National Institute for Health and Care Excellence

Single Technology Appraisal

Eplontersen for treating hereditary transthyretin amyloidosis [ID6337]
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	AstraZeneca	AstraZeneca wishes to propose eplontersen for the cost-comparison process compared to vutrisiran. Vutrisiran represents the only relevant comparator for patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) in England; indirect treatment comparisons demonstrate that eplontersen is associated with at least comparable clinical efficacy to vutrisiran. Of note, eplontersen would provide these health benefits at similar or lower costs and resource use compared to vutrisiran, since eplontersen can be self-administered and does not require ongoing healthcare professional (HCP) administration. In 2023, vutrisiran received a positive recommendation for the treatment of patients with Stage 1 or Stage 2 ATTRv-PN.[1] Vutrisiran is the current standard of care treatment, with UK clinical experts confirming that, at the National Amyloidosis Centre (NAC; where all patients with ATTRv-PN in England, Wales and Northern Ireland are treated), [redacted] of [redacted] patients receive vutrisiran whilst only [redacted] and [redacted] patients remain on patisiran and inotersen,	Thank you for your comments. No action needed.

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		respectively.[2] Additionally, feedback from clinical experts at the NAC advised that all newly diagnosed and treated patients will be initiated on vutrisiran. Collectively, these data demonstrate that vutrisiran is established in clinical practice and has substantial use within the NHS and is therefore the only relevant comparator for the treatment of patients with ATTRv-PN in England.[2] In the absence of head-to-head evidence, the comparative effectiveness of eplontersen versus vutrisiran was assessed via unanchored indirect treatment comparisons (ITCs) using population-adjustment approaches. Unanchored population-adjustment approaches were considered to represent the most robust ITC methodology, given the lack of a common control arm across the eplontersen and vutrisiran trials. Despite the pivotal trials for vutrisiran (HELIOS-A) and eplontersen (NEURO-TTRansform) both using external placebo arms, the placebo groups were not considered as comparable since the external placebo for HELIOS-A used pre-medication which was not permitted in NEURO-TTRansform. The ITC results showed [redacted]	

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		Overall, the ITC results demonstrate that the efficacy of eplontersen is at least equal to the efficacy profile of vutrisiran. When presented with these results, UK clinical experts confirmed the comparability of eplontersen and vutrisiran.[2] [redacted] The resource use associated with eplontersen differs to vutrisiran since eplontersen can be self-administered and does not require HCP administration. Eplontersen would reduce the administration burden on patients and HCPs and administration-related costs, associated with administration of vutrisiran by HCPs. To conclude, eplontersen is anticipated to provide similar or greater health benefits at a similar or lower cost than those provided by vutrisiran in the identical patient population. NICE guidance states that a cost-comparison is appropriate if the intervention is clinically similar to its relevant comparator, which must be established, and used substantially, in clinical practice in England for the same indication. In line with this guidance, AstraZeneca proposes a cost-comparison submission for eplontersen versus vutrisiran.[3]	
	Alnylam Pharmaceuticals	Alnylam considers the proposed evaluation of eplontersen to be appropriate.	Thank you for your comment. No action needed.
	Genetic Alliance UK	We have no specific comments to make other than that hereditary transthyretin amyloidosis is a rare condition that can have a significant impact on quality of life. As this technology has been routed through an STA rather	Thank you for your comments. The committee will consider

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		than HST pathway, its evaluation may be disadvantaged by the evidence constraints of smaller population numbers therefore this would be a good case for the committee to exercise flexibility in their decision making.	the entire evidence in its decision making. No action needed.
Wording	AstraZeneca	AstraZeneca notes that the remits of the vutrisiran, patisiran and inotersen submissions do not align with the draft remit proposed here. As this submission will be in the same indication, the draft remit/evaluation objective should be aligned with the previous submissions, and updated to state: “To appraise the clinical and cost effectiveness of eplontersen within its marketing authorisation for treating hereditary transthyretin-related amyloidosis.” To align with the remit, the submission title should also be adjusted to: “Eplontersen for treating hereditary transthyretin-related amyloidosis”	Thank you for your comments. The title and remint have been updated as suggested.
	Alnylam Pharmaceuticals	Alnylam regards the wording of the remit as being appropriate.	Thank you for your comment. No action needed.
Timing Issues	AstraZeneca	Eplontersen is an alternative to vutrisiran, the current standard of care treatment for patients with Stage 1 or Stage 2 ATTRv-PN. Compared to vutrisiran, eplontersen offers an alternative administration route for patients. Patients, or their carers, can administer eplontersen, which removes the need for HCP involvement. Consequently, eplontersen will reduce the burden of treatment on patients, their caregivers and the healthcare system.	Thank you for your comment. The topic has been scheduled into NICE programme. No action needed.

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		To prevent delays in access, eplontersen should be prioritised for evaluation.	
	Alnylam Pharmaceuticals	Alnylam notes that hereditary transthyretin amyloidosis (hATTR amyloidosis) patients with polyneuropathy in England currently have access to three NICE-recommended treatments (vutrisiran, TA8681; patisiran, HST102; inotersen, HST93).	Thank you for your comment. No action needed.
	UK ATTR amyloidosis patients' association (UKATPA)	This is an urgent issue, due to the progressive and fatal nature of the disease, improved treatment options are desperately needed by the patient community.	Thank you for your comment. The topic has been scheduled into NICE programme. No action needed.
Additional comments on the draft remit	AstraZeneca	N/A – no additional comments.	Thank you for your comment. No action needed.
	Alnylam Pharmaceuticals	Alnylam does not have any additional comments on the draft remit.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	The Background is accurate, however AstraZeneca would like to note that UK prevalence estimates for ATTRv-PN vary in the published literature. The submission will utilise the most up-to-date estimate ([redacted] diagnosed and treated Stage 1 or Stage 2 ATTRv-PN patients in England, Northern Ireland and Wales), that is supported by UK clinical expert opinion from the NAC.	Thank you for your comment. No action needed.

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	Alnylam Pharmaceuticals	Alnylam suggests the following edit to the disease description to avoid confusing the familial amyloid polyneuropathy (FAP) staging system of Coutinho et al. 1980[4] with the polyneuropathy disability (PND) scoring system of Suhr et al. 1994[5]: Change: "The condition is progressive. Based on polyneuropathy disability score it can be classified into 4 stages (Coutinho et al. 1980)." To: "The condition is progressive and the neuropathy can be classified into 4 stages (Coutinho et al. 1980)." This proposed edit aligns with the text used by NICE in the scope for the appraisal of vutrisiran. Alnylam notes that the bulleted list of the three NICE-approved treatments in the Background section does not mention their mechanisms of action, in contrast to the paragraph describing diflunisal, a drug that lacks marketing authorisation in this patient population. We suggest that NICE revise the descriptions of vutrisiran and patisiran to specify that they are small interfering ribonucleic acid (siRNA) therapeutics, and the description of inotersen to state that it is an antisense oligonucleotide.	Thank you for your comment. We have made the suggested change to the staging system. We have removed the description of mechanism of action from the diflunisal paragraph.
	UKATPA	The background information does not fully reflect the full gravity of the patient's plight. Suggest changing the first line to read: *Hereditary transthyretin amyloidosis is a progressive, debilitating, and ultimately fatal condition that affects people born with inherited mutations…'*	Thank you for your comment. We have added your addition into the beginning of the second paragraph.
Population	AstraZeneca	In line with the proposed cost-comparison approach, this submission will be made in the same indication as vutrisiran. As such, the population should be amended to: "Adults with hereditary transthyretin-related amyloidosis and stage 1 or stage 2 polyneuropathy."	Thank you for your comment. The population was changed to 'Adults with hereditary ATTR amyloidosis who have

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			stage 1 or stage 2 polyneuropathy.'
	Alnylam Pharmaceuticals	Alnylam notes that the pivotal trial for eplontersen in hATTR amyloidosis with polyneuropathy, NEURO-TTRansform, enrolled adults with stage 1 or stage 2 polyneuropathy exclusively,[6] and therefore it may be appropriate for NICE to specify these stages in the population definition for eplontersen as was done in the final NICE recommendations for vutrisiran, patisiran, and inotersen.[1-3] The population definition may also need to be aligned with the wording of the indication in the eplontersen SmPC, once approved by the Medicines and Healthcare products Regulatory Agency (MHRA), if this differs from the draft scope population definition.	Thank you for your comments. The population was changed to 'Adults with hereditary ATTR amyloidosis who have stage 1 or stage 2 polyneuropathy.'
	UKATPA	Given the increasing evidence demonstrating the benefits to ATTR amyloidosis patients with cardiomyopathy (ATTR-CM) coupled with the urgency for these patients, who currently have no treatments available, we would like to see ATTR-CM patients included in this appraisal. Significantly this group includes the V122i population who are almost exclusively of African-Caribbean descent.	Thank you for your comment. NICE can only appraise treatments within their marketing authorisation. Although currently unknown, based on the NEURO-TTRansform trial population it is not expected that people with cardiomyopathy will be included in the marketing authorisation.
Subgroups	AstraZeneca	No subgroups are expected to be relevant for separate consideration in this submission.	Thank you for your comment. No action needed.

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	Alnylam Pharmaceuticals	Alnylam regards the population definition without subgroups as likely to be appropriate, but notes that this may need to be aligned with any subgroup restrictions that may be identified in the MHRA-approved SmPC.	Thank you for your comment. No action needed.
Comparators	AstraZeneca	NICE guidance states that the chosen comparator for a cost-comparison submission must be established, and have substantial use, in clinical practice in England.[3] Therefore, the list of relevant comparators included in the draft scope should be adjusted as vutrisiran represents the only standard of care in UK clinical practice for patients with Stage 1 or Stage 2 ATTRv-PN. As such, vutrisiran is the only relevant comparator to eplontersen in this indication, and these assumptions have been confirmed with UK clinical experts, including an expert from the NAC. Vutrisiran offers comparable efficacy to patisiran, but does not require time-consuming intravenous administration, monitoring during infusion by HCPs and premedication due to the risk of infusion-related reactions.[1] Additionally, vutrisiran only requires administration every three months, compared to every three weeks for patisiran.[1] Given its advantages, vutrisiran has replaced patisiran as the standard of care treatment in the UK. This is demonstrated by UK clinical expert feedback indicating that, at the NAC, [redacted] patients receive vutrisiran and only [redacted] receive patisiran.[2] Additionally, the clinical experts highlighted all new patients would be initiated on vutrisiran.2 The clinician input is aligned with England prescribing data from Blueteq, which show that [redacted] patients commenced treatment with vutrisiran in Q2 and Q3 of 2023, and [redacted] initiated treatment on patisiran or inotersen.[4]	Thank you for your comments. We agree vutrisiran is the key comparator, but for completeness all NICE recommended treatments are included in the list of comparators.

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		Inotersen is also recommended by NICE for the treatment of ATTRv-PN but is associated with numerous real-world challenges and consequently is rarely used in clinical practice. UK clinical expert opinion from the NAC confirmed that inotersen is "associated with significant toxicity and is rarely prescribed", with only [redacted] patients at the NAC receiving inotersen.[1, 2] Patisiran and inotersen do not meet the criteria for relevant comparators, as defined by NICE, due to their limitations and negligible use in clinical practice. Therefore, these treatments should not be considered relevant comparators for this submission.	
	Alnylam Pharmaceuticals	Alnylam considers that all potentially relevant comparators have been mentioned in the draft scope. More detailed input is provided below in response to specific questions posed in the NICE draft scope (italicised text below indicates the questions from NICE): *Where do you consider eplontersen will fit into the existing care pathway for hereditary ATTR amyloidosis?* Based on the similar mechanism of action of eplontersen and inotersen, both of which are antisense oligonucleotides,[6,7] it is plausible that clinicians might consider eplontersen as a treatment option for patients who would otherwise receive inotersen. • *Are there differences between vutrisiran, patisiran and inotersen used for hereditary ATTR amyloidosis in terms of patient use?* Although all three of these drugs are transthyretin (TTR) gene silencers, they represent two fundamentally different approaches: patisiran and vutrisiran are double-stranded siRNAs whilst inotersen is a single-stranded antisense oligonucleotide. Below, we summarise important efficacy and safety differences between vutrisiran, patisiran, and inotersen pertinent to patient use, including key distinctions that have previously been highlighted by NICE in prior appraisals.	Thank you for your comments. We would encourage you to submit your assessment of the clinical and safety evidence in your submission for this topic so committee can review it in its consideration. Please note, although vutrisiran is the key comparator, for completeness all NICE recommended treatments are included in the list of comparators.

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		Efficacy In HST9 for inotersen, the committee stated that:[3] "Clinical trial evidence shows that inotersen slows progression of the disease considerably, although its long-term benefits are uncertain." This conclusion reflects evidence from the pivotal NEURO-TTR trial that inotersen treatment only slowed, but did not halt, polyneuropathy progression and HRQoL decline on average relative to pretreatment baseline.[7] The most recent publication of data from the NEURO-TTR open-label extension (OLE) reveals that, over 3 years, patients treated with inotersen continued to experience progression of neuropathy and further decline in HRQoL on average.[8] In contrast, in HST10 for patisiran, the committee stated that:[2] "Clinical trial evidence shows that patisiran reduces disability and improves quality of life, by enabling patients to return to work, carry out daily activities, participate in a more active family and social life, and maintain their independence and dignity. There is also evidence suggesting that patisiran may provide long-term benefits by stopping the progression of amyloidosis and potentially reversing it." These conclusions were based on findings from the phase 3 APOLLO study, in which patisiran halted or reversed polyneuropathy progression and improved HRQoL relative to baseline on average; polyneuropathy and HRQoL were significantly improved compared with placebo.[9] Like patisiran, vutrisiran is a siRNA therapeutic, and these two drugs have demonstrated comparable clinical efficacy in this patient population in the pivotal HELIOS-A study[10] and through a network meta-analysis (NMA).[11] In TA868 for vutrisiran, NICE concluded:[1] "Evidence from a clinical trial and an indirect comparison shows that vutrisiran works as well as patisiran."	

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		Though vutrisiran and patisiran have similar clinical benefit in halting or reversing polyneuropathy progression and HRQoL decline, the formulation of vutrisiran reduces the treatment burden on patients, caregivers, and the NHS relative to patisiran by enabling subcutaneous (SC) administration every 3 months (Q3M) rather than intravenous (IV) infusion every 3 weeks (Q3W).[12,13] <u>Safety</u> Inotersen has safety issues not shared with vutrisiran or patisiran. Contraindications exclusive to inotersen include: platelet count < 100 x 10^9/L prior to treatment [because inotersen can cause a reduction in the number of platelets, posing a risk of bleeding]; urine protein to creatinine ratio (UPCR) ≥ 113 mg/mmol (1 g/g) prior to treatment; estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 [moderate to severe loss of kidney function]; and severe hepatic impairment.[14] Inotersen also has multiple monitoring requirements, including at least biweekly platelet monitoring.[14] The European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) noted:[15] "In contrast, the SmPC for vutrisiran does not have these contraindications [of inotersen], thus broadening the patient population addressable by vutrisiran compared to inotersen. Vutrisiran SmPC also does not require monitoring since there were no effects seen on platelet counts or any evidence of renal toxicity in the HELIOS-A study, which included 4 patients with eGFR 30-45 mL/min/1.73m^2 at baseline [i.e., patients who would be ineligible for treatment with inotersen per its labelled contraindications]." The single listed contraindication for vutrisiran is identical to that of patisiran, namely hypersensitivity to the active ingredient or excipients.[12,13] The safety profiles of vutrisiran and patisiran are generally similar; however, unlike patisiran, vutrisiran is not associated with infusion-related reactions (IRRs) by virtue of its SC administration, and thus does not require premedication to reduce the risk of IRRs as does patisiran.[12,13] • *Which treatment(s) are part of established clinical practice?*	

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		• *Which treatment(s) have a substantial market share?* • *Is inotersen a relevant comparator based on use in practice?* Following its introduction in 2023, vutrisiran has replaced patisiran as the standard of care for patients with hATTR amyloidosis in the UK. Vutrisiran is now the sole first-choice therapy for this patient population. Currently, vutrisiran has almost complete market share in the UK for hATTR amyloidosis with polyneuropathy. Alnylam estimates that vutrisiran has more than [redacted] of market share for this indication. Before the introduction of vutrisiran, patisiran had a similarly high market share. Consistent feedback from UK clinical experts has been that inotersen has been used only under exceptional circumstances over the last few years; specifically, prior to the launch of vutrisiran, inotersen was reserved only for patients who were unable to receive patisiran for non-clinical reasons. In the current era of vutrisiran, inotersen continues to have only limited use in the UK. • *How clinically similar would eplontersen be considered to vutrisiran and patisiran?* Alnylam notes the absence of head-to-head data comparing eplontersen with either vutrisiran or patisiran. Although all three of these drugs are TTR gene silencers, they represent two different approaches: single-stranded antisense oligonucleotide versus double-stranded siRNA.[16] These two distinct mechanisms of action are associated with important pharmacokinetic and pharmacodynamic differences that could result in clinical differences.[17,18] Vutrisiran and patisiran are both siRNA therapeutics, and this identical mechanism of action underlies their comparable clinical efficacy. In contrast, both eplontersen and inotersen are antisense oligonucleotides that have an identical sequence.[16] It is, therefore, plausible that the clinical profile of eplontersen would be more similar to that of inotersen than to the profiles of either vutrisiran or patisiran.	

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		A naïve comparison based solely on visual inspection of the published pivotal trial data for eplontersen (NEURO-TTRansform), vutrisiran (HELIOS-A) and patisiran (APOLLO) suggests a slower reduction of serum TTR with eplontersen than with either vutrisiran or patisiran.[6,10,19] Of course, naïve indirect comparisons of results across these trials should be interpreted with caution, given the lack of adjustment for potential differences in the trial populations, including a higher prevalence in NEURO-TTRansform of patients with the V30M *TTR* genotype,[6,10,19,20] which is associated with slower disease progression compared with other variants.[21] Alnylam is aware that AstraZeneca and Ionis Pharmaceuticals have presented an indirect treatment comparison (ITC) of eplontersen and vutrisiran at the 2023 meetings of the American Academy of Neurology,[22] the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[23] and ISPOR Europe.[24] Alnylam notes that the ITC is based on aggregate data at month 9 from HELIOS-A and APOLLO, and individual patient data (IPD) from NEURO-TTRansform and NEURO-TTR at week 35, extrapolated to week 39 (approximately month 9).[22-24] Although the ITC considers only these short-term results, longer-term data are available as the prespecified primary endpoint assessment times were weeks 65/66 (approximately 16 months) in NEURO-TTRansform and week 66 in NEURO-TTR, and the latest placebo-controlled assessment time point was month 18 in HELIOS-A and APOLLO.[6,7,10,19] The AstraZeneca/Ionis ITC employed an unanchored approach because premedication was administered in the external placebo control arm for vutrisiran but not in the external placebo control arm for eplontersen (i.e., in the APOLLO and NEURO-TTR trials, respectively), and the investigators proposed that this difference violated the requirement of a common control arm for an anchored ITC.[22-24] Premedication in APOLLO, which was intended to limit the risk of IRRs, consisted of dexamethasone, oral acetaminophen/paracetamol, an H_2 blocker, and an H_1 blocker.[25] None of these drugs target the disease process in hATTR amyloidosis, and therefore	

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		their use in the external placebo control arm for vutrisiran would not be expected to substantially influence the long-term trajectory of polyneuropathy outcomes that would be of interest in an ITC. Applying an anchored approach would require less speculative assumptions than an unanchored ITC regarding knowledge of potential confounding variables. The AAN 2023 and ISPOR international 2023 presentations presented ITC results solely for the Norfolk QoL-DN endpoint,[22,23] while the ISPOR Europe 2023 presentation also included a comparison of mNIS+7.[24] Aside from these two measures, other endpoints were defined similarly or even identically across the pivotal trials of eplontersen and vutrisiran (e.g., mBMI, percent serum TTR reduction) and could therefore be compared between the two trials to provide a clearer picture of the relative efficacy of these drugs. In addition, a key difference between eplontersen and vutrisiran that could impact their respective HRQoL benefits lies in their dosing regimens. Eplontersen is associated with a heavier treatment burden, requiring administration every 4 weeks (Q4W),[6] three times as often as the Q3M dosing of vutrisiran.[12] Another potential differentiator between eplontersen on the one hand and vutrisiran and patisiran on the other is their safety profiles. Whereas there were no safety signals regarding haematology or liver function tests related to vutrisiran in HELIOS-A[10] or patisiran in APOLLO,[19] thrombocytopenia and glomerulonephritis were designated as adverse events of special interest for eplontersen in NEURO-TTRansform based on the safety profile of inotersen, which belongs to the same drug class as eplontersen.[6]	
	UKATPA	Yes	Thank you for your comments.
Outcomes	AstraZeneca	AstraZeneca confirms that all relevant outcomes relating to the benefits and adverse effects of eplontersen will be presented as part of the clinical effectiveness evidence, but will not be considered in the economic model, if	Thank you for your comments. No action needed.

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		the proposed cost-comparison approach is considered suitable for this appraisal. Overall survival, cardiac function and effects of amyloid deposits in other organs and tissues were not measured in the eplontersen clinical trial and consequently, will not be presented. These outcomes were not presented in the vutrisiran clinical trial, so this is not expected to represent a source of uncertainty when compared to previous NICE submissions in this indication.[5, 6] The primary and secondary endpoints from NEURO-TTRansform will be presented as part of the clinical effectiveness evidence of the submission, covering the following key aspects: • Neurological impairment • Symptoms of polyneuropathy • Weight loss • Serum transthyretin • Motor function • Adverse effects of treatment • Health-related quality of life These outcomes are aligned with those presented in the vutrisiran submission, as well as others in this disease area.[1, 7, 8] Additional exploratory endpoints from NEURO-TTRansform will be presented in the Clinical Study Report (CSR), which will be provided in confidence alongside the submission.	

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	Alnylam Pharmaceuticals	Alnylam considers that the proposed outcome measures are generally appropriate and should capture the most important health-related benefits and harms of eplontersen.	Thank you for your comment. No action needed.
	UKATPA	For patients 'fewer hospital visits' and 'improved mental/psychological health' are both important outcomes that are not currently listed in scope. We welcome having 'Overall survival' listed as an outcome as this captures the idea of 'living longer' which is also very important to patients.	Thank you for your comment. Health-related quality of life includes a measure of anxiety/depression and hospital visits are included in the calculation of costs. No action needed.
Equality	AstraZeneca	No equality issues were identified.	Thank you for your comment. No action needed.
	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 needed.
	UKATPA	Only assessing this technology for ATTR-PN patients excludes the V122I population and the non-hereditarty Wild Type which both present mainly as cardiomyopathy with very low incidence and currently have no access to treatment. The V122I gene mutation is found almost exclusively in individuals of African-Caribbean descent. There is increasing evidence that this technology is safe and effective for ATTR-CM patients. As this is a progressive and fatal condition time matters. Any delay in making this technology available to ATTR-CM patients is costs lives. Excluding ATTR-CM	Thank you for your comment. NICE can only appraise treatments within their marketing authorisation. Although currently unknown, based on the

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		patients from the appraisal, at this time, raises equality issues on both racial and age grounds. "The fourth most common cause of heart failure in Afro-Caribbeans was cardiac amyloidosis (11.4%). The prevalence may have been even higher as not all patients were tested for amyloidosis. Patients with ATTR V122I had the worst prognosis compared with other causes of Afro-Caribbean heart failure and white patients." Dungu, J.N., et al (2016). Afro-Caribbean Heart Failure in the United Kingdom. Circulation: Heart Failure, 9(9).	NEURO-TTRansform trial population, it is not expected that people with cardiomyopathy will be included in the marketing authorisation. We have added your comments to the Equality Impact Assessment form.
Other considerations	AstraZeneca	AstraZeneca notes the clinical trial investigating eplontersen (NEURO-TTRanform) based its efficacy analyses on the comparison of eplontersen with an external placebo arm, rather than eplontersen versus inotersen. As such, the description of the trial should be updated to: "It [eplontersen] has been studied in a clinical trial and compared with an external placebo group in patients with hereditary ATTR amyloidosis who have Stage 1 or Stage 2 polyneuropathy."	Thank you for your comment. We have made the proposed changes.
	Alnylam Pharmaceuticals	Alnylam does not have any additional issues to suggest.	Thank you for your comment. No action needed.
	UKATPA	As stated above, we believe this evaluation should be expanded to include ATTR-CM patients.	Thank you for your comment.

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			NICE can only appraise treatments within their marketing authorisation. Although currently unknown, based on the NEURO-TTRansform trial population, it is not expected that people with cardiomyopathy will be included in the marketing authorisation. No action needed.
Questions for consultation	AstraZeneca	**Where do you consider eplontersen will fit into the existing care pathway for hereditary ATTR amyloidosis?** As noted above, vutrisiran has replaced patisiran as the current standard of care for patients with Stage 1 or Stage 2 ATTRv-PN in UK clinical practice. Vutrisiran holds the majority of the market share – a NAC clinical expert confirmed that [redacted] % of patients receive vutrisiran and all new patients are initiated on it, whereas only [redacted] % of patients receive patisiran and [redacted] % of patients receive inotersen.[1, 2] In the context of the existing NICE clinical pathway, eplontersen is anticipated to provide similar or greater health benefits than vutrisiran in the same population. Unlike vutrisiran, eplontersen can be self-administered and does not require ongoing HCP administration and therefore will provide these health benefits at a similar or lower cost. As such, eplontersen is expected to be an alternative to vutrisiran, as the standard of care treatment for patients	Thank you for your comments. No action needed.

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		with Stage 1 or Stage 2 ATTRv-PN. UK clinician feedback was aligned with this proposed positioning.[2] **How distinct or similar are the current clinical pathways for polyneuropathy and cardiomyopathy caused by hereditary ATTR amyloidosis?** Many patients with ATTRv present with mixed phenotypes, whereby patients experience both neurological and cardiac impairment and, in clinical practice, a wide range of overlapping phenotypes are observed.[9] The clinical trial investigating eplontersen (NEURO-TTRansform) included patients with 'pure' ATTRv-PN (i.e., no cardiac impairment) and patients with mixed phenotypes (i.e., both neurological and cardiac impairment) and consequently, the clinical efficacy of eplontersen is proven to be applicable to both groups.[6] This is aligned with the positioning of vutrisiran as the standard of care therapy for the treatment of ATTRv-PN, which encompasses patients presenting with 'pure' neuropathy in addition to the mixed phenotype.[10] **Would eplontersen be a candidate for managed access?** The pivotal trial informing the efficacy and safety of eplontersen (NEURO-TTRansform) is complete, with no further data-cuts planned.[6] The comparative efficacy data to be presented in this submission are anticipated to be suitably robust to allow eplontersen to be considered for routine commissioning and eplontersen is not anticipated to be a candidate for managed access. Instead, AstraZeneca wishes to propose eplontersen for the cost-comparison process versus vutrisiran.	

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		Do you consider that the use of eplontersen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? As described above, AstraZeneca propose the cost-comparison route for this submission and consequently, QALYs would not be captured in the economic model. The advantageous administration profile of eplontersen is anticipated to have quality of life (QoL) benefits over vutrisiran. The ITC results showed a [redacted]. Additionally, eplontersen offers an alternative mode of administration compared to vutrisiran since, following the initial injection, eplontersen can be self-administered, or administered by a carer, at home via an auto-injector pen. Conversely, vutrisiran must be injected by an HCP, which requires nurses to travel to the patients' home up to four times a year. A UK clinical expert confirmed that the administration route of eplontersen would be particularly important for active patients (and their caregivers) who prefer not to wait at home for nurse-administered treatments or those who wish to avoid taking time off work, potentially impacting employment. This is particularly significant given that approximately [redacted] of patients with ATTRv-PN are of working age,[2] and this benefit will not be captured in the economic model.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Consequently, the evaluation of eplontersen versus vutrisiran utilises conservative assumptions since the gain in QoL is not captured. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** As described above, the [redacted] will be included in the submission as part of the clinical effectiveness evidence, but not in the economic model. The Norfolk QoL-DN is a validated QoL instrument, tailored to measure QoL for patients with neuropathy. **Please provide comments on the appropriateness of appraising this topic through the cost-comparison process.** As explained in comment 1, vutrisiran is considered to present the only relevant comparator for eplontersen for the treatment of patients with Stage 1 or Stage 2 ATTRv-PN. Eplontersen is anticipated to provide similar or greater health benefits at a similar or lower cost than those provided by vutrisiran and as such, AstraZeneca proposes a cost-comparison submission for eplontersen versus vutrisiran is the most appropriate appraisal process.	
	Alnylam Pharmaceuticals	• *How distinct or similar are the current clinical pathways for polyneuropathy and cardiomyopathy caused by hereditary ATTR amyloidosis?* • *Should people with polyneuropathy who also have symptoms of cardiomyopathy be considered separately?* • *Would tafamidis for treating transthyretin amyloidosis with cardiomyopathy (subject to NICE guidance) be a relevant comparator for eplontersen?* Based on discussions with key UK experts in transthyretin amyloidosis, Alnylam believes that tafamidis (in its formulation as 61 mg micronised tafamidis[26]) will be the first-line therapy for patients with wild-type (wt)ATTR	Thank you for your comments. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		amyloidosis and for patients with hATTR amyloidosis with exclusively cardiomyopathy symptoms, assuming a positive recommendation emerges from the NICE appraisal currently in development (ID6327). These experts indicate that vutrisiran will continue to be the first-line therapy for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, including those who present exclusively with neuropathy as well as those with mixed symptomology of polyneuropathy and cardiomyopathy. Notably, experts believe that in patients with mixed polyneuropathy and cardiomyopathy symptoms, the polyneuropathy symptoms are more aggressive and debilitating than the cardiomyopathy symptoms, thus driving their decision to prescribe vutrisiran. Alnylam does not consider that tafamidis is relevant to include in the present scope for patients with hATTR amyloidosis with polyneuropathy, considering the expected indication of eplontersen will be limited to treatment of polyneuropathy in patients with hATTR amyloidosis. As noted above, UK clinicians would not consider tafamidis as a treatment option in these patients, since its use in hATTR amyloidosis is restricted to patients with exclusively cardiomyopathy symptoms. Although tafamidis formulated as 20 mg of micronised tafamidis meglumine is licensed for hATTR amyloidosis with polyneuropathy,[27] it is not currently used in the NHS for hATTR amyloidosis patients with polyneuropathy or for hATTR amyloidosis patients with neuropathy and cardiomyopathy (mixed symptomology) because it received a negative reimbursement decision from the Advisory Group for National Specialised Services (AGNSS) in 2013.[28] This negative decision reflects the Evidence Review Group's conclusion of 'the lack of a significant difference between tafamidis and placebo in the primary analysis' of the pivotal FX-005 trial and a lack of trial evidence in patients with mutations other than V30M.[29] To our knowledge, there are no reasons for NICE or the NHS to reverse this reimbursement decision and so we assume that tafamidis	

Section	Consultee/ Commentator	Comments [sic]	Action
		will continue to not be used to treat the neurological impairment of patients with hATTR amyloidosis.	
Additional comments on the draft scope	AstraZeneca	N/A	-
	Alnylam Pharmaceuticals	Alnylam does not have any additional comments on the draft scope.	Thank you for your comment. No action needed.
	UKATPA	We believe this product is appropriate for appraisal through the cost comparison process.	Thank you for your comment. No action needed.
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The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

National Amyloidosis Centre, Royal Free Hospital

British Liver Trust