NICE National Institute for Health and Care Excellence

NICE guidance

Volanesorsen for treating familial chylomicronaemia syndrome

Highly specialised technologies guidance
Published: 21 October 2020

www.nice.org.uk/guidance/hst13

Your responsibility

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All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Volanesorsen is recommended, within its marketing authorisation, as an option 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. It is recommended only if the company provides volanesorsen according to the commercial arrangement.

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. People with the condition 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 short-term benefits with volanesorsen, including reduced triglyceride (a type of fat found in the blood) levels. It is uncertain whether this is maintained in the longer term, particularly at the licensed dose, which was not used in clinical trials.

There are also other uncertainties, especially around volanesorsen's effect on acute pancreatitis and the utility values used in the economic model. Despite these, 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.

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, liver and spleen enlargement, 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, about a quarter of the normal daily intake suggested for an adult) 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, at the time of evaluation, 20 people were 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) production. ApoC-III inhibits the metabolism of triglycerides via the actions of both the lipoprotein lipase and lipoprotein lipase-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 '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, as described in the summary of product characteristics, 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 per 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 140×10^9 per litre, another measurement should be taken about a week later to reassess. If platelet count remains below 140×10^9 per 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 and in clinical practice. 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. This makes volanesorsen available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 have 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 worrying for their families and carers. Unpredictable hospital admissions can disrupt 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 strict dietary restrictions. 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, particularly if diabetes develops. 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 have delayed diagnosis, or misdiagnosis and inappropriate treatment. 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 would 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) compared 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 is considered 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 once every 2 weeks) 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 people in the trials and the clinical population in England. These included levels of abdominal pain, which was high in APPROACH compared with the population in England. Also, 11% of patients in APPROACH had previously had alipogene tiparvovec (a gene therapy for treating 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, although the level of additional uncertainty was unclear. The committee agreed that this introduced uncertainty into consideration of the clinical data, but concluded that it was acceptable for decision making.

Generalisability of the trial population to clinical practice

4.5 Most of the patients in the company's clinical trials had a genetic diagnosis of FCS, in line with the marketing authorisation. The committee discussed whether the trial populations would represent 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 currently be identified, and such patients may have entered the trial. However, because the marketing authorisation requires a genetic diagnosis of FCS, these patients would not be part of the NHS population potentially eligible for treatment with volanesorsen. 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 interpret this in clinical practice. The ERG explained that anyone with high TG levels could be considered to be at high risk of pancreatitis but queried whether clinicians might interpret the marketing authorisation 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 vary across and within patients with FCS and fluctuate 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 marketing authorisation was not used in the

clinical trials or for the population in the EAMS (see section 4.4). The committee discussed the implications of this for interpreting the evidence on 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 the EAMS and the clinical trials, than in clinical practice. It also considered the effect of these on patients, TG levels and clinical outcomes. It understood that, in the EAMS, patients all started on once every 2 weeks dosing but could up titrate to the licensed dose if response was not sufficient. The committee considered that the reason given for the dose adjustments and pauses was understandable from a general pharmacological point of view. But in the clinical trials the dose adjustments and pauses added uncertainty to 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 and initially less-intensive monitoring in trials, volanesorsen's short-term effect on clinical and safety outcomes may have been overestimated and there are uncertainties in interpreting its clinical benefits in the long term.

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 is considered academic in confidence by the company, so cannot be presented here. However, the company stated that the results showed a substantial decrease in TG levels with volanesorsen at month 3. 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 levels is a commonly used and important outcome that shows an effect of volanesorsen. The ERG explained that, at subsequent time points, the decrease in TG levels was generally lower than that seen at month 3 in APPROACH, but that any possible waning effect of

volanesorsen is probably small. This was supported by additional evidence from APPROACH OLE that became available during consultation, although 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 were uncertain. The committee concluded that volanesorsen was effective in lowering TG levels in people with FCS, although the extent of the effect in the long term was unclear.

Relationship between TG levels and AP in people with FCS

4.9 The committee considered the company's evidence on a possible dose-response relationship between TG levels and the risk of AP, suggesting that increased TG levels lead to an increased risk of AP. TG levels below 10 mmol per litre are associated with a low risk of AP. Risk increases with TG levels above 10 mmol per litre, becoming particularly high at levels of 22.6 mmol per litre or more. These assumptions were used in the company's economic model to define certain health states (see section 4.17). 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. TG levels can be variable and volatile among people with FCS (see section 4.6), and they are likely to have individual thresholds at which they are at high risk of developing AP. The clinical experts also suggested that people with FCS may have AP at lower TG levels than patients with raised TG levels from other causes.

4.10 During consultation, the company provided further information on the possible relationship between TG and AP in people with FCS. It explained that people with FCS are at a higher risk of AP compared with those with other hypertriglyceridaemia disorders. This is because they have chronically higher mean serum TG levels, their TG levels are more volatile and they have higher rates of previous AP. The ERG argued that the peaks in TG concentration may simply be a function of higher average TGs, and that there is no evidence linking incidence of AP to peak TG levels. The clinical experts noted that TG concentration alone may not be an adequate surrogate for AP in people with FCS. This is because the relationship between TGs and chylomicrons (the lipoprotein particles that transport triglycerides derived from dietary fat from the intestine to

the rest of the body via lipoprotein lipase activity) may be more relevant for this condition. Because FCS is caused by a defect in lipoprotein lipase, TGs cannot be converted in people with this condition, resulting in chylomicron accumulation and consequently pancreatitis. There are no clinical data supporting this argument because chylomicrons are less readily quantified. However, a reduction in both TGs in chylomicrons and AP events in people having volanesorsen was seen in APPROACH. The committee accepted that there is a general linear relationship between TG levels and risk of AP, but it remained uncertain whether this was generalisable to people with FCS. It concluded that, although it is uncertain whether the linear relationship applies in FCS, reduced TG levels may be associated with reduced risk of AP in this population, as shown in the clinical trials.

Study outcomes

Responder analysis

4.11 The company did several responder analyses. The committee particularly looked at 2 of them. This is because they were highly relevant to the decision making for TG level bands as defined in the company's economic model (see section 4.17) and to volanesorsen's stopping rule in the summary of product characteristics (see section 3.1 and section 4.17). These analyses included:

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

In APPROACH, 76.7% (23 out of 33) of patients having volanesorsen and 9.7% (3 out of 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 more patients on volanesorsen (87.9%, 29 out of 33) met the endpoint compared with those on placebo (9.1%, 3 out of 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 substantial proportion of patients were likely to continue treatment after stopping rules are applied (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 someone is unlikely to have pancreatitis, so it is appropriate to consider that people whose TG levels reach the endpoints defined above are at 'lower risk'. The ERG highlighted that the evidence showed that response rates wane over time, so the treatment effect may vary. But the committee concluded that, based on the evidence, TG levels would likely fall to levels at which pancreatitis is less likely in a substantial proportion of patients. However, it remained uncertain whether this benefit would last in the long term.

Acute pancreatitis

4.12 Evidence from a preplanned 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 the event rate of AP 5 years before treatment with that while on treatment in APPROACH OLE gave a rate ratio of 0.13 (p value not reported). The ERG highlighted that this risk estimate was highly uncertain because it was derived from a before–after comparison using patients as their own control, so there was a high risk of recollection bias. In general, the ERG noted that volanesorsen might reduce AP events, but the effect size was unclear. The committee agreed with the ERG and noted that the company's risk estimate of AP was uncertain and subject to risk of bias because of the methods used.

Abdominal pain

4.13 The preplanned 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 (17 out of 66 patients across the 2 arms), patients having volanesorsen (7 out of 33) had a statistically significant reduction in the average maximum intensity of abdominal pain, compared with those on placebo (10 out of 33; 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 some patients continued to have a certain level of abdominal pain while on volanesorsen, which made its effect on abdominal pain unclear. However, it acknowledged that, because abdominal pain is a frequent symptom associated with FCS, the reduction in pain seen in the trial would be beneficial for people with the condition.

Overall study results

4.14 The committee concluded that the clinical trial evidence showed that volanesorsen would likely provide benefits in lowering TG levels and on clinical outcomes (AP and abdominal pain). It also considered the additional data from APPROACH OLE and the EAMS that became available during consultation (mostly confidential, therefore cannot be presented here). These data showed a trend towards a TG-lowering benefit in people having the treatment at weekly and fortnightly dosing. The ERG noted 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 concluded that volanesorsen would likely provide some long-term benefits, although this was associated with substantial uncertainty, particularly at the licensed dose.

Health-related quality of life

4.15 Health-related quality of life 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 at month 3 (p=0.2920 and p=0.6627 respectively), at month 6 (p=0.5923 and p=0.9226 respectively) and at month 12 (p=0.4079 and p=0.7912 respectively). Baseline EQ-5D values were very high for both treatment arms (utility more than 0.97) in APPROACH. The committee noted that this was not in line with the patient testimonies, which indicated that FCS substantially affects every aspect of their

lives. One patient expert explained that the EQ-5D does not measure the aspects of quality of life that FCS affects, for example, strict adherence to a 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 because living with the condition is 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 symptoms of FCS might explain why a one-off questionnaire might not fully capture its effect on quality of life. But it did not think that the clinical trial results showed that volanesorsen had no effect on quality of life.

Adverse events

4.16 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 of stopping treatment, was uncertain at the licensed dose in the long term.

Cost to the NHS and value for money

Company's economic model

4.17 The company presented an economic model comparing volanesorsen alongside a low-fat diet with standard 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, developed 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 treatment was stopped or death (in line with the dosing schedule in the summary of product characteristics). All patients who had standard care in the initial phase progressed to the standard-care Markov model. Patients who had volanesorsen had to meet continuation criteria (a TG level reduced by 25% or more or below 22.6 mmol per litre, or both) to remain on volanesorsen, otherwise they progressed to the standard-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:

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

4.18 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 year 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 (see section 4.10).

Model assumptions

Assumptions on volanesorsen's indirect and direct effects on AP

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

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

In the company's original base case, the risk estimate associated with volanesorsen's direct protective effect on the risk of AP (0.13, p value not reported) 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 (see section 4.12). The rate ratio of 0.13 was applied to patients with historical and recurrent APs in the model. The ERG noted this would represent double counting of the benefits because it was calculated from a population in whom there was already potential for reducing TG levels (via the indirect effect of volanesorsen on TG levels). It was also subject to risk of bias because patients were their own control and because of regression to the mean. 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 specific TG-risk bands. The committee preferred the ERG's assumption, given the lack of clinical trial data, but acknowledged that volanesorsen was likely to have some protective effect on risk of AP.

4.20 At consultation, the company explained that using an additional multiplication factor was necessary because the size of the reduction in risk of AP with volanesorsen was not adequately captured in the model. Therefore, in its updated model, a rate ratio of 0.27 (to low or medium TG health states) and 0.28 (to high TG health states) was applied. The company noted these ratios were midpoints between 0.13 (original submission) and 0.35 (the ratio of pooled event rates of volanesorsen once every 2 weeks dosing from APPROACH, APPROACH OLE and COMPASS compared with the pooled event rates of placebo from APPROACH and COMPASS in patients with a history of AP). The ERG highlighted that both

estimates were subject to considerable risk of bias because 0.13 was derived from a before–after comparison using patients as their own controls, and 0.35 may be confounded because there was no placebo arm in APPROACH OLE. It also suggested that some double counting will remain irrespective of the rate ratio selected. The committee recalled the concern about the relationship between TG level and risk of AP. It recognised the limitations of developing an evidence base for an ultra-rare disease, and around estimating the most plausible rate-ratio values associated with using volanesorsen given the lack of trial data. In the absence of robust evidence, the committee considered that a rate ratio of 0.29, applied to all patients in the model, was reasonable.

Stopping treatment

4.21 The committee noted that relatively high stopping rates were seen across the clinical studies. In APPROACH, 42% (14 out of 32) of patients stopped treatment before month 12, and 79% stopped before week 104. It understood that adverse events were the most common reason for stopping. Stopping rates from APPROACH OLE were considered 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 section 3.1 and section 4.17). The ERG explained that the stopping rate at the licensed dose in clinical practice was currently unknown but was unlikely to be zero.

4.22 At consultation, the ERG clarified 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 committee understood that stopping treatment in trials was not only because of the stopping rules in the summary of product characteristics (see section 3.1). Stopping rates (including rate of dose pauses and missed doses) from the EAMS are commercial in confidence by the company, so cannot be presented here. However, the committee noted that the data suggested some people would stop treatment or pause doses in the trials and the EAMS, regardless of dosing regimen even after being on treatment for 2 or 3 years. Therefore, this trend seems to support some late treatment stopping.

4.23 The company explained that, because of the strengthened monitoring schemes put in place since APPROACH, fewer people in the EAMS have stopped treatment. This is perhaps because these patients have the highest risk of AP and it is difficult to manage the disease on diet alone. The ERG noted the uncertainties about stopping treatment because of the limited follow-up time for patients in the EAMS. The committee noted that, because of the relatively high drop-out rate seen in the clinical trials, some stopping would be likely in clinical practice, even with education and monitoring in place. It concluded that there were likely to be dose pauses and people stopping treatment in the long term, but at a much lower rate than in clinical trials.

Time on treatment

4.24 The committee recognised that the rate of stopping treatment affected the model results. Stopping could happen in the model because of not meeting the continuation criteria (see section 4.17), death, lack of adherence to the treatment and monitoring, or adverse events. In the company's original model, stopping was modelled by fitting parametric survival functions to time-on-treatment data for 32 patients on volanesorsen once every 2 weeks within APPROACH OLE and using log-normal curves to predict when treatment would stop. After consultation, the company capped the stopping rate at 20%. The committee understood that relatively high stopping rates were seen across the clinical studies (see section 4.21) and considered this cap implausible. However, it was also aware that only 1 person stopped treatment in the EAMS even though patients had volanesorsen once every 2 weeks from the start in the scheme (see section 4.21). The committee recalled the discussion on declining stopping rates in the long term, and that there may be differences in the stopping rate between clinical trials and the EAMS because of the different settings as explained by the company (see section 4.14). Based on this, it preferred the ERG's exponential function, which does not suggest that most patients continue after a high initial rate of drop out. The committee agreed that the ERG's initial stopping rate of 10% per year (see section 4.22) was more likely in clinical practice than the low rate in the EAMS. It therefore concluded that the ERG's exponential curve best reflected the likely change in stopping rate with volanesorsen in clinical practice over time, and that this assumption should be used in the model.

Source of utility data

4.25 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 it considered them implausible. Instead, the utility values for the base case were derived from a vignette study commissioned by the company. In response to concerns raised by the committee about the vignette study, the company provided additional information on the methodology after consultation. Substantial information about this study is considered academic in confidence by the company, so cannot be discussed in detail here. The committee noted several methodological issues associated with the study, including the process of constructing the vignettes, uncertainties in the dimensions that defined health states and value-laden language used throughout the vignette. The committee concluded that the source of utility values was subject to risk of bias and that this would contribute to uncertainty in the incremental cost-effectiveness ratio (ICER).

Using utility values derived from the vignette study

4.26 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 and whether an AP event occurred. This contrasted with how the utility values were used in the company's model. In the model, utility for a patient was determined by whether they were having volanesorsen or standard care on the basis that mean TG levels were considerably lower in patients who were having treatment. The ERG had concerns about this approach. It 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 preferred the ERG's approach of linking utility values to TG levels and health states.

4.27 After consultation, the company changed the allocation of utility values in its model. It assigned the high TG utility value from the vignette to those with a TG level of more than 22.6 mmol per litre, and the low TG utility value from the vignette to remaining patients. The ERG explained that this logic was not

consistent with the vignette or the original submission, pointing out that people with TG levels between 10 mmol per litre or more to less than 22.6 mmol per litre 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.

Utility for carers

4.28 The company included utility decrements for carers in the economic model, based on estimates from the literature. In the company's original base case, it used the values from NICE highly specialised technology submission (metreleptin for treating lipodystrophy) as a proxy for carers of people with FCS, assuming a 0.1 utility decrement for carers. In the evaluation consultation document, the committee and ERG highlighted concerns about the source of the proxy value and around the value itself. The committee asked the company to explore alternative values.

4.29 After consultation, the company presented an alternative utility value, decreasing the decrement from 0.1 to 0.04 in the updated model. The company explained that the decrement was a midpoint value between the effect on family utility for patients with new musculoskeletal conditions (0.03) and the utility decrement between treated and untreated groups (0.05) in the metreleptin submission. The company believed that this was a fair valuation of quality-adjusted life year (QALY) gain with volanesorsen treatment for the families of people living with FCS. The committee discussed the appropriateness of applying the new value. It 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). It noted that people with FCS are often unable to participate in usual family activities because of strict dietary restrictions. This can have a substantial emotional and psychological effect on them and their families. The patient experts explained that the effect of volanesorsen on social interaction, including engaging with their families, was substantial. They also explained that not getting recurrent pain and being able to go out and socialise with their families made a lot of difference to them and their families.

4.30 The ERG was concerned that the new decrement may be an overestimation. It noted that, in the literature, the loss in utility with existing mental or musculoskeletal conditions would be 0.01. It also noted that volanesorsen does not remove the need for a low-fat diet, so some social isolation for the family could remain and 0.01 may be more appropriate than 0.04. The committee acknowledged the positive psychological effect that volanesorsen may have on patients and carers, and on their lifestyle. It agreed that there would be some effect of FCS on the utility for carers but thought that applying the 0.04 utility decrement may be unrealistic. It considered that it may be smaller than 0.03, which represents a family decrement for patients with new musculoskeletal conditions. It concluded that it would prefer a utility decrement of 0.02 applied in the model.

Factors not considered by the committee: comorbidities and malnutrition

4.31 The company explained that some comorbidities and symptoms such as joint pain, numbness or tingling of digits, use of corticosteroids and opioids, and nutritional status were not included in the model. It pointed out that these can all seriously affect the quality of life of people with FCS, but were not captured in the model because of similar features with either the vignette descriptions or other symptoms. The committee understood that these factors could have affected quality of life and therefore cost effectiveness. However, it considered that, if these factors were associated with either a decrease or increase in TGs, it would have preferred to see them in the vignette study. It also noted that it was not presented with sufficient evidence on this in the clinical trials. The committee concluded that, because no empirical data were provided, the possible effect of these factors on the cost-effectiveness estimate was unknown.

Applying QALY weighing

4.32 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 analysis that was 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.

Cost-effectiveness results

4.33 The committee considered the results of the economic analysis, taking into account the company's base case and the ERG's exploratory scenario analyses. It acknowledged that neither the company's base case nor the ERG scenarios were without flaws. The committee's preferred base case included the following assumptions:

- a rate ratio of 0.29 for volanesorsen's protective effect on AP risk
- a stopping rate of 10% per year (exponential model)
- applying utility data in the model using the ERG's approach of linking utility values to TG levels and health states
- a carer utility decrement of 0.02.

The committee acknowledged that substantial uncertainties remained about volanesorsen's protective effect on AP risk and applying utility data from the vignette study in the model. It noted that, because of the outstanding uncertainties, the company revised its commercial offer for volanesorsen. This brought the ICER down to £98,013 per QALY gained compared with best supportive care and using the committee's preferred assumptions. Taking this into account, the committee concluded that the most plausible ICER could be considered an effective use of NHS resources for highly specialised

technologies.

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

4.34 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 it noted that the full effect of these benefits had not been quantified. The committee considered these benefits in its decision making.

Other factors

4.35 The committee noted a potential equality issue raised by clinical experts, recognising that FCS 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.

4.36 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 contraindicated 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 pregnant women as a specific subgroup. It also noted

that it was not presented with data on the use of volanesorsen during pregnancy, or how the drug could influence the outcome of pregnancy (it does not cross the blood barrier). The committee concluded that any recommendations would apply equally, regardless of pregnancy, so this does not represent an equality issue.

4.37 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 managing 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

4.38 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 volanesorsen was associated with improved TG levels and likely reduced the risk of clinical outcomes such as AP and abdominal pain in the short term. It concluded that volanesorsen would likely provide some long-term benefits too. However, this was associated with substantial uncertainty, particularly at the licensed dose, which was not used in the clinical trial that provided the evidence base for decision making.

4.39 Overall, the committee considered that the available evidence suggested that volanesorsen could provide important clinical benefits. It considered that there were uncertainties in interpreting the evidence and the company's assumptions in the model, especially around volanesorsen's protective effect on AP and the utility values used in the model. It also noted that volanesorsen did not meet the criteria for a QALY weighting to be applied. Acknowledging the uncertainties and taking into account other benefits of volanesorsen that may not be fully captured in the analysis, the committee concluded that volanesorsen can be considered a cost-effective use of NHS resources for highly specialised technologies. Therefore, the committee recommended volanesorsen as an option for treating FCS.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication. Because volanesorsen has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has familial chylomicronaemia syndrome and the doctor responsible for their care thinks that volanesorsen is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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ISBN: 978-1-4731-3887-2