NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Akcea
   - LPLD Alliance
   - NHS England

3. **Comments on the Evaluation Consultation Document from experts:**
   - Charlotte Dawson – clinical expert, nominated by LPLD Alliance
   - [redacted] - patient expert, nominated by LPLD Alliance
   - Karishma Patel – patient expert, nominated by LPLD Alliance

   No Comments on the Evaluation Consultation Document received through the NICE website

4. **Evidence Review Group critique company ECD response**

5. **Evidence Review Group critique – Addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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

Comments received from consultees

Consultee	Comment	Response
Akcea Therapeutics	Akcea has ordered its response to the Evaluation Consultation Document (ECD) in line with what we understand to be the most critical elements for the NICE committee in its decision making. Therefore, we address first the economic assumptions that are the biggest drivers of the ICER estimate and follow this with comments on clinical efficacy. The four parameters that have the largest impact on the ICER estimate in the economic model: • Patient QoL • Family/carer QoL • Discontinuation rates and • AP event rates are addressed first. We then consider the clinical issues of efficacy in the longer-term at the licenced dose in relation to TG and AP event rates.	Thank you for your comment. The evaluation committee considered evidence submitted by the company. The committee also noted that the company revised its commercial offer for volanesorsen, this brought the incremental cost-effectiveness ratio (ICER) down to £98,013 per QALY gained compared with best supportive care which can be considered an effective use of NHS resources for highly specialised technologies. Although there were uncertainties the committee recommended volanesorsen as an

Consultee	Comment	Response
		option for treating familial chylomicronaemia syndrome. Please see sections 4.33; 4.34; 4.38 and 4.39 of the final evaluation document (FED).
Akcea Therapeutics	FCS patient quality of life The vignette study accurately describes the burden of FCS using a sound methodology that values health states using appropriate general population methods. Revising the implementation of the low and high TG vignette values in the economic model so that they align with the health states leads to a discounted QALY gain of [redacted] and an ICER of £252,847 The vignette study The vignette project is a carefully designed study following commonly used methodology to estimate the impact on quality of life of FCS. Utility values were elicited for FCS health states varying by TG level (high or low) and prior AP experience. We hope we have addressed the request from ECD section 4.33 with the information provided below. If any additional information or clarification is needed, please let us know so that we can provide it. This response is provided in two parts. Part 1 provides summary information about the vignette study methodology, with the full draft manuscript (currently under submission to a peer-reviewed journal) provided in Appendix 1. Part 2 addresses the use of the vignette data in the economic model. The vignette study was led by Louis Matza. Dr. Matza has authored more than 80 peer-reviewed health outcomes studies including over 25 vignette-based utility valuation studies published in journals such as *Value in Health*, *Quality of Life Research*, *European Journal of Health Economics*, and *Medical Decision Making*. This FCS study was conducted in line with previously published vignette-based studies. NICE's preference is that utilities are derived from the EQ-5D completed by patients. However, in	Thank you for your comment. The committee acknowledged the company's comments. It understood that there were advantages and disadvantages with every source of utility data. The committee noted several methodological issues associated with the vignette study, including the process of constructing the vignettes, uncertainties in the dimensions that defined health states, and value laden language used throughout the vignette.

Consultee	Comment	Response
	the current situation, the EQ-5D does not appear to be appropriate for this purpose. First, to derive utilities from patients, a sufficiently large sample is needed within health states that are include in the economic model. For rare diseases like FCS, it is challenging to recruit a large enough sample of patients living in each of the relevant health states. In addition, it can be difficult to gather a sample of patients with rare conditions like FCS to validate generic instruments for use in the target population (Benjamin et al., 2017; Slade et al., 2018). Second, although the EQ-5D was administered in the APPROACH study, the instrument does not appear to be sensitive to variation in quality life in patients with FCS. The EQ-5D results from APPROACH were not plausible due to a likely ceiling effect of the baseline values. The ECD acknowledges that the EQ-5D baseline values were not in line with the patient testimonies. The ceiling effect may be due to the fact that the EQ-5D does not assess the quality of life impact of key aspects of FCS, such as cognitive symptoms and impact of the extremely restrictive diet (ECD section 4.14). Due to the lack of clinical validity of the EQ-5D data, the vignette study was initiated. Vignette-based methods can be used to estimate utilities for rare diseases when it is not feasible to collect preference-based data from a large enough sample of patients. In vignette-based utility studies, health state descriptions (often called vignettes or health states) can be drafted based on the best available information to ensure that the health states accurately represent the typical patient experience. In this case, the health states were based on published literature, interviews with patients with FCS, and interviews with clinicians who treat patients with FCS. Then, utilities for each health state were elicited in a valuation study with general population respondents, using preference-based methods similar to those used to derive the original EQ-5D tariffs (e.g., time trade-off interviews with a 10-year time horizon). Part 1: The vignette study methodology [redacted] 1 [redacted]	The committee concluded that the source of utility values was subject to risk of bias and this would contribute to uncertainty in the incremental cost-effectiveness ratio. Please see section 4.25 of the FED.

Consultee	Comment	Response
	[redacted]	

Consultee	Comment	Response
	[redacted] Summary results are reported in *** 1 below. 1 [redacted] [redacted] The full draft manuscript of the study and a table responding to specific points in the ERG report	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
that comments on the vignette study are provided in Appendix 1 and Appendix 2, respectively.
Part 2: Implementation of the vignette values in the economic model

The mean TG value predicted by the generalized linear mixed modelling (GLMM) (following implementation of the stopping rule) in the economic model was 12.1 vs 26.2 mmol/L, volanesorsen Q2W vs SoC respectively. The probability of an FCS patient having a TG reading within a particular category after application of the stopping rule is reported in Table 2.

Table 2: Probability of having a TG reading in a particular category in the economic model
<table>
<tr><th>Health State</th><th>Volanesorsen Q2W</th><th>SoC</th></tr>
<tr><td>>22.6mmol/L</td><td>7.7%</td><td>61%</td></tr>
<tr><td>>10-<22.6mmol/L</td><td>50.4%</td><td>29%</td></tr>
<tr><td><10 mmol/L</td><td>41.9%</td><td>10%</td></tr>
<tr><td>Mean</td><td>12.1</td><td>26.2</td></tr>
</table>

This distribution represents ‘time in state’ as opposed to proportion of cohort in state due to the transience of serum TG levels. Based on the predictions from the GLMM, the 12.1 mmol/L (volanesorsen Q2W) and 26.2 mmol/L (SoC) represent a ‘rolling average’ of TG readings, with 61% of SoC TG readings substantially above 26 mmol/L and 42% of TG readings on volanesorsen Q2W below 10 mmol/L.

In the economic base case, Akcea wanted to reflect the difference these TGs have on day-to-day HRQoL experienced by the two patient cohorts: those on treatment with a mean serum TG level of 12.1 mmol/L compared with those on SoC with a mean serum TG level of 26.2 mmol/L.

Given the very high TG levels associated with FCS, Akcea took the view that 12.1 mmol/L represents a ‘low TG’ for FCS patients while a mean serum TG of 26.2 mmol/L represents a ‘high TG’, for patients on treatment after the 3-month stopping rule. As a simple ‘work around’ in the model this was implemented as *on* versus *off* treatment. It is important to make clear that Akcea does not contend that being on volanesorsen itself results in a utility value of 0.77 compared with
</td><td></td></tr>
</table>

Consultee	Comment	Response
	0.53 for patients in the Historical AP health state. Instead, that the mean serum TG level for the volanesorsen cohort is a low TG value for an FCS population. As such, the utility value of 0.77 was applied. There is a small body of literature categorising TG thresholds, i.e. the thresholds at which clinical events are more or less likely to happen. Differences in the standard units for reporting serum TG in Europe compared with North America demonstrate that these thresholds are indicative rather than absolute. Europe tends to categorise <10 mmol/L, while the equivalent threshold in North America is <1000 mg/dL. One thousand milligrammes per decilitre converts to 11.3 mmol/L which, again, supports the argument that 12.1 mmol/L can very plausibly be considered a low serum TG level for FCS patients. We acknowledge that we could have explained the rationale for implementing the vignettes in the model better than we did. We apologise for this lack of clarity. We hope that the above provides a better explanation as to what was done and why. A clearer way of applying the vignette utilities in the model would be to allocate the high TG vignette utilities to the >22.6 mmol/L TG health states and the low TG utilities to both <22.6 mmol/L health states. This approach also aligns with a study in patients with Type V hyperlipoproteinemia, in which a decrease in the number and severity of pain episodes (HTG abdominal crisis) and frequency of attacks of pancreatitis correlated well with TG levels of ≤2,000 mg/dL (22.6 mmol/L) (Scherer et al., 2014). Applying the vignette utilities in this way reduces the committee's preferred base case ICER to £252,847.	Thank you for your comment. The committee reviewed the method of applying utility values in the model. It heard from the ERG that this logic was not consistent with the vignette or the original submission (people with TG levels between 10 mmol/L or more to less than 22.6 mmol/L should not be considered as having non-elevated TGs). The committee considered that the company's approach in allocating the utility values for the intermediate group was problematic. It concluded that the ERG's approach of linking utility values to TG levels and health states was acceptable for decision making and

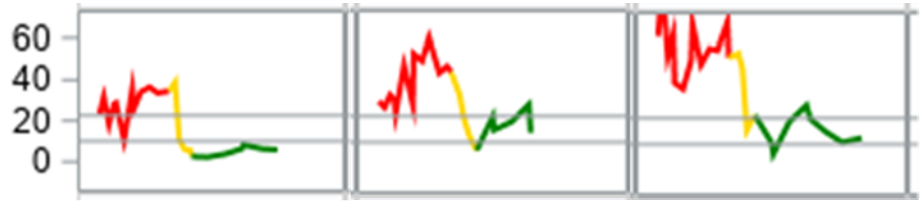
Consultee	Comment	Response
		therefore preferred to see this method in the modelling. Please see section 4.27 of the FED.
Akcea Therapeutics	Impact on health-related quality of life for family members of FCS patients.	Thank you for your comment. The committee acknowledged the new evidence provided by the company and discussed the appropriateness of applying the new value. It recognised the debilitating aspects of the disease but thought that applying the 0.04 utility decrement may be unrealistic. It considered that the value may be smaller than 0.03, which represents a family decrement for patients with new musculoskeletal conditions. It therefore concluded that it would prefer a utility decrement of 0.02 applied in the model. Please see section 4.30 of the FED.
	A revised family/carer utility gain of 0.04 is proposed that results in an ICER of £314,412. This recognises two elements: one, that volanesorsen is indicated for an adult population and two, that there is an impact on the family as a whole of having a family member with FCS. This value for the utility gain lies between 0.05 (metreleptin including paediatric patients) and 0.03 (adult musculoskeletal patients in non-rare, non-genetic diseases with pre-existing treatment options, Wittenberg et al., 2013). A family utility gain of 0.04 results in an ICER of £314,412and an incremental QALY gain of [redacted], based on the Committee's preferred base case.	
	Akcea reviewed the Decision Support Unit's (DSU) report on modelling carer health-related quality of life (HRQoL) as suggested in section 4.33. None of the sources were exactly applicable to this evaluation. However, informed by the information contained therein we suggest an alternative family and carer HRQoL utility value due to FCS of 0.04. We recognise limitations in the application of the metreleptin utility value in this assessment, however we think this remains a relevant reference disease due to the similarity of lipodystrophy and FCS. The metabolic abnormalities associated with lipodystrophy share striking similarities with FCS, including: insulin resistance with resultant hyperinsulinemia and diabetes; hepatic steatosis or steatohepatitis; and dyslipidaemia with severe hypertriglyceridaemia. Patients also have to follow a strict low-fat diet and may receive lipid-lowering drugs (for example, fibrates and statins) and antidiabetic therapy (for example, metformin, insulin, sulphonylureas, and thiazolidinediones) (NICE, 2019). Akcea located a copy of the, now withdrawn, NICE metreleptin Final Evaluation Document (FED). Metreleptin was eventually awarded a relative utility decrement of 0.05 between treated and untreated groups (NICE, 2019). Volanesorsen is indicated for an adult population, while the metreleptin population includes children (section 4.23). Akcea agrees that the mean ages of the different cohorts impact total	

Consultee	Comment	Response
	family/carer HRQoL. As such, we are proposing a lower evidence-informed utility value. Referencing the DSU document, the Wittenberg and Prosser, 2013 and Wittenberg et al., 2013 papers highlight the 'spillover' effect, and conclude this is not restricted to the family/carers of paediatric patients but can include the immediate family members and spouses of adult patients. Documented spillover effects are varied and often condition-specific, ranging from specific symptomology (e.g., anxiety, sleep disturbance), to psychological well-being and physical health. These effects have been measured in the context of a variety of specific health conditions and family or caregiving relationships, such as spouses, parents, children and siblings of cancer patients, and family members and caregivers of individuals with mental illness (e.g., bipolar disorder, schizophrenia, and dementia) (Wittenberg et al., 2013). This spillover effect is clearly relevant to FCS, as described in the ECD section 4.1: "This can be depressing for (patients), and worrisome for their families and carers. Unpredictable hospitalisations can cause disruptions to both a patient's and carer's work. Also, the children of people with FCS often have to be carers for their parents and siblings. The committee also heard that people with FCS are often unable to participate in usual family activities because of the strict dietary restrictions they must stick to. This can have a substantial emotional effect on them and their families." The daily FCS symptom burden, including abdominal pain, fatigue, anxiety and depression, the constant vigilance at every meal and the impact on social life has a spillover effect on family members and partners. This was reported in a survey conducted by Gelrud et al. (2017) in which it was stated that "Caregivers reported that their social life was limited by symptoms of FCS, particularly fatigue," and "Caregivers reported using their own vacation time to care for patients during complications of FCS. Caregivers also expressed anxiety about seeing their loved ones going to work while sick to avoid missing a day of work." The impact on families of different conditions is presented in Wittenberg and Prosser et. al., 2013 study: • existing mental or musculoskeletal conditions, -0.01 (95 % CI -0.02, -0.00); • new mental conditions, -0.02 (95 % CI -0.04, -0.00); • new musculoskeletal conditions, -0.03 (95 % CI -0.05, -0.01)	

Consultee	Comment	Response
	The above disutilities relate to conditions that are not ultra-rare, familial *and* that have existing effective treatments. The carers and family members of FCS patients have lived their entire lives believing that that there is no effective treatment for FCS. The psychological impact of knowing that there is at last an effective treatment, is likely to have an additional QALY benefit beyond simply reducing the disutilities obtained by Wittenberg et al. in non-familial, non-ultra-rare conditions. The relief experienced by the family members of FCS was articulated by the FCS patient representatives and was also captured in the survey by Gelrud et al. (2017): "Both patients with FCS and caregivers were asked what any future therapy developed for FCS would do for them. Patients expressed the hope that a future therapy would reduce their pain and symptoms, improve their quality of life, and help them stay out of the hospital. Several patients also expressed a wish for a less stressful, more normal lifestyle that includes socialization and a more normal diet. Five of the patients hoped that any future therapy would improve their TG values and treat the underlying disease, not just the symptoms. When caregivers were asked what they hoped a future therapy could do for their loved ones, their replies echoed those of the patients." Akcea believes that a fair valuation of QALY gain for carers lies at 0.04, the mid-point between the 0.05 value awarded for metreleptin and 0.03 for a family member of an adult with newly diagnosed musculoskeletal disorder from (Wittenberg et al., 2013). Application of a carer utility of 0.04 in the model reduces the committee base case ICER from £355,235to £314,412.	
Akcea Therapeutics	Treatment continuation rates on volanesorsen: 80% plateau in routine UK clinical practice	Thank you for your comment. The ERG clarified during consultation that based on clinical expert opinion it would expect a stopping rate of 10% per year and up to 20% continuing treatment in total.
	The ECD discontinuation rate is not reflective of clinician feedback in the ERG report. Using the committee's preferred lognormal curve and capping discontinuation at 20%, in line with clinician feedback, over the model lifetime reduces the ICER from £355,235to £341,606	
	The ERG report indicates that the clinical advisors consulted about treatment discontinuation felt that no more than 20% of the patient population would discontinue. This is not reflected in the ERG's base case model. Clinical advisors to the ERG were of the opinion that there would be discontinuations in clinical practice, with estimates up to 10% per annum and 20% in total. The	

Consultee	Comment	Response
	main reasons for these were thought to be the burden of monitoring and adverse events including injection site reactions and thrombocytopaenia (ERG report page 44, section 4.2.4.2). The ERG reflected the 10% annual value as an exponential distribution in their base case but did not capture the likelihood that this would plateau at 20%. Akcea agrees with the clinical advisors that 1) some discontinuation is likely, and 2) that discontinuation is unlikely to exceed 20% in total. This is for two reasons. Firstly, in the UK only patients with the greatest potential to benefit from treatment are likely to be prescribed treatment; these are likely to be patients with the most significant symptom burden. These patients are also likely to be more adherent to treatment over the longer term. Secondly, Akcea's patient support programme is likely to lead to better retention, as evidenced by the good retention rates in EAMS.	The committee acknowledged this and also understood that stopping treatment in trials was not only because of the stopping rules in the summary of product characteristics. The evidence also suggested that a proportion of people would stop treatment in the trials and EAMS regardless of dosing regimen even after being on treatment for 2 or 3 years. Therefore, noted that a trend seems to be supportive of some late treatment stopping. It concluded that it is likely to be dose pauses and people stopping treatment in the long term but at a much lower rate than in clinical trials Please see sections 4.21-4.24 of the FED.
Akcea	Volanesorsen's impact on acute pancreatitis event rates	Thank you for your

Consultee	Comment	Response
Therapeutics	The ECD queries assumptions in the economic model relating to the effect of volanesorsen around 1) the relationship between TG reduction and AP *in FCS patients* and 2) the direct effect of volanesorsen on the risk of AP. In order to address these concerns, we describe below: 1) The relationship between TG and AP in FCS patients based on the literature and clinical trial data 2) The impact of volanesorsen on TG and AP 3) Implementation of TG mediated AP effect in the economic model 4) The implementation of direct impact of volanesorsen on AP in the economic model *The relationship between TG and AP in FCS patients*	comment. Please see response to the comments in the sections below.
	Patients with FCS are at higher risk of AP compared to those with other high HTG disorders for the following three reasons: FCS patients have chronically higher mean serum TG levels, there is greater volatility in their TG levels (higher 'peaks' experienced more frequently) and they have higher rates of prior APs. Together these increase the risk of AP in FCS patients compared with HTG patients.	Thank you for your comment. The committee reviewed the further information on the possible relationship between TG and AP in people with FCS provided by the company during consultation. It considered views of the ERG and clinical experts and accepted that there is a general linear relationship between TG levels and risk of AP. Although it still remained uncertain whether this relationship was generalisable to people
	The incidence of AP in FCS is higher than in other hypertriglyceridemia (HTG) disorders. In a study by Gaudet et al. (2016a), there were 67 AP hospitalisations in 251 FCS patients vs. only 14 AP hospitalisations in 1,981 patients with multifactorial chylomicronaemia. One reason for this is that the TG levels experienced by FCS patients are much higher than in other causes of HTG (up to 70 mmol/L in some patients) (Scherer et al., 2014). Similarly, only 15% of the HTG patients with readings above 10 mmol/L in the CALIBER study had serum TG levels above 22.6 mmol/L (Akcea data on file, 2018), whereas TG levels above 22.6 mmol were observed in over 50% of the TG readings in the APPROACH trial placebo arm. FCS patients present with consistently and chronically elevated serum TG levels that are higher than in other HTG disorders. There also appears to be greater TG volatility (peaks and troughs) in patients with FCS compared with other HTG disorders. This pattern of extremely high and highly variable TG is predicted by the GLMM, with SoC TG level of 26 mmol/L, and can be seen in the patient traces below, see Figure 1.	

Consultee	Comment	Response
	Additionally, one of the known risk factors for an AP event is a prior AP event (Sankaran et al., 2015; Akcea CALIBER study). FCS patients report high rates of AP. Therefore, while the dose-response relationship between TGs and AP is generalisable to FCS patients, it is likely that patients with FCS are at higher risk of AP compared to those with other high HTG disorders for the following three reasons: higher mean serum TG levels than other HTG disorders, greater volatility in TG levels, including higher peak readings and higher rates of prior APs, all predisposing FCS patients to repeat events. *Volanesorsen's impact on AP events*	with FCS. Please see section 4.10 of the FED.
	For patients with a history of AP there is a compelling body of evidence for the benefit of volanesorsen. For patients who suffer frequent AP events and live with the constant fear and anxiety of a further attack volanesorsen's reduction of AP events can be life changing.	Thank you for your comment. The committee noted that it is uncertain whether the linear relationship applies in FCS. Although, reduced TG levels may be associated with reduced risk of AP in this population, as shown in the clinical trials. Please see section 4.10 of the FED.
	Volanesorsen appears to confer effect by both reducing mean serum TG level and reducing the 'height of the peaks'. We hypothesise this reduction in 'spiking' (i.e., particularly high TG levels) may explain why a switch to Q2W is associated with a smaller % reduction in TG from baseline without an increase in AP event rate. This impact can be observed in the individual patients traces which are notably subject to fewer and less extreme fluctuations in TG level during the on-treatment period (Figure 1) and in the GLMM, lower variance in the on-treatment model coefficients. Figure 1: Individual patient plots of TG level by dosing group 	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
Key: Y axis represents TG value in mmol/L. Colour coding: Red: off treatment; Yellow, weekly dosing; Green, Q2W dosing

Data from the clinical trial as relates to AP is also compelling, particularly in patients with a high risk of recurrence (Table 3).

Table 3: Pancreatitis in patients at high risk of recurrent attacks (≥2 adjudicated pancreatic events in the past 5 years)
<table>
<tr><td></td><td colspan="2">Volanesorsen (n = 33)</td><td colspan="2">Placebo (n = 33)</td></tr>
<tr><td></td><td>Patients</td><td>Events</td><td>Patients</td><td>Events</td></tr>
<tr><td>5-year medical history</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Patients with multiple (2 or more) adjudicated events in the past 5 years</td><td>7</td><td>24</td><td>4</td><td>17</td></tr>
<tr><td>Events during study</td><td>0</td><td>0</td><td>3</td><td>4</td></tr>
<tr><td></td><td colspan="4">P = 0.0242</td></tr>
</table>
The effect of volanesorsen in individual patients prone to recurrent AP has been remarkable. One patient with a five-year medical history of three APs enrolled in the placebo arm of APPROACH and experienced a further four APs over the following year. The patient enrolled into APPROACH OLE on weekly dosing, reduced dose to Q2W within 3 months, and completed approximately 18 months of Q2W dosing before being recruited into EAMS 6 months later where they’ve received a further year of Q2W dosing. This patient has had no AP attacks since they initiated volanesorsen over three years ago.
The rate ratio for the risk of an AP event with or without volanesorsen treatment was calculated in a number of ways, see Table 4:

Table 4: Any FCS patient, regardless of AP history
</td><td></td></tr>
</table>

Consultee	Comment	Response

	APPROACH	APPROACH OLE (Feb 2019 data cut)	Pooled APPROACH, APPROACH OLE and COMPASS[2,3]	Glybera observational study[4]
	AP rate (patient years of exposure)			
Medical history	0.21 (330)	[redacted]	[redacted]	0.27
Placebo	0.11 (31.8)	[redacted]	[redacted]	
Volanesorsen (any dose)	0.09 (29)	[redacted]	[redacted]	
Volanesorsen (Q2W)[1]			[redacted]	
	Calculated AP rate ratios			
Rate ratio, any dose vol vs. medical history	0.43	0.13	-	
Rate ratio, any dose vol vs. placebo	0.82	0.17 (vs. 0.19 pooled trial placebo)	0.19	
Rate ratio, Q2W vol[1] vs. placebo	-	-	0.39	

1. after at least 3 months of Q2W dosing
2. FCS patients only
3. July 2019 data cut
4. European Medicines Agency, 2017

Data are also now available for the rate ratio comparing the risk of an AP event with and without volanesorsen in the population of patients with a history of AP, see Table 5.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
Table 5: Patients with a history of AP
<table>
<tr><td></td><td>Pooled APPROACH, APPROACH OLE and COMPASS[2,3]</td></tr>
<tr><td></td><td>AP rate (patient years of exposure)</td></tr>
<tr><td>Placebo</td><td>[redacted]</td></tr>
<tr><td>Volanesorsen (any dose)</td><td>[redacted]</td></tr>
<tr><td>Volanesorsen (Q2W)[1]</td><td>[redacted]</td></tr>
<tr><td></td><td>Calculated AP rate ratios</td></tr>
<tr><td>Rate ratio, any dose (vs. placebo)</td><td>0.18</td></tr>
<tr><td>Rate ratio, Q2W[1] (vs. placebo)</td><td>0.35</td></tr>
</table>
1. after at least 3 months of Q2W dosing
2. FCS patients only
3. July 2019 data cut

Modelling in the impact of volanesorsen on AP events in the economic analysis

The ERG's multiplication factor of 0.5 results in a rate ratio (0.45) for volanesorsen's effect on rate of AP that is not reflective of the available clinical data, particularly in patients with a history of AP or with recurrent AP. The clinical evidence demonstrates volanesorsen has a positive impact on AP rates, particularly in patients with a history of AP. We suggest an effect size estimate between 0.13 and 0.35 is more appropriate. Using values of 0.27 and 0.28 in the low/medium TG and high TG health states respectively, reduces the ICER from the committee base case of£355,235to £333,849

The ECD queries two assumptions in the economic model relating to the effect of volanesorsen on acute pancreatitis events. These queries are specifically:

1) the direct effect of volanesorsen on the risk of acute pancreatitis
</td><td>Thank you for your comment. The committee noted the company's revised approach to modelling volanesorsen's effect on acute pancreatitis. It also acknowledged comments from the ERG, explaining that both estimates were subject to considerable risk of bias.

Although, the committee</td></tr>
</table>

Consultee	Comment	Response
	2) the relationship between triglyceride levels and risk of acute pancreatitis in people with familial chylomicronaemia syndrome We assume that there are three risk factors for acute pancreatitis in FCS: 1) high mean TG levels 2) volatile TG levels / 'spiking' in TG and 3) previous AP events. The economic model explicitly addresses points 1) and 3) in its structure. As a reminder, there are nine main health states (plus chronic pancreatitis and the absorbing state death). The nine health states result from a three by three matrix of TG level (low, medium and high) and AP history (naive, historical and recurrent). In the company base case a rate ratio of 0.13 was applied to patients in the historical and recurrent AP categories based on a comparison between AP event rates in the 5 years prior to the APPROACH OLE trial with the rates on treatment during the trial (tables Table 4 and Table 5). The ERG suggested this would overestimate the benefit and tested an arbitrary multiplication factor of 0.5. The reasons they suggested there would be over-estimation are 1) double counting in a population that already has the potential to reduce AP via TG reduction 2) regression to the mean and 3) recollection bias. Addressing these in reverse order: AP events from the APPROACH OLE medical histories were definitely adjudicated, therefore there is no risk of recollection bias in the 5-year medical history rate of AP. In a clarification response in 2018 we suggested these prior AP were not adjudicated. We have now confirmed that they were, we apologise for any confusion caused. With regards to regression to the mean, we understand the risk would be that patients enrol in the trial because they have just had a bad AP event, and therefore may have naturally been going to enter a period of time with fewer APs, and that being in the trial itself will have encouraged patients to adhere to the required diet, and therefore they have fewer AP events. We are not able to comment either way on the point about motivation to join the trial, we do not have that information.	recognised the limitations of developing an evidence base for an ultra-rare disease and around estimating the most plausible rate ratio values associated with the use of volanesorsen given the lack of trial data. In the absence of robust evidence, the committee considered that a rate ratio of 0.29, applying to all in the model, was reasonable. Please see section 4.20 of the FED.

Consultee	Comment	Response
	With regards to being in the trial improved adherence to the diet, we suggest this is not the case on the basis that there is no notable change in TG results between screening for entry into the trial and the baseline TG measure: mean TG at screening was 26.8mmol/L and 25.0mmol/L at baseline. In this run-in period patients were expected to ensure they were adhering to the required diet. The lack of variation between screening and baseline suggests there was no substantial change in adherence to diet. It is also important to note that a number of patients have now been on volanesorsen for a substantial period of time in OLE and EAMS. We heard in the committee meeting that these patients *have* adjusted their diet. They were keen to point out the adjustment was a nutritionally better adjustment that is still part of a safe diet for FCS patients, but towards the higher permissible fat consumption range. These patients are not reporting AP events. Therefore, this suggests reduced AP events is a true treatment effect and not a statistical artefact: volanesorsen does reduce AP event rates. Akcea acknowledges that there was some double counting, however this was only in the Historical AP health states applicable to 54% of the patient cohort and only up until the first AP event. The additional multiplication factor was necessary because moving from the high TG health state (on SoC) to the medium TG health state (on volanesorsen) did not adequately capture the magnitude of reduction on risk of AP observed in the clinical trials. This is likely because 1) FCS patients on SoC have higher AP rates in the high TG health state than predicted by the CALIBER data (for reasons explained previously) and 2) patients on volanesorsen have lower AP rates than predicted by the CALIBER data (because a large proportion of readings are <10 mmol/L). Furthermore, once patients in the Historical AP health states experience an AP event, they move into the Recurrent AP health states. Therefore, the impact of the double-counting is low. We tested the impact of the ERG adjustment of 0.5 in a scenario in the economic model by comparing the rate of AP predicted by each arm. The scenario equalises the number of patients at risk of AP in the arms by: • removing transition to chronic pancreatitis • removing mortality from AP	

Consultee	Comment	Response
	• removing mortality from diabetes • setting discontinuation on volanesorsen to zero - to capture a long-term on-treatment effect. Under this scenario, that isolates the impact of the ERGs adjustment to the rate ratio for AP, the model predicts a rate ratio of 0.45 between volanesorsen and standard of care (SoC). This is a significant underestimate compared with available evidence. Akcea would suggest that a rate ratio of 0.27 (for the low/medium TG health states) and 0.28 (for the high TG health states) is a reasonable mid-point between 0.13 (APPROACH OLE on-treatment vs. natural history, Table 4) and the value of 0.35 (volanesorsen Q2W vs. trial placebo rates in patients with a history of AP, Table 5), and that this should be used in place of this arbitrary 0.5 rate ratio. Using 0.27 and 0.28 reduces the ICER from the committee base case of £355,235to £333,849.	
Akcea Therapeutics	Triglyceride (TG) lowering effect of volanesorsen at once every week (Q1W) and once every two weeks (Q2W) dosing Volanesorsen demonstrates transformational triglyceride (TG) lowering benefit for patients with FCS in the short and long-term at every week (Q1W) and every two week (Q2W) dosing.	Thank you for your comment. The committee considered the evidence provided by the company during consultation. It acknowledged that the clinical trial evidence showed that volanesorsen would likely provide benefits in lowering TG levels. It also considered the additional data from APPROACH OLE and EAMS which showed a trend toward TG lowering
	For a novel product for treatment of an ultra-rare disease, volanesorsen has a robust data package for its triglyceride (TG) lowering effect in both the short- and long-term at either Q1W or Q2W doses.	
	This benefit is substantial, clinically meaningful and sustained with a reduction in mean serum TG of 70-80% with Q1W dosing and a reduction of 40% with Q2W. The SmPC for volanesorsen recommends a starting dose of 285mg Q1W for 3 months and a reduction to Q2W at 3 to 6 months and thereafter allows clinical discretion for longer term use at either the Q1W or Q2W dosing frequency. Evidence from EAMS would suggest that in the UK patients will stay on Q2W dosing. Data for the efficacy of volanesorsen at both Q1W and Q2W dosing for up to 4 years is provided below. *Triglyceride lowering efficacy: 0-3months efficacy at Q1W dosing* Volanesorsen's triglyceride lowering benefit is seen in the primary endpoint of the pivotal phase 3	

Consultee	Comment	Response
	study APPROACH: • In the APPROACH phase 3 study, treatment with volanesorsen was associated with a 94% benefit compared to standard of care, in reduction from baseline in serum triglyceride (TG) level at 13 weeks: -77% vs +18% respectively, (p<0.0001). • The absolute reduction in TG level at 3 months was 19.3 mmol/L on volanesorsen vs. an increase of 1 mmol/L on placebo (p=<0.001), from a baseline TG level of 25 mmol/L. This is a substantial and clinically meaningful reduction in TG. Levels above 22.6 mmol/L are considered 'ultra-high' and associated with a particularly high risk of acute pancreatic (AP) (Scherer at al., 2014). • All patients in the first three months of APPROACH received weekly dosing, the licensed dose. 91% (30/33) of patients maintained Q1W dosing for the first 3 months. *Triglyceride lowering efficacy: post-3months efficacy at Q2W dosing* For a novel product there is a substantial body of data demonstrating clinically meaningful and sustained long-term triglyceride lowering efficacy at the Q2W dose. While there is a divergence from the trial dosing protocol at 3 months, there is a substantial body of evidence supporting a sustained reduction in TGs of approximately 40% on Q2W dosing. This includes the APPROACH and APPROACH OLE trials (July 2019 data cut, new data), EAMS and the GLMM. Triglyceride (TG) lowering efficacy: 3-6m at Q2W dosing, after initiation at Q1W *APPROACH OLE* o 14 treatment naïve patients from the APPROACH OLE study commenced treatment with volanesorsen 285 mg Q1W and were then down-titrated to Q2W dosing at 3 months +/- 2 weeks; the dosing schedule recommended in the SmPC.	benefit in people receiving the treatment at weekly and fortnightly dosing. The committee heard from the ERG that the evidence raised the possibility that response to the treatment may wane over time, but any reduction was likely to be small. The committee therefore concluded that volanesorsen would likely provide some long-term benefits, although this was associated with substantial uncertainty, particularly at the licensed dose. Please see sections 4.11 to 4.14 of the FED.

Consultee	Comment	Response
	o After a total of 6 months of volanesorsen treatment (~3m at Q1W and ~3 months at Q2W dosing), the observed reduction in serum TG was mean [redacted] o The absolute reduction in serum TG was [redacted] mmol/L at 6 months. Triglyceride (TG) lowering efficacy: post-6m at Q2W dosing *APPROACH OLE* o The latest data cut from the ongoing APPROACH OLE study (July 2019 data cut 1) provides data for additional patients who have received more than 3 months treatment with volanesorsen 285 mg Q2W. o In this cohort, treatment with volanesorsen Q2W produced a reduction in serum TG from baseline of: - [redacted] after 6 months of treatment with volanesorsen 285 mg Q2W ([redacted]) - [redacted] after 12 months of treatment with volanesorsen 285 mg Q2W ([redacted]) - [redacted] after 18 months of treatment with volanesorsen 285 mg Q2W ([redacted]) - [redacted] after 24 months of treatment with volanesorsen 285 mg Q2W ([redacted]) *UK Volanesorsen Early Access to Medicines Scheme (EAMS)* The UK volanesorsen EAMS also provides additional information into the efficacy of volanesorsen 285mg Q2W (the dose mandated within the treatment protocol for the first 6 months of treatment). Data is currently available from 20 patients (October 4th 2019 Data Cut) who have been treated with volanesorsen for a minimum of 3 months in the UK EAMS, comprising 9 patients who were previously treated with volanesorsen within the clinical development programme and 11 treatment-naïve patients (see Appendix 4).	

Consultee	Comment	Response
	o In patients previously treated with volanesorsen within the clinical development programme, after 3 months of treatment with volanesorsen 285 mg Q2W, the percentage change in serum TG was [redacted] (mean) or [redacted] (median) from the *clinical trial* baseline ([redacted]). - 3 patients in this cohort had been on volanesorsen treatment for ~4 years at the time of the data cut o A similar reduction in serum TG was observed in the treatment-naïve patients in the EAMS who initiated treatment at the Q2W dose: In this cohort, 3m of treatment with volanesorsen 285 mg Q2W reduced the serum TG by [redacted] (mean) or [redacted] (median) from baseline ([redacted]). *Generalised Linear Mixed Model (GLMM)* o The generalised linear mixed model (GLMM) was a post-hoc statistical analysis used to predict absolute TG values on Q2W dosing using 1,508 unique TG observations from 90 patients up to the February 2019 cut-off. o The mean of the predicted TG values on volanesorsen Q2W dosing compared with the mean TG on standard of care was associated with a mean TG reduction on Q2W of 44%. Triglyceride (TG) lowering efficacy: post-3m *at Q1W* dosing The licence dosing posology permits up-titration, should that be clinically appropriate. In EAMS, only one patient has up titrated from Q2W to Q1W dosing. They maintained the higher dose for only a few weeks before dose pausing due to platelet levels. Therefore, we think that in routine UK clinical practice, up-titration is very unlikely. However, there are data demonstrating the efficacy of the product at the Q1W dose. *APPROACH pivotal Phase 3 Study*	

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>

In the APPROACH study, 6 patients completed the 12-month study on volanesorsen 285 mg Q1W without any dose adjustment.
In this cohort, 12 months of treatment with volanesorsen 285 mg Q1W produced a reduction in serum TG of 76.2%, an absolute reduction in serum TG of was 17.9 mmol/L.

The submitted evidence demonstrates the substantial short and long-term efficacy of volanesorsen in FCS at Q1W and Q2W.
Efficacy in the long-term at the label recommended dosing is supported by three sets of analyses, conducted independently in three cohorts of patients, all consistently supporting a long-term reduction on fasting TGs of approximately 40% by Q2W volanesorsen.
</td><td></td></tr>
<tr><td>Akcea Therapeutics</td><td>
Uncertainty in favour of volanesorsen: evidence not considered by the committee
A number of co-morbidities were not included in the economic model, as the company was concerned about the risk of double-counting due to shared features with either the vignette descriptions or symptoms of diabetes and/or chronic pancreatitis and/or due to a lack of robust data. These co-morbidities and their symptoms are summarised in Error! Reference source not found. in Appendix 3.
Similarly, the vignette health state descriptions did not capture all the aspects of FCS symptomology which could be expected to add additional decrements. These symptoms are summarised in
Table 6, below.
Table 6: FCS symptoms not included in the vignette descriptions
<table>
<tr><th>Symptom</th><th>Proportion of FCS patients reporting symptoms</th><th>Utility decrement</th></tr>
<tr><td>Joint pain[1]</td><td>22%</td><td>-0.15 associated with rheumatoid arthritis</td></tr>
</table>
</td><td>Thank you for your comment. The committee acknowledged the company’s comments and understood that these factors could have affected patients’ quality of life and therefore cost effectiveness.

It also considered that if these factors were associated with either a decrease or increase in TGs, then it would have preferred to see them in</td></tr>
</table>

1. ID1326 Familial chylomicronaemia - comments table [redacted]

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>(Sullivan et al., 2011)</td></tr>
<tr><td>Feeling cold all the time in extremities[1]</td><td>18%</td><td>Unknown, possibly tied in with the numbness or tingling</td></tr>
<tr><td>Numbness or tingling of digits[1]</td><td>14%</td><td>Possibly links with neuropathy. The smallest disutility associated with peripheral neuropathy in cancer was 0.094 (Peasgood et al., 2010)</td></tr>
<tr><td>Use of steroids[2]</td><td>[redacted]</td><td>Not possible to provide a utility estimate</td></tr>
<tr><td>Use of opioids</td><td>[redacted]</td><td>Not possible to provide a utility estimate</td></tr>
</table>
1 % reporting symptoms in InFOCUS
2 baseline in APPROACH OLE

Akcea points out the high proportions of patients taking prescription opioids ([redacted]) and corticosteroids ([redacted]) at baseline in the APPROACH OLE study. Five percent of patients in the InFOCUS study reported being addicted to opioid and non-opioid painkillers. Once a prescription opioid use disorder is established, the negative impacts on quality of life and health, as well as economic impacts to individuals, families, and society, are substantial. Every year, drug misuse costs the NHS in England £488m, with additional societal costs of up to £15.4 billion (Public health England, 2013). In the ReFOCUS study volanesorsen was found to reduce pancreatitis pain (Arca et al., 2018) and thus could prevent use of opioids and potential addiction in these patients. Importantly, if the committee considers these relevant to FCS patients, then it should also consider that volanesorsen would reduce these symptoms/concomitant medication use which would result in a lower ICER.

Malnutrition, dietary deficiencies and maintaining the FCS diet
Patient representatives at the first committee meeting explained that they had been able to make small modifications to their diet since being on volanesorsen, including for example “being able to eat a small yoghurt”. Guideline dietary fat requirements for normal individuals are between 70 g (women) and 95 g (men) per day, of which just under a third should be saturated (British Nutrition Foundation, 2012), whereas FCS patients on current SoC are restricted to 10–20 g per day. This</td><td>the vignette study.

Since no empirical data were provided, the possible effect of these factors on the cost-effectiveness estimate remained unknown and therefore the committee could not take these into account during decision-making. Please see section 4.31 of the FED.</td></tr>
</table>

Consultee	Comment	Response
	strict diet can lead to malnutrition and deficiency in fat-soluble vitamins. Bone compromise due to a lack of vitamin D is seen in UK FCS patients. In addition, eating disorders such as bulimia, or eating nutritionally worthless food (e.g., surviving on one MacDonald's meal a day) are not uncommon in these patients. Although patients on volanesorsen are still required to adhere to a low-fat diet, appropriate dietary support as described in the FCS Best Practice Guide (Appendix 5) and being able to maximise your permitted fat could improve their nutritional status and help relieve the psychological burden of the strict diet.	
	We ask that the committee considers the potential QALY implications of these additional conditions and symptoms in their deliberations regarding the potential QALY gain from volanesorsen.	
Akcea Therapeutics	To summarise the information provided above: • There is strong evidence that the reduction in TG with volanesorsen treatment leads to an improvement in daily quality of life by keeping mean TG levels notably below 22.6 mmol/L. • There is evidence from peer-reviewed publications and patient representatives that the family members of patients with FCS experience significant 'spillover' effects on HRQoL due to patients' daily burden of disease. • The CALIBER data used in the model potentially under predicts risk of AP in patients with historical AP. • There is consistent evidence of a treatment effect on risk of AP ranging from 0.13 to 0.35 in patients with historical or recurrent AP. • Treatment discontinuation in the UK is unlikely to exceed 20% due to selection of severe patients and a strong patient support program. • Benefits very likely to be associated with volanesorsen treatment are not captured in the model, therefore there are missing elements that would reduce the ICER.	Thank you for your comment. The evaluation committee considered evidence submitted by the company. The committee also noted that the company revised its commercial offer for volanesorsen, which brought the incremental ICER down to £98,013 per QALY gained compared with best supportive care which can be considered an effective use of NHS resources for highly specialised technologies. Although there were

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
As such, Akcea would like to propose alternative ICERs to the committee's base case that capture what the company believes are more plausible estimates of economic value. These are summarised in Table 7 and lead to a gain of 13.45 undiscounted QALYs and a revised ICER estimate of £210,487 or [redacted] with QALY modifiers applied.

Table 7: One-way results of incorporating Akcea's proposed changes to the committee's base case economic analysis
<table>
<tr><th>Scenario</th><th>Incremental costs</th><th>Incremental QALYs (undiscounted)</th><th>Incremental QALYs (discounted)</th><th>ICER [redacted] per syringe)</th><th>REVISED ICER [redacted] per syringe)</th></tr>
<tr><td>Committee base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£481,508</td><td>£355,235</td></tr>
<tr><td>Low TG vignette values applied to TG health states < 22.6 mmol/L</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£342,725</td><td>£252,847</td></tr>
<tr><td>Carer (family member) utility benefit of 0.04 applied on volanesorsen</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£426,174</td><td>£314,412</td></tr>
<tr><td>Adjustment of 0.27 and 0.28 applied to risk of AP in the low/medium TG and high TG health states</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£454,703</td><td>£333,849</td></tr>
<tr><td>Capping discontinuation at 20%</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£462,683</td><td>£341,606</td></tr>
<tr><td>All of the above changes incorporated</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£286,295</td><td>£210,487</td></tr>
<tr><td>Assuming a QALY modifier of [redacted]</td><td></td><td></td><td></td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>uncertainties the committee recommended volanesorsen as an option for treating familial chylomicronaemia syndrome. Please see sections 4.33; 4.34; 4.38 and 4.39 of the FED.</td></tr>
</table>

Consultee	Comment	Response
Akcea Therapeutics	Conclusion The data submitted in the HST dossier and in this ECD response provide robust evidence of effectiveness of volanesorsen in reducing serum triglyceride (TG) levels at every week (Q1W) and every two week (Q2W) dosing. This TG reduction is sustained, clinically meaningful and statistically significant. It is associated with improvement in day-to-day health related quality of life (HRQoL) for patients and their families, the prevention of acute pancreatitis events and a reduction in the long-term sequalae of FCS including chronic pancreatitis and diabetes. This evidence underscores our belief that volanesorsen is a transformational treatment in the management of FCS, an ultra-rare, genetic, chronic, burdensome disease for which there is no effective treatments available in routine NHS care.	Thank you for your comment. The evaluation committee considered evidence submitted by the company.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical expert nominated by LPLD Alliance	We write in response to the above evaluation issued in December 2019. We are former investigators for the APPROACH study and/or health professionals overseeing the care of patients taking Volanesorsen under the Early Access to Medicines Scheme (EAMS). We accept the reservations of the committee regarding the limitations of the clinical trial evidence in demonstrating Volanesorsen's long term efficacy in sustained reduction of triglycerides and incidence of pancreatitis, as well as uncertainties around the relationship between reduction in triglycerides and incidence of pancreatitis. We also acknowledge that the dosing regimen used in the APPROACH trial was different from that subsequently used in EAMS and from that proposed for routine clinical use. We accept that there was lack of clarity in the study about the effect of Volanesorsen on quality of life of participants and carers.	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the ERG. Taking into account all information and evidence the committee concluded

Nominating organisation	Comment	Response
	We aim to clarify the points which led to the committee's decision not to recommend Volanesorsen for the treatment of familial chylomicronaemia syndrome: 1. *The relationship between triglyceride levels and risk of acute pancreatitis in people with familial chylomicronaemia syndrome (FCS)* In the APPROACH trial triglyceride concentration was the primary outcome measure. The trial demonstrated a significant reduction in triglyceride concentration with volanesorsen treatment. However triglyceride concentration does not correlate directly with pancreatitis because chylomicronaemia, *not* hypertriglyceridaemia, is the direct cause of pancreatitis. Chylomicrons are lipoprotein particles responsible for transporting triglycerides derived from dietary fat to organs for metabolism to free fatty acids by the enzyme lipoprotein lipase. In the majority of people with high triglycerides, lipoprotein lipase activity is normal and triglycerides are converted to free fatty acids. FCS is caused by an inherited defect of lipoprotein lipase activity. Hence in patients with the condition triglycerides cannot be converted to free fatty acids resulting in accumulation of unmetabolised chylomicrons. Unmetabolised chylomicrons and chylomicron remnants lodge in the small vessels of the pancreas triggering inflammation and necrosis causing pancreatitis. Chylomicrons cannot be readily quantified hence triglycerides are used as a surrogate measurement of chylomicronaemia. This has its limitations because the two are not directly related - triglyceride concentration fluctuates day-to-day in response to recent dietary fat intake however chylomicronaemia depends not only on dietary fat intake but also on lipoprotein lipase activity. Additionally, the day-to-day fluctuation of triglycerides in response to diet makes it an unreliable marker of long term metabolic control (akin to using glucose measurements for diabetes monitoring).	that clinical trial evidence showed short-term benefits with volanesorsen, including a reduction in triglyceride (a type of fat found in the blood) levels. It was uncertain whether this is maintained in the longer term, particularly at the licensed dose which was not used in clinical trials. The committee also considered other uncertainties, especially around volanesorsen's effect on acute pancreatitis and the utility values used in the economic model. It agreed that despite the uncertainties volanesorsen is likely to provide important clinical and psychological benefits for people with familial

Nominating organisation	Comment	Response
	A patient with FCS carries a higher residual burden of unmetabolised chylomicrons (visible as the milky appearance of their blood samples) than a patient with hypertriglyceridaemia from other causes who does not have FCS. Therefore at any given triglyceride concentration a patient with FCS is at higher risk of pancreatitis than someone with high triglycerides who does not have FCS. Even within an FCS population the triglyceride threshold triggering an episode of pancreatitis will be highly variable depending on an individual's the degree of residual chylomicronaemia which in turn depends on their long-term adherence to a low fat diet. *2. The direct effect of volanesorsen on the risk of acute pancreatitis* In the APPROACH study, Volanesorsen lowers triglycerides and this would be predicted to reduce chylomicronaemia and hence pancreatitis risk. However as stated above triglyceride concentration is not directly related to chylomicronaemia and therefore also not to risk of pancreatitis. *Because chylomicrons cannot be directly quantified there is no direct measure of pancreatitis risk.* *Trial participants were on average at lower baseline risk of pancreatitis than a non-trial FCS population for the following reasons:* i. Trial participants are a generally more adherent group than others with the same condition, and specifically therefore likely to have been more adherent to the low fat diet and have a lower chylomicron burden; ii. Genetic confirmation of FCS was not an inclusion criterion for the trial, some trial participants had hypertriglyceridaemia of other aetiologies Therefore the APPROACH trial is *likely to have underestimated the effect of Volanesorsen on incidence of pancreatitis in FCS and study data cannot be used to determine the effect of Volanesorsen on incidence of pancreatitis in this condition.*	chylomicronaemia syndrome and value for money within the context of a highly specialised service. It is therefore recommended for use in the NHS.

Nominating organisation	Comment	Response
	In order to assess the effect of Volanesorsen on pancreatitis the incidence of pancreatitis must be compared in treated vs. untreated patients, or in individuals before and after starting Volanesorsen. *3. The quality of life values used in the model* The questionnaire-based tools for assessing quality of life (QoL) used in APPROACH, though validated for clinical and research use, were not sufficiently sensitive or specific to capture QoL issues specifically affecting patients with FCS. These include but are not necessarily limited to: i. Impact of a highly restrictive and exceptionally demanding diet (typically less than 20g fat daily, equivalent to 1 ½ tablespoons of vegetable oil daily) • social and societal – eating out, eating with others • requirement for constant vigilance around content of food • weight loss and nutritional deficiencies • dietary fat replaced by carbohydrates which are bulky and may cause bloating • additional dietary restrictions for patients with diabetes ii. Impact of living with symptoms of FCS (fatigue, poor concentration, forgetfulness, pain) iii. Impact of living with a condition that could cause you to be acutely and unpredictably unwell with a life-threatening complication (pancreatitis) iv. Consequences of analgesia dependence, including opiates Conclusions *Triglyceride concentration alone is inadequate as an outcome measure for assessing clinical efficacy of Volanesorsen. Clinically meaningful outcome measures include incidence of pancreatitis and its complications (pancreatic insufficiency, diabetes, mortality) and prevalence of other symptoms affecting quality of life to include the impact of dietary restriction on quality of life. These data were not captured in the APPROACH trial and are not currently formally captured within EAMS.*	

Nominating organisation	Comment	Response
	EAMS has given us the opportunity to prescribe Volanesorsen for patients with FCS in a 'real world' setting. We have seen at first hand the benefit to patients on quality of life. Two examples are provided in the patient vignettes in *Appendix A*. We propose that NICE provisionally approve the medication for treatment of people with genetically confirmed FCS for a defined period during which these data are captured in a real world setting as part of a managed access programme. *Our experience with the EAMS scheme so far suggests that the 2-weekly dosing is effective at reducing the risk of pancreatitis and improving quality of life and propose that this is the dosing schedule used in the managed access programme.* We are optimistic that with this additional data NICE and Akcea will be able to work together to agree an NHS price for the drug which will enable its use for people with genetically confirmed FCS living with such a high burden of illness and lifestyle management.	
[redacted] Patient Expert	I agree with the response to the committee submitted by LPLD Alliance regarding the draft guidance on volanesorsen for treating familial chylomicronaemia syndrome (ID 1326). I would like to make these additional comments relating to the impact of FCS on carers, based on my personal experience. My life has been completely shaped by having FCS. Throughout my life it has caused me to experience a great deal of physical pain, fear of pain, stress, loneliness and depression and hugely restricted the choices I have been able to make. My husband and three children are also very affected by my having FCS. When the children were little, I was at home cooking for them and was often cooking something I was unable to taste. They have told me my efforts were often unsuccessful. As I didn't know how to cook 'fatty' food, or know what it tasted like, I was very limited in what I prepared for them. As they grew older, rather than have me eat differently all the time or making two separate meals, we ate the same thing. This has always meant that the range of food we have at home is extremely limited.	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the ERG. Taking into account all information and evidence

Nominating organisation	Comment	Response
	Having FCS has made me very unconfident and uncomfortable in the kitchen, so my husband has always cooked the evening meals. He works hard to think of ways of preparing the limited range of food I can eat which tastes good and offers variety. Eating out is difficult and can create a lot of stress and anxiety for me which can impact my family. We rarely eat out with friends or go to a restaurant. If we go to a restaurant it invariably means a Japanese restaurant serving sushi so that I can eat at least some of the sushi toppings without having to make special arrangements with all the uncertainty and stress that this creates. This again restricts the family's choice of foods and experiences. Not eating out has the biggest impact on my husband who rarely gets to eat food with the family that he hasn't had to make himself. Our holidays have always been self-catered and nearly all within driving distance. Travelling distances without a car is difficult with FCS as airports and aeroplanes do not offer any suitable food, and travel delays can be very difficult to manage. The same is true when travelling by train. We also need to go to somewhere where there is an accessible good-sized supermarket so that we know we will be able to buy suitable food for me. As a family we have been far less sociable and adventurous than we would have been were our lives not dominated by what and where I can eat. The impact of FCS has affected my earning potential over the years and has had a big impact on our family finances and on our future financial security. FCS has a big impact on me emotionally. When my triglyceride levels began to rise after developing diabetes and going through the menopause, I had frequent episodes of abdominal pain and lived in constant fear that this would get worse and I would have pancreatitis. This made me extremely stressed around food and eating. I felt very hopeless and depressed and scared of what the future would bring. This had a big impact on my husband and children. I was not easy to	the committee concluded that clinical trial evidence showed short-term benefits with volanesorsen, including a reduction in triglyceride (a type of fat found in the blood) levels. It was uncertain whether this is maintained in the longer term, particularly at the licensed dose which was not used in clinical trials. The committee also considered other uncertainties, especially around volanesorsen's effect on acute pancreatitis and the utility values used in the economic model. It agreed that despite the uncertainties volanesorsen is likely to provide important clinical and psychological benefits for people with

Nominating organisation	Comment	Response
	be around. Since taking volanesorsen my triglycerides are much reduced, and I have not experienced any abdominal pain. I have lost my fear of a possible pancreatitis attack. The absence of pain and of this fear feels amazing. I am more relaxed than I think I have ever been and have far more energy and feel far more alert. This is having a very positive impact on my husband and children and on our family life. These benefits are hard to capture and measure, but they have made a huge difference to my life and to the lives of my close family. I am far more emotionally available to them and able to participate more fully in family life. We are more sociable as a family and I am better able to plan ahead and work out ways for me to access things for us all to enjoy together. The future now looks far less scary and I think it will mean that I will be able to continue to work and be far less of a burden as I get older. I am very scared by the prospect of volanesorsen not being available to me in the future and the impact that will have on me and my family. It has made a massive difference to my life and has hugely improved the lives of my children and my husband. We are desperate for these improvements to continue and hope the committee can reconsider their initial decision and recommend volanesorsen for patients with FCS.	familial chylomicronaemia syndrome and value for money within the context of a highly specialised service. It is therefore recommended for use in the NHS.
Dr Karishma Patel Patient Expert	I agree with the response from LPLD Alliance to the committee regarding the draft guidance on Volanesorsen for treating familial chylomicronaemia syndrome, but I would like to make these additional comments as a patient expert based on my personal experience. I understand the committee have concerns with the efficacy of Volanesorsen over the long term. I have been taking Volanesorsen for over four years now and it has been nothing short of a lifeline for me and my family. I have had no attacks of abdominal pain or pancreatitis since taking this medication, when previously I was being admitted to hospital every two months. This was incredibly destabilising and distressing for not only myself but my family and friends. There was also disruptive to my work and a hindrance to my developing career as a Doctor. Without this treatment, I fear that I would not be employable due to ill-health and this would have financial ramifications for not only myself, but my fiancé and my parents.	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the ERG.

Nominating organisation	Comment	Response
	I am the happiest I have ever been with regards to my personal life. Before this drug, I was contemplating moving back to live with my parents so they could help support me with my health and FCS diet. Now I don't have to burden them with my ill-health and they can enjoy their retirement stress free. Perhaps more importantly though, it strikes me as no coincidence that after taking the drug for less than a year I found myself a long-term partner and this year we are planning our wedding. Being able to go to university or work, move out of the childhood/ family home and get married are, for most people, expected life events. For me however, these were almost never events. Volanesorsen has not only been a “pancreatitis stopper” but it has enabled me to have opportunities which would not otherwise be possible. I am GP now and I am desperate to have a treatment which enables me to stay well and live life rather than focusing on the burden on FCS. Though the exact link between triglyceride levels and acute pancreatitis are not well understood, I do not believe this to be a good enough reason to withhold the treatment. There are many conditions where the pathology is not fully understood but the benefit of the treatment has been demonstrated.	Taking into account all information and evidence the committee concluded that clinical trial evidence showed short-term benefits with volanesorsen, including a reduction in triglyceride (a type of fat found in the blood) levels. It was uncertain whether this is maintained in the longer term, particularly at the licensed dose which was not used in clinical trials. The committee also considered other uncertainties, especially around volanesorsen’s effect on acute pancreatitis and the utility values used in the economic model. It agreed that despite the uncertainties volanesorsen is likely to provide important clinical

Nominating organisation	Comment	Response
		and psychological benefits for people with familial chylomicronaemia syndrome and value for money within the context of a highly specialised service. It is therefore recommended for use in the NHS.
LPLD Alliance	The board of LPLD Alliance is disappointed that following the recent Highly Specialised Technologies evaluation NICE does not recommend re-imbursement of the treatment volanesorsen in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate. (ID 1326) Our comments in response to the Evaluation Consultation Document (ECD) are as follows: Has all the evidence been taken into account? the ECD raises questions about longer-term benefits of volanesorsen while acknowledging that trial evidence shows some short-term benefits. We think that in the absence of long term usage of the therapy and the uncertainty of the clinical evidence, the lived experience of people who have been on the therapy since the clinical trial, and the testimony of treating clinicians has not been fully acknowledged. "I have been taking Volanesorsen for over four years and in that time I have not had one single hospital admission or day off work related to FCS. Before, I was in hospital every two months, anywhere from a few days to a couple of weeks. It feels incredible to being living my life now with such stability." Patients report the absence of abdominal pain and pancreatitis, an increased ability to work to socialise and to maintain relationships, all of which have had a positive effect on their mental health. These benefits have a direct impact on those close to them as acknowledged by the committee in the ECD (4.1 and 4.2).	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the ERG. Taking into account all information and evidence the committee concluded that clinical trial evidence showed short-term benefits with volanesorsen, including a reduction in triglyceride

Nominating organisation	Comment	Response
	We think the continued discussions between the patient and their treating clinician will enable close monitoring of the impact of the therapy and allow both patient and the clinician to decide if the therapy is continuing to offer value. Diabetes: we think that not enough attention has been given to the impact that continually high triglycerides has on potential long-term damage to the pancreas with its increased risk of pancreatitis, and any complications from pancreatic damage including the onset of diabetes and pancreatic cysts. One patient who sustained very high triglyceride levels for most of their life did not have a pancreatitis attack until after their diagnosis of diabetes, indicating that the high triglycerides caused damage to their pancreas and the subsequent development of diabetes (this patient had experienced frequent bouts of abdominal pain) "However, in 2003 I was diagnosed with Type II diabetes brought about by living most of my life on a low fat, high carbohydrate diet…. Following the type II diagnosis, I have been hospitalised with pancreatitis spending between 6 and 8 days each time." FCS and diabetes are two conditions which work against each other, with each carrying a separate symptom and huge self-management burden. Blood glucose levels turn to triglycerides in the blood, meaning that the diet is further restricted and near impossible to manage as low fat foods are carbohydrates which in turn worsens the diabetes. We think that there has not been enough consideration of the benefits that lowering triglycerides has on minimising potential long-term damage to the patient's pancreas. The relationship between triglyceride levels and risk of acute pancreatitis and the direct effect of volanesorsen on the risk of acute pancreatitis in people with familial chylomicronaemia syndrome: we appreciate the committee's concern about the lack of evidence of the relationship between triglyceride levels and pancreatitis and the direct effect on the risk of volanesorsen on the risk of acute pancreatitis. We think the issue is complicated by the fact that many patients manage pancreatitis at home and so it is very difficult to capture triglyceride level at the beginning of an attack. "I have only admitted myself on two occasions, preferring to manage such attacks at	(a type of fat found in the blood) levels. It was uncertain whether this is maintained in the longer term, particularly at the licensed dose which was not used in clinical trials. The committee also considered other uncertainties, especially around volanesorsen's effect on acute pancreatitis and the utility values used in the economic model. It agreed that despite the uncertainties volanesorsen is likely to provide important clinical and psychological benefits for people with familial chylomicronaemia syndrome and value for money within the context of a highly specialised service. It is therefore

Nominating organisation	Comment	Response
	home, as I have always done over the years. The experience in hospital has been unpleasant, with inappropriate remarks from nursing staff about alcoholism, and inappropriate food served up once I could eat again." 'Now when I go in, it's normally only for a few days because I've slightly controlled it myself at home. I have more medication to control pain relief, it's only when I can't control the vomiting that I have to go into hospital. I do have anti-sickness at home...' Patients also tolerate severe abdominal pain and possibly do not realise they are having an episode of pancreatitis "I've never been diagnosed with pancreatitis. I'd go into my room and fast for five days, drinking only water and taking pain killers. It was only when I met another patient who had been in hospital with pancreatitis who told me they'd been fasted for five days on a drip with morphine that I thought that maybe I'd had pancreatitis." This acceptance of severe pain as part of life can have potentially serious consequences "I had my appendix out at 16. I didn't contact the doctor for over a day because I was so used to having severe stomach aches – even though it felt different." Patients have also reported that pancreatitis attacks can occur without warning "As there is no current home testing kit available for FCS, as with diabetes, you have no idea whether you are about to have pancreatitis or not. That unpredictability, and fear, is very limiting and impacts massively on your social life, and life choices." Other patients report that their pancreatitis attacks seem to occur at lower levels than previously "First triglycerides measured were 43 – didn't have pancreatitis with that. If I go to that level now, I definitely would have pancreatitis." The picture is further complicated by the fact that FCS is caused by a mutation on at least five different genes and there has been very little research (if any) on the impact of each gene on triglyceride levels. We think that this non-reporting and potential non-recognition of pancreatitis attacks and the lack of research, makes it much harder for the link between AP and triglyceride levels to be identified, and therefore the impact of volanesorsen on the risk of AP. The committee have acknowledged that acute pancreatitis is a symptom of FCS and that acute	recommended for use in the NHS.

Nominating organisation	Comment	Response
	pancreatitis is a life-threatening condition for which intensive care may be needed. The ECD also acknowledges that repeated attacks of acute pancreatitis may lead to chronic pancreatitis and diabetes (2.1). Patients taking the therapy have reported the absence of pain and no pancreatitis attacks since taking the drug. We think this evidence is very relevant when it is virtually impossible to gain a true measurement of the triglyceride level at which acute pancreatitis occurs. One patient reported "I'm not tired, not bloated – in a matter of three weeks I felt better, felt healthier, can I say I felt normal? It made a massive difference, a massive improvement on my life. I felt better in myself, felt more outgoing…. No time off work, no problems with anything at all mentally and physically so good. I felt normal, that I could do anything. I slept better…. I picked up extra hours, they noticed a difference in me. I didn't have to take pain relief…. It was a big relief for all my family – they've all noticed a big difference." The quality of life values used in the model: we think that the quality of life values used in the model were not fit for purpose and did not capture the actual experience of patients. The measures used were very general and did not capture the relentless impact of managing the chronic burden of FCS. Also, patients often do not fully recognise the impact of the condition on their lives relative to someone who is 'normal'. Patients with FCS have a different version of 'normal' which encompasses a much lower quality of life when compared to someone who has good health both in terms of their physical experience - their tolerance of pain fatigue and reduced energy levels, and in terms of their levels of stress and anxiety about the daily management of their condition. Patients don't tend to have a vested interest in viewing their lives relative to others as that path leads only to depression and misery. Many take the stoical approach of 'I just get on with it'. All these factors combined mean that the evidence from the quality of life values used in the model were not reflective of the impact of the drug as this patient testimony demonstrates 'I feel 100% well with regard to my physical health since starting the treatment. Prior to this I felt about 20% well as I was being admitted to hospital recurrently for severe abdominal pain/pancreatitis. It has improved my emotional well-being ten-fold! I feel happier about myself and Volanesorsen has allowed me to feel less anxious when around	

Nominating organisation	Comment	Response
	food/making decisions around eating out.' How the effect on the quality of life of carers is accounted for: the ECD acknowledges that the burden of disease falls on both the patient and their families and carers (4.1) and that a new treatment option would offer considerable hope to them and to their families (4.2). We recognise that the daily impact of the condition on the quality of life of carers could have been further explored and would like to take the opportunity to provide more evidence demonstrating this impact. To do this we have returned to our original interviews of 20 patients and eight caregivers and asked for caregivers to contact us again. Six caregivers did so, all of whom live in England and Wales. We think that the following demonstrates that the devastating impact of FCS on the patient has a hugely negative impact on people close to them. We think we have demonstrated that the absence of any therapeutic option to support patients to manage their symptoms exacerbates the negative effects on carers and that volanesorsen can help ease the burden on carers significantly. Impact of FCS on caregivers (we have defined caregivers as anyone who is close to the patient): The impact on carers was best summed by the following quotations from caregivers: "This is a life-time condition. You are aware of this condition all your waking hours and plan your days around avoiding anything that might cause a problem…. It is a constant presence." "I think we could have been a lot happier if we hadn't had this constant worry because it does affect every area of your life…" "I am very much aware of the patient's FCS, for two main reasons: 1) I am the primary provider of food for the patient, so have to be aware of the dietary limitations at all times. 2) The patient's attention is very much focused on the condition much of the time, so it is a frequent topic of conversation. The limitations imposed by the condition also affect many of our choices in family and social life generally." "We can't just eat at wherever we like, order takeaway because we're just tired, go on holidays without seriously planning how, if at all, in a particular country of choice, my wife	

Nominating organisation	Comment	Response
	would be able to manage her diet." One adult patient reported the impact on her parents "Particularly for my parents, the diagnosis and living with the challenge of FCS has been worrying and draining for them." One adult child reported the impact of her mother's FCS "We try not to let FCS define Mum or us, but it becomes impossible because it is a part of everything she does or can't do. It has caused a lot of anxieties over the year, not just to her, but to everyone around her because of the impact that it causes." Taking responsibility for the patient's health and well-being Many partners/spouses have taken responsibility for the well-being of the patient. While this can be very positive, it can also add an extra, sometimes negative dimension to the relationship. This ambivalence is expressed in the following quotation: "She's always asking me what I had to eat other than the food she provides. I do sometime get angry because I feel it's almost like I'm not allowed to eat anything without her permission but she's only doing it to keep me as healthy as possible" While the positive impact of this concern is expressed here: "Now he's quite strict with me about what I can and can't have. He's now my eyes at the back watching me. He'll say. 'no, we can't do that, or we can but we'll have to do this first'. He'll ring the place we're eating and bring a plate for me." Sharing the restrictions Many of the patients' spouses had taken on the restrictions of the diet in order to make the patient feel less isolated in their eating, and to make catering at home easier. The effect on one carer is as follows "I generally eat the same as her. It does mean that when I escape the regime, I tend to overdose on the fatty foods she avoids. This can have an adverse effect. I am pretty sure a binge on all-day breakfasts triggered an attack of gall stones." Many carers also acknowledged that there was some benefit to them in being exposed to the FCS	

Nominating organisation	Comment	Response
	diet. One 16-year old says "I eat far healthier than all of my friends – I can't believe how much fat they use when cooking! And as an athlete, it's been really easy to adjust my diet to support my training." Impact on social life All patients and carers reported an extremely reduced or divided social life "It tends to mean largely sticking to a core group of those who are able to understand and accommodate the differences imposed." "The condition forces the patient to focus very often on their own needs, in order to ensure their survival and good health in situations where others would simply be at ease and eating as they please. This can have a negative impact on those who are close to the patient." "Not eating 'normally' creates problems with my partner. I avoid social activities and he's very social." Eating out is very problematic. "We rarely eat out. We have to keep control of every aspect of my wife's diet. Generally, we socialise with friends but only dine with them if my wife prepares the meal." If patients and caregivers do eat out, carers often take the lead. "When we go out to eat, he shoulders a lot for me. I still get quite emotional when a salad arrives, and it's got dressing on it and I don't want to deal with it. He does it for me." "He makes sure restaurants are fully informed about what I can and can't eat if we go out." Uncertainty Uncertainty surrounding the impact of FCS on the patient has a huge effect on the carer	

Nominating organisation	Comment	Response
	"The 'not knowing' when the pain will start, if I will be attending functions alone, if my partner can plan anything, if I support my partner or leave her alone as most of the time she deals with this alone…" Carers talk about feeling helpless in the face of the burden of FCS: "I can't help or change anything. Numerous times she has told me to find someone else that's less of a problem." Financial impact Carers share the financial impact that FCS places on the patient. Our previous submission discussed the impact of FCS on patients' ability to work, on the jobs they can manage, on whether they attempt promotion. Income (or lack of it) generated by a patient will have an impact on the overall finances of those close to them. One carer says "I might have been bolder in my choices and if my partner had been more able to earn, I might have been able to retire earlier if it had not been for the condition." Others talk about the impact on budget that the condition imposes "Financially there's things we cannot do and because this upsets my partner it upsets me." "Cost of food shopping is higher as we have to buy low fat products which are not usually the cheapest on the market." One parent says of her adult child that due to her FCS "I have always helped her financially." Being away from home/taking holidays Patients and their carers talk about the near impossibility of being away from home without being able to self-cater. "It also affected our holiday choices as we always went self-catering, this also meant making and taking packed lunches on trips.	

Nominating organisation	Comment	Response
	The future The future is viewed with trepidation by carers in the context of the lack of awareness and knowledge of FCS: "I really worry about the future as my wife's health has got worse as she's got older despite all we do to manage her diet." "The great concern is as we age, if my wife's mental capacity diminishes, how do you educate carers if I'm not there or incapacitated." An adult child of a patient said "If we need a care home for mum in the future, we'd have to work hard to ensure they were able to feed her properly." The impact of volanesorsen on caregivers We previously described the very positive impact on the lives of patients in terms of their experience of the absence or reduction of abdominal pain and pancreatitis, on the fear and anxiety that imminent attacks of both my bring, and therefore on their ability to engage more fully and consistently in all areas of their lives. Patients have reported being able to work, to work more hours and to go for promotion all of which generate higher levels of income. These benefits to the patient have a very positive impact on caregivers and on the patients' families. Greater levels of income can bring its own reduction of stress and anxiety which can improve relationships, but for patients with FCS also allows the patient greater flexibility with their food shopping – more able to afford the very low-fat protein options and products which are always	

Nominating organisation	Comment	Response
	more expensive and which add much needed variety. With the patient's greater flexibility, more 'headspace' to be creative about the management of the condition, their ability to be consistent and able to plan all create a benefit for their caregivers. The lessening of the dominance of the impact of FCS on the patients' life and the subsequent improvement in their mental health can allow relationships to be more enjoyable for the caregivers and lessen the stress and anxiety they feel about the health of the patient. A key impact on caregivers of patients taking volanesorsen was on feelings for the future "Now she's using the drug we have a lot more fun together and she's far more ready to make plans to see people and go out and about. I'm also not worrying so much about the future and how the FCS will affect us as we get older." Are the summaries of the criteria considered by the committee, and the evidence and economic considerations reasonable interpretations of the evidence? We feel that the report from the committee was balanced and even, but our concern is that of a patient community of any ultra-rare condition for which there has been very little attention paid from researchers and clinicians. FCS has an added complication as it is caused by a mutation on at least five different genes and there is little understanding of the impact of each gene and so it becomes harder to make decisions purely on the evidence available. We hope that the committee will give due weight to the patient testimonies and the evidence of clinicians when reconsidering their decision. Are the provisional recommendations sound and a suitable basis for guidance on the use of volanesorsen in the context of national commissioning by NHS England? No. We think that volanesorsen should be recommended in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate. Without this technology, patients would be left with little hope of alleviating the symptom burden that the condition imposes which impacts negatively not only on the patient but on all those close	

Nominating organisation	Comment	Response
	to them. Patients will be left to cope with their lives in fear of, or with unpredictable pain and pancreatitis, with the resulting disruption each episode of pain and pancreatitis causes including hospital admissions and time off work and high levels of fatigue which inevitably impacts on those close to them. Patients report feeling far more relaxed since taking volanesorsen "I have not changed my eating habits at all, but my fear and stress around eating has largely disappeared and I am generally far more relaxed than I ever have been in my life. Consequently, I am more able to participate in social events, am more able to work, and have the ability to keep in touch with and see my friends." These benefits can be seen by those close to the patient "My wife is now a little more clear-headed and relaxed, particularly when she has the results of blood tests that show triglyceride levels being well controlled. Her energy levels are improved" Patients' life choices, whether the ability to work, their choice of job and their participation in social occasions would remain severely limited all of which, again, have a negative impact on caregivers. They would continue to be isolated, stressed and at high risk of depression – again, negatively impacting on those close to them. Paramount for patients and their caregivers is preventing abdominal and pancreatic pain and long-term damage to the pancreas, thereby avoiding unnecessary surgical procedures and other complications like diabetes which impacts not only the patient but on all those close to them. This therapy offers the only option able to do this and so offers the possibility for a healthier and potentially longer life for the patient and a huge reduction of the fear and anxiety about the future for both the patient and caregivers. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We don't believe this to be the case and agree with the committee's summaries in points 4.28 and 4.29. Conclusion	

Nominating organisation	Comment	Response
	This therapy has the potential to profoundly change the lives of many patients, enabling them to live without pain and pancreatitis and the overwhelming and dominating fear of both which creates such anxiety and stress in their lives and in the lives of all those around them. We urge the committee to reconsider their decision and recommend the use of volanesorsen in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate.	

Comments received from commentators

Commentator	Comment	Response
NHS England	NHS England's Highly Specialised Services has reviewed the evaluation consultation document for the above mentioned consultation. NHS England's Highly Specialised Services considers the Highly Specialised Technology Programme to have made a fair assessment of the clinical and cost effectiveness evidence provided. In response to the Evaluation Committee's specific questions NHS England's Highly Specialised Services has made the following assessments: 1. Has all of the relevant evidence been taken into account? Yes 2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence? Yes 3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England: Yes, they provide a sound basis for guidance	Thank you for your comment. The evaluation committee considered evidence submitted by the company, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the ERG. It agreed that volanesorsen is likely to provide important clinical and psychological benefits for people with familial chylomicronaemia syndrome and value for money within the context of a highly specialised service. It is therefore recommended for use in the NHS.

Comments received from members of the public

Role*	Section	Comment	Response
NA	NA	NA	NA

Summary of comments received from members of the public

Theme	Response
NA	NA

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Feb 2020

Dear Helen,

Re: Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Akcea would like to thank NICE for the opportunity to respond to the Evaluation Consultation Document for volanesorsen in the treatment of familial chylomicronaemia syndrome (FCS).

We believe volanesorsen is a transformational treatment in the management of FCS, an ultra-rare, genetic, chronic, burdensome disease for which there is no effective treatment available in routine NHS care. Akcea is keen to align with NICE and NHSE on the value this product offers FCS patients and the NHS, in a timely manner. This will ensure the benefit of this treatment is expanded from the currently treated 20 Early Access to Medicines Scheme (EAMS) patients to all those with FCS in England and Wales for whom the treatment is considered appropriate.

The data submitted in the HST dossier and in this ECD response provide robust evidence of the effectiveness of volanesorsen in reducing serum triglyceride (TG) levels at once every week (Q1W) and once every-two-week (Q2W) dosing. This TG reduction is sustained, clinically meaningful and statistically significant. It is associated with improvement in day-to-day health related quality of life (HRQoL) for patients and their families, the prevention of acute pancreatitis events and a reduction in the long-term sequalae of FCS including chronic pancreatitis and diabetes.

In line with the ECD and a clarification call with NICE, we focus in our response on the elements of the submission identified as being the most important and that have most impact on the ICER estimate:

1) Patient health related quality of life
2) Family and carer health related quality of life
3) Long-term efficacy of volanesorsen with the final label dosing regimen

In the following document we also comment on a number of other points raised in the ECD.

Patient health related quality of life

The FCS vignette study that underpins the patient QoL estimates in the economic analysis was conducted to a high standard using appropriate methodologies. In line with the request in section 4.33 of the ECD we provide more detail on the study methodology. Should any queries remain unaddressed, please don't hesitate to contact us.

We acknowledge that the implementation of the vignette's utility values in the company base case could have been better explained. It was not Akcea's intention to suggest, for example, a utility value of 0.77 compared with 0.53 in the Historical AP health states solely on the basis of being on versus off treatment. Instead, this was a simple implementation 'short-cut' in the model to reflect the utility benefit of a cohort of FCS patients with a mean serum TG level of 12.1mmol/L (with volanesorsen) compared with a mean serum level of 26.2 mmol/L (with standard of care, SoC). In

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

this response we propose an alternative implementation of the vignette values that assigns the high TG utility value to the >22.6mmol/L health state and the low TG utility value to the health states <10mmol/L and 10-22.6mmol/L. This results in [redacted] discounted incremental QALYs compared with the committee's preferred base case of [redacted] resultant estimated ICER of £252,847.

We believe this appropriately values the benefit that volanesorsen can bring to this highly burdensome, genetic disease, that is invisible to others.

Family and carer health related quality of life

The company recognises the committee's concern regarding the family and carer HRQoL estimate and proposes a revised utility gain for family members of patients on volanesorsen of 0.04. We reference the new DSU document (NICE DSU, 2019), specifically the publications by Wittenberg and Prosser, 2013 and Wittenberg et al., 2013 and the 'spillover effect', i.e. the impact on the family of having a family member with FCS. Spillover is particularly relevant for families of FCS patients in which each shared meal is a reminder of the disease, the need for constant vigilance and the fear of pancreatitis.

The utility value we propose is lower than the initial base case and higher than the -0.03 disutility quoted in the TSD for adults with musculoskeletal diseases (Wittenberg et al., 2013) that are non-rare, non-genetic diseases and that do have alternative treatment choices available. We believe this reflects the HRQoL burden for families taking into account the rarity of the disease; the stress due to no treatment options being available for a loved one; social isolation for the family that results from the patient's diet. This revised family and carer utility produces an ICER estimate of £314,412 and is a much better reflection of the day- to-day, meal-to-meal worry and stress for a family of an FCS patient.

Uncertainty in the economic evaluation

Akcea acknowledges that there are uncertainties in the economic evaluation for volanesorsen, however, it is important to note that not all the uncertainty results in a higher ICER estimate. Due to a lack of robust data or a risk of double counting a number of very relevant aspects of the disease are not included in the economic model. This includes steroid [redacted] and opioid use [redacted], joint pain, neuropathy, eating disorders and malnutrition. If the committee considers these as relevant to FCS, then the ICER is reduced.

FCS service pathway

In addition to the NICE submission, Akcea has been working with therapy area experts in the development of an FCS Best Practice Implementation Guide that we hope will be of value to NHS England. The aim of the Guide is to identify the crucial disciplines required within the NHS to provide an optimal FCS service. A key specialty identified is highly specialised dietetic support. Any FCS patient (including those on volanesorsen) needs to adhere to a very low-fat diet. Without appropriate dietician support this diet can lead to malnutrition and/or deficiencies in fat soluble vitamins, amino acids and minerals. With the correct dietetic support risk of malnutrition can be mitigated as can the risk of patients developing diabetes. Akcea's intent is to support the NHS in England and Wales to support FCS patients through provision of care that best meets their

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

complex needs. We provide a copy of the draft guide as an appendix to this document, which has also been shared with NHS England prior to a surgery with NHS England to discuss its implementation.

Budget Impact

Finally, having spent two years understanding the FCS patient population in the UK, Akcea estimates that there are around [redacted] patients likely to be treated with volanesorsen in England over five years. This results in a relatively low, predictable and stable budget for NHS England to manage. We respectfully request this is part of NICE Committee consideration in this very rare disease with no current treatment options.

Akcea thanks NICE for the opportunity to respond to the ECD. We kindly ask the committee to reconsider its decision, not to recommend volanesorsen. We suggest that a number of modelling assumptions in the ECD do not fully represent the value of volanesorsen to FCS patients, their family or the NHS. Akcea would suggest that taking into account revised patient and carer HRQoL estimates, amending the discontinuation rule in line with the clinician feedback in the ERG report and adjusting the risk rate for acute pancreatitis, the most plausible ICER estimate is £210,487. Importantly, this comes with an undiscounted QALY gain of [redacted] which would mean that this product is eligible for consideration under the ultra-orphan modifiers and a true ICER estimate of [redacted] (weighted by [redacted]). In this ultra-rare disease with a very significant health burden and no effective treatment options, a treatment with a stable, predictable and relatively low budget impact on the NHS in England provides good value for money.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Table of Contents

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Response to the Evaluation Consultation Document on

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Akcea has ordered its response to the Evaluation Consultation Document (ECD) in line with what we understand to be the most critical elements for the NICE committee in its decision making. Therefore, we address first the economic assumptions that are the biggest drivers of the ICER estimate and follow this with comments on clinical efficacy. The four parameters that have the largest impact on the ICER estimate in the economic model:

- Patient QoL
- Family/carer QoL
- Discontinuation rates and
- AP event rates

are addressed first. We then consider the clinical issues of efficacy in the longer-term at the licenced dose in relation to TG and AP event rates.

FCS patient quality of life

The vignette study accurately describes the burden of FCS using a sound methodology that values health states using appropriate general population methods. Revising the implementation of the low and high TG vignette values in the economic model so that they align with the health states leads to a discounted QALY gain of [redacted] and an ICER of £252,847

The vignette study

The vignette project is a carefully designed study following commonly used methodology to estimate the impact on quality of life of FCS. Utility values were elicited for FCS health states varying by TG level (high or low) and prior AP experience. We hope we have addressed the request from ECD section 4.33 with the information provided below. If any additional information or clarification is needed, please let us know so that we can provide it.

This response is provided in two parts. Part 1 provides summary information about the vignette study methodology, with the full draft manuscript (currently under submission to a peer-reviewed journal) provided in Appendix 1. Part 2 addresses the use of the vignette data in the economic model.

The vignette study was led by Louis Matza. Dr. Matza has authored more than 80 peer-reviewed health outcomes studies including over 25 vignette-based utility valuation studies

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

published in journals such as *Value in Health*, *Quality of Life Research*, *European Journal of Health Economics*, and *Medical Decision Making*. This FCS study was conducted in line with previously published vignette-based studies.

NICE's preference is that utilities are derived from the EQ-5D completed by patients. However, in the current situation, the EQ-5D does not appear to be appropriate for this purpose. First, to derive utilities from patients, a sufficiently large sample is needed within health states that are include in the economic model. For rare diseases like FCS, it is challenging to recruit a large enough sample of patients living in each of the relevant health states. In addition, it can be difficult to gather a sample of patients with rare conditions like FCS to validate generic instruments for use in the target population (Benjamin et al., 2017; Slade et al., 2018).

Second, although the EQ-5D was administered in the APPROACH study, the instrument does not appear to be sensitive to variation in quality life in patients with FCS. The EQ-5D results from APPROACH were not plausible due to a likely ceiling effect of the baseline values. The ECD acknowledges that the EQ-5D baseline values were not in line with the patient testimonies. The ceiling effect may be due to the fact that the EQ-5D does not assess the quality of life impact of key aspects of FCS, such as cognitive symptoms and impact of the extremely restrictive diet (ECD section 4.14). Due to the lack of clinical validity of the EQ-5D data, the vignette study was initiated.

Vignette-based methods can be used to estimate utilities for rare diseases when it is not feasible to collect preference-based data from a large enough sample of patients. In vignette-based utility studies, health state descriptions (often called vignettes or health states) can be drafted based on the best available information to ensure that the health states accurately represent the typical patient experience. In this case, the health states were based on published literature, interviews with patients with FCS, and interviews with clinicians who treat patients with FCS. Then, utilities for each health state were elicited in a valuation study with general population respondents, using preference-based methods similar to those used to derive the original EQ-5D tariffs (e.g., time trade-off interviews with a 10-year time horizon).

Part 1: The vignette study methodology

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

[redacted]

[redacted]

Summary results are reported in Table 1 below.

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

The full draft manuscript of the study and a table responding to specific points in the ERG report that comments on the vignette study are provided in Appendix 1 and Appendix 2, respectively.

Part 2: Implementation of the vignette values in the economic model

The mean TG value predicted by the generalized linear mixed modelling (GLMM) (following implementation of the stopping rule) in the economic model was 12.1 vs 26.2 mmol/L, volanesorsen Q2W vs SoC respectively. The probability of an FCS patient having a TG reading within a particular category after application of the stopping rule is reported in Table 2.

Table 2: Probability of having a TG reading in a particular category in the economic model

Health State	Volanesorsen Q2W	SoC
>22.6mmol/L	7.7%	61%
>10-<22.6mmol/L	50.4%	29%
<10 mmol/L	41.9%	10%
Mean	**12.1**	**26.2**

This distribution represents 'time in state' as opposed to proportion of cohort in state due to the transience of serum TG levels. Based on the predictions from the GLMM, the 12.1 mmol/L (volanesorsen Q2W) and 26.2 mmol/L (SoC) represent a 'rolling average' of TG readings, with 61% of SoC TG readings substantially above 26 mmol/L and 42% of TG readings on volanesorsen Q2W below 10 mmol/L.

In the economic base case, Akcea wanted to reflect the difference these TGs have on day-to-day HRQoL experienced by the two patient cohorts: those on treatment with a mean serum TG level of 12.1 mmol/L compared with those on SoC with a mean serum TG level of 26.2 mmol/L.

Given the very high TG levels associated with FCS, Akcea took the view that 12.1 mmol/L represents a 'low TG' for FCS patients while a mean serum TG of 26.2 mmol/L represents a 'high TG', for patients on treatment after the 3-month stopping rule. As a simple 'work around' in the model this was implemented as *on* versus *off* treatment. It is important to make clear that Akcea does not contend that being on volanesorsen itself results in a utility value of 0.77 compared with 0.53 for patients in the Historical AP health state. Instead, that the mean serum TG level for the volanesorsen cohort is a low TG value for an FCS population. As such, the utility value of 0.77 was applied.

There is a small body of literature categorising TG thresholds, i.e. the thresholds at which clinical events are more or less likely to happen. Differences in the standard units for reporting serum TG in Europe compared with North America demonstrate that these thresholds are indicative rather than absolute. Europe tends to categorise <10 mmol/L, while the equivalent

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

threshold in North America is <1000 mg/dL. One thousand milligrammes per decilitre converts to 11.3 mmol/L which, again, supports the argument that 12.1 mmol/L can very plausibly be considered a low serum TG level for FCS patients. We acknowledge that we could have explained the rationale for implementing the vignettes in the model better than we did. We apologise for this lack of clarity. We hope that the above provides a better explanation as to what was done and why.

A clearer way of applying the vignette utilities in the model would be to allocate the high TG vignette utilities to the >22.6 mmol/L TG health states and the low TG utilities to both <22.6 mmol/L health states. This approach also aligns with a study in patients with Type V hyperlipoproteinemia, in which a decrease in the number and severity of pain episodes (HTG abdominal crisis) and frequency of attacks of pancreatitis correlated well with TG levels of ≤2,000 mg/dL (22.6 mmol/L) (Scherer et al., 2014). Applying the vignette utilities in this way reduces the committee's preferred base case ICER to £252,847.

Impact on health-related quality of life for family members of FCS patients.

A revised family/carer utility gain of 0.04 is proposed that results in an ICER of £314,412. This recognises two elements: one, that volanesorsen is indicated for an adult population and two, that there is an impact on the family as a whole of having a family member with FCS. This value for the utility gain lies between 0.05 (metreleptin including paediatric patients) and 0.03 (adult musculoskeletal patients in non-rare, non-genetic diseases with pre-existing treatment options, Wittenberg et al., 2013). A family utility gain of 0.04 results in an ICER of £314,412 and an incremental QALY gain of [redacted] based on the Committee's preferred base case.

Akcea reviewed the Decision Support Unit's (DSU) report on modelling carer health-related quality of life (HRQoL) as suggested in section 4.33. None of the sources were exactly applicable to this evaluation. However, informed by the information contained therein we suggest an alternative family and carer HRQoL utility value due to FCS of 0.04. We recognise limitations in the application of the metreleptin utility value in this assessment, however we think this remains a relevant reference disease due to the similarity of lipodystrophy and FCS.

The metabolic abnormalities associated with lipodystrophy share striking similarities with FCS, including: insulin resistance with resultant hyperinsulinemia and diabetes; hepatic steatosis or steatohepatitis; and dyslipidaemia with severe hypertriglyceridaemia. Patients also have to follow a strict low-fat diet and may receive lipid-lowering drugs (for example, fibrates and statins) and antidiabetic therapy (for example, metformin, insulin, sulphonylureas, and thiazolidinediones) (NICE, 2019). Akcea located a copy of the, now withdrawn, NICE metreleptin Final Evaluation Document (FED). Metreleptin was eventually awarded a relative utility decrement of 0.05 between treated and untreated groups (NICE, 2019).

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Volanesorsen is indicated for an adult population, while the metreleptin population includes children (section 4.23). Akcea agrees that the mean ages of the different cohorts impact total family/carer HRQoL. As such, we are proposing a lower evidence-informed utility value.

Referencing the DSU document, the Wittenberg and Prosser, 2013 and Wittenberg et al., 2013 papers highlight the 'spillover' effect, and conclude this is not restricted to the family/carers of paediatric patients but can include the immediate family members and spouses of adult patients. Documented spillover effects are varied and often condition- specific, ranging from specific symptomology (e.g., anxiety, sleep disturbance), to psychological well-being and physical health. These effects have been measured in the context of a variety of specific health conditions and family or caregiving relationships, such as spouses, parents, children and siblings of cancer patients, and family members and caregivers of individuals with mental illness (e.g., bipolar disorder, schizophrenia, and dementia) (Wittenberg et al., 2013).

This spillover effect is clearly relevant to FCS, as described in the ECD section 4.1: "This can be depressing for (patients), and worrisome for their families and carers. Unpredictable hospitalisations can cause disruptions to both a patient's and carer's work. Also, the children of people with FCS often have to be carers for their parents and siblings. The committee also heard that people with FCS are often unable to participate in usual family activities because of the strict dietary restrictions they must stick to. This can have a substantial emotional effect on them and their families."

The daily FCS symptom burden, including abdominal pain, fatigue, anxiety and depression, the constant vigilance at every meal and the impact on social life has a spillover effect on family members and partners. This was reported in a survey conducted by Gelrud et al. (2017) in which it was stated that "Caregivers reported that their social life was limited by symptoms of FCS, particularly fatigue," and "Caregivers reported using their own vacation time to care for patients during complications of FCS. Caregivers also expressed anxiety about seeing their loved ones going to work while sick to avoid missing a day of work."

The impact on families of different conditions is presented in Wittenberg and Prosser et. al., 2013 study:

- existing mental or musculoskeletal conditions, -0.01 (95 % CI -0.02, -0.00);
- new mental conditions, -0.02 (95 % CI -0.04, -0.00);
- new musculoskeletal conditions, -0.03 (95 % CI -0.05, -0.01)

The above disutilities relate to conditions that are not ultra-rare, familial *and* that have existing effective treatments. The carers and family members of FCS patients have lived their entire lives believing that that there is no effective treatment for FCS. The psychological impact of knowing that there is at last an effective treatment, is likely to have an additional QALY benefit beyond simply reducing the disutilities obtained by Wittenberg et al. in non-familial, non-ultra-rare conditions.

The relief experienced by the family members of FCS was articulated by the FCS patient representatives and was also captured in the survey by Gelrud et al. (2017):

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

"Both patients with FCS and caregivers were asked what any future therapy developed for FCS would do for them. Patients expressed the hope that a future therapy would reduce their pain and symptoms, improve their quality of life, and help them stay out of the hospital. Several patients also expressed a wish for a less stressful, more normal lifestyle that includes socialization and a more normal diet. Five of the patients hoped that any future therapy would improve their TG values and treat the underlying disease, not just the symptoms. **When caregivers were asked what they hoped a future therapy could do for their loved ones, their replies echoed those of the patients**."

Akcea believes that a fair valuation of QALY gain for carers lies at 0.04, the mid-point between the 0.05 value awarded for metreleptin and 0.03 for a family member of an adult with newly diagnosed musculoskeletal disorder from (Wittenberg et al., 2013). Application of a carer utility of 0.04 in the model reduces the committee base case ICER from £355,235 to £314,412.

Treatment continuation rates on volanesorsen: 80% plateau in routine UK clinical practice

The ECD discontinuation rate is not reflective of clinician feedback in the ERG report. Using the committee's preferred lognormal curve and capping discontinuation at 20%, in line with clinician feedback, over the model lifetime reduces the ICER from £355,235 to £341,606

The ERG report indicates that the clinical advisors consulted about treatment discontinuation felt that no more than 20% of the patient population would discontinue. This is not reflected in the ERG's base case model. Clinical advisors to the ERG were of the opinion that there would be discontinuations in clinical practice, with estimates up to 10% per annum and 20% in total. The main reasons for these were thought to be the burden of monitoring and adverse events including injection site reactions and thrombocytopaenia (ERG report page 44, section 4.2.4.2).

The ERG reflected the 10% annual value as an exponential distribution in their base case but did not capture the likelihood that this would plateau at 20%. Akcea agrees with the clinical advisors that 1) some discontinuation is likely, and 2) that discontinuation is unlikely to exceed 20% in total. This is for two reasons. Firstly, in the UK only patients with the greatest potential to benefit from treatment are likely to be prescribed treatment; these are likely to be patients with the most significant symptom burden. These patients are also likely to be more adherent to treatment over the longer term. Secondly, Akcea's patient support programme is likely to lead to better retention, as evidenced by the good retention rates in EAMS.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Volanesorsen's impact on acute pancreatitis event rates

The ECD queries assumptions in the economic model relating to the effect of volanesorsen around 1) the relationship between TG reduction and AP *in FCS patients* and 2) the direct effect of volanesorsen on the risk of AP.

In order to address these concerns, we describe below:

1) The relationship between TG and AP in FCS patients based on the literature and clinical trial data
2) The impact of volanesorsen on TG and AP
3) Implementation of TG mediated AP effect in the economic model
4) The implementation of direct impact of volanesorsen on AP in the economic model

The relationship between TG and AP in FCS patients

Patients with FCS are at higher risk of AP compared to those with other high HTG disorders for the following three reasons: FCS patients have chronically higher mean serum TG levels, there is greater volatility in their TG levels (higher 'peaks' experienced more frequently) and they have higher rates of prior APs. Together these increase the risk of AP in FCS patients compared with HTG patients.

The incidence of AP in FCS is higher than in other hypertriglyceridemia (HTG) disorders. In a study by Gaudet et al. (2016a), there were 67 AP hospitalisations in 251 FCS patients vs. only 14 AP hospitalisations in 1,981 patients with multifactorial chylomicronaemia. One reason for this is that the TG levels experienced by FCS patients are much higher than in other causes of HTG (up to 70 mmol/L in some patients) (Scherer et al., 2014). Similarly, only 15% of the HTG patients with readings above 10 mmol/L in the CALIBER study had serum TG levels above 22.6 mmol/L (Akcea data on file, 2018), whereas TG levels above 22.6 mmol were observed in over 50% of the TG readings in the APPROACH trial placebo arm. FCS patients present with consistently and chronically elevated serum TG levels that are higher than in other HTG disorders.

There also appears to be greater TG volatility (peaks and troughs) in patients with FCS compared with other HTG disorders. This pattern of extremely high and highly variable TG is predicted by the GLMM, with SoC TG level of 26 mmol/L, and can be seen in the patient traces below, see Figure 1.

Additionally, one of the known risk factors for an AP event is a prior AP event (Sankaran et al., 2015; Akcea CALIBER study). FCS patients report high rates of AP. Therefore, while the dose-response relationship between TGs and AP is generalisable to FCS patients, it is likely

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

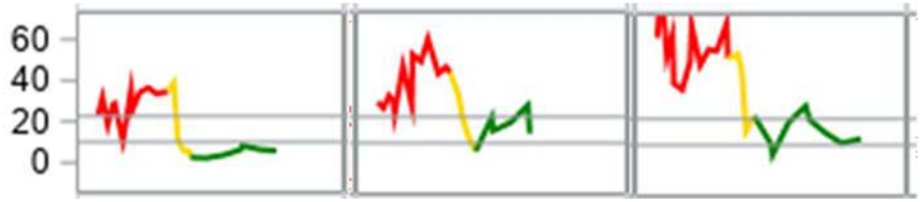
that patients with FCS are at higher risk of AP compared to those with other high HTG disorders for the following three reasons: higher mean serum TG levels than other HTG disorders, greater volatility in TG levels, including higher peak readings and higher rates of prior APs, all predisposing FCS patients to repeat events.

Volanesorsen's impact on AP events

For patients with a history of AP there is a compelling body of evidence for the benefit of volanesorsen. For patients who suffer frequent AP events and live with the constant fear and anxiety of a further attack volanesorsen's reduction of AP events can be life changing.

Volanesorsen appears to confer effect by both reducing mean serum TG level and reducing the 'height of the peaks'. We hypothesise this reduction in 'spiking' (i.e., particularly high TG levels) may explain why a switch to Q2W is associated with a smaller % reduction in TG from baseline without an increase in AP event rate. This impact can be observed in the individual patients traces which are notably subject to fewer and less extreme fluctuations in TG level during the on-treatment period (Figure 1) and in the GLMM, lower variance in the on-treatment model coefficients.

Figure 1: Individual patient plots of TG level by dosing group



Key: Y axis represents TG value in mmol/L. Colour coding: Red: off treatment; Yellow, weekly dosing; Green, Q2W dosing

Data from the clinical trial as relates to AP is also compelling, particularly in patients with a high risk of recurrence (Table 3).

Table 3: Pancreatitis in patients at high risk of recurrent attacks (≥2 adjudicated pancreatic events in the past 5 years)

	Volanesorsen (n = 33)		Placebo (n = 33)	
	Patients	**Events**	**Patients**	**Events**
5-year medical history				
Patients with multiple (2 or more) adjudicated	7	24	4	17

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

events in the past 5 years				
Events during study	0	0	3	4
	P = 0.0242			

The effect of volanesorsen in individual patients prone to recurrent AP has been remarkable. One patient with a five-year medical history of three APs enrolled in the placebo arm of APPROACH and experienced a further four APs over the following year. The patient enrolled into APPROACH OLE on weekly dosing, reduced dose to Q2W within 3 months, and completed approximately 18 months of Q2W dosing before being recruited into EAMS 6 months later where they've received a further year of Q2W dosing. This patient has had no AP attacks since they initiated volanesorsen over three years ago.

The rate ratio for the risk of an AP event with or without volanesorsen treatment was calculated in a number of ways, see Table 4:

Table 4: Any FCS patient, regardless of AP history

	APPROACH	**APPROACH OLE (Feb 2019 data cut)**	**Pooled APPROACH, APPROACH OLE and COMPASS[2,3]**	**Glybera observational study[4]**
	AP rate (patient years of exposure)			
Medical history	0.21 (330)	[redacted]	[redacted]	0.27
Placebo	0.11 (31.8)	[redacted]	[redacted]	
Volanesorsen (any dose)	0.09 (29)	[redacted]	[redacted]	
Volanesorsen (Q2W)[1]			[redacted]	
	Calculated AP rate ratios			
Rate ratio, any dose vol vs. medical history	**0.43**	**0.13**	**-**	
Rate ratio, any dose vol vs. placebo	**0.82**	**0.17 (vs. 0.19 pooled trial placebo)**	**0.19**	
Rate ratio, Q2W vol[1] vs. placebo	**-**	**-**	**0.39**	

1. after at least 3 months of Q2W dosing
2. FCS patients only

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

3. July 2019 data cut
4. European Medicines Agency, 2017

Data are also now available for the rate ratio comparing the risk of an AP event with and without volanesorsen in the population of patients with a history of AP, see Table 5.

Table 5: Patients with a history of AP

	Pooled APPROACH, APPROACH OLE and COMPASS[2,3]
	AP rate (patient years of exposure)
Placebo	[redacted]
Volanesorsen (any dose)	[redacted]
Volanesorsen (Q2W)[1]	[redacted]
	Calculated AP rate ratios
Rate ratio, any dose (vs. placebo)	**0.18**
Rate ratio, Q2W[1] (vs. placebo)	**0.35**

1. after at least 3 months of Q2W dosing
2. FCS patients only
3. July 2019 data cut

Modelling in the impact of volanesorsen on AP events in the economic analysis

The ERG's multiplication factor of 0.5 results in a rate ratio (0.45) for volanesorsen's effect on rate of AP that is not reflective of the available clinical data, particularly in patients with a history of AP or with recurrent AP. The clinical evidence demonstrates volanesorsen has a positive impact on AP rates, particularly in patients with a history of AP. We suggest an effect size estimate between 0.13 and 0.35 is more appropriate. Using values of 0.27 and 0.28 in the low/medium TG and high TG health states respectively, reduces the ICER from the committee base case of £355,235 to £333,849.

The ECD queries two assumptions in the economic model relating to the effect of volanesorsen on acute pancreatitis events. These queries are specifically:

1) the direct effect of volanesorsen on the risk of acute pancreatitis

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

2) the relationship between triglyceride levels and risk of acute pancreatitis in people with familial chylomicronaemia syndrome

We assume that there are three risk factors for acute pancreatitis in FCS: 1) high mean TG levels 2) volatile TG levels / 'spiking' in TG and 3) previous AP events. The economic model explicitly addresses points 1) and 3) in its structure. As a reminder, there are nine main health states (plus chronic pancreatitis and the absorbing state death). The nine health states result from a three by three matrix of TG level (low, medium and high) and AP history (naive, historical and recurrent).

In the company base case a rate ratio of 0.13 was applied to patients in the historical and recurrent AP categories based on a comparison between AP event rates in the 5 years prior to the APPROACH OLE trial with the rates on treatment during the trial (tables Table 4 and Table 5). The ERG suggested this would overestimate the benefit and tested an arbitrary multiplication factor of 0.5. The reasons they suggested there would be over-estimation are 1) double counting in a population that already has the potential to reduce AP via TG reduction 2) regression to the mean and 3) recollection bias.

Addressing these in reverse order: AP events from the APPROACH OLE medical histories were definitely adjudicated, therefore there is no risk of recollection bias in the 5-year medical history rate of AP. In a clarification response in 2018 we suggested these prior AP were not adjudicated. We have now confirmed that they were, we apologise for any confusion caused.

With regards to regression to the mean, we understand the risk would be that patients enrol in the trial because they have just had a bad AP event, and therefore may have naturally been going to enter a period of time with fewer APs, and that being in the trial itself will have encouraged patients to adhere to the required diet, and therefore they have fewer AP events. We are not able to comment either way on the point about motivation to join the trial, we do not have that information.

With regards to being in the trial improved adherence to the diet, we suggest this is not the case on the basis that there is no notable change in TG results between screening for entry into the trial and the baseline TG measure: mean TG at screening was 26.8mmol/L and 25.0mmol/L at baseline. In this run-in period patients were expected to ensure they were adhering to the required diet. The lack of variation between screening and baseline suggests there was no substantial change in adherence to diet. It is also important to note that a number of patients have now been on volanesorsen for a substantial period of time in OLE and EAMS. We heard in the committee meeting that these patients *have* adjusted their diet. They were keen to point out the adjustment was a nutritionally better adjustment that is still part of a safe diet for FCS patients, but towards the higher permissible fat consumption range. These patients are not reporting AP events. Therefore, this suggests reduced AP events is a true treatment effect and not a statistical artefact: volanesorsen does reduce AP event rates.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea acknowledges that there was some double counting, however this was only in the Historical AP health states applicable to 54% of the patient cohort and only up until the first AP event. The additional multiplication factor was necessary because moving from the high TG health state (on SoC) to the medium TG health state (on volanesorsen) did not adequately capture the magnitude of reduction on risk of AP observed in the clinical trials. This is likely because 1) FCS patients on SoC have higher AP rates in the high TG health state than predicted by the CALIBER data (for reasons explained previously) and 2) patients on volanesorsen have lower AP rates than predicted by the CALIBER data (because a large proportion of readings are <10 mmol/L). Furthermore, once patients in the Historical AP health states experience an AP event, they move into the Recurrent AP health states. Therefore, the impact of the double-counting is low.

We tested the impact of the ERG adjustment of 0.5 in a scenario in the economic model by comparing the rate of AP predicted by each arm. The scenario equalises the number of patients at risk of AP in the arms by:

- removing transition to chronic pancreatitis
- removing mortality from AP
- removing mortality from diabetes
- setting discontinuation on volanesorsen to zero - to capture a long-term on-treatment effect.

Under this scenario, that isolates the impact of the ERGs adjustment to the rate ratio for AP, the model predicts a rate ratio of 0.45 between volanesorsen and standard of care (SoC). This is a significant underestimate compared with available evidence.

Akcea would suggest that a rate ratio of 0.27 (for the low/medium TG health states) and 0.28 (for the high TG health states) is a reasonable mid-point between 0.13 (APPROACH OLE on-treatment vs. natural history, Table 4) and the value of
0.35 (volanesorsen Q2W vs. trial placebo rates in patients with a history of AP, Table 5), and that this should be used in place of this arbitrary 0.5 rate ratio. Using 0.27 and 0.28 reduces

Triglyceride (TG) lowering effect of volanesorsen at once every week (Q1W) and once every two weeks (Q2W) dosing

with FCS in the short and long-term at every week (Q1W) and every two-week (Q2W) dosing.

For a novel product for treatment of an ultra-rare disease, volanesorsen has a robust data package for its triglyceride (TG) lowering effect in both the short- and long-term at either Q1W or Q2W doses.

This benefit is substantial, clinically meaningful and sustained with a reduction in mean serum TG of 70-80% with Q1W dosing and a reduction of 40% with Q2W.

The SmPC for volanesorsen recommends a starting dose of 285mg Q1W for 3 months and

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

a reduction to Q2W at 3 to 6 months and thereafter allows clinical discretion for longer term use at either the Q1W or Q2W dosing frequency. Evidence from EAMS would suggest that in the UK patients will stay on Q2W dosing. Data for the efficacy of volanesorsen at both Q1W and Q2W dosing for up to 4 years is provided below.

Triglyceride lowering efficacy: 0-3months efficacy at Q1W dosing

Volanesorsen's triglyceride lowering benefit is seen in the primary endpoint of the pivotal phase 3 study APPROACH:

- In the APPROACH phase 3 study, treatment with volanesorsen was associated with a 94% benefit compared to standard of care, in reduction from baseline in serum triglyceride (TG) level at 13 weeks: -77% vs +18% respectively, ($p<0.0001$).
- The absolute reduction in TG level at 3 months was 19.3 mmol/L on volanesorsen vs. an increase of 1 mmol/L on placebo ($p=<0.001$), from a baseline TG level of 25 mmol/L. This is a substantial and clinically meaningful reduction in TG. Levels above 22.6 mmol/L are considered 'ultra-high' and associated with a particularly high risk of acute pancreatic (AP) (Scherer at al., 2014).
- All patients in the first three months of APPROACH received weekly dosing, the licensed dose. 91% (30/33) of patients maintained Q1W dosing for the first 3 months.

Triglyceride lowering efficacy: post-3months efficacy at Q2W dosing

For a novel product there is a substantial body of data demonstrating clinically meaningful and sustained long-term triglyceride lowering efficacy at the Q2W dose.

While there is a divergence from the trial dosing protocol at 3 months, there is a substantial body of evidence supporting a sustained reduction in TGs of approximately 40% on Q2W dosing. This includes the APPROACH and APPROACH OLE trials (July 2019 data cut, new data), EAMS and the GLMM.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Triglyceride (TG) lowering efficacy: 3-6m at Q2W dosing, after initiation at Q1W

APPROACH OLE

- 14 treatment naïve patients from the APPROACH OLE study commenced treatment with volanesorsen 285 mg Q1W and were then down-titrated to Q2W dosing at 3 months +/- 2 weeks; the dosing schedule recommended in the SmPC.

- After a total of 6 months of volanesorsen treatment (~3m at Q1W and ~3 months at Q2W dosing), the observed reduction in serum TG was mean [redacted]

- The absolute reduction in serum TG was [redacted] mmol/L at 6 months.

Triglyceride (TG) lowering efficacy: post-6m at Q2W dosing

APPROACH OLE

- The latest data cut from the ongoing APPROACH OLE study (July 2019 data cut 1) provides data for additional patients who have received more than 3 months treatment with volanesorsen 285 mg Q2W.

- In this cohort, treatment with volanesorsen Q2W produced a reduction in serum TG from baseline of:
  - [redacted] after 6 months of treatment with volanesorsen 285 mg Q2W [redacted]
  - [redacted] after 12 months of treatment with volanesorsen 285 mg Q2W [redacted]
  - [redacted] after 18 months of treatment with volanesorsen 285 mg Q2W [redacted]
  - [redacted] after 24 months of treatment with volanesorsen 285 mg Q2W [redacted]

UK Volanesorsen Early Access to Medicines Scheme (EAMS)

The UK volanesorsen EAMS also provides additional information into the efficacy of volanesorsen 285mg Q2W (the dose mandated within the treatment protocol for the first 6 months of treatment).

Data is currently available from 20 patients (October 4th 2019 Data Cut) who have been treated with volanesorsen for a minimum of 3 months in the UK EAMS, comprising 9 patients who were previously treated with volanesorsen within the clinical development programme and 11 treatment-naïve patients (see Appendix 4).

- In patients previously treated with volanesorsen within the clinical development programme, after 3 months of treatment with volanesorsen 285 mg Q2W, the percentage change in serum TG was [redacted] (mean) or [redacted] (median) from the *clinical trial* baseline [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

- 3 patients in this cohort had been on volanesorsen treatment for ~4 years at the time of the data cut

o A similar reduction in serum TG was observed in the treatment-naïve patients in the EAMS who initiated treatment at the Q2W dose: In this cohort, 3m of treatment with volanesorsen 285 mg Q2W reduced the serum TG by [redacted] (mean) or [redacted] (median) from baseline [redacted].

Generalised Linear Mixed Model (GLMM)

o The generalised linear mixed model (GLMM) was a post-hoc statistical analysis used to predict absolute TG values on Q2W dosing using 1,508 unique TG observations from 90 patients up to the February 2019 cut-off.

o The mean of the predicted TG values on volanesorsen Q2W dosing compared with the mean TG on standard of care was associated with a mean TG reduction on Q2W of 44%.

Triglyceride (TG) lowering efficacy: post-3m *at Q1W* dosing

The licence dosing posology permits up-titration, should that be clinically appropriate. In EAMS, only one patient has up titrated from Q2W to Q1W dosing. They maintained the higher dose for only a few weeks before dose pausing due to platelet levels. Therefore, we think that in routine UK clinical practice, up-titration is very unlikely. However, there are data demonstrating the efficacy of the product at the Q1W dose.

APPROACH pivotal Phase 3 Study

o In the APPROACH study, 6 patients completed the 12-month study on volanesorsen 285 mg Q1W without any dose adjustment.

o In this cohort, 12 months of treatment with volanesorsen 285 mg Q1W produced a reduction in serum TG of 76.2%, an absolute reduction in serum TG of was 17.9 mmol/L.

The submitted evidence demonstrates the substantial short and long-term efficacy of volanesorsen in FCS at Q1W and Q2W.

Efficacy in the long-term at the label recommended dosing is supported by three sets of analyses, conducted independently in three cohorts of patients, all consistently supporting a long-term reduction on fasting TGs of approximately 40% by Q2W volanesorsen.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Uncertainty in favour of volanesorsen: evidence not considered by the committee

A number of co-morbidities were not included in the economic model, as the company was concerned about the risk of double-counting due to shared features with either the vignette descriptions or symptoms of diabetes and/or chronic pancreatitis and/or due to a lack of robust data. These co-morbidities and their symptoms are summarised in Table 9 in Appendix 3.

Similarly, the vignette health state descriptions did not capture all the aspects of FCS symptomology which could be expected to add additional decrements. These symptoms are summarised in

Table 6, below.

Table 6: FCS symptoms not included in the vignette descriptions

Symptom	Proportion of FCS patients reporting symptoms	Utility decrement
Joint pain[1]	22%	-0.15 associated with rheumatoid arthritis (Sullivan et al., 2011)
Feeling cold all the time in extremities[1]	18%	Unknown, possibly tied in with the numbness or tingling
Numbness or tingling of digits[1]	14%	Possibly links with neuropathy. The smallest disutility associated with peripheral neuropathy in cancer was 0.094 (Peasgood et al., 2010)
Use of steroids[2]	[redacted]	Not possible to provide a utility estimate
Use of opioids	[redacted]	Not possible to provide a utility estimate

1 % reporting symptoms in InFOCUS
2 baseline in APPROACH OLE

Akcea points out the high proportions of patients taking prescription opioids ([redacted]) and corticosteroids ([redacted] at baseline in the APPROACH OLE study. Five percent of patients in the InFOCUS study reported being addicted to opioid and non-opioid painkillers. Once a prescription opioid use disorder is established, the negative impacts on quality of life and health, as well as economic impacts to individuals, families, and society, are substantial. Every year, drug misuse costs the NHS in England £488m, with additional societal costs of up to £15.4 billion (Public health England, 2013). In the ReFOCUS study volanesorsen was found to reduce pancreatitis pain (Arca et al., 2018) and thus could prevent use of opioids and potential addiction in these patients.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Importantly, if the committee considers these relevant to FCS patients, then it should also consider that volanesorsen would reduce these symptoms/concomitant medication use which would result in a lower ICER.

Malnutrition, dietary deficiencies and maintaining the FCS diet

Patient representatives at the first committee meeting explained that they had been able to make small modifications to their diet since being on volanesorsen, including for example "being able to eat a small yoghurt". Guideline dietary fat requirements for normal individuals are between 70 g (women) and 95 g (men) per day, of which just under a third should be saturated (British Nutrition Foundation, 2012), whereas FCS patients on current SoC are restricted to 10–20 g per day. This strict diet can lead to malnutrition and deficiency in fat-soluble vitamins. Bone compromise due to a lack of vitamin D is seen in UK FCS patients. In addition, eating disorders such as bulimia, or eating nutritionally worthless food (e.g., surviving on one MacDonald's meal a day) are not uncommon in these patients. Although patients on volanesorsen are still required to adhere to a low-fat diet, appropriate dietary support as described in the FCS Best Practice Guide (Appendix 5) and being able to maximise your permitted fat could improve their nutritional status and help relieve the psychological burden of the strict diet.

We ask that the committee considers the potential QALY implications of these additional conditions and symptoms in their deliberations regarding the potential QALY gain from volanesorsen.

Summary

To summarise the information provided above:

- There is strong evidence that the reduction in TG with volanesorsen treatment leads to an improvement in daily quality of life by keeping mean TG levels notably below 22.6 mmol/L.
- There is evidence from peer-reviewed publications and patient representatives that the family members of patients with FCS experience significant 'spillover' effects on HRQoL due to patients' daily burden of disease.
- The CALIBER data used in the model potentially under predicts risk of AP in patients with historical AP.
- There is consistent evidence of a treatment effect on risk of AP ranging from 0.13 to 0.35 in patients with historical or recurrent AP.
- Treatment discontinuation in the UK is unlikely to exceed 20% due to selection of severe patients and a strong patient support program.
- Benefits very likely to be associated with volanesorsen treatment are not captured in the model, therefore there are missing elements that would reduce the ICER.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

As such, Akcea would like to propose alternative ICERs to the committee's base case that capture what the company believes are more plausible estimates of economic value. These are summarised in Table 7 and lead to a gain of [redacted] undiscounted QALYs and a revised ICER estimate of £210,487 or [redacted] with QALY modifiers applied.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Please find below a revised table 7, incorporating both Akcea's proposed changes to the committee base case economic analysis and the revised PAS, submitted 6 Feb 2020.

Table 7: One-way results of incorporating Akcea's proposed changes to the committee's base case economic analysis

Scenario	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER [redacted] per syringe)	REVISED ICER [redacted] per syringe)
Committee base case	[redacted]	[redacted]	[redacted]	£481,508	£355,235
Low TG vignette values applied to TG health states < 22.6 mmol/L	[redacted]	[redacted]	[redacted]	£342,725	£252,847
Carer (family member) utility benefit of 0.04 applied on volanesorsen	[redacted]	[redacted]	[redacted]	£426,174	£314,412
Adjustment of 0.27 and 0.28 applied to risk of AP in the low/medium TG and high TG health states	[redacted]	[redacted]	[redacted]	£454,703	£333,849
Capping discontinuation at 20%	[redacted]	[redacted]	[redacted]	£462,683	£341,606
All of the above changes incorporated	[redacted]	[redacted]	[redacted]	**£286,295**	**£210,487**
Assuming a QALY modifier of [redacted]				[redacted]	[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Conclusion

The data submitted in the HST dossier and in this ECD response provide robust evidence of effectiveness of volanesorsen in reducing serum triglyceride (TG) levels at every week (Q1W) and every two-week (Q2W) dosing. This TG reduction is sustained, clinically meaningful and statistically significant. It is associated with improvement in day-to-day health related quality of life (HRQoL) for patients and their families, the prevention of acute pancreatitis events and a reduction in the long-term sequalae of FCS including chronic pancreatitis and diabetes.

This evidence underscores our belief that volanesorsen is a transformational treatment in the management of FCS, an ultra-rare, genetic, chronic, burdensome disease for which there is no effective treatments available in routine NHS care.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

References

AKCEA 2018a. Data on file: CALIBER

ARCA, M., HSIEH, A., SORAN, H., ROSENBLIT, P., O'DEA, L. & STEVENSON, M. 2018. The effect of volanesorsen treatment on the burden associated with familial chylomicronemia syndrome: the results of the ReFOCUS study. Exp Rev Cardiovasc Ther Jul;16(7):537-546

BENJAMIN K, VERNON MK, PATRICK DL, PERFETTO E, NESTLER-PARR S, BURKE L. 2017. Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report. Value in health: 20(7):838-855.

BRAZIER J, RATCLIFFE J, SALOMON JA, TSUCHIYA A. Measuring and Valuing Health Benefits for Economic Evaluation. Second ed. Oxford, UK: Oxford University Press; 2017.

BRITISH NUTRITION FOUNDATION. 2012. Fat: Key points. https://www.nutrition.org.uk/nutritionscience/nutrients-food-and-ingredients/fat.html

DAVIDSON, M., STEVENSON, M., HSIEH, A., AHMAD, Z., CROWSON, C. & WITZTUM, J. L. 2017. The burden of familial chylomicronemia syndrome: interim results from the IN-FOCUS study. Expert Rev Cardiovasc Ther, 15, 415-423.

EUROPEAN MEDICINES AGENCY. 2017. Glybera Public assessment report EMEA/H/C/002145 S/0057. https://www.ema.europa.eu/en/medicines/human/EPAR/glybera

GELRUD, A., WILLIAMS, K. R., HSIEH, A., GWOSDOW, A. R., GILSTRAP, A. & BROWN, A. 2017. The burden of familial chylomicronemia syndrome from the patients' perspective. Expert Rev Cardiovasc Ther, 15, 879-887

GRETCHEN A. 2007. Anxiety, Depression, and Quality of Life in Primary Care Patients. Prim Care Companion J Clin Psychiatry: 9(6): 437–443

JANSSEN MF, LUBETKIN EI, SEKHOBO JP, PICKARD AS. 2011. The use of the EQ-5D preference-based health status measure in adults with Type 2 diabetes mellitus. Diabetic medicine. Apr 2011;28(4):395-413.

KUPPERMANN, M., SHIBOSKI, S., FEENY, D., ELKIN, E.P., WASHINGTON, A.E. 1997: Can preference scores for discrete states be used to derive preference scores for an entire path of events? An application to prenatal diagnosis. Med. Decis. Making. 17(1), 42–55

MACKEIGAN, L.D., O'BRIEN, B.J., OH, P.I. 1999: Holistic versus composite preferences for lifetime treatment sequences for type 2 diabetes. Med. Decis. Making. 19(2), 113–121

MATZA, L.S., STEWART, K.D., GANDRA, S.R., DELIO, P.R., FENSTER, B.E., DAVIES, E.W., et al. 2015: Acute and chronic impact of cardiovascular events on health state utilities. BMC Health Serv. Res. 15, 173

MORRIS, S., GURUSAMY, K. S., PATEL, N. & DAVIDSON, B. R. 2014. Cost-effectiveness of early laparoscopic cholecystectomy for mild acute gallstone pancreatitis. Br J Surg, 101, 828-35.

NICE. 2013. Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#measuring-and-valuing-health-effects

NICE. 2019. Final evaluation document, Metreleptin for treating lipodystrophy.

NICE DSU. 2019. Modelling carer health-related quality of life. http://nicedsu.org.uk/modelling-carer-health-related-quality-of-life/

PEASGOOD, T., WARD, S. AND BRAZIER, J. 2010. A review and meta analysis of health state utility values in breast cancer. Discussion Paper. (Unpublished). HEDS Discussion Paper 10/15 http://eprints.whiterose.ac.uk/11227/1/HEDS_DP_10-15.pdf

PUBLIC HEALTH ENGLAND. 2013. Alcohol and drugs prevention, treatment and recovery: why invest?
https://webarchive.nationalarchives.gov.uk/20170807160639/http://www.nta.nhs.uk/uploads/why-invest-2014-alcohol-and-drugs.pdf

SANKARAN, S. J., XIAO, A. Y., WU, L. M., WINDSOR, J. A., FORSMARK, C. E. & PETROV, M. S. 2015. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology, 149, 1490-1500.e1.

SLADE A, ISA F, KYTE D, ET AL. 2018. Patient reported outcome measures in rare diseases: a narrative review. Orphanet journal of rare diseases. 13(1):61.

SULLIVAN, P. W., SLEJKO, J. F., SCULPHER, M. J. & GHUSHCHYAN, V. 2011. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making, 31, 800-4.

WITTENBERG E, RITTER G, AND PROSSER LA. 2013. Evidence of spillover effects of illness among household members: EQ-5D scores from a US population sample. Med Decis Making. 2013 February ; 33(2): 235–243.

WITTENBERG E. AND PROSSER LA. 2013. Disutility of Illness for Caregivers and Families: A Systematic Review of the Literature. PharmacoEconomics (2013) 31:489–500

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

APPENDICES

Appendix 1: The FCS vignette study

Estimating Health State Utilities Associated with a Rare Disease: Familial Chylomicronemia Syndrome (FCS)

Running Head: "Utilities Associated with a Rare Disease: FCS"

Louis S. Matza, PhD[1] (Louis.Matza@evidera.com)
Glenn A. Phillips, PhD[2] (gphillips@akceatx.com)
Timothy A. Howell, MA[1] (Timothy.Howell@evidera.com)
Nicole Ciffone, MSN, NP[3] (nixciffone@gmail.com)
Zahid Ahmad, MD[4] (Zahid.Ahmad@utsouthwestern.edu)

[1]Patient-Centered Research, Evidera, Bethesda, MD, USA
[2]Health Economics and Outcomes Research, Akcea Therapeutics, Boston, MA, USA
[3]Arizona Center for Advanced Lipidology, Tucson, AZ, USA
[4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

09 October 2019

Word count = 2499
Number of tables: 2
Appendix: 5 pgs

Corresponding author:

Louis S. Matza, PhD
Evidera, 7101 Wisconsin Avenue, Suite 1400,
Bethesda, MD 20814
P: 301-664-7263; F: 301-654-9864;
E: louis.matza@evidera.com

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Acknowledgements: The authors would like to thank Hayley Syrad and Gordon Parola for assistance with the pilot study; Haylee Andrews, Ella Brookes, Christopher Langelotti, and Natalie Taylor for assistance with participant recruitment; Kristen Deger, Meredith Hoog, Christopher Langelotti, Haylee Andrews, Melissa Garcia, and Ella Brookes for assistance with the UK data collection; Beenish Nafees, Carole Charland, Karen Hofman, and Matthew Sparks for assistance with the Canadian data collection; Benjamin Arnold and the FACITtrans team for performing the translations; Ray Hsieh and Christine Thompson for statistical programming; and Amara Tiebout for editorial assistance.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

ABSTRACT (current word count = 249)

Objectives

[redacted]

Methods

[redacted]

Results

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Conclusions

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

INTRODUCTION

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

[redacted]

Participants

[redacted]

Pilot Study

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

Utility Interview Procedures and Scoring

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Statistical Analysis Procedures

[redacted]

RESULTS

Sample Characteristics

[redacted]

Health State Utilities

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

DISCUSSION

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

COMPLIANCE WITH ETHICAL STANDARDS

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

REFERENCES

1. Aronson JK. Rare diseases and orphan drugs. *British journal of clinical pharmacology.* Mar 2006;61(3):243-245.

2. Deticek A, Locatelli I, Kos M. Patient Access to Medicines for Rare Diseases in European Countries. *Value in health.* May 2018;21(5):553-560.

3. Fonseca DA, Amaral I, Pinto AC, Cotrim MD. Orphan drugs: major development challenges at the clinical stage. *Drug discovery today.* Mar 2019;24(3):867-872.

4. Miller KL, Lanthier M. Investigating the landscape of US orphan product approvals. *Orphanet journal of rare diseases.* Oct 22 2018;13(1):183.

5. Nestler-Parr S, Korchagina D, Toumi M, et al. Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group. *Value in health.* May 2018;21(5):493-500.

6. Ollendorf DA, Chapman RH, Pearson SD. Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers. *Value in health.* May 2018;21(5):547-552.

7. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. *Lancet.* Jun 14 2008;371(9629):2039-2041.

8. Smith BP. Challenges and Opportunities in Rare Disease Drug Development. *Clinical pharmacology and therapeutics.* Oct 2016;100(4):312-314.

9. Food and Drug Administration (FDA). Rare Diseases: Common Issues in Drug Development Guidance for Industry. Silver Spring, MD. January 2019; 22 pgs, Revision 1; www.fda.gov/media/119757/download. Accessed October 1, 2019.

10. Pearson I, Rothwell B, Olaye A, Knight C. Economic Modeling Considerations for Rare Diseases. *Value in health.* May 2018;21(5):515-524.

11. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa, CAN: Mar 2017:71.

12. Haute Autorite de Sante (HAS). A Methodological Guide: Choices in Methods for Economic Evaluation. Department of Economics and Public Health Assessment. La Plaine Saint-Denis, France: October 2012:55

13. Kind P, Brooks R, Rabin R. *EQ-5D concepts and methods: a developmental history.* Dordrecht, the Netherlands: Springer; 2010.

14. National Institute for Health and Care Excellence (NICE). Process and methods guides: Guide to the methods of technology appraisal 2013 (PMG9). London, UK: April 2013:93.

15. Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. *Australian Government, Department of Health.* Version 5. Canberra, Australia: September 2016:216.

16. Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report. *Value in health.* Jul - Aug 2017;20(7):838-855.

17. Slade A, Isa F, Kyte D, et al. Patient reported outcome measures in rare diseases: a narrative review. *Orphanet journal of rare diseases.* Apr 23 2018;13(1):61.

18. Davidson M, Stevenson M, Hsieh A, Ahmad Z, Crowson C, Witztum JL. The burden of familial chylomicronemia syndrome: interim results from the IN-FOCUS study. *Expert review of cardiovascular therapy.* May 2017;15(5):415-423.

19. Gaudet D, Brisson D, Tremblay K, et al. Targeting APOC3 in the familial chylomicronemia syndrome. *The New England journal of medicine.* Dec 4 2014;371(23):2200-2206.

20. Burnett JR, Hooper AJ, Hegele RA. Familial Lipoprotein Lipase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews((R))*. Seattle (WA)1993.

21. Pouwels ED, Blom DJ, Firth JC, Henderson HE, Marais AD. Severe hypertriglyceridaemia as a result of familial chylomicronaemia: the Cape Town experience. *South African medical journal.* Feb 2008;98(2):105-108.

22. Rare Disease Report. Familial Chylomicronemia Syndrome - Proper Management of FCS is Critical. FDA; Silver Spring, MD. Available at: http://fcs.raredr.com/diet-opt.html. Accessed May 30, 20182017b.

23. Yang X, Lee SR, Choi YS, et al. Reduction in lipoprotein-associated apoC-III levels following volanesorsen therapy: phase 2 randomized trial results. *Journal of lipid research.* Apr 2016;57(4):706-713.

24. Brahm AJ, Hegele RA. Chylomicronaemia--current diagnosis and future therapies. *Nature reviews. Endocrinology.* Jun 2015;11(6):352-362.

25. Pejic RN, Lee DT. Hypertriglyceridemia. *Journal of the American Board of Family Medicine : JABFM.* May-Jun 2006;19(3):310-316.

26. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *Journal of clinical gastroenterology.* Mar 2014;48(3):195-203.

27. Al Azkawi H, Alalwan I. Two siblings with familial chylomicronemia syndrome: disease course and effectiveness of early treatment. *Case reports in medicine.* 2010;2010:807434.

28. Chen YH, Ke ZL, Wang YX, Wang Y, Zheng YZ. Two case reports of familial chylomicronemia syndrome. *Case reports in pediatrics.* 2012;2012:384719.

29. Patil M, Pratinidhi SA, Ghadage D. Familial chylomicronemia syndrome. *Case Study Case Rep.* 2011;1(2):92-98.

30. Sugandhan S, Khandpur S, Sharma VK. Familial chylomicronemia syndrome. *Pediatric dermatology.* May-Jun 2007;24(3):323-325.

31. Gelrud A, Williams KR, Hsieh A, Gwosdow AR, Gilstrap A, Brown A. The burden of familial chylomicronemia syndrome from the patients' perspective. *Expert review of cardiovascular therapy.* Nov 2017;15(11):879-887.

32. Rare Disease Report. Familial Chylomicronemia Syndrome - Understanding FCS. FDA; Silver Spring, MD 2017a.

33. United States Department of Agriculture, Agricultural Research Service. USDA Food Composition Databases. Available at: https://ndb.nal.usda.gov/ndb/search/list. Accessed May 30, 2018.2017.

34. Mayerle J, Hlouschek V, Lerch MM. Current management of acute pancreatitis. *Nature clinical practice. Gastroenterology & hepatology.* Oct 2005;2(10):473-483.

35. Schorn S, Ceyhan GI, Tieftrunk E, Friess H, Demir IE. Pain Management in Acute Pancreatitis. *Pancreapedia.* May 30, 2015;American Pancreatic Association, Version 1.0:1-13.

36. Symersky T, van Hoorn B, Masclee AA. The outcome of a long-term follow-up of pancreatic function after recovery from acute pancreatitis. *JOP.* Sep 10 2006;7(5):447-453.

37. Tenner S, Baillie J, DeWitt J, Vege SS, American College of G. American College of Gastroenterology guideline: management of acute pancreatitis. *The American journal of gastroenterology.* Sep 2013;108(9):1400-1415; 1416.

38. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. *Measuring and Valuing Health Benefits for Economic Evaluation.* Second ed. Oxford, UK: Oxford University Press; 2017.

39. Rowen D, Brazier J. Health Utility Measurement. In: Glied S, Smith P, eds. *The Oxford Handbook of Health Economics*. New York, NY: Oxford University Press; 2011:788-813.

40. Janssen MF, Lubetkin EI, Sekhobo JP, Pickard AS. The use of the EQ-5D preference-based health status measure in adults with Type 2 diabetes mellitus. *Diabetic medicine.* Apr 2011;28(4):395-413.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

41. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. *Health and quality of life outcomes.* Oct 16 2003;1:54.

42. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. *Health economics.* Mar-Apr 1996;5(2):141-154.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

TABLES

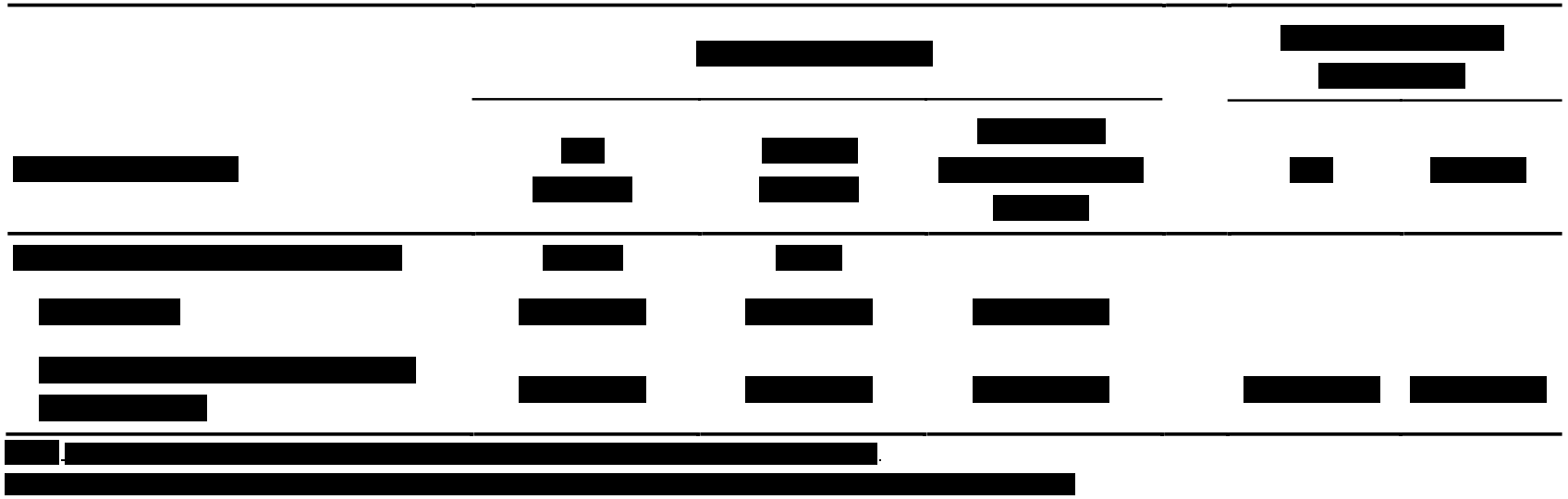
Table 1. Sample Characteristics

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Table 2. Health State Utilities[a]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT



Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

SUPPLEMENTAL MATERIAL

Appendix A. Introductory Information Page

[redacted]

- [redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Appendix B. Health Sates

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

- [redacted]
- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

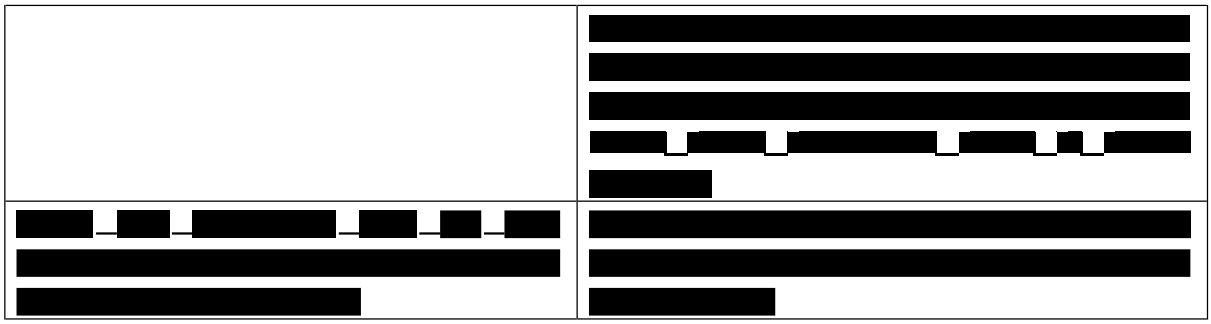
Appendix 2: Comments on the vignette study in the committee papers

The ERG raised several concerns regarding the vignette in the ERG report. We have addressed these in Table 8 below.

Table 8: concerns raised by the ERG with respect to the vignette study methodology (page 79 of the ERG report)

ERG concern raised	Company response
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT



Appendix 3: FCS co-morbidities not included in the cost-effectiveness model

Table 9: FCS co-morbidities not included in the economic model (Davidson et al., 2018)

Co-morbidity	% reporting symptoms in InFOCUS	Symptoms
Eating disorder	23	spending a lot of time worrying about your weight and body shape avoiding socialising when you think food will be involved eating very little food deliberately making yourself sick or taking laxatives after you eat exercising too much having very strict habits or routines around food changes in your mood
Hepatomegaly	11	Abdominal pain Fatigue Nausea and vomiting Yellowing of the skin and the whites of the eyes (jaundice)
splenomegaly	10	No symptoms in some cases Pain or fullness in the left upper abdomen that may spread to the left shoulder Feeling full without eating or after eating only a small amount from the enlarged spleen pressing on your stomach

		Anemia Fatigue Frequent infections Easy bleeding
Hypertension	10	Shortness of breath (dyspnea), initially while exercising and eventually while at rest Fatigue Dizziness or fainting spells (syncope) Chest pressure or pain Swelling (edema) in your ankles, legs and eventually in your abdomen (ascites) Bluish color to your lips and skin (cyanosis) Racing pulse or heart palpitations
peripheral neuropathy	7	Gradual onset of numbness, prickling or tingling in feet or hands Sharp, jabbing, throbbing or burning pain Extreme sensitivity to touch Pain in feet when putting weight on them or when they're under a blanket Lack of coordination and falling Muscle weakness Paralysis if motor nerves are affected The smallest disutility associated with peripheral neuropathy in cancer was 0.094 (Peasgood et al., 2010)
Malnutrition	Reported by patient representatives and IMD clinic expert dietitian (personal communication)	FCS patients are at risk of: • Fat soluble vitamins deficiency • Amino acid deficiency • Mineral deficiency • Insufficient calorific intake • Poor dietetic advice - not all FCS services have access to the appropriately qualified dietitian

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Addiction to pain medication such as opioids	5	

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Appendix 4: Analysis of Early Access for Medicines Scheme (EAMS) data

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Baseline Characteristics, Efficacy & Safety Data from the Volanesorsen EAMS

October 4th 2019 data cut (last patient 3m exposure) to support the Waylivra NICE HST Submission

The data contained herein is **not for public release**. It is provided to NICE in line with the discussion between Akcea and NICE prior to the dossier submission in August 2019.

A second EAMS data cut is planned before the end of 2019. This later data cut will be used to support the FDA regulatory submission. It is anticipated that this second data cut *will* be published in 2020. Akcea will share this second data cut with NICE, time and appraisal process permitting.

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

EAMS analysis

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Measuring TG

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Methodology

ETHICS

[redacted]

SITES AND PATIENTS

[redacted]

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Methodology

PROCEDURE

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Methodology

ANALYSIS

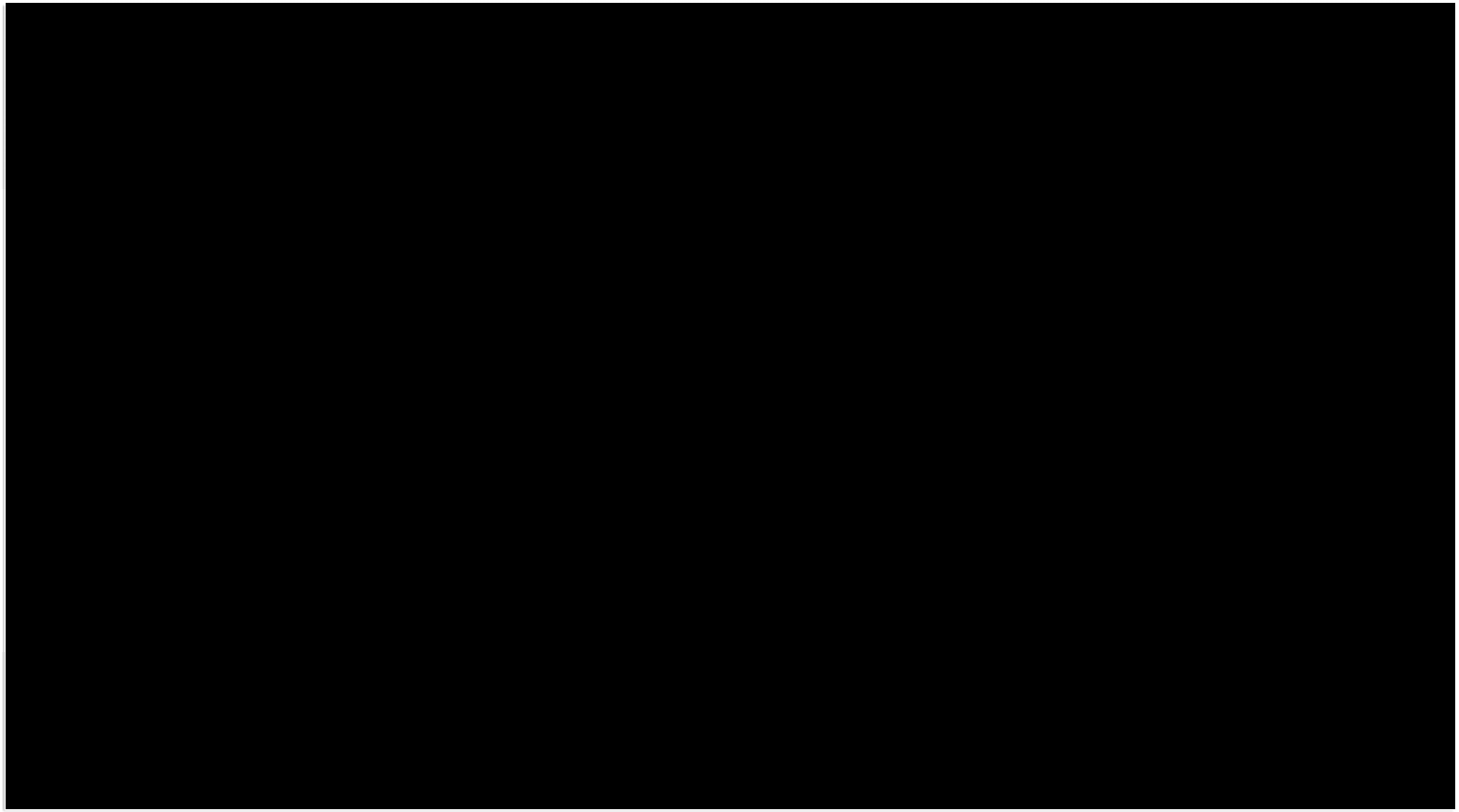
Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

RESULTS

Baseline characteristics
Drug exposure
Summary TG data
Individual patient platelet data

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT



Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

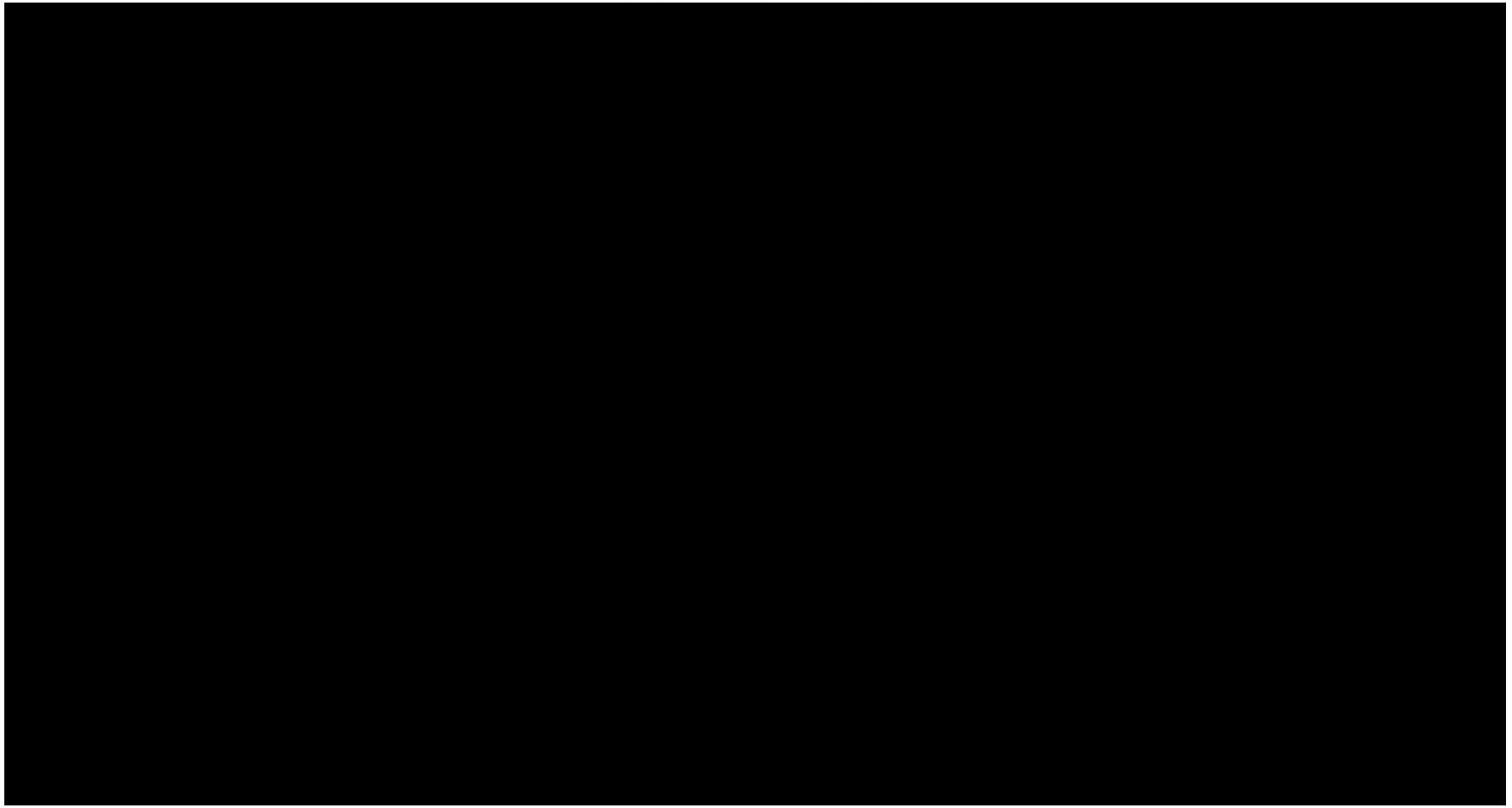
Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Change in Triglyceride at 3m (By Prior Exposure)

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

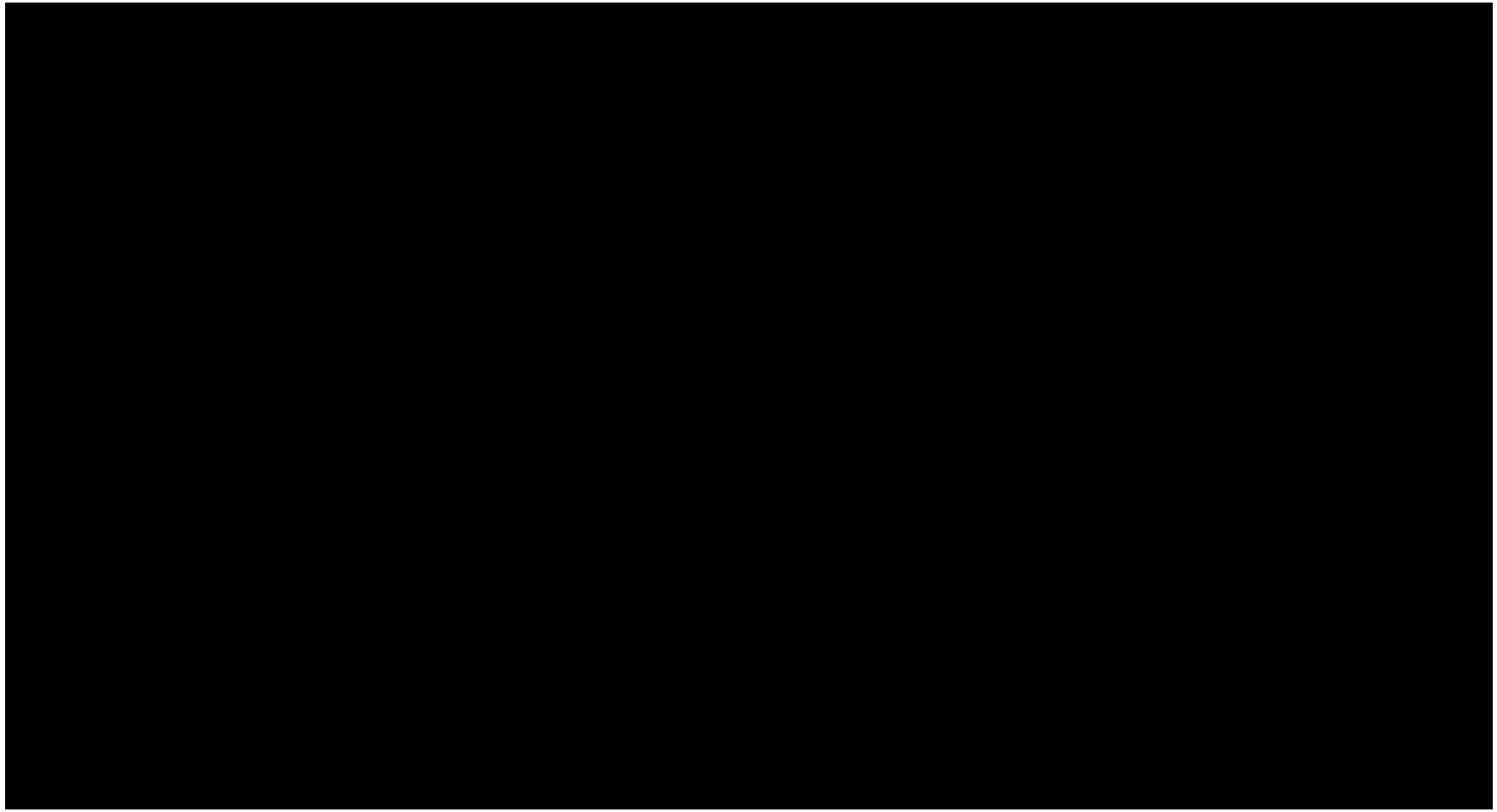
Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT



Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT



Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Discussion

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Discussion continued

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Conclusion

Akcea Therapeutics UK Ltd
Regus Building
Wellington Way
Weybridge
Surrey
KT13 0TT

Appendix 5: Draft FCS Best Practice Guide

Please see the pdf document submitted separately.

Familial Lipoprotein Lipase Deficiency
Familial Chylomicronaemia Syndrome

36 Gaskell Street, London, SW4 6NS
lpldalliance@gmail.com +44 (0)7517 752168
www.lpldalliance.org

23rd January 2020

Dear Evaluation Committee

LPLD Alliance response to draft guidance on volanesorsen for treating familial chylomicronaemia syndrome (ID 1326).

The board of LPLD Alliance is disappointed that following the recent Highly Specialised Technologies evaluation NICE does not recommend re-imbursement of the treatment volanesorsen in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate. (ID 1326)

Our comments in response to the Evaluation Consultation Document (ECD) are as follows:

Has all the evidence been taken into account? the ECD raises questions about longer-term benefits of volanesorsen while acknowledging that trial evidence shows some short-term benefits. We think that in the absence of long term usage of the therapy and the uncertainty of the clinical evidence, the lived experience of people who have been on the therapy since the clinical trial, and the testimony of treating clinicians has not been fully acknowledged.

> "I have been taking Volanesorsen for over four years and in that time I have not had one single hospital admission or day off work related to FCS. Before, I was in hospital every two months, anywhere from a few days to a couple of weeks. It feels incredible to being living my life now with such stability."

Patients report the absence of abdominal pain and pancreatitis, an increased ability to work to socialise and to maintain relationships, all of which have had a positive effect on their mental health. These benefits have a direct impact on those close to them as acknowledged by the committee in the ECD (4.1 and 4.2).

We think the continued discussions between the patient and their treating clinician will enable close monitoring of the impact of the therapy and allow both patient and the clinician to decide if the therapy is continuing to offer value.

Diabetes: we think that not enough attention has been given to the impact that continually high triglycerides has on potential long-term damage to the pancreas with its increased risk of pancreatitis, and any complications from pancreatic damage including the onset of diabetes and pancreatic cysts.

One patient who sustained very high triglyceride levels for most of their life did not have a pancreatitis attack until after their diagnosis of diabetes, indicating that the high triglycerides caused damage to their pancreas and the subsequent development of diabetes (this patient had experienced frequent bouts of abdominal pain)

> "However, in 2003 I was diagnosed with Type II diabetes brought about by living most of my life on a low fat, high carbohydrate diet…. Following the type II diagnosis, I have been hospitalised with pancreatitis spending between 6 and 8 days each time."

FCS and diabetes are two conditions which work against each other, with each carrying a separate symptom and huge self-management burden. Blood glucose levels turn to triglycerides in the blood, meaning that the diet is further restricted and near impossible to manage as low fat foods are carbohydrates which in turn worsens the diabetes.

We think that there has not been enough consideration of the benefits that lowering triglycerides has on minimising potential long-term damage to the patient's pancreas.

The relationship between triglyceride levels and risk of acute pancreatitis and the direct effect of volanesorsen on the risk of acute pancreatitis in people with familial chylomicronaemia syndrome: we appreciate the committee's concern about the lack of evidence of the relationship between triglyceride levels and pancreatitis and the direct effect on the risk of volanesorsen on the risk of acute pancreatitis. We think the issue is complicated by the fact that many patients manage pancreatitis at home and so it is very difficult to capture triglyceride level at the beginning of an attack.

> "I have only admitted myself on two occasions, preferring to manage such attacks at home, as I have always done over the years. The experience in hospital has been unpleasant, with inappropriate remarks from nursing

> staff about alcoholism, and inappropriate food served up once I could eat again."
>
> 'Now when I go in, it's normally only for a few days because I've slightly controlled it myself at home. I have more medication to control pain relief, it's only when I can't control the vomiting that I have to go into hospital. I do have anti-sickness at home...'

Patients also tolerate severe abdominal pain and possibly do not realise they are having an episode of pancreatitis

> "I've never been diagnosed with pancreatitis. I'd go into my room and fast for five days, drinking only water and taking pain killers. It was only when I met another patient who had been in hospital with pancreatitis who told me they'd been fasted for five days on a drip with morphine that I thought that maybe I'd had pancreatitis."

This acceptance of severe pain as part of life can have potentially serious consequences

> "I had my appendix out at 16. I didn't contact the doctor for over a day because I was so used to having severe stomach aches – even though it felt different."

Patients have also reported that pancreatitis attacks can occur without warning

> "As there is no current home testing kit available for FCS, as with diabetes, you have no idea whether you are about to have pancreatitis or not. That unpredictability, and fear, is very limiting and impacts massively on your social life, and life choices."

Other patients report that their pancreatitis attacks seem to occur at lower levels than previously

> "First triglycerides measured were 43 – didn't have pancreatitis with that. If I go to that level now, I definitely would have pancreatitis."

The picture is further complicated by the fact that FCS is caused by a mutation on at least five different genes and there has been very little research (if any) on the impact of each gene on triglyceride levels.

We think that this non-reporting and potential non-recognition of pancreatitis attacks and the lack of research, makes it much harder for the link between AP

and triglyceride levels to be identified, and therefore the impact of volanesorsen on the risk of AP.

The committee have acknowledged that acute pancreatitis is a symptom of FCS and that acute pancreatitis is a life-threatening condition for which intensive care may be needed. The ECD also acknowledges that repeated attacks of acute pancreatitis may lead to chronic pancreatitis and diabetes (2.1).

Patients taking the therapy have reported the absence of pain and no pancreatitis attacks since taking the drug. We think this evidence is very relevant when it is virtually impossible to gain a true measurement of the triglyceride level at which acute pancreatitis occurs. One patient reported

> "I'm not tired, not bloated – in a matter of three weeks I felt better, felt healthier, can I say I felt normal? It made a massive difference, a massive improvement on my life. I felt better in myself, felt more outgoing…. No time off work, no problems with anything at all mentally and physically so good. I felt normal, that I could do anything. I slept better…. I picked up extra hours, they noticed a difference in me. I didn't have to take pain relief…. It was a big relief for all my family – they've all noticed a big difference."

The quality of life values used in the model: we think that the quality of life values used in the model were not fit for purpose and did not capture the actual experience of patients. The measures used were very general and did not capture the relentless impact of managing the chronic burden of FCS. Also, patients often do not fully recognise the impact of the condition on their lives relative to someone who is 'normal'. Patients with FCS have a different version of 'normal' which encompasses a much lower quality of life when compared to someone who has good health both in terms of their physical experience - their tolerance of pain fatigue and reduced energy levels, and in terms of their levels of stress and anxiety about the daily management of their condition.

Patients don't tend to have a vested interest in viewing their lives relative to others as that path leads only to depression and misery. Many take the stoical approach of 'I just get on with it'. All these factors combined mean that the evidence from the quality of life values used in the model were not reflective of the impact of the drug as this patient testimony demonstrates

> 'I feel 100% well with regard to my physical health since starting the treatment. Prior to this I felt about 20% well as I was being admitted to hospital recurrently for severe abdominal pain/pancreatitis. It has improved my emotional well-being ten-fold! I feel happier about myself and Volanesorsen has allowed me to feel less anxious when around food/making decisions around eating out.'

How the effect on the quality of life of carers is accounted for: the ECD acknowledges that the burden of disease falls on both the patient and their families and carers (4.1) and that a new treatment option would offer considerable hope to them and to their families (4.2). We recognise that the daily impact of the condition on the quality of life of carers could have been further explored and would like to take the opportunity to provide more evidence demonstrating this impact. To do this we have returned to our original interviews of 20 patients and eight caregivers and asked for caregivers to contact us again. Six caregivers did so, all of whom live in England and Wales.

We think that the following demonstrates that the devastating impact of FCS on the patient has a hugely negative impact on people close to them. We think we have demonstrated that the absence of any therapeutic option to support patients to manage their symptoms exacerbates the negative effects on carers and that volanesorsen can help ease the burden on carers significantly.

Impact of FCS on caregivers (we have defined caregivers as anyone who is close to the patient):

The impact on carers was best summed by the following quotations from caregivers:

> "This is a life-time condition. You are aware of this condition all your waking hours and plan your days around avoiding anything that might cause a problem…. It is a constant presence."

> "I think we could have been a lot happier if we hadn't had this constant worry because it does affect every area of your life…"

> "I am very much aware of the patient's FCS, for two main reasons: 1) I am the primary provider of food for the patient, so have to be aware of the

> dietary limitations at all times. 2) The patient's attention is very much focused on the condition much of the time, so it is a frequent topic of conversation. The limitations imposed by the condition also affect many of our choices in family and social life generally."

> "We can't just eat at wherever we like, order takeaway because we're just tired, go on holidays without seriously planning how, if at all, in a particular country of choice, my wife would be able to manage her diet."

One adult patient reported the impact on her parents

> "Particularly for my parents, the diagnosis and living with the challenge of FCS has been worrying and draining for them."

One adult child reported the impact of her mother's FCS

> "We try not to let FCS define Mum or us, but it becomes impossible because it is a part of everything she does or can't do. It has caused a lot of anxieties over the year, not just to her, but to everyone around her because of the impact that it causes."

Taking responsibility for the patient's health and well-being

Many partners/spouses have taken responsibility for the well-being of the patient. While this can be very positive, it can also add an extra, sometimes negative dimension to the relationship. This ambivalence is expressed in the following quotation:

> "She's always asking me what I had to eat other than the food she provides. I do sometime get angry because I feel it's almost like I'm not allowed to eat anything without her permission but she's only doing it to keep me as healthy as possible"

While the positive impact of this concern is expressed here:

> "Now he's quite strict with me about what I can and can't have. He's now my eyes at the back watching me. He'll say. 'no, we can't do that, or we can but we'll have to do this first'. He'll ring the place we're eating and bring a plate for me."

Sharing the restrictions

Many of the patients' spouses had taken on the restrictions of the diet in order to make the patient feel less isolated in their eating, and to make catering at home easier. The effect on one carer is as follows

> "I generally eat the same as her. It does mean that when I escape the regime, I tend to overdose on the fatty foods she avoids. This can have an adverse effect. I am pretty sure a binge on all-day breakfasts triggered an attack of gall stones."

Many carers also acknowledged that there was some benefit to them in being exposed to the FCS diet. One 16-year old says

> "I eat far healthier than all of my friends – I can't believe how much fat they use when cooking! And as an athlete, it's been really easy to adjust my diet to support my training."

Impact on social life

All patients and carers reported an extremely reduced or divided social life

> "It tends to mean largely sticking to a core group of those who are able to understand and accommodate the differences imposed."

> "The condition forces the patient to focus very often on their own needs, in order to ensure their survival and good health in situations where others would simply be at ease and eating as they please. This can have a negative impact on those who are close to the patient."

> "Not eating 'normally' creates problems with my partner. I avoid social activities and he's very social."

Eating out is very problematic.

> "We rarely eat out. We have to keep control of every aspect of my wife's diet. Generally, we socialise with friends but only dine with them if my wife

prepares the meal."

If patients and caregivers do eat out, carers often take the lead.

> "When we go out to eat, he shoulders a lot for me. I still get quite emotional when a salad arrives, and it's got dressing on it and I don't want to deal with it. He does it for me."

> "He makes sure restaurants are fully informed about what I can and can't eat if we go out."

Uncertainty

Uncertainty surrounding the impact of FCS on the patient has a huge effect on the carer

> "The 'not knowing' when the pain will start, if I will be attending functions alone, if my partner can plan anything, if I support my partner or leave her alone as most of the time she deals with this alone…"

Carers talk about feeling helpless in the face of the burden of FCS:

> "I can't help or change anything. Numerous times she has told me to find someone else that's less of a problem."

Financial impact

Carers share the financial impact that FCS places on the patient. Our previous submission discussed the impact of FCS on patients' ability to work, on the jobs they can manage, on whether they attempt promotion. Income (or lack of it) generated by a patient will have an impact on the overall finances of those close to them. One carer says

> "I might have been bolder in my choices and if my partner had been more able to earn, I might have been able to retire earlier if it had not been for the condition."

Others talk about the impact on budget that the condition imposes

> "Financially there's things we cannot do and because this upsets my partner

it upsets me."

"Cost of food shopping is higher as we have to buy low fat products which are not usually the cheapest on the market."

One parent says of her adult child that due to her FCS

"I have always helped her financially."

Being away from home / taking holidays

Patients and their carers talk about the near impossibility of being away from home without being able to self-cater.

"It also affected our holiday choices as we always went self-catering, this also meant making and taking packed lunches on trips.

The future

The future is viewed with trepidation by carers in the context of the lack of awareness and knowledge of FCS:

"I really worry about the future as my wife's health has got worse as she's got older despite all we do to manage her diet."

"The great concern is as we age, if my wife's mental capacity diminishes, how do you educate carers if I'm not there or incapacitated."

An adult child of a patient said

"If we need a care home for mum in the future, we'd have to work hard to ensure they were able to feed her properly."

The impact of volanesorsen on caregivers

We previously described the very positive impact on the lives of patients in terms of their experience of the absence or reduction of abdominal pain and pancreatitis, on the fear and anxiety that imminent attacks of both my bring, and therefore on their ability to engage more fully and consistently in all areas of their lives. Patients have reported being able to work, to work more hours and to go for promotion all

of which generate higher levels of income.

These benefits to the patient have a very positive impact on caregivers and on the patients' families.

Greater levels of income can bring its own reduction of stress and anxiety which can improve relationships, but for patients with FCS also allows the patient greater flexibility with their food shopping – more able to afford the very low-fat protein options and products which are always more expensive and which add much needed variety.

With the patient's greater flexibility, more 'headspace' to be creative about the management of the condition, their ability to be consistent and able to plan all create a benefit for their caregivers.

The lessening of the dominance of the impact of FCS on the patients' life and the subsequent improvement in their mental health can allow relationships to be more enjoyable for the caregivers and lessen the stress and anxiety they feel about the health of the patient.

A key impact on caregivers of patients taking volanesorsen was on feelings for the future

> "Now she's using the drug we have a lot more fun together and she's far more ready to make plans to see people and go out and about. I'm also not worrying so much about the future and how the FCS will affect us as we get older."

Are the summaries of the criteria considered by the committee, and the evidence and economic considerations reasonable interpretations of the evidence? We feel that the report from the committee was balanced and even, but our concern is that of a patient community of any ultra-rare condition for which there has been very little attention paid from researchers and clinicians.

FCS has an added complication as it is caused by a mutation on at least five different genes and there is little understanding of the impact of each gene and so it becomes harder to make decisions purely on the evidence available. We hope

that the committee will give due weight to the patient testimonies and the evidence of clinicians when reconsidering their decision.

Are the provisional recommendations sound and a suitable basis for guidance on the use of volanesorsen in the context of national commissioning by NHS England? No. We think that volanesorsen should be recommended in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate.

Without this technology, patients would be left with little hope of alleviating the symptom burden that the condition imposes which impacts negatively not only on the patient but on all those close to them. Patients will be left to cope with their lives in fear of, or with unpredictable pain and pancreatitis, with the resulting disruption each episode of pain and pancreatitis causes including hospital admissions and time off work and high levels of fatigue which inevitably impacts on those close to them.

Patients report feeling far more relaxed since taking volanesorsen

> "I have not changed my eating habits at all, but my fear and stress around eating has largely disappeared and I am generally far more relaxed than I ever have been in my life. Consequently, I am more able to participate in social events, am more able to work, and have the ability to keep in touch with and see my friends."

These benefits can be seen by those close to the patient

> "My wife is now a little more clear-headed and relaxed, particularly when she has the results of blood tests that show triglyceride levels being well controlled. Her energy levels are improved"

Patients' life choices, whether the ability to work, their choice of job and their participation in social occasions would remain severely limited all of which, again, have a negative impact on caregivers. They would continue to be isolated, stressed and at high risk of depression – again, negatively impacting on those close to them.

Paramount for patients and their caregivers is preventing abdominal and pancreatic pain and long-term damage to the pancreas, thereby avoiding unnecessary surgical procedures and other complications like diabetes which impacts not only the patient

but on all those close to them. This therapy offers the only option able to do this and so offers the possibility for a healthier and potentially longer life for the patient and a huge reduction of the fear and anxiety about the future for both the patient and caregivers.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We don't believe this to be the case and agree with the committee's summaries in points 4.28 and 4.29.

Conclusion

This therapy has the potential to profoundly change the lives of many patients, enabling them to live without pain and pancreatitis and the overwhelming and dominating fear of both which creates such anxiety and stress in their lives and in the lives of all those around them. We urge the committee to reconsider their decision and recommend the use of volanesorsen in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate.

Yours sincerely

[redacted]

[redacted], LPLD Alliance

Highly Specialised Technology Programme
National Institute for Health and Care Excellence
Level 1A
City Tower
Piccadilly Plaza
Manchester
M1 4BT

Specialised Commissioning
NHS England
Skipton House
80 London Road
London
SE1 6LH

[redacted]
28 January 2020

Dear Ms Ekeledo,

RE: Familial chylomicronaemia syndrome – volanesorsen [ID1326]

NHS England's Highly Specialised Services has reviewed the evaluation consultation document for the above mentioned consultation. NHS England's Highly Specialised Services considers the Highly Specialised Technology Programme to have made a fair assessment of the clinical and cost effectiveness evidence provided.

In response to the Evaluation Committee's specific questions NHS England's Highly Specialised Services has made the following assessments:

1. Has all of the relevant evidence been taken into account?
   Yes
2. Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?
   Yes
3. Are the provisional recommendations sound and a suitable basis for guidance to NHS England:
   Yes, they provide a sound basis for guidance

Kind regards,

[redacted]
Highly Specialised Services

National Institute for Health and Care Excellence evaluation consultation on

Volanesorsen for treating familial chylomicronaemia syndrome

We write in response to the above evaluation issued in December 2019.

We are former investigators for the APPROACH study and/or health professionals overseeing the care of patients taking Volanesorsen under the Early Access to Medicines Scheme (EAMS).

We accept the reservations of the committee regarding the limitations of the clinical trial evidence in demonstrating Volanesorsen's long term efficacy in sustained reduction of triglycerides and incidence of pancreatitis, as well as uncertainties around the relationship between reduction in triglycerides and incidence of pancreatitis.
We also acknowledge that the dosing regimen used in the APPROACH trial was different from that subsequently used in EAMS and from that proposed for routine clinical use.
We accept that there was lack of clarity in the study about the effect of Volanesorsen on quality of life of participants and carers.

We aim to clarify the points which led to the committee's decision not to recommend Volanesorsen for the treatment of familial chylomicronaemia syndrome:

1. *The relationship between triglyceride levels and risk of acute pancreatitis in people with familial chylomicronaemia syndrome (FCS)*

In the APPROACH trial triglyceride concentration was the primary outcome measure. The trial demonstrated a significant reduction in triglyceride concentration with volanesorsen treatment. However triglyceride concentration does not correlate directly with pancreatitis because chylomicronaemia, *not* hypertriglyceridaemia, is the direct cause of pancreatitis.

Chylomicrons are lipoprotein particles responsible for transporting triglycerides derived from dietary fat to organs for metabolism to free fatty acids by the enzyme lipoprotein lipase. In the majority of people with high triglycerides, lipoprotein lipase activity is normal and triglycerides are converted to free fatty acids. FCS is caused by an inherited defect of lipoprotein lipase activity. Hence in patients with the condition triglycerides cannot be converted to free fatty acids resulting in accumulation of unmetabolised chylomicrons. Unmetabolised chylomicrons and chylomicron remnants lodge in the small vessels of the pancreas triggering inflammation and necrosis causing pancreatitis.

Chylomicrons cannot be readily quantified hence triglycerides are used as a surrogate measurement of chylomicronaemia. This has its limitations because the two are not directly related - triglyceride concentration fluctuates day-to-day in response to recent dietary fat intake however chylomicronaemia depends not only on dietary fat intake but also on lipoprotein lipase activity.
Additionally, the day-to-day fluctuation of triglycerides in response to diet makes it an unreliable marker of long term metabolic control (akin to using glucose measurements for diabetes monitoring).

A patient with FCS carries a higher residual burden of unmetabolised chylomicrons (visible as the milky appearance of their blood samples) than a patient with

hypertriglyceridaemia from other causes who does not have FCS. Therefore at any given triglyceride concentration a patient with FCS is at higher risk of pancreatitis than someone with high triglycerides who does not have FCS.

Even within an FCS population the triglyceride threshold triggering an episode of pancreatitis will be highly variable depending on an individual's the degree of residual chylomicronaemia which in turn depends on their long-term adherence to a low fat diet.

2. The direct effect of volanesorsen on the risk of acute pancreatitis

In the APPROACH study, Volanesorsen lowers triglycerides and this would be predicted to reduce chylomicronaemia and hence pancreatitis risk. However as stated above triglyceride concentration is not directly related to chylomicronaemia and therefore also not to risk of pancreatitis. Because chylomicrons cannot be directly quantified there is no direct measure of pancreatitis risk.

Trial participants were on average at lower baseline risk of pancreatitis than a non-trial FCS population for the following reasons:

i. Trial participants are a generally more adherent group than others with the same condition, and specifically therefore likely to have been more adherent to the low fat diet and have a lower chylomicron burden;
ii. Genetic confirmation of FCS was not an inclusion criterion for the trial, some trial participants had hypertriglyceridaemia of other aetiologies

Therefore the APPROACH trial is likely to have underestimated the effect of Volanesorsen on incidence of pancreatitis in FCS and study data cannot be used to determine the effect of Volanesorsen on incidence of pancreatitis in this condition.

In order to assess the effect of Volanesorsen on pancreatitis the incidence of pancreatitis must be compared in treated vs. untreated patients, or in individuals before and after starting Volanesorsen.

3. The quality of life values used in the model

The questionnaire-based tools for assessing quality of life (QoL) used in APPROACH, though validated for clinical and research use, were not sufficiently sensitive or specific to capture QoL issues specifically affecting patients with FCS. These include but are not necessarily limited to:

i. Impact of a highly restrictive and exceptionally demanding diet (typically less than 20g fat daily, equivalent to 1 ½ tablespoons of vegetable oil daily)
    - social and societal – eating out, eating with others
    - requirement for constant vigilance around content of food
    - weight loss and nutritional deficiencies
    - dietary fat replaced by carbohydrates which are bulky and may cause bloating
    - additional dietary restrictions for patients with diabetes
ii. Impact of living with symptoms of FCS (fatigue, poor concentration, forgetfulness, pain)

iii. Impact of living with a condition that could cause you to be acutely and unpredictably unwell with a life-threatening complication (pancreatitis)
iv. Consequences of analgesia dependence, including opiates

Conclusions

Triglyceride concentration alone is inadequate as an outcome measure for assessing clinical efficacy of Volanesorsen. Clinically meaningful outcome measures include incidence of pancreatitis and its complications (pancreatic insufficiency, diabetes, mortality) and prevalence of other symptoms affecting quality of life to include the impact of dietary restriction on quality of life. These data were not captured in the APPROACH trial and are not currently formally captured within EAMS.

EAMS has given us the opportunity to prescribe Volanesorsen for patients with FCS in a 'real world' setting. We have seen at first hand the benefit to patients on quality of life. Two examples are provided in the patient vignettes in *Appendix A*.

We propose that NICE provisionally approve the medication for treatment of people with genetically confirmed FCS for a defined period during which these data are captured in a real world setting as part of a managed access programme.

Our experience with the EAMS scheme so far suggests that the 2-weekly dosing is effective at reducing the risk of pancreatitis and improving quality of life and propose that this is the dosing schedule used in the managed access programme.

We are optimistic that with this additional data NICE and Akcea will be able to work together to agree an NHS price for the drug which will enable its use for people with genetically confirmed FCS living with such a high burden of illness and lifestyle management.

Charlotte Dawson MRCP, FRCPath, PhD, Consultant in inherited metabolic disorders, University Hospitals Birmingham

[redacted]

Appendix A

Patient 1: [redacted] has genetically confirmed FCS. She was 55 when she started Volanesorsen under the EAMS programme. In the five years prior to starting Volanesorsen she had had 15 hospital admissions with acute pancreatitis and an uncountable number of ‘bed days’ with abdominal pain. She had pancreatic insufficiency (treated with Creon) and was dependent on opiate analgesia to manage pain. In the two years since being on Volanesorsen she has had no hospital admissions or ‘bed days’ and her opiate requirement is one third of that prior to treatment. She has recently returned from her first oversees holiday in over a decade. We are now working with her to wean her off opiates entirely.

Patient 2: [redacted] has genetically confirmed FCS. She was 18 when she started Volanesorsen under the EAMS programme. In the five years prior to treatment she had had six hospital admissions with acute pancreatitis and had dropped out of college because of so many days missed with recurrent abdominal pain. Since starting the medication she has had no hospital admissions and lost no further days of education to ill health. This has allowed her to gain the qualifications required for university which she started last September. She has also started a part-time job.

23rd January 2020

Dear Evaluation Committee

I agree with the response to the committee submitted by LPLD Alliance regarding the draft guidance on volanesorsen for treating familial chylomicronaemia syndrome (ID 1326). I would like to make these additional comments relating to the impact of FCS on carers, based on my personal experience.

My life has been completely shaped by having FCS. Throughout my life it has caused me to experience a great deal of physical pain, fear of pain, stress, loneliness and depression and hugely restricted the choices I have been able to make.

My husband and three children are also very affected by my having FCS. When the children were little, I was at home cooking for them and was often cooking something I was unable to taste. They have told me my efforts were often unsuccessful. As I didn't know how to cook 'fatty' food, or know what it tasted like, I was very limited in what I prepared for them. As they grew older, rather than have me eat differently all the time or making two separate meals, we ate the same thing. This has always meant that the range of food we have at home is extremely limited. Having FCS has made me very unconfident and uncomfortable in the kitchen, so my husband has always cooked the evening meals. He works hard to think of ways of preparing the limited range of food I can eat which tastes good and offers variety.

Eating out is difficult and can create a lot of stress and anxiety for me which can impact my family. We rarely eat out with friends or go to a restaurant. If we go to a restaurant it invariably means a Japanese restaurant serving sushi so that I can eat at least some of the sushi toppings without having to make special arrangements with all the uncertainty and stress that this creates. This again restricts the family's choice of foods and experiences. Not eating out has the biggest impact on my husband who rarely gets to eat food with the family that he hasn't had to make himself.

Our holidays have always been self-catered and nearly all within driving distance. Travelling distances without a car is difficult with FCS as airports and aeroplanes do not offer any suitable food, and travel delays can be very difficult to manage. The same is true when travelling by train. We also need to go to somewhere where there is an accessible good-sized supermarket so that we know we will be able to buy suitable food for me.

As a family we have been far less sociable and adventurous than we would have been were our lives not dominated by what and where I can eat.

The impact of FCS has affected my earning potential over the years and has had a big impact on our family finances and on our future financial security.

FCS has a big impact on me emotionally. When my triglyceride levels began to rise after developing diabetes and going through the menopause, I had frequent episodes of abdominal pain and lived in constant fear that this would get worse and I would have pancreatitis. This made me extremely stressed around food and eating. I felt very hopeless and depressed and scared of what the future would bring. This had a big impact on my husband and children. I was not easy to be around.

Since taking volanesorsen my triglycerides are much reduced, and I have not experienced any abdominal pain. I have lost my fear of a possible pancreatitis attack. The absence of pain and of this fear feels amazing. I am more relaxed than I think I have ever been and have far more energy and feel far more alert. This is having a very positive impact on my husband and children and on our family life.

These benefits are hard to capture and measure, but they have made a huge difference to my life and to the lives of my close family. I am far more emotionally available to them and able to participate more fully in family life. We are more sociable as a family and I am better able to plan ahead and work out ways for me to access things for us all to enjoy together. The future now looks far less scary and I think it will mean that I will be able to continue to work and be far less of a burden as I get older.

I am very scared by the prospect of volanesorsen not being available to me in the future and the impact that will have on me and my family. It has made a massive difference to my life and has hugely improved the lives of my children and my husband. We are desperate for these improvements to continue and hope the committee can reconsider their initial decision and recommend volanesorsen for patients with FCS.

With thanks.

[redacted]

Patient Expert

21st January 2020

Dear Evaluation Committee,

I agree with the response from LPLD Alliance to the committee regarding the draft guidance on Volanesorsen for treating familial chylomicronaemia syndrome, but I would like to make these additional comments as a patient expert based on my personal experience.

I understand the committee have concerns with the efficacy of Volanesorsen over the long term. I have been taking Volanesorsen for over four years now and it has been nothing short of a lifeline for me and my family. I have had no attacks of abdominal pain or pancreatitis since taking this medication, when previously I was being admitted to hospital every two months. This was incredibly destabilising and distressing for not only myself but my family and friends. There was also disruptive to my work and a hindrance to my developing career as a Doctor. Without this treatment, I fear that I would not be employable due to ill-health and this would have financial ramifications for not only myself, but my fiancé and my parents.

I am the happiest I have ever been with regards to my personal life. Before this drug, I was contemplating moving back to live with my parents so they could help support me with my health and FCS diet. Now I don't have to burden them with my ill-health and they can enjoy their retirement stress free. Perhaps more importantly though, it strikes me as no coincidence that after taking the drug for less than a year I found myself a long-term partner and this year we are planning our wedding.

Being able to go to university or work, move out of the childhood/ family home and get married are, for most people, expected life events. For me however, these were almost never events. Volanesorsen has not only been a “pancreatitis stopper” but it has enabled me to have opportunities which would not otherwise be possible.

I am GP now and I am desperate to have a treatment which enables me to stay well and live life rather than focusing on the burden on FCS. Though the exact link between triglyceride levels and acute pancreatitis are not well understood, I do not believe this to be a good enough reason to withhold the treatment. There are many conditions where the pathology is not fully understood but the benefit of the

treatment has been demonstrated.

I hope the committee can reconsider their initial decision and recommend Volanesorsen for FCS patients.

With thanks

Dr Karishma Patel

Patient Expert

Volanesorsen for treating familial chylomicronaemia syndrome: A Highly Specialised Technology Appraisal. The ERG's critique of the company's response to the ECD.

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Sue Harnan, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Andrew Rawdin, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
	Anthony Wierzbicki, Consultant in Metabolic Medicine / Chemical Pathology, Guy's & St Thomas' Hospitals, London, UK
Correspondence Author	Sue Harnan, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed 07/02/2020

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 17/141/14.

Declared competing interests of the authors and clinical advisors

Anthony Wierzbicki was a site investigator for the Volanesorsen CS7 study in familial chylomicroneamia syndrome (Akcea), the evanicumab R1500-TG studies in familial chylomicroneamia syndrome (Regeneron) and the evolocumab VESALIUS trial in cardiovascular disease. He also has publications relating to treatment of familial chylomicronaemia syndrome and high triglycerides. Paul Downie has received consultancy fees from Akcea for attending advisory boards. No other authors or clinical advisors declared competing interests.

Acknowledgements

We would like to thank Paul Downie, Graham Bayly and Anthony Wierzbicki for their clinical advice and input to the project. We would like to thank Gill Rooney, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report. We would like to thank Allan Wailoo, ScHARR, for providing comments on the vignette study conducted by the company.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Harnan SE, Stevenson M, Rawdin A Wierzbicki A. Volanesorsen for treating familial chylomicronaemia syndrome: A Highly Specialised Technology Appraisal. The ERG's critique of the company's response to the ECD. School of Health and Related Research (ScHARR), 2020.

Contributions of authors and clinical advisors

Sue Harnan was the project lead. Sue Harnan summarised and critiqued the clinical effectiveness data reported within the company's submission. Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Graham Bayly, Anthony Wierzbicki and Paul Downie provided clinical advice to the project. All authors were involved in drafting and commenting on the final report.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 Background

NICE appraised volanesorsen at a Highly Specialised Technology (HST) appraisal committee on the 28th of November 2019. This resulted in an Evaluation Consultation Document (ECD),[1] which did not recommend the use of volanesorsen for treating familiar chylomicronaemia syndrome (FCS) in adults with genetically confirmed familial chylomicronaemia syndrome who are at high risk of pancreatitis, and when response to diet and triglyceride-lowering therapy has been inadequate.

On the 28th of January 2020 the Evidence Review Group (ERG) received comments from the company (Akcea) which responded to NICE's ECD. This comprised a written report[2] with a number of appendices, including a separate Appendix 4[3] which details the Early Access to Medicines (EAMS) study data, and an executable model in excel. In this document, the ERG attempts to summarise the main points raised by the company and to provide an ERG critique of these issues.

Akcea made a submission to the National Institute for Health and Care Excellence's (NICE) for volanesorsen in 2018.[4] However, a European Medicines Agency (EMA) license was not acquired in 2018 and the submission was paused. An EMA license was acquired in 2019, for a different dosing and monitoring schedule than originally proposed, or used in the pivotal trials. A revised submission was made to NICE in 2019.[5]

In this report we summarise and critique the company's response to the ECD consultation[2]. We comment on the clinical evidence in Section 2, and then move on to comments relating to the cost-effectiveness evidence in Section 3.

2 Key clinical points raised by the company in its response to the ECD, and the ERG's critique of these

2.1 Treatment continuation rates on volanesorsen

The company highlight a sentence within the ERG report which stated "*Clinical advisors to the ERG were also of the opinion that there would likely be discontinuations in clinical practice, with estimates up to 10% per annum and 20% in total*" (p39 ERG report).[6] The issue of discontinuations is important, not due to its effect on the incremental cost effectiveness ratio (ICER) but on its impact on quality adjusted life year (QALY) gains which could lead to additional weighting of QALYs under the HST process.

The ERG apologises for poor wording. The sentence that appeared in the clinical section should have stated "with estimates of up to 10% per annum and up to 20% continuation in total". We revisited the issue of discontinuations with clinicians since it was of some importance to the cost-effectiveness of the treatment. All three clinicians agreed that a rate of 10% per year was a reasonable estimate.

In our original report,[6] we provided a summary of the evidence from the clinical studies relating to discontinuations. This is summarised here in Table 1. Estimates range from [redacted] to [redacted]. There were limitations to all analyses. Estimates 1-3 were from patients who received weekly dosing, and the ERG speculates that this will overestimate discontinuation rates, since discontinuations are often due to adverse events (AEs) and AEs are thought to be reduced with less frequent dosing. Estimates 4 and 5 were from patients who were receiving doses every two weeks, [redacted]. The data that is reported by the company relating to the EAMS study (estimate 6) is limited in two ways. Firstly, patients did not receive weekly dosing in the first three months, and may therefore be less likely to discontinue, and secondly the analysis is fairly immature, with [redacted] having completed less than 52 weeks on treatment. [redacted]

The ERG also considered whether the discontinuation rate was likely to decrease over time, or stop altogether. There are not much data to inform this question since the EAMS data are immature and the clinical study data, which follows some patients up for 3 years across APPROACH and APPROACH OLE, are at risk of bias as described above. Data across APPROACH and APPROACH OLE [redacted] For simplicity, COMPASS data (n=3) are not considered here since COMPASS was only 6 months long, making the

timelines incompatible. However, it showed similar trends ([redacted]).

Discontinuations have been often due to AEs (n=14/28 (50%) discontinuations in APPROACH, [redacted]). Clinical advisors indicate that patients have also voluntarily withdrawn due to the burden of monitoring, or a poor profile between clinical efficacy and adverse events. The extent to which a reduction in dose frequency may ameliorate these reasons is unclear.

The ERG concludes that the empirical evidence relating to discontinuations at the licensed dose is inconclusive.
[redacted], and since
[redacted], there is evidence to suggest that discontinuations are likely with doses every two weeks, and may continue in the longer term. As such, the rate preferred by the ERG was informed by clinical advice, which indicated that a 10% discontinuation per annum at the licensed dose was a reasonable estimate.

The company states that they expect retention to be better than in the clinical studies due to the selection of more severe patients, and a patient support programme. The ERG considers the extent to which these two factors will lead to treatment continuation to be uncertain, and continues to prefer the estimates provided by clinical advisors, which were based on experience with the treatment in a UK setting.

Table 1 Discontinuations across APPROACH, APPROACH OLE and the EAMS study

No.	Data source	Patients	Dose	Critique of data source	Discontinuation rate
1	APPROACH (n=33)	All recruited	Weekly dosing with dose pauses for AEs	Higher dose than indicated	14/33, 42% in one year
2	APPROACH OLE [redacted])	Those continuing into OLE from APPRAOCH	Weekly dosing with dose pauses for AEs	Higher dose than indicated	[redacted]

No.	Data source	Patients	Dose	Critique of data source	Discontinuation rate
3	APPROACH OLE ([redacted])	Treatment Naïve	Weekly dosing with dose pauses for AEs, enhanced monitoring	Enhanced monitoring more in line with EMA license	At week 52: [redacted] At week 104: [redacted]
4	APPROACH OLE ([redacted])	Conformed to licensed dosing schedule	3 months weekly dosing, followed by dosing every two weeks	Conforms to licensed dose Selected for patients with AEs so may overestimate discontinuation	[redacted]
5	APPROACH and APPRAOCH OLE ([redacted])	Patients who changed to every two weeks dosing any time after 3 months	Weekly dosing followed by dosing every two weeks	Somewhat similar to licensed dose Selected for patients with AEs so may overestimate discontinuation	[redacted] discontinued (time point unclear)
6	EAMS [redacted]	Patients receiving volanesorsen in the UK under the EAMS programme	Dosing every two weeks	Somewhat similar to licensed dose, but lower in first 3 months [redacted]	[redacted]

* WCS assumes voluntary withdrawal and regulatory delay patients discontinued treatment; BCS assumes they did not discontinue, e.g. continued on EAMS

2.2 The impact of volanesorsen on acute pancreatitis event rates

The company highlights that the ECD identified concerns relating to the effect of volanesorsen with respect to "*1) the relationship between TG reduction and AP in FCS patients and 2) the direct effect of volanesorsen on the risk of AP*." (p9, ECD response).[2] The company then goes on to consider four items, which we will consider in turn (2.3.1 to 2.3.4).

2.2.1 The relationship between TG and AP in FCS patients based on the literature and clinical trial data

The company describes three reasons why the risk of AP is higher in FCS than in other hypertriglyceridemia (HTG) conditions:

a) Chronically higher TG levels in FCS patients. The company cites two studies demonstrating higher TG levels in FCS patients than in HTG patients (Scherer et al. 2014[7]; CALIBER study).[8]
b) Higher peak TG levels that occur more frequently (volatility). The company provides three patient traces from APPROACH (Figure 1, company ECD response,[2] reproduced here as Figure 1) which show that patients appear to have more volatile TG levels prior to treatment with volanesorsen.
c) Higher rates of previous APs, which is a risk factor for AP. The company also cites two studies demonstrating that prior AP is a risk factor for experiencing a subsequent AP.

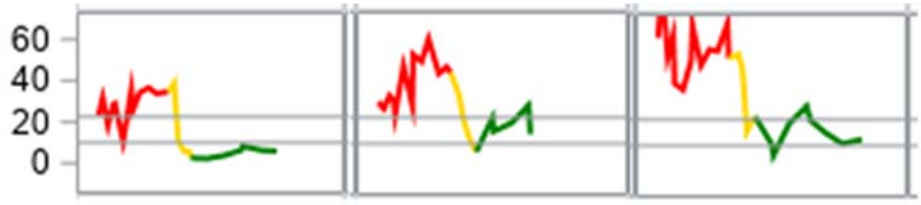
The company then states "*Therefore, while the dose-response relationship between TGs and AP is generalisable to FCS patients, it is likely that patients with FCS are at higher risk of AP compared to those with other high HTG disorders for the following three reasons: higher mean serum TG levels than other HTG disorders, greater volatility in TG levels, including higher peak readings and higher rates of prior APs, all predisposing FCS patients to repeat events*." (p10-11, company ECD response).[2]

The ERG does not agree with these reasons:

a) If the relationship between TGs and APs is generalisable to FCS patients as the company states, and, so long as the data includes the range of TG levels experienced by FCS patients, which appears to be the case since CALIBER included [redacted], then the higher mean TG levels of FCS patients should be taken into account within the modelled estimates.
b) Clinical advice to the ERG suggests that a) there is no proof that incidence of pancreatitis episodes is related to peak TG as opposed to any other variable, and b) that the spikes may be a function of high TG levels, not of FCS itself.

c) Means will include a proportion of patients who have a prior AP history. Currently, the license for volanesorsen is for patients at high risk of AP, but this is not limited to patients who have a prior history of AP. The higher risk associated with prior AP history should already be taken into account within the modelled estimates.

Figure 1 Individual patient plots of TG level by dosing group. Reproduction of Figure 1 from the company ECD response[2]



Key: Y axis represents TG value in mmol/L. Colour coding: Red: off treatment; Yellow, weekly dosing; Green, Q2W dosing

2.2.2 The impact of volanesorsen on TG and AP

The company states that "*Volanesorsen appears to confer effect by both reducing mean serum TG level and reducing the 'height of the peaks'*. (p11 company ECD response)[2] The traces provided for three patients (Figure 1, company ECD response)[2] do show greater volatility before volanesorsen treatment. However, clinical advice to the ERG notes that the mathematics of biological variables would suggest greater instability with higher levels. Notably, the periods of volatility are at higher TG levels, and the periods of less volatility may simply be a characteristic of lower TG levels, rather than an additional clinical effect of volanesorsen. However, this remains unclear.

The company goes on to state "*We hypothesise this reduction in 'spiking' (i.e., particularly high TG levels) may explain why a switch to Q2W is associated with a smaller % reduction in TG from baseline without an increase in AP event rate*." (p11 company ECD response).[2] The company provides AP event rates from the clinical studies, for patients on any dose (up to weekly dosing) and on doses every two weeks (Table 4, company ECD response,[2] reproduced here as Table 2). In the opinion of the ERG, the empirical data (rates and rate ratios) do not appear to support the company's hypothesis, since patients in APPROACH, APPROACH OLE and COMPASS on any dose experienced APs at a rate of [redacted] whilst those on doses every two weeks experienced APs at a rate of [redacted]

Corresponding AP rates off-treatment (either from the placebo arms of the trials, or from pre-treatment medical history) for the patients in these two analyses were not provided in Table 4. The available alternative off-treatment AP estimates were the 5-years prior to treatment medical history rate for APPROACH patients (0.21, 330 patient years of exposure) and APPROACH OLE patients ([redacted]

patient years of exposure) or the placebo arm patients from APPROACH (0.11, 31.8 patient years of exposure) or the placebo arm of APPROACH and COMPASS (patient years of exposure). The company only provides rate ratios for both any dose and every two-week dosing using the placebo rate of APPROACH and COMPASS as a comparator. This results in rate ratios of 0.19 (volanesorsen any dose rate, , divided by placebo rate,) and 0.39 (volanesorsen two-weekly dosing rate, , divided by placebo rate,) for APPROACH, APPROACH OLE and COMPASS patients for any dose and every two week dosing respectively. Very similar data were presented for patients with a history of AP (Table 5, company ECD response).[2]

The ERG notes that off-treatment rates vary somewhat, with the lowest estimates being from the clinical studies. These have the advantage of being comparable in terms of any potential study effects, such as greater adherence to diet, which may not persist beyond the confines of the trial and regression to the mean. However, the 5-year medical history rate has the advantage of drawing on several years of data. As detailed in the initial ERG report,[6] it is possible that the effects of volanesorsen persist for 6 months after dose discontinuation (or reduction). Since it is also unclear how many patients had been on every two-week doses for longer than 6 months, the rate may be an underestimate of the AP rate of patients on doses every two weeks, and therefore the rate ratio (0.39) may be an overestimate of treatment effect.

Table 2 AP event rates in APPROACH, APPROACH OLE and COMPASS. Reproduction of Table 4 of the company ECD response[2]

	APPROACH	**APPROACH OLE (Feb 2019 data cut)**	**Pooled APPROACH, APPROACH OLE and COMPASS**[2,3]	**Glybera observational study**[4]
	AP rate (patient years of exposure)			
Medical history	0.21 (330)			0.27
Placebo	0.11 (31.8)			
Volanesorsen (any dose)	0.09 (29)			
Volanesorsen (Q2W)[1]				
	Calculated AP rate ratios			
Rate ratio, any dose vol vs. medical history	**0.43**	**0.13**	**-**	
Rate ratio, any dose vol vs. placebo	**0.82**	**0.17 (vs. 0.19 pooled trial placebo)**	**0.19**	

Rate ratio, Q2W vol[1] vs. placebo	**-**	**-**	**0.39**	

1. after at least 3 months of Q2W dosing
2. FCS patients only
3. July 2019 data cut
4. European Medicines Agency, 2017

The company also describe a case report of one patient who had three APs in the 5 years prior to treatment, who has no APs since commencing treatment, which includes at least a 30-month period on every two-week dosing.

The company also reports AP rates in a subgroup analysis of patients who had ≥2 adjudicated pancreatic events in the past 5 years, which showed a statistically significant difference in favour of volanesorsen. However, this analysis was for patients receiving the more frequent dosing schedule.

The ERG concludes that the hypothesis that volanesorsen reduces "spikes" and that the reduction of "spikes" leads to no loss of efficacy on AP event rates at the licensed dose of volanesorsen cannot be definitively confirmed or refuted by the available evidence. However, on balance, the ERG considers the available evidence to largely not support the hypothesis.

2.2.3 Implementation of TG-mediated AP effect in the economic model

This is discussed in Section 3.3.

2.2.4 The implementation of direct impact of volanesorsen on AP in the economic model

This is discussed in Section 3.3.

2.3 Triglyceride (TG) lowering effect of volanesorsen at once every week (Q1W) and once every two weeks (Q2W) dosing

The company states "*Volanesorsen demonstrates transformational triglyceride (TG) lowering benefit for patients with FCS in the short and long-term at every week (Q1W) and every two week (Q2W) dosing. For a novel product for treatment of an ultra-rare disease, volanesorsen has a robust data package for its triglyceride (TG) lowering effect in both the short- and long-term at either Q1W or Q2W doses. This benefit is substantial, clinically meaningful and sustained with a reduction in mean serum TG of 70-80% with Q1W dosing and a reduction of 40% with Q2W.*" (p15 company ECD response).[2]

APPROACH, APPROACH OLE and COMPASS were all designed to treat patients weekly, with dose pauses for adverse events. The key adverse events that led to dose pauses were thrombocytopaenia (low platelet counts) and injection site reactions. Given the frequency and severity of the adverse events, the

SmPC recommends a different dose. This is 3 months at weekly dosing, and at 3 months, patients should down-titrate to 285 mg every 2 weeks or stop treatment if the reduction in serum triglycerides is <25%, or the patient fails to achieve serum triglycerides below 22.6 mmol/L. At 6 months patients can up-titrate to weekly dosing if the response is inadequate, and at 9 months they should down-titrate if the response remains inadequate.

Since the trial evidence generally used weekly dosing, the ERG highlighted uncertainty in their original report[6] around the TG reduction when dosing every two weeks. The company presented a number of analyses in their CS[5] to evidence the reduction in TG levels when dosing every two weeks.

In their response to the ECD,[2] the company summarise key data that was in the CS, relating to:

- Weekly dosing for the first three months (as per the SmPC). Data from APPROACH showed substantial and clinically meaningful reductions in TG levels (-77% compared to +18% mean change from baseline, and absolute mean reduction of 19.3mmol/L compared to increase of 1mmol/L from a baseline of 25mmol/L in volanesorsen arm and placebo arms respectively).

[redacted]

- The GLMM analysis from the CS, which predicted a 44% mean reduction in TG levels from baseline

The company also present new evidence in their response to the ECD,[2] relating to:

- A new analysis from APPROACH OLE (July 2019 data cut), for patients who have received more than 3 months of doses every two weeks. Mean change from baseline in TG levels were reported as:
    - [redacted] after 6 months of treatment with volanesorsen 285 mg Q2W ([redacted])
    - [redacted] after 12 months of treatment with volanesorsen 285 mg Q2W ([redacted])
    - [redacted] after 18 months of treatment with volanesorsen 285 mg Q2W ([redacted])
    - [redacted] after 24 months of treatment with volanesorsen 285 mg Q2W ([redacted])
- The EAMS study (October 4th 2019 data cut), where patients were treated with doses every two weeks from study inception.
    - Nine patients were previously treated within APPROACH, APPROACH OLE or COMPASS and had a mean change in TG from clinical trial baseline of [redacted]
    - Seven patients were treatment naïve and had doses every two weeks from inception (a departure from the SmPC). Mean change in TG at 3 months was [redacted]
    - Data were not reported for four patients, presumably due to being in EAMS for only a short period

- The ERG also notes from the appendix[3] containing EAMS data ([redacted]) supplied as appendix 4 to the company's ECD response[2] that:

[redacted]

Error! Reference source not found.

[redacted]

[2]

[redacted]

[2]

[redacted]

[redacted]

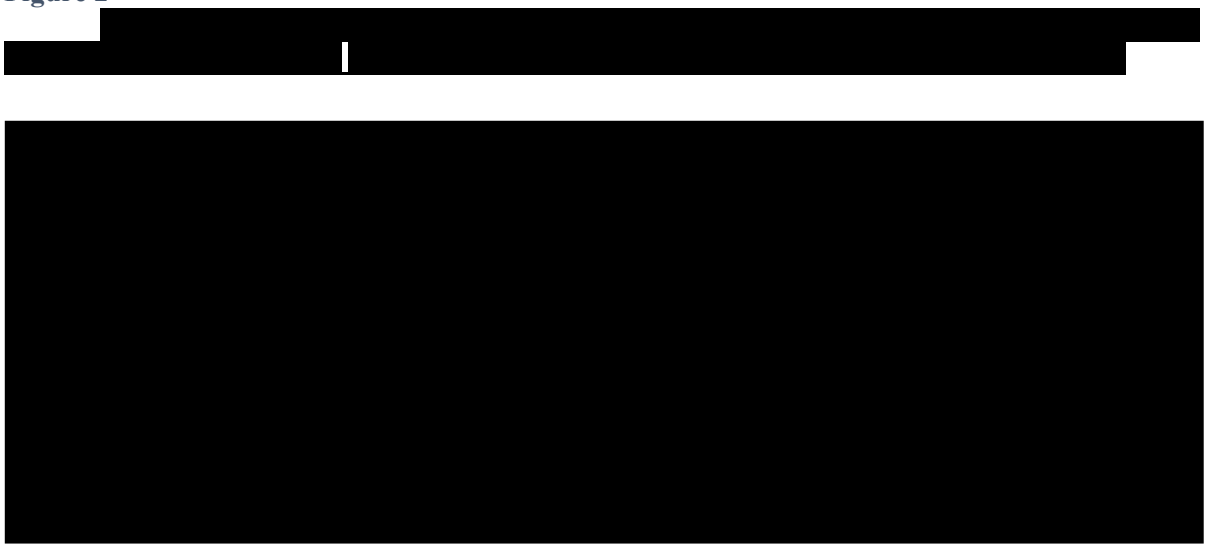
[redacted]

NB: Platelet levels trigger dose frequency changes when they dip below 140 x 10^9/L in the first three months of treatment (from weekly to every two weeks), and dose pauses when they dip below 100 x 10^9/L thereafter (from every two weeks to a ≥4 weeks pause, and resume after platelet levels ≥100 x 10^9/L). Treatment discontinuation is indicated when platelets go below 50 x 10^9/L.

During the appraisal, the ERG received clarification data[9] that showed a more variable picture of TG levels for patients, with an 18-month efficacy low with a mean change from baseline of [redacted]. This is reproduced here as Figure 2.

The company also considered that up-titration to weekly dosing at 6 months was unlikely in the UK, since only one EAMS patient had done so. They note that 6/33 patients in APPROACH completed the study without any dose adjustments, and achieved a mean reduction in TG of 76.2%.

Figure 2



The ERG agrees that weekly dosing produces a clinically meaningful change in TG levels at 3 months. The new data presented by the company (APPROACH OLE July 2019 data cut, and EAMS) suggest that the mean change in TG levels when receiving doses every two weeks is around 40%.

The ERG note that this is unlikely to result in all patients achieving TG levels that could be categorised as "low risk" by cut-offs generally accepted in the literature, which vary around 8.5-11.4mmol/L, since baseline TG levels in APPROACH were around 25mmol/L, and 40% reduction would lead to a mean TG of around 15mmol/L. The data presented in Figure 2 are still relevant, and . The ERG speculate that this may be due to dose pauses and missed doses.

The ERG agrees that up-titration is unlikely, and clinical advice to the ERG suggested that some patients might even benefit from dosing less than every two weeks. That 6/33 patients completed 12 months with no dose pauses suggests there may be some patients who can tolerate higher doses than others can. However, data are not presented beyond 12 months, and it is not clear if these patients experienced adverse events that did not lead to dose adjustments.

The ERG concludes that the mean reduction in TG levels at the SmPC dosing is likely to produce a mean TG reduction of around 40%. However, the ERG also notes that AEs continue to lead to dose pauses and patients appear to miss a proportion of doses voluntarily, and this may lead to poor or no TG reductions in some patients at some time points. Patients still appear to be at some risk of APs, as discussed in Section 2.2

2.4 Uncertainty: evidence not considered by the committee

The company notes that certain co-morbidities and symptoms were not included in the model or the vignette. These include joint pain, feeling cold all the time, numbness or tingling of digits, use of steroids and use of opioids.

The ERG notes that no quantification of these symptoms has been submitted, or of the reduction in symptoms when volanesorsen is provided, and therefore the impact they may have on the cost-effectiveness of the treatment is unknown.

The company state "*Although patients on volanesorsen are still required to adhere to a low-fat diet, appropriate dietary support as described in the FCS Best Practice Guide (Appendix 5) and being able to maximise your permitted fat could improve their nutritional status and help relieve the psychological burden of the strict diet*" (p20, response to ECD)[2]

The ERG notes that no empirical evidence is provided for this statement, and the extent to which this will occur in practice and the associated improvement in the health of patients are unknown. Therefore, the impact of potentially better nutritional status on the cost-effectiveness of the treatment is unknown.

3 The impact of the clinical points raised in the company response to the ECD on the incremental cost per QALY gained

In this section, the ERG details the impact on the incremental cost-effectiveness ratio (ICER) in terms of cost per QALY gained of the changes made by the company in response to the ECD. Each point also has an ERG critique and where appropriate an ERG-preferred estimate. The section concludes with a summary of the company's estimate of budget impact. On the 6th of February 2020 the ERG received notification that a further patient access scheme (PAS) had been submitted which reduced the price per vial of volanesorsen from the previous PAS price of £[redacted] per syringe to a price of £[redacted] per syringe. As the ERG does not know whether the PAS has been officially signed off both results with the old PAS, and with the new PAS are presented. The committee's preferred deterministic ICER was £481,508 with a probabilistic value of £492,072. The deterministic ICER becomes £355,235 when the new PAS is applied.

3.1 Impact on health-related quality of life for FCS patients

The ERG was pleased to see further details of the vignette study and acknowledge a typographical error in the ERG report[6] where it was intended to state that the generalisability of people who largely answered adverts in newspaper to members of the 'public' was uncertain, rather than 'FCS patients'. Additional details on how the wording for the states was established were provided by the company and that the statements were "[redacted]". It remains our view that the vignettes contain some elements of value-laden language that may affect the valuations obtained and that alternative more neutral language would have been preferable, but we would accept that this is relatively minor. The ERG believes that the duration of events should not affect the valuation of the utility of the health state and comments that some time periods are described in a vague way, for example pain "[redacted]". However, this perceived limitation is not believed to impact markedly on the results.

The company has changed the method used to assign utility to people with FCS description whilst clarifying its intention within the previous submission. The new method assigns the high TG utility value from the vignette to those in the TG>22.6mmol/L health state, whilst assigning the low TG utility value from the vignette to remaining patients (i.e. those with a TG level ≤22.6 mmol/L). This change reduced the ICER from the committee's deterministic base case value of £481,508 per QALY gained to an ICER of £342,725 per QALY gained (£252,847 when the new PAS is applied).

The ERG comments that this logic does not seem consistent with the vignette or the company submission. The vignette is explicit that in the 'low TG health state' TGs are not elevated whereas the company submission states that "*FCS is characterised by markedly elevated levels of triglycerides in the plasma (>8.4 mmol/L was the threshold in APPROACH, the pivotal phase 3 APPROACH trial)*"

and that values above 22.6 mmol/L are considered 'ultra-high' by Scherer et al. suggesting that values below, but close to this, would be considered high.[7] Therefore, the ERG does not believe that people who have TG levels in the band of ≥10 mmol/L to <22.6 mmol/L would qualify as having non-elevated TGs. Given this, the ERG maintains that its preference is for the method used in the ERG's base case. This assigns the 'low TG health state' vignette utility value to those with TG levels <10 mmol/L, the 'high TG health state' vignette utility value to those with a TG level >22.6mmol/L and the mean of the two values for those with a TG level ≥10 mmol/L to <22.6 mmol/L. Were the company wanting to distinguish between patients with TG levels of 11 mmol/L from patients with TG levels of 21 mmol/L then a model with finer gradation of TG level bands would be required.

Whilst it is not stated in the company's response to the ECD,[2] the utility values for those with an historic AP (one within the last five years) is further adjusted, as in the model considered at the Appraisal Committee, to take into consideration that some patients (assumed to be 50%) have fully recovered and do not have the lingering effects assumed in the vignette. The ERG is content with this adjustment.

3.2 Impact on health-related quality of life for family members / carers of FCS patients

The company has adjusted the value assigned to carer disutility that was 0.10 in the initial submission but has now been reduced to 0.04. The reduction was said to be informed by two elements, 1) that volanesorsen is indicated for an adult population and 2), that there would be an impact on the whole family when a family member has FCS.

The company stated that it had "*located a copy of the, now withdrawn, NICE metreleptin Final Evaluation Document (FED). Metreleptin was eventually awarded a relative utility decrement of 0.05 between treated and untreated groups*" This value could not be verified by the ERG. As metreleptin includes children, the company propose a lower value than 0.05. Having identified that the impact on family utility for patients with new musculoskeletal conditions was -0.03[10] the company proposed a disutility of 0.04, midway between 0.03 (for musculoskeletal conditions) and 0.05 (that stated by the company to be accepted for metreleptin). This change reduced the incremental cost-effectiveness ratio from the committee's deterministic base case value of £481,508 per QALY gained to an ICER of £426,174 per QALY gained.

The ERG believes that the carer disutility of 0.04 is likely to be an overestimate for the following reasons.

- That the carer disutility associated with treatments that have been displaced and are no longer funded have not been considered. For example, were funding for treatment of a new

musculoskeletal condition withdrawn, this would be associated with a utility loss of 0.03,[10] meaning a net effect of 0.01.

- That temporal issues have not been considered within the estimate as the loss in utility associated with existing mental or musculoskeletal conditions was 0.01 (with new mental conditions estimated as a loss of 0.02) thus indicating that the utility loss decreases over time.
- That as volanesorsen does not remove the need for a low fat diet that stresses such as the "*social isolation for the family that results from the patient's diet*" would not be impacted on by the use of volanesorsen.

Having considered these factors the ERG believes that a net societal disutility value of 0.01 may be more appropriate than 0.04. However, the impact of using alternative values between 0.00 and 0.04 has been tested. (£314,412 when the new PAS is applied)

3.3 AP event rate

In the company's base case of its original submission, it was assumed that a rate ratio of 0.13 could be used to estimate the impact of volanesorsen on AP. This value was calculated based on a comparison between AP event rates in the five years prior to the APPROACH OLE trial with the rates on treatment observed in the volanesorsen arm of the APPROACH trial. The ERG was critical of the use of these values for three reasons:

First, that the methodology would double-count benefits when patients with an historical AP were simulated to move to a better TG level, as better TG levels were assumed to have a reduced underlying risk of AP. Second, that there could be regression to the mean, in that patients are more likely to enter a study following a period where there were multiple APs and that enrolment in a study may improve patient behaviour; and third, that the data could be prone to recollection bias.

The company elected to address these points in reverse order, which has the advantage of leaving the more complex issue to last, which also uses information on the two other points. The company provided revised information to state that the medical histories of patients were 'definitively adjudicated' amending an error in a previous clarification response, and stating that there is no risk of recall bias. The ERG is content with this response.

With respect to regression to the mean, the company stated that "*We are not able to comment either way on the point about motivation to join the trial, we do not have that information.*" The company did address the potential issue of improvement due to being within a trial, suggesting that there was not an improved adherence to a low-fat diet "*on the basis that there is no notable change in TG results between screening for entry into the trial and the baseline TG measure: mean TG at screening was 26.8mmol/L*

and 25.0mmol/L at baseline. In this run-in period, patients were expected to ensure they were adhering to the required diet. The lack of variation between screening and baseline suggests there was no substantial change in adherence to diet." The ERG comments that there still may be an overestimation of the efficacy of volanesorsen due to regression to the mean, but would accept that if there were improvement due to being enrolled in a trial that this could be slight.

The company accepted that the method that had been used would have resulted in double counting in those with historical AP, which accounted for 54% of the starting patient cohort. This double counting did not apply to those with a recurrent AP (more than one AP within the last five years) as the underlying rate of AP was assumed independent of TG level. The company performed an analysis to assess the impact of the arbitrary value of 0.5 selected by the ERG and stated that this predicted a risk ratio of 0.45 for volanesorsen compared with placebo. This value was higher than the rate ratio of 0.35 estimated when comparing the pooled rates of AP observed in APPROACH, APPROACH OLE and COMPASS when using fortnightly dosing of volanesorsen for at least three months compared with the rate of AP observed in APPROACH and COMPASS for patients on placebo. The company stated that they had selected rate ratios of 0.27 for those with an historical AP and 0.28 for those with a recurrent AP claiming that these were reasonable midpoints between the 0.13 value in the original submission and the 0.35 obtained when comparing fortnightly dosing of volanesorsen for at least three months with placebo. On clarification, it was confirmed that the 0.27 and 0.28 rate ratios were actually for the low / medium TG bands and the high TG band respectively. This change reduced the ICER from the committee's deterministic base case value of £481,508 per QALY gained to an ICER of £454,703 per QALY gained (£333,849 when the new PAS is applied).

Estimating the most plausible values for the rate ratio associated with the use of volanesorsen is complex and the ideal data do not exist. The lower value of 0.13 is taken from a self-control cohort and there could be biases due to regression to the mean and more frequent doses of volanesorsen than fortnightly for a sizeable proportion of the population. The higher value of 0.35 has some comparative data between volanesorsen and placebo although this may be confounded by patients enrolled into APPROACH OLE who do not have a corresponding placebo group. Further to this, regardless of the rate ratio chosen, there will still be double counting of the reduction in AP levels in patients with an historical AP due to the assumed reduction in TG levels associated with the use of volanesorsen. The ERG did not have sufficient resources to reprogram the company model to allow the rate ratio to differ between those with an historical AP and those with a recurrent AP so this limitation could not be removed.

To provide the committee with indication of the sensitivity of the incremental cost-effectiveness ratio (ICER) to the assumed rate ratio the ERG has conducted analyses varying the value from 0.15 to 0.38 assuming an equal rate ratio for both historic and recurrent APs.

3.4 Discontinuation rates

The impact of the company capping discontinuation rates at 20% reduced the from the committee's deterministic base case value of £481,508 per QALY gained to an ICER of £462,683 per QALY gained but had a larger impact on the estimated number of undiscounted QALYs gained (increasing these from [redacted] to [redacted]). As stated, the ERG does not support a cap at 20% but prefers an assumption that 10% of those on treatment discontinue each year. However, the NICE appraisal committee preferred the use of the lognormal function and there has been no strong additional evidence on discontinuation presented since (see Section 2.1). As such, the ERG believes that this should not be changed although comments, for information, that the use of the exponential function increased the deterministic ICER from £481,508 to £483,814.

3.5 Summary of the changes in the results based on the amendments made by the company

The company present a summary of the impact of its proposed changes on the ICER. This is reproduced in Table 4. It can be seen that the company estimate a cost per QALY gained of £286,295 (£210,487 with the new PAS) compared with the NICE appraisal committee's preferred estimate of £481,508.

Table 4: A summary of the changes in the results based on the amendments made by the company. Reproduced from Table 7 of the company response to the ECD[2]

Scenario	Incremental costs	Incremental QALYs (undiscounted)	Incremental QALYs (discounted)	ICER [redacted] per syringe)	ICER [redacted] per syringe)
Committee base case	[redacted]	[redacted]	[redacted]	£481,508	£355,235
Low TG vignette values applied to TG health states < 22.6 mmol/L	[redacted]	[redacted]	[redacted]	£342,725	£252,847
Carer (family member) utility benefit of 0.04 applied on volanesorsen	[redacted]	[redacted]	[redacted]	£426,174	£314,412
Adjustment of 0.27 and 0.28 applied to risk of AP in the low/medium TG and high TG health states	[redacted]	[redacted]	[redacted]	£454,703	£333,849
Capping discontinuation at 20%	[redacted]	[redacted]	[redacted]	£462,683	£341,606
All of the above changes incorporated	[redacted]	[redacted]	[redacted]	£286,295	£210,487
Assuming a QALY modifier of [redacted]				[redacted]	[redacted]

3.6 Budget impact

The company states that there are around [redacted] patients likely to be treated with volanesorsen in England over five years. The ERG has no reason to dispute this statement. Assuming 26 doses of volanesorsen per year the costs would be approximately [redacted] per year at the initial PAS price and £[redacted] per year at the newly proposed PAS price.

4 ERG exploratory analyses

The results of the ERG's exploratory analyses using the original PAS price are presented in Table 5 with the results using the new PAS price presented in Table 6. These are deterministic values. The utility for people with FCS and the discontinuation rate has been left at the NICE appraisal committee's preferred values, with two-way sensitivity analyses performed altering the assumed treatment effect of volanesorsen on AP rates and the assumed carer disutility. In all of the ERG's analyses, the undiscounted QALYs gained were below [redacted].

Table 5: Cost per QALY gained results from the ERG's deterministic exploratory analyses (original PAS price).

Treatment effect of volanesorsen on AP rate	Carer disutility value				
	0.00	**0.01**	**0.02**	**0.03**	**0.04**
0.14	£440,188	£427,168	£414,895	£403,308	£392,351
0.17	£443,480	£430,294	£417,869	£406,142	£395,055
0.20	£446,798	£433,445	£420,867	£408,998	£397,780
0.23	£450,144	£436,621	£423,888	£411,876	£400,526
0.26	£453,517	£439,823	£426,933	£414,776	£403,293
0.29	£456,917	£443,051	£430,001	£417,698	£406,080
0.32	£460,346	£446,304	£433,094	£420,643	£408,888
0.35	£463,802	£449,583	£436,210	£423,609	£411,716
0.38	£467,286	£452,888	£439,350	£426,598	£414,566

Table 6: Cost per QALY gained results from the ERG's deterministic exploratory analyses (new PAS price).

Treatment effect of volanesorsen on AP rate	Carer disutility value				
	0.00	**0.01**	**0.02**	**0.03**	**0.04**
0.14	£322,342	£312,807	£303,820	£295,335	£287,311
0.17	£324,946	£315,285	£306,181	£297,588	£289,465
0.20	£327,575	£317,785	£308,563	£299,862	£291,637
0.23	£330,229	£320,309	£310,967	£302,155	£293,829
0.26	£332,907	£322,855	£313,393	£304,469	£296,040
0.29	£335,610	£325,425	£315,840	£306,803	£298,270
0.32	£338,338	£328,018	£318,309	£309,158	£300,518
0.35	£341,091	£330,634	£320,799	£311,533	£302,786
0.38	£343,869	£333,274	£323,312	£313,928	£305,073

As expected, the ICERs using the newly proposed PAS price are lower than those using the previous PAS price. Considering the new PAS price, it is seen that in the range of scenario analyses run by the ERG that the deterministic ICER was never below £285,000 per QALY gained (£390,000 for the old PAS price).

Using the values for AP rate ratio proposed by the company (0.27 for low/medium TG levels and 0.28 for high TG levels), and the carer disutility proposed by the company (0.04), it is estimated that the deterministic cost per QALY gained would be between £296,000 and £298,000 for the new PAS price. (£403,000 and £406,000 for the old PAS price).

The ERG believes that the net carer disutility is lower than proposed by the company and that the company's preferred estimates of the AP rate ratios are potentially favourable to the company. As such, the ERG believe that plausible combinations of treatment effect on APs and carer disutility are likely to generate a deterministic cost per QALY gained in excess of £315,000 using the new PAS (in excess of £430,000 using the old PAS price). The probabilistic values are likely to be greater than the deterministic values for all presented analyses. To test this, the most favourable and least favourable deterministic ICERs in Table 6 were run probabilistically. Both increases were moderate (< £5000 per QALY gained) with the probabilistic ICER for the most favourable assumption being £291,324 and the probabilistic ICER for the least favourable assumption being £348,343.

There may be increased uncertainty in the ICERs due to the impact of dose pauses/missed doses and potential up-titrating of volanesorsen to once-weekly dosing. Dose pausing/missed doses will be associated with lower volanesorsen acquisition costs whereas up-titrating would be associated with higher volanesorsen acquisition costs. These changes may also have impact on clinical outcomes, the magnitude of which is uncertain, but it is plausible that reduced costs of volanesorsen would be associated with worse clinical outcomes whereas increased costs of volanesorsen would be associated with better clinical outcomes. The net effects of dose pausing/missed doses and up-titrating could not be quantified by the ERG and it has only commented on the increased uncertainty.

The company makes a claim that the ICER may be overestimated due to elements, such as joint pain, use of opioids and improved nutritional status, which were omitted from the decision problem. In Section 2.4 the ERG detail that the evidence for the improvement in these elements is lacking. Therefore, the impact on the ICER is unknown, and could be small.

References

1. National Institute for Health & Care Excellence. Evaluation consultation document. Volanesorsen for treating familial chylomicronaemia syndrome. In; 2020.
2. Therapeutics A. Company Response to ECD. In; 2020.
3. Therapeutics A. Appendix 4: Baseline Characteristics, Efficacy & Safety Data from the Volanesorsen EAMS. In; 2020.
4. National Institute for Health and Care Excellence. Volanesorsen for the treatment of familial chylomicronaemia syndrome (FCS). Company submission of evidence. In: Highly Specialised Technologies Evaluation Programme 2018.
5. National Institute for Health and Care Excellence. Volanesorsen for the treatment of familial chylomicronaemia syndrome (FCS) - Company submission of evidence. In: Highly Specialised Technologies Evaluation Programme 2019.
6. Harnan S, Stevenson M, Ren S, Rawdin A, Orr M, Clowes M*, et al.* Volanesorsen for treating familial chylomicronaemia syndrome: A Highly Specialised Technology Appraisal. School of Health and Related Research, (ScHARR). 2019.
7. Scherer J, Singh V, Pitchumoni C, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. *Journal of Clinical Gastroenterology* 2014;48:195-203.
8. Akcea Therapeutics. Clinical Study Report (CALIBER). In. Akcea Company submission to NICE; 2018.
9. Akcea Therapeutics. Volanesorsen for treating familial chylomicronaemia syndrome [ID1326] - Response to clarification questions. In; 2019.
10. Wittenberg E, Prosser L. Disutility of Illness for Caregivers and Families: A Systematic Review of the Literature. *PharmacoEconomics* 2013;31:489-500.

This addendum has been requested by NICE following the second Appraisal Committee meeting (26th February 2020). It uses the PAS as submitted at the time of the meeting and makes the following changes from the committee's preferred assumptions as detailed in the ACD.

1) Setting the value of carer disutility to 0.02
2) Assuming a direct effect of volanesorsen on APs using a rate ratio of 0.29 independent of TG levels
3) Assuming that the discontinuation rate for people having volanesorsen was 10% per year in perpetuity

The results generated by these assumptions are provided in Table 1.

Table 1: Results based on the committee's new preferred assumptions

Description	Discounted Costs	Discounted QALYs	Incremental Discounted Costs	Incremental Discounted QALY	Cost per QALY gained
Deterministic					
SoC	[redacted]	[redacted]			
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	£317,477
Probabilistic					
SoC	[redacted]	[redacted]			
Volanesorsen	[redacted]	[redacted]	[redacted]	[redacted]	£321,413

The undiscounted QALY gains were [redacted] in the deterministic analyses and were [redacted] in the probabilistic analyses

Document written by Matt Stevenson (28th February 2020)