National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation (HST)

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Akcea Therapeutics UK Ltd	Whilst we believe the Highly Specialised Technology (HST) process is a valuable addition to NICE's assessment pathways, a cost per QALY assessment and threshold forms part of the assessment which demands a breadth of patient data and level of economic certainty that is very challenging to meet in familial chylomicronemia syndrome (FCS), where the patient numbers are very small and where the disease does not lend itself easily to traditional EQ5D-style utility estimation. Whilst we believe that volanesorsen for FCS meets the criteria for HST (please see points a. to g. below), we also believe that the CSP process may be a more appropriate mechanism to assess the drug as this still demands high quality clinical data but is sometimes a better approach where economic data is inevitably limited. a) ***The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;*** FCS is a very rare disease with a prevalence of approximately 55 -110 people in England. Currently the majority of	Comments noted. This topic will be evaluated through the HST programme. No action required.

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		patients are managed through the existing lipid clinic network, mainly in tertiary referral centres in 3 geographical areas (Birmingham, Manchester and London). Management requires specialist services (specialist dietician & nurse support in addition to consultant led service) to ensure the delivery of an effective service for patients. *b)* ***The target patient group is distinct for clinical reasons;*** FCS is a serious, rare genetic disorder of lipid metabolism characterized by inability to process dietary fat and extremely high serum TG (> 750 mg/dL, 8.5 mmol/L) that are carried primarily in chylomicrons (dietary lipids). Chylomicrons are large (~ one micron in diameter) lipoprotein particles that if elevated, can result in clinically significant manifestations, including reduction of blood flow though the pancreatic microcirculation leading to severe abdominal pain and pancreatitis. Risks of chylomicronemia include acute pancreatitis, which can be fatal or lead to pancreatic damage, resulting in permanent exocrine or endocrine insufficiency and, on occasion, death. Whilst chylomicronemia and severe hypertriglyceridemia are not uncommon, in the vast majority of cases, these arise as a consequence of established secondary causes such as poor lifestyle, excessive alcohol consumption, poorly controlled type 2 diabetes etc. Correction of these secondary causes and treatment with established lipid lowering therapies usually results in a marked improvement in serum triglyceride levels for such individuals. In patients with FCS, because the hypertriglyceridemia is a consequence of mutations within the lipoprotein lipase gene (or associated genes), fibrates and other lipid lowering therapies are only minimally effective as they depend on the presence of the enzyme (LPL) to be effective. The mainstay of treatment is to maintain the patient on a low-fat diet (typically comprising <20g of fat per day), which is extremely challenging for the patient, and specialist dietician	

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		support is needed to manage the disease. Despite this severe dietary restriction, patients commonly still exhibit triglyceride levels >8.5mmol/L and remain at significant risk of acute pancreatitis. c) ***The condition is chronic and severely disabling;*** FCS is characterised by the risk of recurrent and potentially fatal pancreatitis due to the build-up of chylomicron particles. Compared to other forms of pancreatitis, cases induced by hypertriglyceridemia (HTG) appear to have significantly worse outcomes. In a systematic literature search Bardia et al found that the burden of disease (hospital length and mortality) was significantly higher in the HTG-induced Acute pancreatitis (AP) patients than other etiological forms of AP. Results of a recent survey of 84 lipidologists responsible for managing patients with FCS found that patients with FCS are at a greater risk of developing recurrent AP, and death from pancreatitis-related complications is not uncommon despite modern medical care. Like other rare and chronic conditions, the impact of FCS goes beyond acute risks and long-term complications and includes significant effects on social and psychological status. In a multicentre study, Gardner et al found a profound impact on the ability to work and interpersonal relationships for patients who experienced chronic pancreatitis. Data from their survey of 111 patients found that 74% of patients had their work life altered by chronic pancreatitis, 60% reported that it affected their social lives, and 46% reported that it had an effect on relationships with family and friends. These findings are supported by The Investigation of Findings and Observations Captured in Burden of Illness Survey in FCS Patients (IN-FOCUS), the first study of this size (60 patients) to capture patient-reported burden of disease Within the cohort, 21% of patients reported experiencing at least 10 symptoms when their FCS symptoms were at their worst or most severe; the five most commonly reported physical symptoms were bloating (35%), generalized abdominal pain (33%), asthenia (33%), fatigue (27%) and indigestion (23%). The most commonly	

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		reported cognitive symptoms were difficulty concentrating (18%), “brain fog” (17%), forgetfulness (10%), impaired judgment (8%) and recent memory loss (8%). Reported emotional symptoms included uncertainty regarding an attack of pain or acute pancreatitis at any time (33%), anxiety, fear or worry (30%), and feeling out of control or powerless because of FCS (25%). Nearly all patients reported at least one FCS-related comorbidity; acute pancreatitis was the most commonly reported (42%). The condition also affected patient employment status, according to the researchers. Most respondents reported that FCS negatively influenced their ability to fulfill their responsibilities at school or work (91%), additionally, 68% of full- or part-time employed patients reported taking time off work because of FCS, missing a mean of 30 days over 12 months ***d) The technology is expected to be used exclusively in the context of a highly specialised service;*** Whilst there is no current service specification for FCS, patients are currently managed through the existing lipid clinic network specifically in those tertiary referral centres for rarer and/or more severe lipid conditions (mainly FH), in 3 geographical areas (Birmingham, Manchester and London). Healthcare professions with expertise in treating patients with FCS have made it clear that without a formal service for FCS there are significant variations in the resources and expertise available, even across specialist centres, to appropriately care for FCS patients. A formally established and resourced consultant led service, anchored around specialist centres with dietician & specialist nurse support is required to ensure the effective delivery of care. In addition, volanesorsen will require the need for regular platelet monitoring as well as injection training for patients so requires specialist support from a number of stakeholders and resources***.***	

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		e) The technology is likely to have a very high acquisition cost; The price for volanesorsen has not been established as yet. Patients with FCS have a significant disease burden in terms of both acute episodes of AP and ongoing impact on QOL. Volanesorsen will be priced at a level that reflects both the extreme rarity of FCS and benefit that this product can bring to this patient population f) ***The technology and has the potential for life long use;*** Volanesorsen is a once weekly sub-cutaneous injection and is intended to be given chronically and has the potential for life long use g) ***The need for national commissioning of the technology is significant;*** FCS is a very rare disease and there is a limited number of clinicians in England, outside of the more specialist centres, with sufficient expertise to appropriately care for these patients, particularly with the introduction of a new novel therapy. Moreover, patients are at significant risk of developing comorbidities due to FCS and may require access to, and care from, different parts of the NHS at different times – some of which is not universally available. We strongly believe that a national specialised commissioned service is required to ensure that FCS patients in England receive sufficiently expert advice and appropriate care from relevant HCPs (including specialist nurses and dieticians) to ensure effective management of the disease. This thinking has been validated with healthcare professionals with expertise managing patients with FCS, who have agreed that a nationally commissioned service (incorporating a	

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		hub and spoke model) would be the most appropriate and effective method to manage these patients.	
	Genetic Alliance UK	This is an appropriate topic for the HST programme, as it meets all the criteria for prioritisation.	Comment noted. No action required.
	LPLD Alliance	Yes, it is very appropriate to refer this topic to NICE for evaluation. People who have FCS struggle daily to manage the symptoms. The only effective treatment currently available, is to severely restrict the intake of fat (from any source) simple carbohydrates, and drink no alcohol. The recommended intake is between 10g-20g fat daily, and many patients' triglycerides remain very high with recurrent abdominal pain and pancreatitis as well as long term complications. For those patients for whom type 2 diabetes has developed, there is a secondary condition which needs management but with the complicating factor that high blood glucose is turned to fat in the body and the restriction on eating becomes more draconian in that attention needs to be paid to both fat and carbohydrates, and also the spacing of meals and snacks. For those with diabetes, restricting dietary fat as well as carbohydrates is practically impossible. The need to adhere to such a restrictive and restricting regime has a profound impact on the participation in 'normal' life for the individual and their families. Even with adherence to the restrictions, people with FCS can experience many symptoms including abdominal pain, often serve, chronic and acute pancreatitis which can be life-threatening (we have cases of people developing necrotising pancreatitis), back-pain, diabetes (mentioned above), fatigue – which is described as 'living in a post-prandial state', depression. People with FCS also experience problems with concentration and memory which they describe as 'brain-fog'. The condition can create difficulties in pregnancy and increases the risk of mortality to both the mother and the unborn child as triglyceride levels rise automatically during the third trimester and the risk of gestational diabetes is	Comments noted. No action required.

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		higher due to a pancreas that has been weakened by managing the condition.	
Wording	Akcea Therapeutics UK Ltd	Yes , the draft remit reflects the issue of clinical and cost effectiveness with this technology	Comment noted. No action required.
	Genetic Alliance UK	This is the standard wording.	Comment noted. No action required.
	LPLD Alliance	They seem to	Comment noted. No action required.
Timing Issues	Akcea Therapeutics UK Ltd	FCS is a very rare disease with a significant disease burden in terms of both pancreatitis risk and impact on QOL. These patients' current treatment options are limited to dietary fat restriction together with the avoidance of alcohol and certain medications that may elevate triglycerides. An FCS advisory board held by Akcea in July 2107 found that a low-fat diet is the primary strategy employed by clinicians to manage FCS; however, access to expert dietary advice is limited with only a few centres having access to dietician teams. Most importantly, even in patients with strict dietary adherence, TG levels may remain at dangerously high levels and episodes of abdominal pain, and recurrent pancreatitis remain common. Management of patients during pregnancy provides a particular challenge due to triglyceride levels rising naturally during the third trimester, a risk which must be balanced against maintaining the nutritional requirements of the mother and foetus. [redacted]	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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		[redacted] These findings clearly underscore the unmet need and clinical ineffectiveness of currently available management and lipid lowering therapies, with TGs remaining considerably above the well-established threshold for increased pancreatitis risk as well as the other symptoms and burdens noted previously. Given the high unmet need in this patient population there is an urgent need to assess this product with a view to making it available in an area where there are no other licensed therapies to treat the disease.	
	Genetic Alliance UK	Volanesorsen has been granted Promising Innovative Medicine designation by the MHRA due to the severity of the condition and the high unmet need. We understand that the marketing authorisation application was submitted to the EMA in July 2017, and that the CHMP opinion is expected in the second or third quarter of 2018. It is appropriate that the medicine be appraised quickly in order for patients who would benefit from the treatment to gain access as soon as possible.	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	LPLD Alliance	This is very urgent. People with FCS live with an extremely difficult to manage condition which causes life-disrupting symptoms, and life-threatening event. Their lives are shaped by the stress of managing their health which impacts on their education, on the choices they make for work and their ability to gain and manage employment. For women, the decision to have a child is a difficult one and managing the pregnancy can mean regular plasmapheresis, or a reduction of fat to as near zero grams as possible. If	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation

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		gestational diabetes develops the women can be given insulin. This all can lead to a very high-stress pregnancy in which the risk of mortality is greatly increased. The lives of people with FCS are overshadowed by the fear of the onset of pain and life-threating pancreatitis, as well as actual pain and or/pancreatitis, and of the many other symptoms the condition brings. The unrelenting nature of having such severely restricted food choices makes daily living stressful. When in control of the meal or snack, the condition is relatively bearable, but once being catered for, the restrictions mean that it is very difficult to eat anything without having checked its ingredients and how it's cooked and many events and occasions can be difficult to access without major pre-planning, or employing strategies to ensure suitable food is available. Many people chose not to drink alcohol, or belong to a culture where alcohol is not a feature, but for those patients for whom alcohol seems an attractive option, having the choice taken away creates a different dynamic and can make events where alcohol is featured, inaccessible and excluding. Volanesorsen offers people with FCS relief from the pain and pancreatitis associated with the condition, and a reduction of the stress associated with living in anticipation of the next attack and the life-disruption it can cause. The reduction in hospital admissions also reduces both the physical and psychological stress for people and enables them to maintain consistency in their daily lives and their employment. It also reduces the burden on the NHS.	for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
Additional comments on the draft remit	Akcea Therapeutics UK Ltd	Volanesorsen has received a PIM designation and [redacted]	Comments noted. No action required.
	LPLD Alliance	None	Noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Akcea Therapeutics UK Ltd	Historically FCS was known as Fredrickson's type 1 hyperlipidaemia and more recently as lipoprotein lipase deficiency (LPLD). However FCS is now deemed to be the most appropriate nomenclature for the disease since it highlights its key distinguishing features; that it is genetic in origin, (Familial), characterised biochemically with the presence of plasma chylomicrons (Chylomicronaemeia) due to severe hypertriglyceridemia as a consequence of being unable to process dietary fats, and that it presents as a group of coexisting symptoms (Syndrome) including chronic abdominal pain, acute and chronic pancreatitis, eruptive xanthoma, arthralgia, lipaemia retinalis, hepatosplenomegaly, plus a diverse array of neurological (e.g. forgetfulness, confusion, difficulty concentrating) and other symptoms (e.g. nausea, vomiting, headache, muscle and joint pain). These symptoms cause significant morbidity for the patient and their families, and have a negative impact upon social functioning, education and employment. As outlined above, the IN-FOCUS study highlighted that over 1 in 5 patients reported experiencing at least 10 symptoms when their FCS symptoms were at their worst or most severe; as well as significant numbers of patients reporting cognitive impairment. Only 22% of respondents were in full time employment, and most respondents reported that FCS negatively influenced their ability to fulfill their responsibilities at school or work (91%). Additionally, 68% of full- or part-time employed patients reported taking time off work because of FCS, missing a mean of 30 days over 12 months. A high proportion of European respondents in the survey felt their disease had influenced their decision on whether to have children, or how many children to have (58%), with 57% of patients reported feeling a burden to those around them because of their FCS. Current pharmaceutical and dietary interventions are generally not effective in reducing the triglyceride levels below the threshold at which chylomicrons form (~10mmol/L) and therefore do little to reduce the patient's	Comments noted. The background section has been updated in light of consultation comments and discussion at the scoping workshop.

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		symptomology, improve their wellbeing, or to reduce the risk of developing acute pancreatitis which can be unpredictable in nature and result in pancreatic necrosis, organ failure mortality in 8-10% of cases	
	Genetic Alliance UK	We understand from our members the LPLD Alliance that familial chylomicronaemia syndrome (FCS) is not the same as familial lipoprotein lipase deficiency (LPLD), as the scope suggests. Rather FCS is the umbrella label for a number of specific disorders of lipid metabolism causing the same clinical symptoms, of which LPLD (cause by mutations in the LDL gene) is the best known and most prevalent. Other genes for which mutations can cause FCS include APOC2, LMF1, APOA5, and GPIHBP1. Currently, the management of FCS in England consists of restriction of dietary fat intake to between 10g and 20g daily, and the amount of fat an individual can consume without causing symptoms varies from individual to individual. The suggestion in the scope that the guidance is 'no more than 20g' is thus inaccurate.	Comments noted. The background section has been updated in light of consultation comments and discussion at the scoping workshop.
	LPLD Alliance	There is an inaccuracy of the definition. FCS is not synonymous with LPLD. LPLD is one of the causes of FCS. **Paragraph one needs to start:** FCS is a clinical condition cause by mutations/deletions in genes known to cause the lack of ability to process triglyceride rich chylomicrons, particles in the blood which then stay in the blood stream of the affected individual. Some of the genes that are known to cause Familial Chylomicronaemia Syndrome include those for familial lipoprotein lipase (LPL) deficiency, apolipoprotein C-II (APO C-II) deficiency or mutations that affect APOA5, GP1HBP1 and LMF1 genes. (1)(2). N some patients other unidentified mutations affecting other genes or pathways may be responsible.	Comments noted. The background section has been updated in light of consultation comments and discussion at the scoping workshop.

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		Lipoprotein lipase deficiency is an inherited disorder….. **Paragraph two needs the addition (at the end):** People with FCS are highly stressed with each day being a challenge in working out whether fat is in the food being eaten, and if so, how much. The impact of this necessary micro-management can be overwhelming. **Paragraph four needs to change to:** Currently, the management of FCS in England consists of restriction of dietary fat intake to between 10g and 20g daily, and no alcohol, in order to keep plasma triglyceride levels low and to have a reduction in symptoms or be symptom-free….. …….The strict dietary regimen is highly restrictive and is very challenging for patients and their families, and even when the diet is closely followed, people often still have high triglyceride levels and experience symptoms.	
The technology/ intervention	Akcea Therapeutics UK Ltd	Yes, the description gives an overview of the technology. However given the novel mode of action and potential benefits for patients of this technology we have expanded the description below: Volanesorsen is a 2′-O-(2 methoxyethyl) chimeric antisense oligonucleotide (2'-MOE ASO) inhibitor of the molecular target apoC-III protein. Antisense technology interrupts the protein production process by degrading the target messenger ribonucleic acid (mRNA) and thus preventing the translation of the specific protein. Antisense oligonucleotides are designed to be sequence specific with a high binding affinity to their unique target RNA. Volanesorsen is designed to bind to the human apoC-III mRNA and promote a reduction in apoC-III protein. Antisense treatment with volanesorsen, an antisense therapy, reduces apoC-III synthesis and production specifically at	Comment noted. This section of the scope aims to provide a brief overview of the technology for the evaluation; additional details may be considered by the committee, if appropriate, at the time of the evaluation. No action required.

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		the genetic level through binding to and causing degradation of apoC-III mRNA. Apolipoprotein C-III, a key regulator of plasma TG levels, is a 79 amino acid glycoprotein synthesized principally in the liver and, to a lesser extent, by the intestines (Ooi, 2008). Multiple apoC-III protein molecules reside on the surface of apoB-containing lipoproteins and high-density lipoprotein (HDL) and exchange rapidly between these particles. The majority of apoC-III is associated with TG-rich lipoproteins (TRL) in hypertriglyceridemic patients (Chan, 2008). FCS is primarily a consequence of impaired TRL clearance, manifested by the severe elevation in plasma TG, very low-density lipoproteins (VLDL) and/or chylomicrons. Prior to our work in FCS, ApoC-III was believed to regulate plasma triglyceride levels principally through the LPL-mediated lipolysis (Norata, 2015). Volanesorsen demonstrated that ApoC-III is also a major regulator of hepatic receptor-mediated clearance pathways, where its suppression led to profound reductions in plasma TG in FCS patients (Gaudet, 2014). Thus, in addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors (Gordts, 2016). [redacted] [redacted] [redacted] is delivered via a weekly sub-cut injection [redacted] should be used as an adjunct to diet	
	Genetic Alliance UK	-	Noted
	LPLD Alliance	Yes, so far as we understand.	Comment noted. No action required.

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Population	Akcea Therapeutics UK Ltd	Yes, the appropriate population is adult patients with familial chylomicronaemia syndrome	Comment noted. No action required.
	Genetic Alliance UK	Yes, though we would consider it appropriate to look at patients with diabetes and women who are or wish to become pregnant separately, as the level of clinical benefit or cost effectiveness may differ in these groups from the patient population as a whole.	Comments noted. If evidence allows, consideration may be given to the subgroup of people with comorbid diabetes. If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues.
	LPLD Alliance	Yes, the population is defined appropriately.	Comment noted. No action required.
Comparators	Akcea Therapeutics UK Ltd	The mainstay and only current option for treatment, is stringent dietary fat restriction (<20g/fat per day) supplemented in some cases with fibrates/lipid lowering. However as mentioned previously, the later are not licensed and are of limited value in this population as they rely on LPL activity which is mostly absent from these patients. Most importantly, even in patients with strict dietary adherence and use of fibrates, TG levels may remain at dangerously high levels and episodes of abdominal pain, and recurrent pancreatitis remain common.	Comments noted. No action required.

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		[redacted]	
	Genetic Alliance UK	-	Noted
	LPLD Alliance	of the standard treatments currently used the 'best alternative care' would be the severe reduction of dietary fat and simple carbohydrates.	Comments noted. No action required.
Outcomes	Akcea Therapeutics UK Ltd	FCS is characterised by extremely high serum triglycerides (TG), carried in chylomicrons. Patients typically present with plasma triglyceride levels ranging from 10 to 100 times normal values and initial assessment of these patients in the NHS is currently based primarily on their TG levels rather than their chylomicrons (which are not routinely measured). The risk of acute pancreatitis has been shown to rise with triglyceride levels by as much as 4% for every 100 mg/dL (1.1mmol/L) increase in triglyceride levels. The 2016 ESC/EAS Guidelines for the Management of Dyslipidemias define Mild-Moderate Hypertriglyceridemia as levels ranging from 1.7mmol/L (~150mg/dL) (the upper limit of normal) to 10mmol/L, and severe hypertriglyceridemia (HTG) as TG >10mmol/L (~885mg/dL).The guidelines also state 'The risk of pancreatitis is clinically significant if TGs exceed 10 mmol/L (~885 mg/dL), and actions to prevent acute pancreatitis are mandatory.	Comments noted. Outcomes have been amended to include triglyceride levels.

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		In the APPROACH study the significant TG reductions seen with volanesorsen (77% reduction in TGs) translated into important clinical outcome benefits such as reduction in abdominal pain intensity and frequency and reduction in pancreatitis attacks. We therefore believe it is more appropriate to look at reductions in TGs than those in chylomicrons. In addition to this, the incidence of acute pancreatitis is also important.	
	Genetic Alliance UK	The outcome measures included are broadly appropriate, however the measurement of triglyceride levels should be included as we understand from patients that this is the primary indicator used in managing the condition. We would also suggest inclusion of other endpoints of importance to patients including dietary fat intake, fatty liver damage, and cognitive symptoms, and perhaps some of the later and rarer features of the condition such as pancreatic necrosis and cardiovascular disease. We are also concerned that the scope lists pain and fatigue as part of the health related quality of life. Pain, particularly abdominal pain, and fatigue in FCS are significant symptoms which can be incapacitating. These aspects of the condition definitely have substantial impact on a patient's health related quality of life, but it diminishes the importance of these symptoms to group them under that heading. health-related quality of life, as well as suggests that the correlation of these symptoms with HRQoL impact is identical for all affected individuals. It is important to distinguish between the symptom and the impact of that symptom on the patient's physical, mental and social well-being, and acknowledge both.	Comments noted. Outcomes have been amended to include triglyceride levels, abdominal pain, fatigue, neurological and psychological impact (including depression and cognitive ability), and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease).
	LPLD Alliance	The measurement of triglyceride levels is what is meaningful to patients in managing the condition.	Comments noted. Outcomes have been amended to include

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		Add: • Health related quality of life should include mental health. • Impact on pregnancy	triglyceride levels and psychological impact. If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues.
Equality and Diversity	Akcea Therapeutics UK Ltd	Akcea is also committed to equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others and as such is supportive of ensuring equal access to effective treatment for all appropriate FCS patients irrespective of their ethnicity or background. In our opinion, the proposed remit and scope would not • exclude any people protected within any equality legislation • lead to any recommendation which would negatively impact any people protected within any equality legislation • have any adverse impact on people with any particular disability Two patient populations which are potentially more adversely affected by FCS, are the South Eastern Asian community (in which the prevalence of FSC would appear to be higher than in other ethnicities), and female patients (since oral contraceptives are recognised to raise triglyceride levels, and triglyceride levels rise naturally during the course of pregnancy, thereby	Comments noted. If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues. If appropriate, consideration may be given to whether factors contributing to or exacerbating hypertriglyceridemia are associated with characteristics that are

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		further increasing the risk of acute pancreatitis (which is already high)). The scope should take this into account.	protected under equality legislation (for example, but not limited to, women using oral contraceptives).
	Genetic Alliance UK	One protected characteristic that is relevant to this evaluation and may need to be considered is pregnancy and maternity. Pregnancy is a particularly challenging time for management of the condition and affected women may experience significant changes in lipid levels, leading to a higher risk of pancreatitis, dangerous to both the mother and her unborn child and potentially requiring even greater dietary restrictions during this period. Women with FCS also have a higher risk of developing gestational diabetes, which can lead to increased difficulties managing the condition in future.	Comments noted. If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues.
	LPLD Alliance	We think that the proposed remit and scope would not exclude any group protected by the equality legislation, or have a different impact on people protected by equality legislation or have an adverse impact on people with a particular disability or disabilities.	Comments noted. No action required.
Other considerations	Akcea Therapeutics UK Ltd	In a recent UK patient advisory meeting held in April 2017, work productivity was reported as an important consideration in FCS. Patients reported experiencing repeated episodes of hospitalization and days lost from work, and/or consequent underemployment/ unemployment. Many felt nervous about moving on from jobs that they are already holding, for fear that new employers will be less sympathetic than existing ones. In The Investigation of Findings and Observations Captured in Burden of Illness Survey in FCS Patients (IN-FOCUS), the first study of this size (60 patients) to capture patient-reported burden of disease, patients reported that FCS negatively	Comments noted. The NICE reference case states that costs should be considered from the NHS and Personal Social Services perspective. No action required.

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		influenced their ability to fulfill their responsibilities at school or work (91%), additionally, 68% of full- or part-time employed patients reported taking time off work because of FCS, missing a mean of 30 days over 12 months. FCS can therefore be very restrictive on day to day work as well as longer term working prospects.	
	LPLD Alliance	There are no other effective therapies for this very rare and very severe condition. This should be taken into consideration.	Comments noted. No action required.
Innovation	Akcea Therapeutics UK Ltd	Yes, Akcea has undertaken ground-breaking work to develop this product and an understanding of the disease it treats. Not only does volanesorsen have a novel mechanism of action as described in the technology section above but patients treated with volanesorsen in the Phase 3 APPROACH study experienced robust reductions in triglycerides and related benefits. Volanesorsen met the primary study endpoint with volanesorsen-treated patients in the FAS achieving a statistically significant ($p<0.0001$) mean reduction in triglycerides of 77% from baseline after three months of treatment, compared with a mean increase of 18% in placebo-treated patients. This represented a mean absolute TG reduction of 19.3mmol/L (1,712mg/dL) in volanesorsen-treated patients. 	Comments noted. Innovation will be considered by the evaluation committee when formulating its recommendations. No action required.

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		Reductions in TGs of this magnitude and subsequent reduction in AP events have not previously been seen in FCS patients so volanesorsen represents a step change to currently available management for these patients	
	Genetic Alliance UK	As the medicine is the first to treat the underlying basis of the condition, we consider it to be innovative in its potential to make a significant and substantial impact on the health of these patients.	Comments noted. Innovation will be considered by the evaluation committee when formulating its recommendations. No action required.
	LPLD Alliance	The impact of the extreme rarity and 'invisible' nature of FCS needs to be recognised. People with the condition often feel their difficulties are not understood and are not validated by the society around them. With very little to offer patients, the input from health services is minimal. Monitoring at lipid clinics usually has nothing practical to offer and many patients fall out of the system as they see no point in wasting the time and energy going to clinic. Professional advice from dieticians can often lack understanding of the extreme nature of the restrictions. This is exacerbated in the case of patients with diabetes. Dieticians managing diabetes usually have no understanding of the interplay of the two conditions and there have been a number of occasions where patients with diabetes have been advised to eat foods unsuitable for the FCS diet. This lack of practical support and input increases feelings of isolation for patients and their families and makes the individual need to find their way forward on their own. Patients can have varying degrees of success with this, and it can often depend hugely on the understanding and support from the	Comments noted. Innovation will be considered by the evaluation committee when formulating its recommendations. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		community around them. There also seems to be a wide variety of susceptibility to symptoms in individual patients, and little is known about the impact of ageing for people with the condition. Psychological support for patients managing such severe restrictions is not routinely offered but would help greatly in validating the difficulties the condition imposes. It would help individuals to come to terms with the life-adjustments that need to be made in order to reduce symptoms as much as possible. We think the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits. Patients currently on the drug have reported a big reduction in pain and a relaxation of the stress involved in anticipating episodes of pain and pancreatitis allowing for better future planning and aspirations. It would improve the way that current need is met in that it will be the first time that a medicine that makes a significant difference to the lives of patients will be available and will bring more patients into the health service where they can be managed by a team of specialists who will have a greater understanding of the condition and will be able to offer good advice. It will be a huge step-change in the management of the condition.	
Questions for consultation	Akcea Therapeutics UK Ltd	Q1: Yes it will be used as an adjunct to low fat diet. In Phase 3 studies combining volanesorsen with low fat diet led to a 77% reduction in TGs from baseline after three months of treatment, compared with a mean increase of 18% in placebo-treated patients. Q2: We would expect that volanesorsen would be made available to adult FCS patients who are [redacted] Q3: There is no currently defined service specified in England for FCS. Patients are managed through the existing lipid clinic network for FH mainly in	Q1: Comment noted. The scope has been amended to specify Volanesorsen in combination with established clinical management (including dietary fat restrictions).

Section	Consultee/ Commentator	Comments [sic]	Action
		tertiary referral centres in 3 geographical areas (Birmingham, Manchester and London). Currently available management is a combination of low fat diet (<20g/day) and fibrates/lipid lowering agents. Fish oils, MCT oil and Medium chain FA are also used by some patients. Q4: FCS can and in most cases is diagnosed clinically through a number of criteria including recurrent high TGs which are refractory to fibrates and other treatment and are not secondary in cause (e.g. alcohol, gallstones) plus the occurrence of acute pancreatitis and/or abdominal pain. The EAS are currently considering a clinical diagnostic scoring system as symptomology is generally considered appropriate to define treatment. Genetic testing and measurement of LPL enzyme activity can be used to confirm diagnosis although they are not routinely available or regularly performed in the NHS. Q5: Please see comments above Q6: Given the rarity of FCS and the limited level of data in these patients, it is difficult to identify a specific sub-population of patients, however, patients with very high TG levels may potentially benefit the most although the evidence for treatment effect in this group is limited and assessment is ongoing. Q7: Please see comments above Q8: Please see comments above. Please also note that volanesorsen has a PIM designation indicating that it is an innovative product with considerable promise in this indication	Q2 and Q3: Comments noted. No action required. Q4: Comments noted. The following has been added to the "Other considerations" section of the scope "Consideration should be given to the precise definition and clinical diagnosis of familial chylomicronaemia syndrome" Q5, Q6, Q7 and Q8: Comments noted. No action required.
	LPLD Alliance	Evidence to be gathered should include the patient reported experience of the burden of disease.	Comment noted. No action required.
Additional comments on the draft scope	Akcea Therapeutics UK Ltd	None	Comment noted. No action required.

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

Department of Health