Slides for public – redacted

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

Chair's presentation

2nd evaluation committee meeting
Highly Specialised Technologies committee

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Company: Akcea Therapeutics
Chair: Peter Jackson
ERG: School of Health and Related Research (ScHARR)
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Overview

- **Recap (ECM1: November 2019)**
  - The condition
  - The technology
  - Decision problem
  - Clinical- and cost-effectiveness evidence presented at ECM1
  - ECD preliminary recommendations and considerations
- **Responses to ECD consultation and ERG comments**
- **Key issues**

The nature of the condition

Familial chylomicronaemia syndrome (FCS)

FCS is a rare, genetic metabolic disorder of lipid metabolism caused by homozygous mutations in the lipoprotein lipase (LPL) gene

- **Characterised by** high levels of triglycerides (TGs) 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**:
  - abdominal pain
  - fatigue
  - impaired cognition
  - numbness or tingling sensation
- **Morbidities/complications associated with FCS:** unpredictable and recurrent acute pancreatitis (AP), which occurs in 60-80% of patients with FCS; chronic pancreatitis (CP); pancreatic necrosis; fatty liver disease; diabetes
  - ➢ All thought to be a consequence of the build-up of chylomicrons particles which reduce blood flow through organs microcirculation (Valdivielso 2014)

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Volanesorsen
(Waylivra, Akcea)

Marketing authorisation	Indicated for an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate
Mechanism of action	Volanesorsen is an antisense oligonucleotide (ASO) inhibitor of apoC-III. ApoC-III inhibits the metabolism of TGs via the actions of LPL and LPL-independent pathway. It selectively binds to apoC-III mRNA, preventing production of the apoC-III protein and allowing metabolism of TGs
Administration & dose	285 mg in 1.5 ml injected subcutaneously once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks
List price	• List price: £11,394 per single-use syringe (285mg) • Simple discount PAS approved
Treatment course length and discontinuation rules	• Starting dose is 285 mg once-weekly for 3 months, followed by down-titration to a maintenance dosing schedule of once every 2 weeks for those after 3 months ○ If the patient has not achieved a >25% reduction in triglyceride levels, or if triglyceride levels remain above 22.6 mmol/L at 3 months, treatment should be discontinued ○ 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 thereafter depending on response to treatment and platelet levels

Apoc-III: apolipoprotein C-III; ASO: antisense oligonucleotide, TG: triglyceride; LPL: Lipoprotein lipase; PAS: Patient access scheme; FCS: Familial chylomicronaemia syndrome

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Decision problem

RECAP

	Final scope issued by NICE	Company deviations
Population	Adults with FCS	Narrower than scope: The population is adult patients with genetically confirmed FCS and at high risk for pancreatitis in whom response to diet and triglyceride-lowering therapy has been inadequate
Intervention	Volanesorsen in combination with established clinical management (incl. dietary fat restrictions)	
Comparator	Established clinical management without volanesorsen (incl. dietary fat restrictions)	
Outcomes	The outcome measures to be considered include: • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability) • incidence of acute pancreatitis (AP), chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis related admissions) • mortality (including all-cause and pancreatitis related mortality) • adverse effects (AEs) of treatment • health-related quality of life (HRQoL) for patients and carers	Data gaps and limitations, and concerns regarding double counting mean that some outcomes are not explicitly considered in the model: e.g. pancreatic necrosis and fatty liver disease Cardiovascular disease (CVD) is not in the economic model as there is no clinical consensus regarding the impact of FCS on CVD outcomes

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Source of evidence presented at ECM1

	Description	Aim of study	Used in clinical effectiveness evidence	Used in cost effectiveness analysis
Clinical trials	APPROACH COMPASS	To evaluate the efficacy and safety of volanesorsen administered subcutaneously to patients with FCS ----	YES YES	YES NO
Ongoing observational studies	APPROACH OLE	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen administered subcutaneously to patients with FCS	YES	YES – except results from the subgroup which used SmPC dosing during the trial (due to AE related dose adjustment)
Single-arm, retrospective survey	Re-Focus	To measure burden of disease before and after volanesorsen treatment	YES	NO
Early Access to Medicines Scheme	EAMS	Provide access to volanesorsen for people living with FCS	NO	No data used, but basis for a scenario analysis: under every 2 weeks dosing and regular platelet monitoring, no patients will experience severe thrombocytopenia
Retrospective analysis	CALIBER	Observational study Data collection	NO	Yes

Clinical evidence presented at ECM1

- **Dosing:** licensed dosing not used in clinical trials
- **Treatment effectiveness**
  - Primary endpoint: % change from baseline in TG levels at month 3 (*surrogate outcome*)
    - Statistically significant ($p<0.05$) change in TG levels compared with placebo
    - Not all patients achieved TG levels below 8.4mmol/L
  - Results relating to AP, abdominal pain and HRQoL less certain
- **Stopping treatment**: relatively high stopping rates seen across clinical studies mostly due to adverse events
  - APPROACH: 42% of patients stopped before week 52, and 79% stopped before week 104
  - APPROACH OLE volanesorsen group: [redacted] of patients stopped before week 52, and [redacted] stopped before week 104
- **The relationship between TG levels and risk of AP:**
  - The underlying relationship between TG levels and AP
  - A change in TG levels is assumed to be associated with a change in risk of AP

- Patient experts explained that benefit seen translated into a marked effect on patients' lives (regaining of family and social life, emotional wellbeing, return to work) → TG levels, experience of abdominal pain and AP (also fear of) attacks reduced

RECAP

Cost-effectiveness evidence presented at ECM1

- **Company modelling approach:**
  - Decision tree model for the initial 3-month; and
  - Markov model for the long-term beyond 3 months;
    - 3 month cycles, 59 year time horizon
- **Health states:** defined based on TG level bands
  - Cut-offs: (low risk: <10 mmol/L; medium risk: ≥10 and <22.6 mmol/L; and high risk: ≥22.6 mmol/L)
  - AP; CP, diabetes or death as events experienced by patients
- **Transition in the model - treatment effectiveness on TG levels:** reduction in TG levels observed in APPROACH up to month 3; GLMM techniques to predict TG levels beyond month 3
- **Treatment duration:** parametric survival functions fitted to time on treatment data for patients who had bi-weekly dosing within the APPROACH OLE study
- **Assumptions on volanesorsen's effects on AP:**
  - Reducing the risk of AP indirectly via reducing patients' TG levels; and directly reducing the risk of AP independent of TG risk bands
- **Utility values**
  - Utility values for health states estimated from a vignette study
  - Carer utility decrement (0.1) derived from NICE HST submission for metreleptin - ID861

ECD preliminary recommendation

Volanesorsen was not recommended for treating FCS

The committee recommended that the company provides further clarification and analyses for consideration at the second evaluation committee meeting, which included:

- 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 TSD on modelling carer HRQoL

ECD considerations

Committee's considerations on the clinical evidence presented

Issue	Conclusion
Population	'High risk of pancreatitis' is likely to include anyone with high TG levels
Difference in dosing	Volanesorsen's effect on clinical and safety outcomes could be overestimated in the short term, it's effect in the long term is uncertain
The relationship between TG and AP	A change in TG levels is assumed to be associated with a change in risk of AP → uncertain whether it is generalisable to people with FCS Acknowledging there may be individual thresholds in people with FCS, under which the risk of AP may be lower
Clinical trial evidence	Some effect seen of volanesorsen on TG levels Response to treatment could wane over time but reduction in TG levels is likely to be small → volanesorsen's impact on risk of AP, especially in the long term is unclear Effect on clinical efficacy and safety outcomes in the long term, particularly at the licensed dose, is uncertain
Safety	Effect of volanesorsen on safety outcomes and stopping treatment is unknown at the licensed dose in the long term
Health-related quality of life	No significant change measured by EQ-5D-5L or SF-36 during the trials → Committee noted that volanesorsen may have an effect on quality of life of people

ECD considerations

Committee's considerations on modelling assumptions

Issue	Conclusion
Model structure	Structure reflects the general course of the condition Uncertainty in relationship between TG levels and risk of AP in people with FCS
Volanesorsen's indirect and direct effects on AP	Effect of volanesorsen on AP that is independent of TG level is uncertain Company's ratio used to inform the risk of AP associated with volanesorsen might represent double counting, is subject to recall bias and regression to the mean ERG's multiplication factor of 0.50 to both historical and recurrent AP rates within a specific TG risk band is preferred
Stopping treatment	ERG suggested it is likely to be between 10% and 20% each year Some stopping likely in clinical practice
Time on treatment	Company's lognormal curve best reflected the likely change in stopping rate with volanesorsen in clinical practice over time
Application of utility data	ERG's approach of linking utility values to TG levels and health states is preferred a) low TG health state values to TG levels <10 mmol/L b) high TG health state values to TG level >22.6mmol/L c) mean of the two values for TG level ≥10 mmol/L to <22.6 mmol/L Further details on vignette study requested
Utility for carers	Using 0.1 utility decrement value for carers is insufficient for decision making Alternative values should be explored by the company

Cost-effectiveness results (including PAS)

Description	Incremental discounted QALY	Cost per QALY gained
Company's preferred analysis	[redacted]	£260,587
ERG's preferred analysis	[redacted]	£483,814
Committee's preferred analysis	[redacted]	£481,508

QALY weighting: volanesorsen does not meet the criteria for applying a QALY weight

ECD consultation responses

- Consultee comments from:
  - Akcea Therapeutics (company)
- Clinical and patient experts; and professional organisations:
  - Clinical expert (endorsed by University Hospitals, Birmingham; in collaboration with other clinical experts)
  - Patient organisation: LPLD Alliance
  - Patient experts
- Other comments: NHSE

- No web comments

- No comment response from:
  - Department of Health and Social Care

Key issues I.

The vignette study and application of utility values:

- Was the vignette study appropriately conducted? Is the committee satisfied with the additional information provided? Which approach of linking the utility values from vignette to health states in the model does the committee prefer? Which values are preferable?

Carer's utilities:

- Company proposed an alternative disutility of 0.04 for carers: midway between 0.03 (for musculoskeletal conditions) and 0.05 (referenced from NICE HST submission for metreleptin - ID861). Which value does the committee prefer between **0.00 to 0.04**?

Volanesorsen's indirect and direct effects on risk of AP:

- Is there sufficient evidence to suggest that volanesorsen confers effect by both reducing mean serum TG level and reducing the 'height of the peaks', therefore the smaller reduction in TG levels associated with the fortnightly dosing is not associated with an increased risk of AP?
- Given the lack of data, is the updated implementation of AP rates sufficient and appropriately modelled? Which is the most plausible value for the rate ratio associated with the use of volanesorsen - **0.50** for all as originally assumed by the ERG; **0.27** (for low/medium TG band) and **0.28** (for high TG band) respectively; or between **0.14** and **0.38**?

Key issues II.

Discontinuation:

- Is the company's assumption on capping discontinuation at **20%** appropriate? Does the clinical evidence available support that?

The relationship between TG levels and risk of AP in people with FCS:

- Does the committee consider the evidence provided by the company supporting the relationship between TG levels and risk of AP in people with FCS sufficient?

Other considerations:

- Has the company addressed all aspects affecting the guidance? Should additional items, e.g. co-morbidities, symptoms or effects of malnutrition also be considered?

ICER and QALY weighting:

- What is the committee's preferred ICER? Does QALY weighting apply?

ECD consultation comments received

Clinical expert: commented on the relationship between TG levels and AP in people with FCS; and volanesorsen's effect on AP

Company*:*

- **Clinical evidence**
  - Further discussion on:
    - The relationship between TG levels and AP in people with FCS
    - Treatment continuation rates
  - Volanesorsen's indirect and direct effects on AP
    - New clinical evidence on volanesorsen's TG lowering effect at once every week (Q1W) and once every two weeks (Q2W) dosing
    - New estimates of volanesorsen's direct effect on risk of AP
  - Additional points for committee's consideration
- **Cost-effectiveness evidence, revised economic model**
  - Further information on methodology of EVA-22200 (vignette study) and new implementation of vignette values
  - Alternative carer utility decrement
  - New implementation of AP rates
  - Updated economic analysis including a new PAS

ECD consultation comments

The relationship between TG levels and AP in FCS patients I.

ECD: linear relationship between TG levels and risk of AP in general population, uncertain whether it is generalisable to people with FCS - there may be individual thresholds in people with FCS, under which the risk of AP may be lower

Clinical expert comment:

TG concentration alone is inadequate as an outcome measure for assessing clinical efficacy of volanesorsen

- Chylomicronaemia (not hypertriglyceridaemia) is the direct cause of pancreatitis →TG concentration does not correlate directly with pancreatitis
- In patients with FCS, triglycerides can't be converted to free fatty acids → accumulation of unmetabolised chylomicrons → triggering inflammation and necrosis causing pancreatitis
- Chylomicrons can't be readily quantified → TGs are used as a surrogate measurement of chylomicronaemia
  - Not directly related - TG concentration fluctuates in response to dietary fat intake (unreliable marker of long term metabolic control), however chylomicronaemia depends not only on dietary fat intake but also on lipoprotein lipase activity
- A patient with FCS carries a higher residual burden of unmetabolised chylomicrons than a patient with hypertriglyceridaemia from other causes who does not have FCS
  - At any given triglyceride concentration a patient with FCS is at higher risk of pancreatitis than someone with high triglycerides who does not have FCS
- In APPROACH: volanesorsen lowers TGs → reduce chylomicronaemia and hence pancreatitis risk
  - TG concentration is not directly related to chylomicronaemia → not to risk of pancreatitis

ECD consultation comments

The relationship between TG levels and AP in FCS patients II.

Company response: the dose-response relationship between TG and AP generalisable to people with FCS, and risk of AP is higher in FCS than in other hypertriglyceridemia (HTG) conditions:

- Chronically higher TG levels in FCS patients than in other HTG patients (Scherer et al. 2014; CALIBER study)
- Greater volatility (higher frequency) in higher peak TG levels - patient traces (n=3) from APPROACH show that patients appear to have more volatile TG levels prior to treatment
- Higher rates of previous APs → risk factor for AP
  - Prior AP is a risk factor for experiencing a subsequent AP (Sankaran et al. 2015, CALIBER study)

ERG comment:

- ***If*** the relationship between TGs and APs is generalisable to FCS patients → higher mean TG levels of FCS patients should already be taken into account within the modelled estimates
- Clinical advice to ERG: a) no proof that incidence of pancreatitis episodes related to peak TG levels as opposed to any other variable, b) the spikes may be a function of high TG levels, not of FCS itself
- Means will include a proportion of patients who have a prior AP history → license for volanesorsen is not limited to patients with prior AP → higher risk associated with prior AP history should already be taken into account within the model

ECD consultation comments

Volanesorsen's effect on TG levels, at Q1W and Q2W dosing I.

Recap: SmPC for volanesorsen recommends a starting dose of 285mg Q1W for 3 months and a reduction to Q2W at 3 to 6 months; thereafter allows clinical discretion for longer term use at either the Q1W or Q2W dosing frequency

ECD: clinical trial evidence showed some effect with volanesorsen on TG levels; because of limitations in the data volanesorsen's effect on clinical efficacy and safety outcomes in the long term, particularly at the licensed dose, is uncertain

Company response: volanesorsen demonstrates transformational TG lowering benefit for patients with FCS in the short and long-term at Q1W and Q2W dosing

0-3months efficacy at Q1W dosing

- Data from APPROACH showed substantial and clinically meaningful reductions in TG levels
  - -77% compared to +18% mean change from baseline; absolute mean reduction of 19.3mmol/L compared to increase of 1mmol/L from a baseline of 25mmol/L in volanesorsen arm and placebo arms respectively

3-6m at Q2W dosing, after initiation at Q1W

- [redacted]

GLMM analysis: post-hoc statistical analysis used to predict absolute TG values on Q2W dosing up to Feb 2019 data-cut

- 44% mean reduction in TG levels from baseline

ECD consultation comments

Volanesorsen's effect on TG levels, at Q1W and Q2W dosing II.

Company:

New evidence at post-6m at Q2W dosing

July 2019 data cut (APPROACH OLE): patients received more than 3 months of doses Q2W

- Mean change from baseline in TG levels reported as:
  - [redacted] after 6 months of treatment with volanesorsen 285 mg Q2W ([redacted])
  - [redacted] after 12 months of treatment with volanesorsen 285 mg Q2W ([redacted])
  - [redacted] after 18 months of treatment with volanesorsen 285 mg Q2W ([redacted])
  - [redacted] after 24 months of treatment with volanesorsen 285 mg Q2W ([redacted])

post-3m at Q1W dosing

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

New evidence from EAMS study:

October 4th 2019 data cut: patients treated with doses Q2W from study inception

- 9 patients previously treated within APPROACH, APPROACH OLE or COMPASS and had a mean change in TG from clinical trial baseline of [redacted]
- 7 patients treatment naïve and had doses Q2W from inception → mean change in TG at 3 months was [redacted]

NICE

ECD consultation comments

ERG comments: volanesorsen's effect on TG levels, at Q1W and Q2W dosing

Based on EAMS data reported in the appendix of company ECD response

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

[redacted]

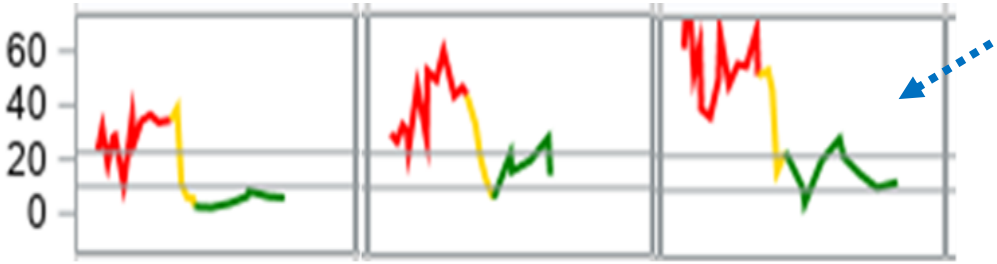
ERG's other considerations:

- [redacted]
- [redacted]
  - Unlikely that all patients achieve TG levels of "low risk" (8.5-11.4mmol/L) since baseline TG levels in APPROACH were around 25mmol/L → [redacted]
- Mean reduction in TG levels at SmPC dosing likely to produce a mean TG reduction [redacted]
- [redacted]
- Up-titration is unlikely, some patients might even benefit from less than Q2W dosing; although some patients might tolerate higher doses
- Patients still appear to be at some risk of APs

ECD consultation comments

Effect of volanesorsen on the risk of AP via reduction in TG levels I.

Company new evidence: volanesorsen appears to confer effect by both reducing mean serum TG level and reducing the "height of the peaks"



Source: Figure 1 – company ECD response document

Patients traces are notably subject to fewer and less extreme fluctuations in TG level during on-treatment period

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

ERG comment: periods of volatility are at higher TG levels, and the periods of less volatility may simply be a characteristic of lower TG levels, rather than an additional clinical effect of volanesorsen → remains unclear

	Volanesorsen (n = 33)		Placebo (n = 33)	
	Patients	Events	Patients	Events
5-year medical history				
Patients with multiple ≥2 events in the past 5 years	7	24	4	17
Events during study	0	0	3	4
P value	P = 0.0242			

Source: Table 3 – company ECD response document

Company: trial data show remarkable results in patients with high risk of recurrence

ERG comment: statistically significant difference seen in favour of volanesorsen, but analysis was for patients receiving the more frequent dosing schedule

ECD consultation comments

Effect of volanesorsen on the risk of AP via reduction in TG levels II.

Company comment:

- Hypothesis: reduction in 'spiking' (particularly high TG levels) may explain why a switch to Q2W is associated with a smaller % reduction in TG from baseline without an increase in AP event rate

ERG comments:

Empirical data don't appear to support company's hypothesis

- AP rates off-treatment (placebo arm, or pre-treatment history) not provided as medical history not recorded for all patients
- **Rate ratios:** using placebo rate of APPROACH and COMPASS as a comparator (no placebo arm in APPROACH OLE study)

: volanesorsen any dose: [redacted]
: volanesorsen Q2W dosing: [redacted]

	APPROACH	APPROACH OLE (Feb 2019 data cut)	Pooled APPROACH, APPROACH OLE and COMPASS, for patients in the analysis only (Feb 2019; July 2019 data-cut)	Glybera observational study
	AP rate (patient years of exposure)			
Medical history	0.21 (330)	[redacted]	[redacted]	0.27
Placebo	0.11 (31.8)	[redacted]	[redacted]	
Volanesorsen (any dose)	0.09 (29)	[redacted]	[redacted]	
Volanesorsen (Q2W) – after ≥3 months			[redacted]	
	Calculated AP rate ratios			
Rate ratio, any dose vol vs. medical history	0.43	0.13	-	
Rate ratio, any dose vol vs. placebo	0.82	0.17 (vs. 0.19 pooled trial placebo)	0.19	
Rate ratio, Q2W vol (≥3 mth) vs. placebo	-	-	***0.39***	

Unclear patient number on Q2W doses >6 months → [redacted] rate may be an underestimate of the AP rate → rate ([redacted]) may be an overestimate of treatment effect

Source: Table 4 – company ECD response document

Key: Q2W: once every two weeks

ECD consultation comments

The direct effect of volanesorsen on the risk of acute pancreatitis

ECD: the direct effect of volanesorsen on the risk of acute pancreatitis was uncertain

Company: risk of AP in population of patients with a history of AP: volanesoresen vs. placebo

	Pooled APPROACH, APPROACH OLE and COMPASS (July 2019 data cut)
AP rate (patient years of exposure)	
Placebo	[redacted]
Volanesorsen (any dose)	[redacted]
Volanesorsen (Q2W) after ≥3 months	[redacted]
Calculated AP rate ratios	
Rate ratio, any dose (vs. placebo)	0.18
Rate ratio, Q2W (vs. placebo) (≥3 mth)	0.35 (0.08/0.23)

Base point for the rate ratio describing the impact of volanesorsen on AP
See slide: 26

Source: Table 5 – company ECD response document

Key: Q2W: once every two weeks

Clinical expert comment:

- Likely that APPROACH underestimated the effect of volanesorsen on incidence of pancreatitis in FCS patients
  - Study data cannot be used to determine effect of volanesorsen on incidence of pancreatitis in this condition
  - Incidence of pancreatitis should be compared in treated and untreated patients, or in individuals before and after starting volanesorsen

ECD consultation comments

AP event rate in the updated economic model I.

*Recap: in original model rate ratio **(0.13)** used to estimate the impact of volanesorsen on AP for both historical and recurrent AP (rate ratio derived from post-hoc analysis comparing event rates of AP 5 years before and on treatment in APPROACH OLE)*

*ECD: double-counting of benefits for patients with an historical AP as better TG levels were assumed to have a reduced underlying risk of AP already; also subject to regression to the mean (e.g., out of better adherence to diet, or entered trial following a period of multiple APs), and recollection bias → **ERG's multiplication factor of 0.50 to both historical and recurrent AP rates within a specific TG risk band is preferred***

Company response and ERG corresponding comments

A) Company re: recall bias: AP events from APPROACH OLE medical histories were adjudicated → no risk of recollection bias in the 5-year medical history rate of AP

ERG : content with the response

B) Company re: regression to the mean: can't comment about motivation of people to join the trial; with regards to being in the trial improved adherence to diet → not the case: no marked change in TG results between screening for entry and baseline TG measure

ERG: there still may be an overestimation of the efficacy of volanesorsen, but accept improvement due to being enrolled in a trial could be slight

ECD consultation comments

AP event rate in the updated economic model II.

Company response and ERG corresponding comments

C) Company re: double counting: some double counting in historical AP health states applicable to 54% of patient cohort and up until the first AP event

- Additional multiplication factor necessary: moving from high TG health state (on SoC) to medium TG health state (on volanesorsen) didn't capture the magnitude of reduction on risk of AP observed in the trials → impact of double-counting is low
- Arbitrary value of 0.5 (by ERG) predicted a rate ratio of 0.45 for volanesorsen compared with placebo
  - Significant underestimate of effect of volanesorsen compared with available evidence

Updated AP rate: rate ratio of ***0.27*** (low/medium TG health states) and ***0.28*** (high TG health states) reasonable mid-point between 0.13 (original submission) and 0.35 (volanesorsen Q2W vs. trial placebo rates with a history of AP – *see on slide 24*) → updated AP rates used in company's model

ERG comment: as data do not exist, estimating most plausible values for rate ratio associated with volanesorsen is complex

- 0.13 taken from a self-control cohort, there could be high risk of biases (regression to the mean; some patients would have received more frequent doses of treatment than fortnightly)
- 0.35 based on comparison between volanesorsen and placebo → but may be confounded by patients enrolled into APPROACH OLE who do not have a corresponding placebo group

There is double counting regardless of the chosen rate ratio

Sensitivity analyses conducted varying the value from 0.14 to 0.38 assuming an equal rate ratio for both historic and recurrent APs

ECD consultation comments

Evidence not considered by the committee

Company comments: ***Co-morbidities and symptoms not included in the model or vignette due to risk of double-counting***

- Symptoms: *joint pain, extreme feeling of cold, numbness or tingling, use of steroids, use of opioids*
- Vignette health state descriptions did not capture all aspects of FCS

= negative economic and health (QoL) impact on individuals, families, and society substantial

- **Volanesorsen would reduce these symptoms/concomitant medication use which would result in a lower ICER**

Malnutrition, dietary deficiencies and maintaining the FCS diet

- Patients on volanesorsen required to adhere to a low-fat diet, but good dietary support (being able to maximise permitted fat) could improve the nutritional status and help relieve the burden of strict diet
- Potential QALY implications of these additional conditions and symptoms shall be considered

ERG comments

- No quantification of the symptoms submitted → impact on cost-effectiveness is unknown but minor
- No empirical evidence provided for issue of malnutrition (extent; associated improvement unknown) → impact on cost-effectiveness is unknown but minor

ECD consultation comments

Treatment continuation rates on volanesorsen

ECD: relatively high drop-out rate seen in clinical trials. ERG: it is likely to be between 10% and 20% each year but no plateau assumed → some stopping would be likely in clinical practice even with proper education and monitoring in place

Company response:

- The ERG used 10% annual value as an exponential distribution in their base case but didn't capture the likelihood (would plateau at 20%)
- Company agrees that 1) some discontinuation is likely, 2) unlikely to exceed 20% in total
  - Patients with greatest potential to benefit from treatment are likely to be prescribed treatment (most significant symptom burden) - likely to be more adherent over the longer term
  - Support programme is likely to lead to better retention, as seen in EAMS
- **80%** plateau in routine UK clinical practice → used in updated economic model (see changes in company base case model on *slide 34*)

ERG comment:

- Correction of description around discontinuation: *'estimates of up to 10% per annum and up to 20% continuation in total'*
  - Discontinuation has an effect on QALYs → **revisited the issue**

ECD consultation comments

ERG comments: Treatment continuation rates on volanesorsen I.

Data source	Patients	Dose	Critique of data source	Discontinuation rate
APPROACH (n=33)	All recruited	Q1W with dose pauses for AEs	Higher dose than indicated	14/33, 42% in one year
APPROACH OLE ([redacted])	Those continuing into OLE from APPRAOCH			52 weeks: [redacted] 104 weeks: [redacted]
APPROACH OLE ([redacted])	Treatment Naïve	Q1W with dose pauses for AEs, enhanced monitoring	Enhanced monitoring more in line with EMA license	52 weeks: [redacted] 104 weeks: [redacted]
APPROACH OLE ([redacted])	Conformed to licensed dosing due to AEs	3 months Q1W, followed by dosing Q2W	Selected for patients with AEs - overestimate discontinuation	104 weeks: [redacted]
APPROACH and APPRAOCH OLE ([redacted])	Patients who changed to Q2W dosing any time after 3 month	Q1W followed by dosing Q2W		[redacted] discontinued (any time after 3 months, time point unclear)
EAMS ([redacted])	Patients receiving volanesorsen in the UK under EAMS	Dosing Q2W	Dose lower in first 3 months [redacted]	[redacted]

Discontinuation rates ranging from [redacted] to [redacted]

Limitations to all analyses: EAMs, under-estimated; all others may be over-estimated

Source: Table 1 – ERG response to company ECD comments

Key: WCS assumes voluntary withdrawal and regulatory delay patients discontinued treatment; BCS assumes they did not discontinue, Q1W: once every week; Q2W: once every two weeks

ECD consultation comments

ERG comments: Treatment continuation rates on volanesorsen II.

- Considered whether discontinuation rate is likely to decrease over time, or stop altogether, but data is limited
  - a) EAMS data are immature b) follow-up data for APPROACH and APPROACH OLE are at risk of bias – *discontinuations are often due to AEs → thought to be reduced with less frequent dosing → may overestimate discontinuation*
- [redacted]
- Patients voluntarily withdrawn due to the burden of monitoring, or a poor profile between clinical efficacy and adverse events → dose adjustments' impact on the alleviation of that unclear
- Evidence on discontinuations at the licensed dose is inconclusive
  - [redacted]
  - [redacted]
- Evidence suggest discontinuations are likely with doses Q2W, may continue in the longer term
  - *10% discontinuation per annum at the licensed dose is a reasonable estimate*
- Treatment continuation is still uncertain → ERG prefers the estimates provided by clinical advisors, based on experience with treatment in a UK setting

ECD consultation comments

Information provided on methodology of EVA-22200 (vignette study)

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

Company response: vignette is a carefully designed study following commonly used methodology to estimate the impact on quality of life of FCS

– [redacted]

Vignette methodology

Extensive details provided as part of an Appendix to the ECD response document

ERG comments:

- Vignettes contain elements of value-laden language → may affect the valuations (*minor issue*)
- Duration of events should not affect valuation of utility of the health state
  - Some time periods are described in a vague way (*minor impact*)

ECD consultation comments

Updated economic model: implementation of vignette values

Recap: in the original model patients on SoC had mean TGs of 26.2 mmol ('high TG' utilities); patients on every 2 weeks volanesorsen had mean TGs of 12.1 mmol ('low TG' utilities) → value predicted by the GLMM model following implementation of the stopping rule

- Method used in company's updated model: High TG utility value assigned to those with ***TG>22.6mmol/L*** health state, low TG utility value from the vignette to remaining patients - ***TG level ≤22.6 mmol/L***
- Aligns with study in patients with type V hyperlipoproteinemia
  - Decrease in number and severity of pain episodes (HTG abdominal crisis) and frequency of attacks of pancreatitis correlated with TG levels of 22.6 mmol/L (Scherer et al., 2014)

ERG comments:

- Logic not consistent with vignette or original submission
  - In vignette study: 'Low TG health state' is associated with non-elevated TGs
  - In original submission: values > 22.6 mmol/L considered 'ultra-high' → values below, but close to this, would be considered high
- People with TG levels between ≥10 mmol/L to <22.6 mmol/L would should *not* qualify as having non-elevated TGs
- ERG maintains its preference for the method used in the ***ERG's original base case*** (***see recap slide 11***)
- A model with finer gradation of TG bands required in order to be able to distinguish between patients with TG levels of 11 mmol/L from patients with TG levels of 21 mmol/L
- *Further comment: not stated in ECD response -- values for historic AP was further adjusted in the model*
  - *Some patients (assumed to be 50%) fully recovered and don't have lingering effects assumed in the vignette →* ***ERG is content with this adjustment***

ECD consultation comments

Updated economic model: carer utility decrement

ECD: using 0.1 utility decrement value for carers is insufficient for decision making → Alternative values should be explored by the company

- Value assigned to carer disutility reduced to 0.04, informed by:
  - Volanesorsen is indicated for an adult population
  - Impact on whole family when a family member has FCS
  - NICE HST submission for metreleptin - ID861 used a utility decrement of 0.05 between treated and untreated groups
    - Population includes children → a lower value proposed than 0.05 for volanesorsen
  - According to literature the impact on family utility for patients with new musculoskeletal conditions is 0.03 (Wittenberg et al. 2013)

= Proposed disutility is **0.04**: midway between 0.03 (for musculoskeletal conditions) and 0.05 (referenced from ID861) – rate of 0.04 used in company's updated model

ERG comments: 0.04 is likely to be an overestimate

- Carer disutility associated with treatments no longer funded were not considered
- Temporal issues not considered within the estimate
  - Loss in utility with existing mental/musculoskeletal conditions is 0.01 (new mental conditions is 0.02) → indicates that utility loss decreases over time
- ERG cannot verify value from metreleptin evaluation
- Volanesorsen doesn't remove need for a low fat diet → social isolation for the family not impacted on by use of volanesorsen → 0.01 may be more appropriate than 0.04

Sensitivity analyses conducted varying the value from 0.00 to 0.04

ECD consultation comments

Company's revised deterministic results (including new PAS price)

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

Key: QALY, Quality-adjusted life year; ICER: Incremental cost effectiveness ratio; PAS: Patient Access Scheme

Source: Table 8 – company ECD response document

ECD consultation comments

ERG exploratory analyses and most plausible ICER (including new PAS price)

- ERG believe that the most plausible deterministic cost per QALY gained would be in excess of **£315,000 (with new PAS)**
  - Net carer disutility should be lower than proposed by the company
  - Estimates of the AP ratios potentially favourable to the company
- There is increased uncertainty in the ICERs due to the impact of dose pauses/missed doses and potential up-titrating of volanesorsen to once-weekly dosing → magnitude is uncertain

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

Source: Table 6 – ERG response to company ECD comments document

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Scenario	QALY gain	
	Undiscounted	Discounted (3.5%)
Company base case	[redacted]	[redacted]

QALY, Quality-adjusted life year

- In all of the ERG's analyses, the undiscounted QALYs gained were below [redacted]

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	Impact beyond direct health benefits
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issues I.

The vignette study and application of utility values:

- Was the vignette study appropriately conducted? Is the committee satisfied with the additional information provided? Which approach of linking the utility values from vignette to health states in the model does the committee prefer? Which values are preferable?

Carer's utilities:

- Company proposed an alternative disutility of 0.04 for carers: midway between 0.03 (for musculoskeletal conditions) and 0.05 (referenced from NICE HST submission for metreleptin - ID861). Which value does the committee prefer between **0.00 to 0.04**?

Volanesorsen's indirect and direct effects on risk of AP:

- Is there sufficient evidence to suggest that volanesorsen confers effect by both reducing mean serum TG level and reducing the 'height of the peaks', therefore the smaller reduction in TG levels associated with the fortnightly dosing is not associated with an increased risk of AP?
- Given the lack of data, is the updated implementation of AP rates sufficient and appropriately modelled? Which is the most plausible value for the rate ratio associated with the use of volanesorsen - **0.50** for all as originally assumed by the ERG; **0.27** (for low/medium TG band) and **0.28** (for high TG band) respectively; or between **0.14** and **0.38**?

Key issues II.

Discontinuation:

- Is the company's assumption on capping discontinuation at **20%** appropriate? Does the clinical evidence available support that?

The relationship between TG levels and risk of AP in people with FCS:

- Does the committee consider the evidence provided by the company supporting the relationship between TG levels and risk of AP in people with FCS sufficient?

Other considerations:

- Has the company addressed all aspects affecting the guidance? Should additional items, e.g. co-morbidities, symptoms or effects of malnutrition also be considered?

ICER and QALY weighting:

- What is the committee's preferred ICER? Does QALY weighting apply?