National Institute for Health and Care Excellence

Health Technology Evaluation

Plozasiran for treating familial chylomicronaemia syndrome [ID6593]

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	Arrowhead	Arrowhead agrees that is it appropriate to refer plozasiran for evaluation via the NICE single technology appraisal (STA) route. While Arrowhead accepts that the highly specialised technologies (HST) route is not appropriate for this appraisal given that volanesorsen is already available in the UK (HST13), we note that volanesorsen was appraised via the HST route, which means it received greater flexibility in decision-making and tolerability of uncertainty. We also note that plozasiran in FCS meets several HST criteria and therefore request that this is acknowledged in NICE's decision-making for this appraisal: • **Criterion 1 and 3:** Familial chylomicronaemia syndrome (FCS) is an ultra-rare disease, with a prevalence rate (1-2 per million people)[1] and total prevalence (57–114 people in England in 2022)[2] that comfortably meets the NICE threshold for the HST route. Arrowhead requests that the NICE appraisal for plozasiran takes into consideration the challenges associated with ultra-rare diseases, including limited published literature in the disease area and limited sample sizes in clinical studies.	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist).

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		• **Criterion 1:** FCS is a lifelong condition and is exceptionally debilitating. Patients suffer from a range of symptoms that have a broad impact on activities of daily living and quality of life (QoL), including unpredictable and recurrent episodes of acute pancreatitis (mean of two episodes per patient per year).[3–9] Acute pancreatitis is life-threatening and is usually associated with hospitalisation.[10] While volanesorsen is available in the UK, it is associated with intensive monitoring requirements due to risk of thrombocytopaenia and associated bleeding events.[11] There is, therefore, an unmet need for new therapies. Arrowhead requests that the debilitating and lifelong nature of the condition is considered in the appraisal. • **Criterion 2:** Plozasiran is a first-in-class small interfering ribonucleic acid (siRNA) therapeutic with a unique mechanism of action in FCS.12 Arrowhead requests that this innovation is acknowledged in the plozasiran STA appraisal. **References** 1. Heart UK. Familial chylomicronaemia syndrome [Internet]. 2025 [cited 2025 Jul 28]. Available from: https://www.heartuk.org.uk/fcs/familial-chylomicronaemia-syndrome-fcs 2. Office for National Statistics. Population estimates for the UK, England, Wales, Scotland and Northern Ireland: mid-2023. [Internet]. 2023 [cited 2025 Jul 28]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2023 3. Orphanet: Familial chylomicronemia syndrome [Internet]. [cited 2024 Nov 13]. Available from: https://www.orpha.net/en/disease/detail/444490 4. Regmi M, Rehman A. Familial Hyperchylomicronemia Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551655/	

Section	Stakeholder	Comments [sic]	Action
		5. Chylomicronemia syndrome: MedlinePlus Medical Encyclopedia [Internet]. [cited 2024 Nov 13]. Available from: https://medlineplus.gov/ency/article/000405.htm 6. What is FCS? [Internet]. [cited 2024 Nov 13]. Available from: https://www.heartuk.org.uk/fcs/familial-chylomicronaemia-syndrome-fcs 7. FCS [Internet]. National Pancreas Foundation. [cited 2024 Nov 13]. Available from: https://pancreasfoundation.org/pancreas-disease/fcs/ 8. Baass A, Paquette M, Bernard S, Hegele RA. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridaemia. J Intern Med. 2020 Apr;287(4):340–8. 9. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Roeters van Lennep J, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907.e2. 10. Gaudet D, Blom D, Bruckert E, Stroes E, Kastelein J, John K, et al. Acute Pancreatitis is Highly Prevalent and Complications can be Fatal in Patients with Familial Chylomicronemia: Results From a Survey of Lipidologist. Journal of Clinical Lipidology. 2016 May 1;10(3):680–1. 11. Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med. 2019 Aug 8;381(6):531–42.	
	Action FCS & Metabolic Support UK	The evaluation is very appropriate as many patients with FCS do not have access to the one existing therapy for FCS, volanesorsen (HST13), due to problems with low platelets, injection site issues, large needle phobias, and allergic reactions provoking flu-like symptoms. This means that they live with many of the symptoms of FCS and are in fear of and/or experience bouts of abdominal pain which can be severe, as well as pancreatitis. Patients with FCS are keen for new therapies to help relieve the symptom burden that FCS brings and are hopeful that there will be choices available which means that all patients with the disease can have a therapy that suits them.	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist). However, this topic will be evaluated by the HST (rare diseases) committee.

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		We have some concerns that using the single technology route for evaluation may not be appropriate. Committees making evaluations through this route may not be as experienced in the ultra-rare disease landscape where there is a paucity of data that can be gathered, and decisions need to be made on a much more marginal evidence base.	
	Genetic Alliance UK	On review of the draft scope, we also suggest that routing plozasiran via the HST pathway is more appropriate than the STA for the same reasons provided [for olezarsen]. As plozasiran is an RNA interference therapy targeting ApoC-III that aims to achieve triglyceride reduction through a different mechanism, it also represents a significant contribution to innovation in the therapeutic options available to people living with FCS. At present, although the evidence base for its use appears to be earlier and less mature than that for olezarsen, it offers promise as another targeted option and would support greater treatment choice for this community.	Thank you for your comments. The HST criteria were not met for this topic (please see separate checklist).
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Appropriate for single technology appraisal	Thank you for your comment.
Wording	Arrowhead	Arrowhead agrees with the wording of the remit.	Thank you for your comment.
	Action FCS & Metabolic Support UK	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? It does.	Thank you for your comment.
	Genetic Alliance UK	No comments.	N/A

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	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? Yes	Thank you for your comment.
Timing issues	Arrowhead	Plozasiran is expected to receive UK regulatory approval in [redacted]. A timely evaluation will ensure that eligible patients will have access to plozasiran at the earliest opportunity.	Thank you for your comments.
	Action FCS & Metabolic Support UK	This evaluation is urgent as there are many patients who have tried volanesorsen and had to stop due to side effects, and others who are unable to take the therapy due to the onerous monitoring requirements (affecting especially those from the South Asian community) and are therefore left with no support other than severely reducing their fat, added sugars, and carbohydrates for those with diabetes, and alcohol intake.	Thank you for your comments.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Important but not urgent	Thank you for your comment.
	Arrowhead	No comments	N/A

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

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Arrowhead	Arrowhead agrees with the overall summary provided in the background information section of the draft scope and confirms that the information is generally accurate. While Arrowhead agrees that there is a Chinese study for plozasiran, the PALISADE Phase 3 trial is the key plozasiran trial relevant to this appraisal. [redacted]	Thank you for your comments. Details of the Chinese study have now been removed from the scope. The US brand name has been removed". The background section of the scope is intended to give a brief overview of

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		Regarding completeness of the information, Arrowhead considers it important to note the following: • The symptoms of FCS are driven by sustained very high triglyceride levels in the blood.[4] The primary goal of FCS therapy is to lower triglyceride levels.[13–18] • Volanesorsen – the only currently recommended treatment – is associated with a risk of thrombocytopenia and associated serious bleeding events. According to its Summary of Product Characteristics (SmPC), it is associated with strict and intensive monitoring requirements, with a minimum of fortnightly monitoring visits (in patients with normal platelet count), increasing to weekly (in patients with mild thrombocytopaenia) and daily in patients with severe thrombocytopaenia (<50,000 platelets per microlitre).[11] There is therefore an unmet need for novel treatment options for patients with FCS. • Plozasiran is a first-in-class siRNA therapeutic designed to silence APOC3.[12,19] The PALISADE Phase 3 study shows that plozasiran is associated with a rapid, deep, sustained, and statistically significant lowering of triglyceride levels compared with baseline and compared with placebo.[12] PALISADE also shows that plozasiran substantially reduced the odds of acute pancreatitis events compared with placebo.[12] Arrowhead requests that the brand name 'Redemplo', currently listed as the US brand name, is removed from the technology description and left as the UK approved name only – plozasiran. **References** 4. Regmi M, Rehman A. Familial Hyperchylomicronemia Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551655/	the condition and treatment pathway. Please include any additional detail in the company evidence submission.

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		11. Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, et al. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med. 2019 Aug 8;381(6):531–42. 12. Watts GF, Rosenson RS, Hegele RA, Goldberg IJ, Gallo A, Mertens A, et al. Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. N Engl J Med. 2024 Sep 2; 13. Handelsman Y, Jellinger PS, Guerin CK, Bloomgarden ZT, Brinton EA, Budoff MJ, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. Endocr Pract. 2020 Oct;26(10):1196–224. 14. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082–143. 15. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. J Clin Lipidol. 2015;9(2):129–69. 16. Sanchez RJ, Ge W, Wei W, Ponda MP, Rosenson RS. The association of triglyceride levels with the incidence of initial and recurrent acute pancreatitis. Lipids Health Dis. 2021 Jul 18;20(1):72. 17. Moulin P, Dufour R, Averna M, Arca M, Cefalù AB, Noto D, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an “FCS score.” Atherosclerosis. 2018 Aug;275:265–72. 18. Falko JM. Familial Chylomicronemia Syndrome: A Clinical Guide For Endocrinologists. Endocr Pract. 2018 Aug;24(8):756–63.	

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		19. Arrowhead Pharmaceuticals. Data on file - Plozasiran DRAFT label.	
	Action FCS & Metabolic Support UK	Suggestion to update the existing background as follows: FCS is managed by an extremely restrictive, very low-fat diet to keep triglyceride levels low. This involves restricting dietary fat intake to between 10 and 20 g/day, limiting added sugars, and not consuming alcohol. For those patients who have developed diabetes, dietary restrictions become more onerous and other factors like the timing of food intake limiting carbohydrates become relevant. The need to manage insulin levels can become a further burden and a further concern for those around them. .....Symptoms of FCS include…… reduced cognition, fatigue, the constant fear of impending pancreatitis, and depression. (Journal of Clinical Lipidology: The burden of familial chylomicronaemia syndrome: Results from the global IN_FOCUS study)	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. A sentence on the psychological impact of the condition has been added. Please include any additional detail in the evidence submission.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	Include psychological impact on the patient and the support needed, even though this is mentioned later in the document. Nicotinic Acid is no longer available in the UK.	Thank you for your comments. The background section of the scope is intended to give a brief overview of the condition and treatment pathway. A sentence on the psychological impact of the condition has been added. Please include any additional detail in

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			the evidence submission. Nicotinic acid has been removed.
	NHS England	Accurate and complete	Thank you for your comment.
Population	Arrowhead	Arrowhead agrees with the population defined in the draft scope, which is aligned to the anticipated licensed indication of plozasiran. Plozasiran is expected to be indicated [redacted]	Thank you for your comment.
	Action FCS & Metabolic Support UK	Once a child begins to be independent from their family (usually when going to secondary school), the dietary restrictions can be harder to manage due to the desire to 'fit in' with their peers and access to inappropriate foods (and potentially alcohol). It would therefore be appropriate to consider the inclusion of children younger than 18 to help them to manage their education without the burden of abdominal pains and pancreatitis.	Thank you for your comment. Plozasiran will be evaluated in line with the current marketing authorisation.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Is the population defined appropriately? Yes	Thank you for your comment

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Subgroups	Arrowhead	Arrowhead considers the full population to be the most robust and relevant to the appraisal, but is happy to present subgroup data to support decision-making. Subgroup analyses of the PALISADE study show that plozasiran is similarly effective across all subgroups explored. However, it should be noted that sample sizes are small for any subgroup analyses given the ultra-rare nature of FCS. Regarding the subgroups specified in the NICE scope, Arrowhead notes the following: • *Triglyceride levels:* Arrowhead can provide subgroup results in the clinical evidence section of the NICE dossier. • *History of pancreatitis:* In PALISADE, 89.3% of patients had prior acute pancreatitis (not caused by alcohol or cholelithiasis), so a subgroup analysis based on prior history of pancreatitis would be based on a very limited sample size and would be exploratory and very limited. In addition, the full intention-to-treat (ITT) population is representative of this subgroup, so Arrowhead does not recommend including this as a specific subgroup in the plozasiran NICE appraisal. • *Risk of pancreatitis*: Arrowhead notes that risk of pancreatitis in HST13 was defined as "prior history of pancreatitis". Our comments related to *history of pancreatitis* therefore apply to the *risk of pancreatitis* subgroup, and we therefore do not recommend including *risk of pancreatitis* as a specific subgroup in the plozasiran NICE appraisal. • *Chinese family background:* Arrowhead does not consider this subgroup to be relevant to decision-making in the UK given that the UK general population is majority White (81.7%)[20] and given that [redacted] We therefore do not recommend including it as a specific subgroup in the plozasiran NICE appraisal. As noted above, however, Arrowhead can provide topline results from the Chinese study as supplementary information in the clinical evidence section of the NICE dossier.	Thank you for your comments. "Risk of pancreatitis" and "Chinese family background" subgroups have been removed. "History of pancreatitis" remains as a subgroup to align with the final scope for olezarsen ID6585.

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		Reference: 20. Office for National Statistics. Ethnic group, England and Wales: Census [Internet]. 2021 [cited 2025 Jul 28]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021#ethnic-groups-in-england-and-wales	
	Action FCS & Metabolic Support UK	Other subgroups to be added are: Patients who have diabetes. People from the South Asian community of whom there is a relatively large population of patients due to consanguinity. These patients have a higher risk of developing diabetes and often their cultural norms make managing food restrictions very difficult. Many of these patients have strong family links in South Asian countries and travel to see family making it difficult for them to take volanesorsen due to the onerous monitoring requirements. Pregnant women. Pregnancy is a high stress period for women with FCS as triglyceride levels rise naturally during the third trimester increasing the risk of pancreatitis which is dangerous for both mother and unborn baby. For women who develop gestational diabetes the impact can be very negative and add huge amounts of stress to the pregnancy as high blood glucose leads to higher triglycerides, Women can often be recommended plasmapheresis (where available) which is a time-consuming, draining and very short-term intervention with some women having the procedure two or three times a week.	Thank you for your comments. The suggested subgroups have been added
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	Triglyceride levels are included but this needs to be clearer what range or above what level you are referring to	Thank you for your comments. This has been left intentionally

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		This is an adult treatment only Consideration needs to be given to effects of injection site or people with needle phobia	broad so the company can propose a cost-effective range. If a recommendation in this subgroup is considered appropriate, this will be specified in the final guidance recommendation wording.
	NHS England	Subgroups are appropriate. Additionally, the technology is expected to be especially clinically effective for patients with FCS for whom volanesorsen is contraindicated e.g. because of significant thrombocytopenia or who can't take volanesorsen for any other reason	Thank you for your comment. The suggested subgroup has been added.
Comparators	Arrowhead	Arrowhead agrees with the proposed comparators of volanesorsen and olezarsen, but considers it inappropriate to include 'Established clinical management without plozasiran (including dietary fat restriction)' as it no longer reflects active management or standard of care in the UK since volanesorsen was recommended by NICE in 2020 (HST13). Feedback from UK clinical experts, solicited as part of an advisory board in 2025, suggested that volanesorsen is the only relevant comparator.	Thank you for your comments. It is our understanding from consultation feedback that there is a group of people who cannot have volanesorsen because of thrombocytopenia (either before starting or while on treatment), injection site issues or allergic reactions. Some people may also

Section	Consultee/ Commentator	Comments [sic]	Action
			choose not to start treatment. For this group, established clinical management is an appropriate comparator. This has now been clarified in the scope.
	Action FCS & Metabolic Support UK	The comparators are comprehensive.	Thank you for your comment.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included? Yes	Thank you for your comment.
Outcomes	Arrowhead	Arrowhead broadly agrees that the listed outcomes are relevant to people with FCS. We would like to emphasise that the symptoms of FCS (including acute pancreatitis) are driven by persistently high triglyceride levels.[4] Triglyceride level should therefore be considered a key outcome in the NICE appraisal.	Thank you for your comments. The list of outcomes has been amended to give more prominence to triglyceride levels.

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		We would also like to note that the PALISADE study primary and key secondary endpoints were triglyceride level, APOC3 level, and incidence of acute pancreatitis.[12] Secondary endpoints included safety (including mortality), while abdominal pain, hospitalisation due to abdominal pain, and health-related quality of life were exploratory endpoints.[12] Some of the outcomes listed in the scope (e.g., fatigue, chronic pancreatitis, diabetes) were not included as specific endpoints in the study. Arrowhead therefore expects some data gaps and limitations in terms of providing data relevant to the outcomes listed in the draft NICE scope. These limitations were also noted by the NICE team during the appraisal for volanesorsen (HST13). **References** 4. Regmi M, Rehman A. Familial Hyperchylomicronemia Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Nov 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551655/ 12. Watts GF, Rosenson RS, Hegele RA, Goldberg IJ, Gallo A, Mertens A, et al. Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. N Engl J Med. 2024 Sep 2;	APOC3 level has been added.
	Action FCS & Metabolic Support UK	The following should be added: **The ability to adhere to the treatment regimen.** From volanesorsen we know that treatment adherence in people with FCS is problematic, regularly leading to discontinuation, due to the numerous side effects associated with volanesorsen. It would be valuable for the community of people living with FCS to understand to what extend adherence would be impacted when treated with plozasiran. **Need for plasmapheresis and stress levels in pregnant women.** The rise in triglyceride levels during pregnancy raises the risk of pancreatitis which is	Thank you for your comments. Adherence has been added as an outcome. Any evidence on the impact of this condition and treatment on carers will be considered during the appraisal. Health-related quality of life (for patients and carers) is

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		potentially life-threatening for both mother and unborn child and can result in premature birth. This leads to substantial stress, as well as the need for plasmapheresis in pregnant women. It would be valuable to understand how plozasiran impacts this. **Time spent in good health.** People with FCS experience frequent, sudden bouts of severe abdominal pain, or in hospital due to pancreatitis. This affects their ability to work, attend school/university (i.e. young adults) and increases social isolation. It would be valuable to understand how l impacts this. **Impact on caring responsibilities** Living with or being a parent to a patient who is liable to develop severe abdominal pain/pancreatitis or is always fatigued, leaves carers and parents constantly concerned about their loved one. For adult partners it can mean they have to carry out family responsibilities, and miss, or attend social events alone. The children of patients can become stressed about their parent's health, and potentially take on extra responsibilities with younger siblings, and taking on the role of a young carer. Parents of patients who do or don't live with them can devote a lot of time to caring for their child with FCS, leaving other siblings without the parental support they may otherwise have had. It would be valuable to understand how plozasiran impacts this.	included as an outcome in the scope. The outcomes listed in the scope are not expected to be exhaustive and additional outcomes may be presented.
	Genetic Alliance UK	The outcomes appear suitable to our knowledge. We support emphasis on: Incidence and severity of acute pancreatitis; pancreatitis-related hospitalisations, including ICU admissions; patient-reported outcomes (including pain, fatigue and mental health) and carer quality of life and burden. In our experience, these reflect what matters most to families affected by rare conditions and are consistent with HST13.	Thank you for your comments

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	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology? Yes	Thank you for your comment
Equality	Arrowhead	Arrowhead is committed to equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with particular protected characteristics and others. We do not foresee any equality issues with the draft scope or with the use of plozasiran.	Thank you for your comment
	Action FCS & Metabolic Support UK	We would like to highlight that people with FCS from the South Asian community in England may be disproportionately affected by the current draft remit and scope. This group forms a relatively large proportion of the FCS population in England, in part due to higher rates of consanguinity. Several factors create specific equality challenges for this group: - Higher risk of comorbidities: People of South Asian heritage are at greater risk of developing type 2 diabetes. The combination of FCS and diabetes compounds the burden of disease, dietary restrictions, and health risks. - Cultural barriers to dietary management: Traditional South Asian diets often include foods that are particularly challenging to restrict for someone living with FCS. This makes adherence to the extremely strict dietary requirements potentially more difficult in practice than for some other groups.	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.

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		- Monitoring requirements and international travel: Many patients maintain strong family links in South Asia and travel abroad regularly. Current onerous monitoring requirements for volanesorsen can make it difficult for this group to access or remain on treatment compared with other groups. These issues mean that the draft scope could inadvertently disadvantage people of South Asian heritage.	
	Genetic Alliance UK	To our knowledge, no protected group appears to be excluded by the current wording, although we defer to condition-specific groups for direct of experiences that may be overlooked. For example, there is likely to be a number of practical concerns around regional access to genetic testing, lipid clinics and dietetic support. The committee may therefore need to consider evidence on geographic and socio-economic factors affecting adherence to very low-fat diet, and ensure arrangements for home administration or shared-care is available, where appropriate.	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Route of administration may be a consideration. Self-injection favours people better able to self-manage, hospital injection may favour those better able to travel (especially if administered in tertiary care).	The equalities issues raised here have been recorded in the equalities impact assessment and will be considered by the committee during the evaluation.

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Other considerations	Arrowhead	None.	N/A
	Action FCS & Metabolic Support UK	Action FCS would welcome the assessment of the socio-economic impact of FCS on people with FCS and their families, including the impact on social isolation felt by patients, the ability of patients to maintain regular employment, uninterrupted by visits to hospital or sick days at home and the impact on carers and children of the patient.	Thank you for your comment. Please include these details in the evidence submission for consideration by committee.
	Genetic Alliance UK	No comments.	N/A
	HEART UK – The Cholesterol Charity	N/A	N/A
	NHS England	Incidence of significant thrombocytopenia with prolonged use compared with volanesorsen	Thank you for your comment. “Incidence of severe thrombocytopenia” has been included as an additional outcome.
Questions for consultation	Arrowhead	**Where do you consider plozasiran will fit into the existing care pathway for familial chylomicronaemia syndrome?** • Plozasiran is anticipated to be indicated as an adjunct to diet for FCS patients. In line with the patient populations enrolled in PALISADE, plozasiran is expected to be used in clinical practice in patients with inadequate response to lipid-lowering therapy. It is therefore positioned	Thank you for your comments.

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		alongside volanesorsen and potentially olezarsen as a first-line option in patients with inadequate response to lipid-lowering therapy. • Plozasiran is expected to be prescribed in secondary/tertiary care, with routine follow-up in secondary/tertiary care. **Would plozasiran be a candidate for managed access?** • No. The PALISADE trial data are mature and Arrowhead does not consider that managed access would help to address any uncertainties in the evidence submitted to NICE. **Do you consider that the use of plozasiran can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** • Yes. There are substantial health-related benefits associated with plozasiran that may not be fully captured in a traditional QALY framework. FCS causes recurrent acute pancreatitis, which is not only physically painful but also emotionally distressing and unpredictable.[9] While acute episodes may be included in QALY estimates, broader impacts, such as the chronic fear of attacks, anxiety over food choices, social withdrawal due to dietary restrictions, and disruptions to family planning, are unlikely to be adequately reflected in utility values derived from generic instruments like EQ-5D, which have been shown to underestimate disease burden in FCS.[21,22] Additionally, plozasiran may deliver significant caregiver benefits. FCS affects not just patients but also their support networks, who often experience emotional strain, missed work, and reduced social and financial stability.[9,23] These carer impacts are rarely incorporated into QALY calculations, despite their relevance in ultra-rare diseases like FCS.[21] Novel treatments such as	

Section	Consultee/ Commentator	Comments [sic]	Action
		plozasiran are therefore expected to provide broader societal benefit by reducing burden on caregivers, enabling patients to live more independent lives, and reducing the disruptive economic and healthcare consequences of acute events. **References** 9. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Roeters van Lennep J, Crowson C, et al. The burden of familial chylomicronemia syndrome: Results from the global IN-FOCUS study. J Clin Lipidol. 2018;12(4):898-907.e2. 21. NICE HST13. Volanesorsen for treating familial chylomicronaemia syndrome. 2020. 2020 Oct 21; Available from: https://www.nice.org.uk/guidance/hst13 22. Matza LS, Phillips GA, Howell TA, Ciffone N, Ahmad Z. Estimating health state utilities associated with a rare disease: familial chylomicronemia syndrome (FCS). J Med Econ. 2020 Sep;23(9):978–84. 23. Williams L, Rhodes KS, Karmally W, Welstead LA, Alexander L, Sutton L. Familial chylomicronemia syndrome: Bringing to life dietary recommendations throughout the life span. Journal of Clinical Lipidology. 2018 Jul;12(4):908–19.	
	Action FCS & Metabolic Support UK	Regarding the care pathway for plozasiran we would defer to the clinical experts. Regarding plozasiran as a candidate for managed access, we would defer to the company and Action FCS would fully support this outcome. The substantial health-related benefits unlikely to be included in QALY calculation are the socio-economic impacts of FCS on people with the condition and their families, including the impact on social isolation felt by patients, the ability of patients to maintain regular employment, uninterrupted	Thank you for your comments.

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

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

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		In practice, volanesorsen is rarely discontinued in patients who fail to achieve a reduction in serum triglycerides >25% or below 22.6 mmol/L – this is because the benefit of volanesorsen in reducing incidence of pancreatitis is evident at higher triglyceride concentrations (and may not be directly related to triglycerides but rather the effect on chylomicrons which is not readily quantifiable). If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. ***Atherosclerosis* 375 (2023) 67-74**	
Additional comments on the draft scope	Arrowhead	Arrowhead would like to reiterate that FCS is an ultra-rare disease. A cost per QALY assessment demands a breadth of patient data and level of economic certainty that is very challenging to meet in FCS where the patient numbers are very small and where the disease does not lend itself easily to traditional EQ5D-style utility estimation.	Thank you for your comment. The committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult, such as rare diseases. In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature

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			of the condition or technology affects the ability to generate high-quality evidence before applying greater flexibility. (NICE health technology evaluations: the manual, section 6.2.34)
	Action FCS & Metabolic Support UK	None	N/A
	Genetic Alliance UK	A Managed access agreement (MAA) could help collect further evidence on pancreatitis incidence, hospital admissions, durability of effect and patient-reported outcomes in NHS practice. Specialist networks are well placed to support this. An MAA arrangement could also help address residual uncertainty on long-term clinical outcomes, real-world adherence and impact on carer burden. Specialist lipid clinics could contribute to national data collection.	Thank you for your comments. The company can submit a managed access proposal if they consider the treatment a candidate for managed access. Arrowhead has not indicated that this topic will be a candidate for managed access.
	HEART UK – The Cholesterol Charity	None	N/A

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	NHS England	None	N/A

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

N/A