Agency (MHRA)-approved for the treatment of patients with hATTR-PN with stage 1 or stage 2 polyneuropathy and received a positive recommendation from the National Institute for Health and Care Excellence (NICE) in this population.[24,25] • A convenient, patient-centric treatment profile that limits the risk of non-adherence to treatment. If approved by the MHRA for ATTR-CM, and positively recommended by NICE, vutrisiran is anticipated to be a new standard-of-care option for the first-line treatment of ATTR-CM in the UK. In this rapidly progressive, debilitating, and ultimately fatal disease, every day that optimally effective treatment remains unavailable translates into irreversible disability and higher risk of premature death. Existing treatment for ATTR-CM has important limitations that are addressed by vutrisiran. Thus, Alnylam regards this evaluation as highly urgent for the NHS to address the current unmet needs of ATTR-CM patients and to allow NICE to render a decision on granting access to vutrisiran for UK patients before they experience further potentially avoidable disease progression. **References**: 1. Dharmarajan K, Maurer MS. Transthyretin cardiac amyloidoses in older North Americans. *J Am Geriatr Soc.* 2012;60(4):765-774. 2. Jain A, Zahra F. Transthyretin amyloid cardiomyopathy (ATTR-CM). Chapter in StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, ed2023.	

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		3. Coelho T, Maurer MS, Suhr OB. THAOS - The transthyretin amyloidosis outcomes survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin.* 2013;29(1):63-76. 4. Rintell D, Heath D, Braga Mendendez F, et al. Patient and family experience with transthyretin amyloid cardiomyopathy (ATTR-CM) and polyneuropathy (ATTR-PN) amyloidosis: results of two focus groups. *Orphanet J Rare Dis.* 2021;16(1):70. 5. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation.* 2019;140(1):16-26. 6. 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. 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. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med.* 2024. 9. Ponti L, Hsu K, Damy T, et al. Burden of untreated transthyretin amyloid cardiomyopathy on patients and their caregivers by disease severity: results from a multicenter, non-interventional, real-world study. *Front Cardiovasc Med.* 2023;10:1238843. 10. Damy T, Adams D, Bridoux F, et al. Amyloidosis from the patient perspective: the French daily impact of amyloidosis study. *Amyloid.* 2022;29(3):165-174. 11. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J.* 2018;39(30):2799-2806.	

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		12. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid.* 2015;22(2):123-131. 13. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol.* 2016;68(10):1014-1020. 14. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation.* 2016;133(3):282-290. 15. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc.* 2013;2(2):e000098. 16. Ruberg FL, Maurer MS, Judge DP, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: The Transthyretin Amyloidosis Cardiac Study (TRACS). *American Heart Journal.* 2012;164(2):222-228.e221. 17. Cheng RK, Levy WC, Vasbinder A, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *JACC CardioOncol.* 2020;2(3):414-424. 18. Jang SC, Nam JH, Lee SA, et al. Clinical manifestation, economic burden, and mortality in patients with transthyretin cardiac amyloidosis. *Orphanet J Rare Dis.* 2022;17(1):262. 19. Damy T, Bourel G, Slama M, et al. Incidence and survival of transthyretin amyloid cardiomyopathy from a French nationwide study of in- and out-patient databases. *Orphanet J Rare Dis.* 2023;18(1):345. 20. Medicines and Healthcare products Regulatory Agency (MHRA). VYNDAQEL (tafamidis) Summary of Product Characteristics. Kent, United Kingdom: Pfizer Limited B.V.; Date 25 May 2023.	

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		21. Hawkins PN, Ando Y, Dispenzeri A, et al. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med.* 2015;47(8):625-638. 22. Habtemariam BA, Karsten V, Attarwala H, et al. Single-dose pharmacokinetics and pharmacodynamics of transthyretin targeting N-acetylgalactosamine-small interfering ribonucleic acid conjugate, vutrisiran, in healthy subjects. *Clin Pharmacol Ther.* 2021;109(2):372-382. 23. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2023;30(1):1-9. 24. European Medicines Agency (EMA). AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; 15 September 2022. 25. National Institute for Health and Care Excellence (NICE). Vutrisiran for treating hereditary transthyretin-related amyloidosis (TA868). 2023. 26. National Institute for Health and Care Excellence (NICE). Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (TA984). 2024.	
	Amyloidosis UK	From the amyloidosis patient perspective this is very urgent. Patients are living with a progressive, ultimately fatal condition. Any delay in accessing new treatments shortens lives.	Thank you for your comment. This topic is currently scheduled into the NICE work programme. For further details, please see the NICE website:

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			https://www.nice.org.uk/guidance/indevelopment/gid-ta11598 No action required.
	British Cardiovascular Society	There is an urgent need to evaluate this therapy - there is still a large unmet need based on the high mortality which persists in this population (see ATTR-ACT trial data) despite existing treatment with tafamidis.	Thank you for your comment. This topic is currently scheduled into the NICE work programme. For further details, please see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta11598 No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Alnylam Pharmaceuticals	The draft scope states that there are 800 patients with ATTR-CM in the UK: 200 with hereditary ATTR-CM (hATTR-CM) and 600 with wild-type ATTR-CM	Thank you for your comment. The scope has been amended to

Section	Consultee/ Commentator	Comments [sic]	Action
		(wtATTR-CM). These prevalence estimates underestimate the true prevalence of ATTR-CM in the UK. Based on discussions with experts at the National Amyloidosis Centre (NAC), Alnylam understands there are approximately [redacted] diagnosed patients with ATTR-CM in the UK.	provide an updated estimate of the number of people in England with ATTR-CM.
	Amyloidosis UK	We welcome the information in the background discussing higher prevalence among specific ethnic groups. However, the detail that these groups are also more likely to develop cardiomyopathy, without neuropathy, is missing. This is highly relevant to this assessment.	Thank you for your comment. The background section of the scope has been amended to reflect this.
	Pfizer	Section states: “In the UK there are thought to be around 600 people with wildtype ATTR-CM and 200 people with hereditary ATTR-CM.” The above estimate is similar to that used in the final scope of TA984 (tafamidis for ATTR-CM). However, as of November 2024, approximately 1,200 patients with ATTR-CM have been initiated on tafamidis treatment. Please can the estimate be updated to more accurately reflect the true size of the UK ATTR-CM population.	Thank you for your comment. The scope has been amended to provide an updated estimate of the number of people in England with ATTR-CM.
Population	Alnylam Pharmaceuticals	Alnylam regards the population definition to be appropriate.	Thank you for your comment. No action required.
Subgroups	Alnylam Pharmaceuticals	Alnylam regards it reasonable that subgroups defined by level of heart failure severity (via New York Heart Association [NYHA] classification) and disease type (hATTR-CM vs wtATTR-CM) may be of potential interest to assess clinical effectiveness and cost effectiveness.	Thank you for your comment. No action required.

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Comparators	Alnylam Pharmaceuticals	Alnylam believes that tafamidis is the appropriate comparator, given: • It is the only MHRA-approved20 NICE-recommended[26] therapy for patients with ATTR-CM. • Patients anticipated to receive vutrisiran would receive tafamidis if vutrisiran were not available.	Thank you for your comment. No action required.
	Amyloidosis UK	Yes, the comparators represent all the standard treatments currently used in the NHS.	Thank you for your comment. No action required.
Outcomes	Alnylam Pharmaceuticals	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.[27] Specifically, longitudinal changes in daily loop diuretic dose have shown prognostic value in patients with ATTR-CM, as patients seen at the NAC (n=1,598) experiencing outpatient diuretic intensification (ODI; defined as 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.[28] Therefore, Alnylam considers that outcomes that incorporate ODI in patients with ATTR-CM should be added to the list of outcomes. **References**: 27. 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-	Thank you for your comment. The list of outcomes is not intended to be exhaustive at this stage. Where relevant, the company is welcome to provide evidence on any additional outcomes that may be relevant for people with the condition during the evaluation. No action required.

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		CM) according to the disease severity [Presented at ISPOR Europe, virtual, Nov 19–Dec 20, 2020]. *Value Health.* 2020;23:S487. 28. 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.	
Equality	Alnylam Pharmaceuticals	Alnylam does not consider that the draft remit and scope need to be modified to meet equality goals.	Thank you for your comment. No action required.
	Amyloidosis UK	As noted in the background, certain ethnic groups (African or Caribbean and Hispanic family backgrounds) have a higher prevalence of this condition compared to the general population. However, what's missing is that, in these patients, the disease primarily manifests as cardiomyopathy rather than neuropathy. In practice, this means these groups of patients have reduced access to treatment options in addition to demonstrably worse outcomes compared to other patient subgroups. The outcome of this assessment will disproportionately impact these groups compared to the general patient population.	Thank you for your comment. This information has been added to the Equality Impact Assessment form issued along with the final scope.
	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. This information has been added to the Equality Impact Assessment form issued along with the final scope.

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Questions for consultation	Alnylam Pharmaceuticals	**Where do you consider vutrisiran will fit into the existing care pathway for ATTR-CM?** Vutrisiran is anticipated to be a new standard-of-care option for the first-line treatment of ATTR-CM in the UK. **Who currently receives established clinical management rather than tafamidis in clinical practice? What is established clinical management for these people?** Despite the several efficacy limitations associated with tafamidis in the treatment of ATTR-CM and its limited therapeutic benefit in some patient types (noted above), Alnylam understands all patients anticipated to receive vutrisiran would receive tafamidis if vutrisiran were not available. **Please select from the following, will vutrisiran 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):** The current and proposed routes for prescription and routine follow-up care align with option “C”. In summary: • Prescribing of vutrisiran in patients with ATTR-CM is anticipated to be overseen by clinicians at the NAC and the Amyloid Network (described further below). • Routine Q3M treatment with vutrisiran is anticipated to be delivered to patients at home.	Thank you for your comments. No action required.

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		• Routine follow-up is anticipated to performed at the NAC or other sites in the Amyloid Network (described further below). A Highly Specialised Service (HSS) is in place for amyloidosis management in the UK.[29] The NAC at the Royal Free Hospital has led innovation in diagnostic testing and treatment internationally. Vutrisiran is anticipated to be prescribed for the treatment of ATTR-CM under oversight of the NAC. This is a continuation of the current prescribing process for vutrisiran in its existing indication (hATTR-PN). Currently, patients with hATTR-PN who are prescribed vutrisiran at the NAC are also seen for follow-up at the NAC. From 2025 onwards, NHS England is considering an amyloidosis service networked model of care (i.e., the UK Amyloidosis Network [UKAN]).[30] The UKAN is proposed to consist of the NAC plus four regional centres. If the UKAN is established, it is anticipated that prescribing and routine follow-up may occur at any one of these centres, enabling greater convenience for patients and further improved efficiency of coordinated care. **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. **Would vutrisiran be a candidate for managed access?** Alnylam does not consider vutrisiran to be a candidate for managed access.	

		Do you consider that the use of vutrisiran 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.** Health states used to model heart failure in ATTR-CM (including NYHA classes, which were used in the submission for tafamidis to NICE) are based on cardiomyopathy-driven disease status. As a result, these health states do not capture the burden of neuropathy-related clinical manifestations that are present as a consequence of systemic TTR amyloid deposition in the peripheral and autonomic nerves in some patients with ATTR-CM. Quality-adjusted life year (QALY) calculations would therefore not capture the likely neuropathy-related clinical benefits of vutrisiran in addressing this burden. Vutrisiran received a positive recommendation from NICE for the treatment of hATTR-PN,[25] and is the current standard-of-care therapy for the treatment of patients with hATTR-PN in the UK. This recommendation was based on results from the HELIOS-A trial, where vutrisiran demonstrated statistically and clinically significant benefits in patients with hATTR-PN in terms of neuropathy disability, HRQoL, ambulatory speed, nutritional status, and the ability to perform everyday activities.[23] To identify the proposed benefits of vutrisiran in neuropathy-related symptoms beyond those captured in QALY calculations, the committee can consider the benefits of vutrisiran in hATTR-PN, as described in the NICE appraisal of vutrisiran (TA868).[25] Furthermore, by virtue of its less frequent administration (i.e., Q3M), vutrisiran provides a convenient, patient-centric treatment profile expected to limit the risk of non-adherence when compared to adherence with tafamidis, which requires frequent daily oral administration. These administration-associated benefits of vutrisiran are not captured in QALY calculations.	

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		[redacted] **References**: 23. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid.* 2023;30(1):1-9. 25. National Institute for Health and Care Excellence (NICE). Vutrisiran for treating hereditary transthyretin-related amyloidosis (TA868). 2023. 29. National Health Service (NHS). Amyloidosis. https://www.royalfree.nhs.uk/services/amyloidosis. Accessed Oct 31 2024. 30. Government of the UK (GOV.UK). Provision of: Amyloidosis Networked Model of Care. 2024. Accessed Oct 30 2024. 31. Medicines and Healthcare products Regulatory Agency (MHRA). AMVUTTRA (vutrisiran) Summary of Product Characteristics. Amsterdam, Netherlands: Alnylam Netherlands B.V.; Date 16 September 2022.	
	Amyloidosis UK	At present the only treatment available is Tafamidis. It is crucial for patients to have more than one treatment option available. It has been shown (Maurer et al, 2018) that individuals with amyloidosis respond differently to therapies, and in cases where the disease is not being controlled with one therapy, a second must be available. This is a chronic, progressive disease for which	Thank you for your comment. No action required.

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		the goal of treatment is to reduce the amount of the causative protein. If this is not being done effectively patients' lives will be shortened. Maurer, M.S., Schwartz, J.H., Gundapaneni, B., Elliott, P.M., Merlini, G., Waddington-Cruz, M., Kristen, A.V., Grogan, M., Witteles, R., Damy, T., Drachman, B.M., Shah, S.J., Hanna, M., Judge, D.P., Barsdorf, A.I., Huber, P., Patterson, T.A., Riley, S., Schumacher, J. and Stewart, M. (2018). Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. New England Journal of Medicine, 379(11), pp.1007–1016. doi:https://doi.org/10.1056/nejmoa1805689.	
	Cardiomyopathy UK	**Where do you consider vutrisiran will fit into the existing care pathway for ATTR-CM?** We expect that the treatment would be prescribed in secondary care with primary care follow up. The committee would need to consider planed changes (due to be in effect from March 2025) to the provision of care and treatment of amyloidosis and the establishment of a network of 4 regional centres connected to the National Amyloidosis Centre in London. **Do you consider that the use of vutrisiran 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 leading to an overall improvement in the recognition of and detection of all forms of cardiomyopathy and amyloidosis. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.**	Thank you for your comment. No action required.

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		Cardiomyopathy UK will be able to provide evidence from its national survey and focus group/s on the impact of ATTR-CM and the experience of people with ATTR-CM of their care and treatment.	
Additional comments on the draft scope	Alnylam Pharmaceuticals	The valine to isoleucine substitution at amino acid position 122 (V122I) and threonine to alanine at amino acid position 60 (T60A) are two common variants in patients with hATTR-CM. Alnylam wishes to note: • The acronyms “Val112Ile”, “Val112Il2”, “Vall112Ile”, and “T60A” are all used in the draft scope. o For consistency, it would be appropriate to use either “Val122Ile” and “Thr60Ala” or “V122I” and “T60A". • These variants have been historically referred to as V122I and T60A; however, nomenclature has been updated due to the incorporation of a signal peptide comprising 20 amino acids into the codon count for the TTR gene (i.e., resulting in “V142I” and “T80A”). o Alnylam is aware that both the old and new definitions for these TTR gene variants continue to be used in the literature, yet they represent the same TTR gene variants.	Thank you for your comment. The background section of the scope has been updated to use the terms “Val122Ile” and “Thr60Ala” throughout the scope.
	British Cardiovascular Society	**Where do you consider vutrisiran will fit into the existing care pathway for ATTR-CM?** Vutrisiran may become the preferred first line option for patients presenting with transthyretin cardiac amyloidosis. In those patients with ATTR-CM in whom there is disease progression despite being on tafamidis, vutrisiran will also need to be considered either in combination therapy, or if costs are prohibitive, then as an alternative disease-modifying therapy to tafamidis. We are unlikely to see a head-to-head trial of TTR knockdown with siRNA therapies (vutrisiran) versus TTR stabilisers (tafamidis). Making comparisons	Thank you for your comment. No action required.

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		between the phase 3 RCTs HELIOS-B and ATTR-ACT is difficult given the baseline differences in the cohorts recruited into the two trials. HELIOS-B does provide data in a contemporaneous population in patients with earlier-stage disease. **What is established clinical management for these people?** All patients currently receive 'established clinical management' which might be better defined as best supportive care. This consists of loop diuretic therapy, mineralocorticoid receptor antagonists, SGLT2 inhibitors and often requires suspension or down titration of beta-blocker therapy. More than half of patients are in atrial fibrillation at the time of diagnosis of ATTR-CM and merit anticoagulation because of high thromboembolic risk. Many patients will develop conduction disease during the course of their disease and require pacemakers for bradycardia. To-date, there are no data to support fitting primary prevention defibrillators in this cohort of patients. Only very rarely are patients offered defibrillators. ATTR-CM is a slowly progressive lethal disease and without access to disease modifying therapy, patients die from congestive cardiac failure at a median of only 4 years from diagnosis. Patients also, therefore, require timely input from palliative care services. **Who currently receives established clinical management rather than tafamidis in clinical practice?** At present in the UK, patients deemed eligible for disease modifying therapy with tafamidis can only be prescribed this therapy by clinicians at the National Amyloidosis Centre, Royal Free London. Tafamidis is safe, well tolerated and has few side effects. Most patients in England diagnosed with ATTR-CM are therefore likely to now benefit from being started on disease-modifying therapy once their diagnosis is secure and AL disease has been safely excluded. This is because patients are now being diagnosed with ATTR-CM at an earlier stage because of increased disease awareness (Ioannou et al Circulation 2022). The importance of being diagnosed early is paramount	

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		because patients do not “get back what they have lost” in terms of functional status as determined by 6MWD. In patients with the most advanced (NAC stage 4) ATTR-CM disease and in those with poor functional status / NYHA Class IV, there is questionable benefit from being started on tafamidis. A small proportion of patients that are deemed unlikely to benefit from being started on tafamidis are not offered therapy on grounds of futility. These patients will typically be elderly with high frailty scores and numerous, concomitant co-morbidities which need to be taken into account before a decision to prescribe disease modifying therapy is made. **Please select from the following, will vutrisiran be:** *D. Other (please give details):* If approved, this therapy is likely to be initially prescribed only by NHSE highly specialised commissioned centres. A national amyloidosis network is currently in development (tendering process is now in progress) with a planned start date of May 2025. The scope is for 4 centres across England outside of London to work closely with the National Amyloidosis Centre, Royal Free London. **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** As is the case now with the National Amyloidosis Centre, the only commissioned centre in England to provide care for patients with this disease, it is envisaged that not all patients with ATTRwt-CM will necessarily need to travel to a future network centre; there will, however, need to be a sharing of patient data and ideally an MDT discussion with the prescribing centre before a prescription for disease modifying therapy can be safely issued. The proposed level of funding for each network centre outside of London (210k/annum) is to cover all aspects of amyloidosis healthcare and is not limited to ATTR-CM. It is therefore unlikely that future network centres will	

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		be able to offer any more than baseline diagnostic assessment and 12 monthly follow-up reviews of patients with ATTR-CM. Routine cardiology care or "established clinical management" will still need to be delivered by the clinical team local to the patient (in most circumstances this will be the original referring cardiology heart failure team). **Would vutrisiran be a candidate for managed access?** Yes. **Do you consider that the use of vutrisiran 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.** In the HELIOS-B trial (Fontana et al, NEJM 2024) patients treated with vutrisiran versus placebo had a significantly lesser decline in their KCCQ-OS score and 6MWD. As ATTR-CM progresses, patients become increasingly reliant on relatives and/or social care for activities of daily living. Values important in palliative care, such as psychosocial and spiritual factors, are missing in standard ways of measuring health-related QoL (Wichman et al. BMC Health Serv Res. 2020). QALY will not take into account improvements in psychosocial health for the patient nor will it take into account the benefit vutrisiran will have on the mental, physical and economic health of the patient's relatives.	

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

None