NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Volanesorsen for treating familial chylomicronaemia syndrome

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using volanesorsen in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- 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?
- 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?

Issue date: December 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using volanesorsen in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 27 January 2020

Second evaluation committee meeting: 26 February 2020

Details of membership of the evaluation committee are given in section 6.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Recommendations

1.1 Volanesorsen is not recommended, within its marketing authorisation, for treating familial chylomicronaemia syndrome 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.

1.2 This recommendation is not intended to affect treatment with volanesorsen that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Familial chylomicronaemia syndrome is a rare and potentially life-threatening condition that has a significant effect on the quality of life of people with the condition, and their families and carers. Patients have severe abdominal pain, unpredictable and recurrent acute pancreatitis and fatigue, and need to have a restricted low-fat diet. Current treatment options are limited.

Clinical trial evidence shows some short-term benefits with volanesorsen treatment, including a reduction in triglyceride (a type of fat found in the blood) levels. But it is uncertain whether this is maintained in the longer term. There is also uncertainty around the evidence because the licensed dose was not used in clinical trials.

The assumptions in the economic modelling are highly uncertain, particularly around:

- the relationship between triglyceride levels and risk of acute pancreatitis in people with familial chylomicronaemia syndrome
- the direct effect of volanesorsen on the risk of acute pancreatitis
- the quality of life values used in the model
- how the effect on the quality of life of carers is accounted for.

The criteria for a quality-adjusted life-year weighting has not been met (that is, the extra health and quality-of-life benefits of volanesorsen are not considered to be substantial). Also, the cost-effectiveness estimates are much higher than what NICE considers acceptable for highly specialised technologies.

Because of the concerns around the clinical evidence and high cost, volanesorsen is not considered an appropriate use of NHS resources within the context of a highly specialised service, so cannot be recommended.

2 The condition

2.1 Familial chylomicronaemia syndrome (FCS) is a rare genetic metabolic disorder of lipid metabolism caused by homozygous mutations in the lipoprotein lipase gene. It is characterised by high levels of triglycerides in the plasma and a build-up of chylomicrons (the lipoprotein particles responsible for transporting dietary fat from the intestine to the rest of the body). Symptoms include repeated episodes of severe abdominal pain, unpredictable and recurrent episodes of acute pancreatitis, enlargement of the liver and spleen, and fatigue. Acute pancreatitis is a life-threatening condition for which intensive care may be needed. Repeated attacks of acute pancreatitis may lead to chronic pancreatitis. Diabetes can develop as a result of pancreatitis and often makes FCS more difficult to manage.

2.2 Current treatment options for people with FCS are limited. To keep plasma triglyceride levels low, management consists of severely restricting dietary fat intake (usually to between 10 g and 20 g daily) and

consuming no alcohol. People with the condition may take several drugs to control pain and other symptoms of FCS, including corticosteroids, analgesics, anxiolytics, antidepressants, diabetes treatments and antithrombotic drugs. People on a fat-restricted diet need supplements of essential fatty acids (linoleic and alpha linolenic acids) and fat-soluble vitamins (vitamins A, D, E and K). In addition, treatments for hypercholesterolaemia (such as fibrates, nicotinic acids and statins) may be prescribed but are of limited value. The strict dietary regimen is highly restrictive and often challenging for people with the condition and their families. Also, people often still have high triglyceride levels even when the diet is closely followed.

2.3 The prevalence of FCS is estimated to be 1 to 2 per million people, which equates to about 55 to 110 people in England. At the time of the evidence submission, there were thought to be around 80 to 100 people with FCS eligible for treatment with volanesorsen in the UK.

2.4 Treatment with volanesorsen has been provided since March 2018 under an Early Access to Medicines Scheme at several specialist centres. The company explained that 20 people are currently having volanesorsen (with treatment duration ranging from 1 to 15 months). A further 5 people have been identified to start treatment.

3 The technology

3.1 Volanesorsen (Waylivra, Akcea) is an antisense oligonucleotide inhibitor of apolipoprotein C-III (apoC-III). ApoC-III inhibits the metabolism of triglycerides via the actions of both the lipoprotein lipase and LPL-independent pathways. It selectively binds to apoC-III mRNA to prevent the production of the apoC-III protein, so increasing metabolism of triglycerides. Volanesorsen has a marketing authorisation that indicates it ‘as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in

whom response to diet and triglyceride-lowering therapy has been inadequate'. Volanesorsen is administered by subcutaneous injection. The recommended starting dosage is 285 mg once weekly for 3 months, followed by down-titration to a maintenance dosing schedule of once every 2 weeks. If there has not been a greater than 25% reduction in triglyceride levels, or if these remain above 22.6 mmol/litre at 3 months, treatment should be stopped. If response is inadequate (in terms of serum triglyceride reduction) after 6 months of treatment, an increase in dosing frequency to 285 mg once weekly should be considered. Dosing may also change at 9 months and later depending on response to treatment and platelet levels.

3.2 The adverse reactions listed as very common (that is, occurring in 1 in 10 people or more) in the summary of product characteristics for volanesorsen include thrombocytopenia and injection site reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Before starting treatment with volanesorsen, platelet count should be measured. If it is below $140x10^9$/litre, another measurement should be taken about a week later to reassess. If platelet count remains below $140x10^9$/litre at a second measurement, treatment should not be started. Because of concerns about thrombocytopenia, an enhanced monitoring scheme has been implemented during clinical trials. For full details of monitoring schedules see the summary of product characteristics.

3.4 The price of volanesorsen for a single-use syringe (285 mg) is £11,394 (excluding VAT; company's evidence submission). The company has a commercial arrangement, which would apply if the technology had been recommended.

4 Consideration of the evidence

The evaluation committee (see section 6) considered evidence submitted by Akcea Therapeutics, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Burden of disease

4.1 The patient and clinical experts explained how the condition affects all aspects of the lives of people with familial chylomicronaemia syndrome (FCS), and their families and carers. It has a significant effect on a person's independence, and their ability to work and take part in a social life. People with FCS live in constant fear of having a life-threatening attack of acute pancreatitis (AP) and recurrent hospital admissions. This can be depressing for them, 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 patient experts explained that FCS is a hidden disease because people who do not have the condition often find it difficult to understand the challenges associated with it. This has made it difficult for people with FCS, and their families and carers to get support. The committee concluded that FCS is a

rare, serious and potentially life-threatening condition that can affect the lives of people with the condition, and their families and carers.

Unmet need

4.2 The clinical experts explained that FCS is a relentless condition, and that currently there are no effective drug treatments available. They noted that, in the absence of treatment targeting FCS, dietary advice is a mainstay of supportive treatment. The patient experts noted their frustration with this because dietary control can be very challenging. They also explained that people may have mixed experiences of symptom and disease management approaches, depending on their triglyceride (TG) levels, but that a new treatment option would offer considerable hope to them and to their families. The committee recognised that there is a significant unmet need for effective treatment options for FCS.

Diagnosis

4.3 The clinical experts explained that, historically, FCS has been diagnosed by several clinical criteria, including abdominal pain, AP and raised TG levels refractory to lipid-lowering therapy (but not due to other causes such as type 2 diabetes or hypothyroidism). Given the rarity of the disease, people with FCS often experience delayed diagnosis, or misdiagnosis and inappropriate treatment. The committee heard that genetic diagnosis is becoming more common. It identifies some mutations in lipoprotein lipase, apolipoprotein 2 and 5, lipase maturation factor 1 or GPIHPB1 genes, which code for proteins involved in lipoprotein lipase activity. The expert from NHS England noted that genetic testing will become available from April 2020, which will help with the identification and genetic confirmation of FCS.

Impact of the new technology

Clinical evidence

4.4 The clinical evidence available for volanesorsen included:

- APPROACH (n=66) – a double-blind randomised placebo-controlled trial that assessed the efficacy and safety of volanesorsen (n=33) in comparison with placebo (n=33). Volanesorsen was administered by subcutaneous injection (285 mg) once weekly. After the 52-week trial period, patients could either have a 13-week follow up or enter the APPROACH OLE open-label extension study.
- COMPASS (n=114) – a multicentre double-blind randomised placebo-controlled trial in patients with hypertriglyceridaemia from many different causes; only 7 patients had FCS. Volanesorsen was administered by subcutaneous injection (285 mg) once weekly. After 26 weeks, patients could either have a 13-week follow up or enter the APPROACH OLE open-label extension study.
- APPROACH OLE – an ongoing single-arm open-label study assessing the safety and efficacy of dosing and extended dosing with volanesorsen. Volanesorsen was administered by subcutaneous injection (285 mg) once weekly. Information about treatment arms and patient numbers have been deemed to be academic in confidence by the company, so cannot be presented.
- The Early Access to Medicines Scheme (EAMS) (n=20) – an ongoing programme that provides access to volanesorsen (administered by subcutaneous injection, 285 mg biweekly) for people with FCS, including those who have previously had treatment in APPROACH and APPROACH OLE.

Emphasis on clinical efficacy outcomes was given to data from APPROACH and APPROACH OLE. The committee noted some small differences in baseline characteristics between the trials and the clinical

population in England, such as level of abdominal pain, which was high in APPROACH compared with what is seen in the English population. Furthermore, 11% of patients in APROACH had previously had alipogene tiparvovec (a gene therapy for the treatment of lipoprotein lipase deficiency). This may have lowered the baseline levels of pancreatitis compared with levels seen in patients in clinical practice in England. The ERG noted that the baseline differences added uncertainty to the estimates of true relative treatment effect, but that the level of uncertainty was unclear. The committee agreed that this introduced uncertainty into the consideration of clinical data, but concluded that it was acceptable for decision making.

Representativeness of study populations in relation to genetic diagnosis of FCS

4.5 Most of the patients in the company's clinical studies had a genetic diagnosis of FCS (a condition of the license). The committee discussed whether the studies' populations would be representative of people with FCS seen in the NHS. It noted that about 50% of patients in APPROACH lacked known functional mutations in the lipoprotein lipase gene. However, it understood that some patients with FCS may have unknown gene mutations that cannot be diagnosed genetically, and such patients may have entered the trial. However, because of the condition of the license, these patients would not be part of the NHS population. The company explained that there is no clear correlation between types of gene mutation and disease prognosis. The committee agreed that, given this, it was reasonable to consider the trial population to be generalisable to clinical practice.

High risk of pancreatitis in relation to TG levels

4.6 The marketing authorisation for volanesorsen stipulates that people must have a high risk of pancreatitis to be able to have the drug. The committee discussed how clinicians would define this in clinical practice. The ERG

explained that anyone with high TG levels could be clinically considered to be at high risk of pancreatitis, but queried whether clinicians might interpret the license differently. The clinical experts explained that TG levels can be variable and volatile in people with FCS, but agreed that they would generally consider people with high TG levels to be at high risk of pancreatitis. They also explained that TG levels in patients with FCS vary across and within individuals with huge fluctuations over time, and that TG levels are high most of the time if they are uncontrolled. The clinical experts explained that the decision to treat is based on discussions with patients and consideration of their needs. The committee concluded that the definition in the marketing authorisation for 'high risk of pancreatitis' is likely to include anyone with high TG levels.

Dosing

4.7 The volanesorsen dose stated in the license was not used in the clinical trials nor in the EAMS population (see section 4.4). The committee discussed the implications of this for interpreting the evidence in relation to volanesorsen's clinical efficacy and safety. It queried the frequent dose adjustments and pauses seen in studies. It concluded that these would be more likely under the intensified monitoring regime of EAMS and the clinical trial, than in clinical practice. It also considered the effect of these on patients, TG levels and clinical outcomes. It understood that, in EAMS, patients all started on biweekly dosing but could uptitrate to the licensed dose if there was not a sufficient response. The committee considered that the reason given for the dose adjustments and pauses was understandable from a general pharmacological point of view. However, it remained concerned that the dose adjustments and pauses seen in the clinical trials increased uncertainty about the long-term efficacy and safety of volanesorsen and the likely rate of stopping treatment. The committee concluded that the difference between the licensed and trialled dosing regimens contributed to further uncertainties. It also concluded that, because of the higher dosing in trials, volanesorsen's effect on clinical and

safety outcomes may have been overestimated in the short term and that, given the lack of evidence, its effect in the long term at any dose is uncertain.

Percentage change in TG level as a surrogate outcome

4.8 The primary outcome measure in APPROACH was the percentage change from baseline in TG levels at month 3 (there were no formally designated primary and secondary outcomes in APPROACH OLE). In APPROACH, at month 3, volanesorsen treatment was associated with a statistically significant and clinically meaningful change in TG levels compared with placebo (percentage difference in change from baseline in TG: 94.1%, 95% confidence interval [CI] -121.7 to -66.6; p<0.0001). Clinical data from APPROACH OLE has been deemed to be academic in confidence by the company, so cannot be presented here. However, the company stated that the results were supportive of an effect with volanesorsen, indicating a substantial decrease in TG levels with volanesorsen at month 3 and over time. The committee was aware that percentage change in TG levels is a surrogate outcome for clinical outcomes such as AP. The company explained that percentage change in TG level is a commonly used and important outcome that shows the effect of volanesorsen. The clinical experts agreed that change in TG levels has been used over time in clinical practice and can be considered predictive of clinical outcome. The ERG explained that, at subsequent time points, evidence showed that the response in TG levels was generally lower than what was seen at month 3 in APPROACH, but that the possible waning effect of volanesorsen is probably small. The ERG also noted that follow up in studies did not appear to go beyond around 3 to 4 years. Therefore, the long-term effects of volanesorsen measured by percentage change in TG levels is uncertain. The committee concluded that volanesorsen is effective in lowering TG levels in people with FCS, but that the extent of the effect and its impact on the risk of pancreatitis, especially in the long term, is unclear.

Dose-response relationship between TG levels and acute pancreatitis

4.9 The committee considered the evidence provided by the company on a possible dose-response relationship between TG levels and AP. The company explained that increased levels of TGs leads to an increased risk of AP. TG levels below 10 mmol/litre are associated with a low risk of AP, and risk increases with TG levels above 10 mmol/litre, becoming particularly high at levels of 22.7 mmol/litre or more. The assumptions are used in the company's economic model to define certain health states (see section 4.18). The clinical experts noted that there is a linear relationship between TG levels and risk of AP in the general population. However, there is a lack of evidence about whether this dose-response relationship is generalisable to FCS. For people with FCS, TG levels can be variable and volatile among individuals (see section 4.8), and they are likely to have individual thresholds at which they are individually at high risk of developing AP. The clinical experts also suggested that people with FCS may experience AP at lower TG levels than patients with raised TG levels from other causes. The committee accepted that there is a general linear relationship between TG levels and risk of AP. It remained uncertain about whether this was generalisable to people with FCS or applicable to individuals, but acknowledged that there may be individual thresholds for people with FCS.

Study outcomes

Responder analysis

4.10 Several responder analyses were conducted by the company. The committee particularly looked at 2 of them. This is because they are closely relevant to the decision making for TG level bands as defined in the company's economic model (see section 4.16) and for the stopping rule for volanesorsen as set out in the summary of product characteristics (see sections 3.1 and 4.16). These include:

- attaining fasting TG levels of below 750 mg/decilitre (8.5 mmol/litre) between baseline and month 3
- a 40% reduction in fasting TG levels between baseline and month 3.

In APPROACH, 76.7% (n=23/33) of patients having volanesorsen and 9.7% (n=3/33) of those on placebo met the first of these endpoints (odds ratio: 186.16, 95% CI 12.86 to not applicable; p<0.0001). Similarly, for the second of these endpoints, evidence from APPROACH showed that statistically significantly more patients on volanesorsen (87.9%, n=29/33) met the endpoint compared with those on placebo (9.1%, n=3/33) at month 3 (odds ratio: 99.69. 95% CI 15.75 to 631.06; p<0.0001). Generally, a reduction in TG levels at month 3 or a moderate-to-high relative reduction in TG levels was seen. The ERG noted that this showed that a good proportion of patients are likely to continue treatment after the assessment of stopping rules (see section 3.1). The clinical experts explained that it is difficult to identify a population threshold in TG levels for clinical events (such as pancreatitis) in FCS. However, they agreed that there is likely to be a level below which individuals are unlikely to have pancreatitis, so it is appropriate to consider people in whom the endpoints as defined above are reached to be at 'lower risk'. The ERG highlighted that the evidence showed that response rates wane over time, so treatment effect may vary. The committee concluded that TG levels would fall to levels at which pancreatitis is less likely in a substantial proportion of patients, but that it remains uncertain whether this benefit lasts.

Acute pancreatitis

4.11 Evidence from a pre-planned safety analysis showed that 1 patient having volanesorsen (n=33) and 3 patients on placebo (N=33) had AP (p=0.6132) in APPROACH. A post-hoc analysis comparing the AP event rate 5 years before treatment with the AP event rate while on treatment in the same trial showed a statistically significant difference in favour of

volanesorsen (p=0.0242). The same post-hoc analysis comparing event rates of AP 5 years before treatment with that while on treatment was conducted in APPROACH OLE (rate ratio 0.13, p value not reported). This rate ratio was used in the economic model to inform the risk of AP associated with volanesorsen (see section 4.19).The ERG highlighted that this risk estimate was highly uncertain because it was derived from a before-after comparison using patients as a self-control, so there was a high risk of recollection bias. In general, the ERG noted that the treatment might reduce AP events, but the effect size is unclear. The committee agreed with the ERG, and noted that risk estimate of AP derived by the company was uncertain and subject to high risk of bias because of the methods employed.

Abdominal pain

4.12 The pre-planned efficacy analyses describing the average maximum intensity of abdominal pain during the on-treatment period in APPROACH did not show a statistically significant difference between treatment arms. However, an exploratory analysis showed that, among those who had abdominal pain at baseline in APPROACH (n=17), patients having volanesorsen (n=7) had a statistically significant reduction in the average maximum intensity of abdominal pain, compared with those on placebo (n=10; p = 0.0227). The ERG commented that this difference may have been because of the higher baseline rates of abdominal pain in this subgroup, making it easier to detect an effect. The committee noted that patients continued to have some abdominal pain while on treatment, and that volanesorsen's effect on abdominal pain is unclear.

Overall study results

4.13 The committee concluded that the clinical trial evidence showed some effect with volanesorsen on TG levels and possibly on clinical events (AP and abdominal pain). The evidence raised the possibility that response to the treatment may wane over time, but that any reduction is likely to be

small. The committee considered that, because of the limitations in the data, volanesorsen' effect on clinical efficacy and safety outcomes in the long term, particularly at the licensed dose, is uncertain.

Health-related quality of life

4.14 Health-related quality of life (HRQoL) was measured using the EQ-5D and SF-36 in APPROACH and APPROACH OLE. In APPROACH, there was no statistically significant change from baseline for the EQ-5D-5L or SF-36 or at month 3 (p=0.2920 and p=0.6627 respectively), at month 6 (p=0.5923 and p=0.9226 respectively) and month 12 (p=0.4079 and p=0.7912 respectively). Baseline values captured by EQ-5D were very high for both treatment arms (utility more than 0.97) in APPROACH. The committee noted that baseline values were not in line with the patient testimonies, which indicated that FCS substantially affects every aspect of their lives. One patient expert explained that part of the reason is that the EQ-5D does not measure the aspects of quality of life that FCS affects, for example, strict adherence to low-fat diet and the effect of that on their family and social lives. The committee noted that the EQ-5D does not contain questions about difficulties posed by the restricted diet, but does measure usual activities, pain and anxiety. Another patient expert noted that people with FCS may have adapted by taking living with the condition as their normal (for example, the fear of having AP, restrictions to usual activities related to dietary restrictions), so no difference from baseline would be detected. The committee recognised that the intermittent nature of symptoms might explain why a one-off questionnaire might not fully capture the effect of FCS on quality of life. Also, it did not think that the clinical trials results indicated that the technology had no effect on quality of life.

Adverse events

4.15 The committee discussed the adverse events reported in the 2 main clinical trials. Common events (occurring in between 1 in 100 or more and

fewer than 1 in 10 patients) in APPROACH were wide ranging, but the most frequent (in 1 in 10 or more patients) were limited to injection site reactions, fatigue, headache and thrombocytopenia. Seven (21%) patients in the volanesorsen group had serious adverse events compared with 5 (15%) patients on placebo. The committee recalled that safety risks had been identified with volanesorsen (see section 3.3), and an intensified routine monitoring scheme had been implemented in clinical trials and the EAMS. It noted, however, that the effect of volanesorsen on safety outcomes and, consequently stopping treatment, is unknown at the licensed dose in the long term.

Cost to the NHS and value for money

Company's economic model

4.16 The company presented an economic model comparing volanesorsen alongside a low-fat diet with standard of care. The model had 2 components: a 3-month decision tree model and a long-term Markov model. In each 3-month model cycle, patients moved between TG bands or remained in the same band, had AP, chronic pancreatitis or died. Patients with historical AP moved to the recurrent AP category when having AP. Treatment with volanesorsen was assumed to be weekly within the initial 3-month period and fortnightly in the Markov stage until stopping treatment or death (in accordance with the summary of product characteristics dosing schedules). All patients who had standard of care in the initial phase progressed to the standard-of-care Markov model. Patients who had volanesorsen had to meet continuation criteria (a TG level reduced by 25% or more; and TG level below 22.6 mmol/litre or both) to remain on volanesorsen, otherwise they progressed to the standard-of-care arm. The population in the model was in line with the indication (see section 3.1). A high risk of pancreatitis was defined as having had a previous AP event in the model. The hypothetical cohort of patients:

- were assumed to be 41 years old
- comprised 54.5% females
- and were assumed to have the same following characteristics as patients in APPROACH:
  - AP history – 0 or 1 or more episodes in the past 5 years
  - baseline TG levels – below 10 mmol/litre (low-risk band); between 10 mmol/litre and below than 22.6 mmol/litre (medium-risk band); 22.6 mmol/litre or more (high-risk band), which were used to define health states in the Markov model.

4.17 The company's economic analysis adopted an NHS perspective and implemented a 59-year time horizon (assumed to represent the maximum remaining lifetime of a patient). A discount rate of 3.5% per annum was used for both cost and health outcomes. The committee was satisfied that the model structure reflected the general course of the condition, although it recalled the uncertainty in the relationship between TG levels and risk of AP in people with FCS.

Model assumptions

Assumptions on volanesorsen's indirect and direct effects on AP

4.18 In the model, the company assumed that volanesorsen would reduce the risk of AP by:

- reducing patients' TG-risk band indirectly
- directly reducing the risk of AP independent of TG-risk bands.

The risk estimate associated with volanesorsen's direct protective effect on AP was estimated from a post-hoc analysis. This compared the event rate of AP in patients 5 years before enrolment in APPROACH OLE with their event rate while on treatment. This produced a rate ratio of 0.13 for patients on volanesorsen compared with those on standard of care (see section 4.11). In the model, the risk

of AP occurrence in the standard-of-care arm was calculated by fitting an accelerated-failure-time model to observational data from the CALIBER study. This contains linked electronic health records from England.

4.19 This rate ratio of 0.13 was applied to patients with historical AP in the company's model. The ERG explained that this estimate was calculated from a population in whom there was already a potential for reducing TG levels (via the indirect effect of volanesorsen on TG levels). This meant it represented a double counting of the benefits. The reduction may have been an overestimate of the effect of a patient enrolling in a study in which a greater adherence to diet was in place. This meant it was subject to regression to the mean (which is a statistical phenomenon that can make natural variation in repeated data look like real change) and a high risk of bias (see section 4.11). The ERG therefore removed some of the double counting by applying a multiplication factor of 0.50 to both historical and recurrent AP rates within a specific TG-risk band. It recognised that this estimate was also arbitrary (that is, not based on evidence). The committee recalled the uncertainty in the relationship between TG level and risk of AP. It was not persuaded that there was an effect with volanesorsen on AP that was independent of TG level. In the absence of robust evidence, it preferred the ERG's assumption because it at least removed some of the double counting of volanesorsen's effect on AP in the model.

Stopping treatment

4.20 The committee noted that relatively high stopping rates were seen across the clinical studies. In APPROACH, 42% (14/32) of patients stopped before month 12, and 79% stopped before week 104. It understood that the most common reason for stopping was adverse events. Stopping rates from APPROACH OLE have been deemed to be academic in confidence by the company, so cannot be presented here. The committee

was also aware that only 1 patient stopped treatment in the EAMS because of cancer recurrence. However, it questioned whether this would be seen in clinical practice because of the different dosing regimen (see sections 3.1 and 4.16). The company explained that, with appropriate education and monitoring in place, stopping will be lower than what was seen in the clinical trials. The ERG noted that the stopping rate at the licensed dose in clinical practice is currently unknown, but is unlikely to be zero in clinical practice. It suggested that it was likely to be somewhere between 10% and 20% each year. The committee understood that stopping treatment seen in trials was not only a result of meeting the stopping rules set out in the summary of product characteristics (see section 3.1). It concluded that, because of the relatively high drop-out rate seen in the clinical trials, some stopping would be likely in clinical practice even with proper education and monitoring in place.

Time on treatment

4.21 The committee recognised that the rate of stopping treatment was an influential factor on the model results. Stopping could happen in the model because of not meeting the continuation criteria (see section 4.16), death, lack of adherence to the treatment and monitoring, or adverse events. In the model, stopping was modelled by fitting parametric survival functions to time on-treatment data for 32 patients on biweekly dosing within APPROACH OLE. The company preferred to use lognormal curves to predict when treatment would stop. This curve allows for a decreasing rate of stopping treatment over time. The committee recalled that relatively high stopping rates were seen across the clinical studies. However, it was also aware that only 1 person stopped treatment in the EAMS even though patients had biweekly dosing from the start in the scheme (see section 4.20). It considered that the lognormal curve was a reasonable fit for stopping rates in the trial over time. However, it also agreed that the initial stopping rate of 10% per annum deemed by the ERG (see section 4.20) is more likely in clinical practice than the low rate

in the EAMS. The committee therefore concluded that the company's lognormal curve best reflected the likely change in stopping rate with volanesorsen in clinical practice over time.

Source of utility data and the vignette study

4.22 The utility data collected in APPROACH were not used in the model. The company explained that this was because utility values for both treatment arms were higher than the average UK index value and deemed them implausible. Instead, the utility values for the base case were derived from a vignette study commissioned by the company. Substantial information available for the vignette study has been deemed to be academic in confidence by the company, so cannot be discussed here. The ERG noted that the vignettes did not distinguish between patients who were on treatment and those who were not, but instead by low- or high-risk TG bands. This contrasted with how the utility values were used in the company's model, in which utility for a patient was determined by whether treatment was with volanesorsen or standard of care. The ERG provided alternative utilities in its base case, which used the vignette results but linked the utility to TG levels rather than treatment. It also assumed that values for patients with historical AP lay halfway between those with no prior AP and those with AP with lingering effects. The committee was concerned about the robustness of the vignettes used to elicit the utility values. This was because of the lack of details on the study methodologies, such as recruitment, description of health states and the ordering of questions asked. The committee preferred the ERG's approach of linking utility values to TG levels and health states. It encouraged the company to provide further details on the vignette study. In the absence of further evidence, it concluded that it would consider utility values based on the ERG's analysis.

Utility for carers

4.23 The company included utility decrements for carers in the economic model. It used the values from a NICE highly specialised technology submission (metreleptin for treating lipodystrophy) as a proxy for carers of people with FCS, assuming a 0.10 utility decrement for carers. The company explained that it believed the assumptions for lipodystrophy to be generalisable because the condition is another metabolic disease with similar outcomes and challenges in terms of daily dietary management as FCS. However, the ERG noted that the source of the carer utility decrement, and the committee's view of it, in the metreleptin submission was unknown. Also, in the volanesorsen model, the average age of patients was assumed to be 41 years, whereas the population for which metreleptin is indicated includes children and young people, when 24-hour caring may be needed. Therefore, the ERG removed this additional decrement from its base case. The committee recalled that the patient and clinical experts explained the substantial effect of FCS on the lives of patients, and their families and carers (see section 4.1). The committee agreed that there could be an effect of FCS on the utility of carers, but thought that applying the 0.1 utility decrement value for carers would be unrealistic. It considered that it may be much smaller than 0.1 and encouraged the company to explore alternative values more reflective of the experience of carers of people with FCS. The committee noted that it would like to see scenarios exploring different utility decrements for carers. It agreed that the Decision Support Unit's report on modelling carer health-related quality of life would be a good basis for the company to explore alternative values. It therefore concluded that the company's utility decrements used for carers was insufficient for decision making, and that it would like to see alternative values explored by the company.

Cost-effectiveness results

4.24 The committee considered the results of the economic analysis, taking into account the company's base case, the ERG's preferred base case

and exploratory scenario analyses. In the company's base case (with an agreed patient access scheme included), volanesorsen was associated with an incremental cost-effectiveness ratio (ICER) of £260,587 per quality-adjusted life year (QALY) gained.

4.25 The committee recalled that the ERG made several changes to the company's base case. The most influential changes were:

- the assumed reduction in APs associated with volanesorsen independent of, and additional to, that related to a reduction in TG levels (see sections 4.18 and 4.19)
- HRQoL – the ERG's preferred utility data incorporated from the vignette study (see section 4.22) and carer disutility (see section 4.23).

The ERG also applied other small changes to the company's model, which affected the ICER, and these were accepted by the committee. Based on these changes and using the company's time on-treatment assumption, the committee's preferred base case was associated with an ICER of £481,508 per QALY gained. It noted that the ICER from its preferred analysis and the ICERs from the company's and ERG's scenario analyses were all substantially higher than what is considered an effective use of NHS resources for highly specialised technologies.

Applying QALY weighing

4.26 The committee understood that the interim process and methods of the highly specialised technologies programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. It

understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee discussed the QALY gains associated with volanesorsen. It highlighted that these were below 10 in the company's and ERG's base cases, and in the ERG's exploratory analysis that was the most plausible to the committee (the exact QALY gains are considered commercial in confidence by the company, so cannot be reported here). The committee concluded that there was no evidence to suggest that volanesorsen would meet the criteria for applying a QALY weight.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.27 The committee discussed the effects of volanesorsen beyond its direct health benefits and the testimony of the patient experts. It understood from patient and clinical experts that all aspects of patients', families' and carers' lives are affected by the condition. It noted that there could be a significant negative financial effect for families if they have to give up work, but considered this less likely because of the age of the patients. The patient experts explained that volanesorsen has changed their experience of living with FCS, although they still have to restrict dietary fat intake. The committee concluded that volanesorsen may affect patients beyond the direct health benefits but quantifying this would be difficult. It concluded that it was highly unlikely that the benefits would be sufficient to overcome its concerns about the most preferred ICERs that can be considered an effective use of NHS resources for highly specialised technologies.

Other factors

4.28 The committee noted a potential equality issue raised by clinical experts, recognising that prevalence can be higher in some cultural and ethnic groups in the UK. However, it concluded that its recommendation applies

equally, regardless of ethnicity, so a difference in disease prevalence does not in itself represent an equality issue.

4.29 The committee was aware that, according to the IN-FOCUS study, having FCS affects the decision of women who may wish to become pregnant. It recognised that people who are pregnant or wish to become pregnant are an important clinical group. However, while not contradicted in pregnancy, the summary of product characteristics advises that the use of volanesorsen should be avoided during pregnancy. Therefore, the committee concluded that it would be inappropriate to consider pregnancy as a specific subgroup. It also noted that it was not presented with data on the use of volanesorsen during pregnancy, nor how it could influence the outcome of pregnancy (the drug does not cross the blood barrier). The committee concluded that any recommendations would apply equally, regardless of pregnancy, so this does not, in itself, represent an equality issue.

4.30 The committee discussed the innovative nature of volanesorsen, noting that the company considered that the drug's mechanism of action represents a step-change in the management of FCS. The patient experts explained that having a treatment available would give people with the condition hope, both for themselves and for family members and carers.

Conclusion

4.31 The committee recognised that FCS is a rare, serious and, at times, life-threatening condition that can substantially affect the lives of patients, and their families and carers. The committee understood that there is an unmet need for an effective treatment. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that some benefits with volanesorsen in the short term have been shown. It also noted that there may be some longer-term effects, but that there is substantial uncertainty about this and around the interpretation of the evidence. This included: the limited follow-up time in

trials; the before-after comparison using patients as self-controls to calculate the risk of AP associated with volanesorsen; and the discrepancy between the dosing schedules used in the trials and those recommended in the summary of product characteristics.

4.32 The committee also agreed that there was a lot of uncertainty about the company's assumptions around:

- the dose-response relationship between TG level bands and AP in patients with FCS (see section 4.9)
- the direct effect of volanesorsen on the risk of AP (see sections 4.18 and 4.19)
- the utility values incorporated in the model and (see section 4.22)
- the utility decrements applied for carers (see section 4.23).

The committee considered that the most plausible ICER was substantially higher than what is usually considered an appropriate use of NHS resources for highly specialised technologies. It also noted that volanesorsen did not meet the criteria for a QALY weighting to be applied. The committee concluded that volanesorsen at its current price was not cost effective compared with standard of care. Therefore, it did not recommend volanesorsen as an option for treating FCS in adults at high risk of pancreatitis, when response to diet and TG-lowering therapy has been inadequate.

4.33 The committee recommended that the company provides further clarification and analyses for consideration at the second evaluation committee meeting, and that this should include:

- further details on the vignette study, including methods used and values applied in the economic model

- scenario analyses using more plausible utility decrements for carers using the Decision Support Unit's report on modelling carer health-related quality of life.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson

Chair, highly specialised technologies evaluation committee

November 2019

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Orsolya Balogh
Technical lead

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ISBN: [to be added at publication]