Slides for public – redacted

Lead team presentation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

1st Evaluation Committee Meeting
Highly Specialised Technology, 28 November 2019
Clinical effectiveness

Lead team member: Paul Arundel
Company: Akcea Therapeutics
Chair: Peter Jackson
Evidence review group: School of Health and Related Research (ScHARR)
NICE team: Orsolya Balogh, Yelan Guo, Melinda Goodall

[redacted]

History of the topic

- Following a submission in 2018 the company advised of changes to its anticipated marketing authorisation (MA)
- Updated submission provided in 2019 using final MA
- **Original anticipated indication:** an adjunct to a low-fat diet for the treatment of patients with FCS

- **Final SmPC indication:** for adults with ***genetically confirmed*** FCS ***at high risk for pancreatitis***
- **SmPC dosing and discontinuation rules:**
  - **Treatment** should ***be discontinued at 3 months*** in patients ***with a reduction in serum triglycerides <25% or who fail to achieve serum triglycerides below 22.6 mmol/L***
  - Posology consists of ***3 months of weekly dosing***, ***followed by down-titration to*** a maintenance dosing schedule of ***once every 2 week***s for those after 3 months; **possible re - up titration at 6 months** to weekly dosing, if response is not acceptable on 2-weekly dosing

- **Platelet monitoring rules** were introduced in company's trial*; with clear indications for dose pausing or discontinuation

** Before treatment imitation, platelet count should be measured (not initiated if <140X10^9/L). During APPROACH trial, a more intensive platelet monitoring plan was implemented because of adverse events (AE) such as thrombocytopenia*

[redacted]

Key issues for consideration

Clinical effectiveness

Population: volanesorsen is indicated for adult patients with genetically confirmed FCS at high risk for pancreatitis. Not all patients in company's trials (APPROACH, APPROACH OLE, COMPASS) were genetically diagnosed (89.13%, 82/92):

- Are the study populations representative to people with FCS seen in the UK practice?
- How would "high risk for pancreatitis" be defined in clinical practice?

Clinical effectiveness and safety of volanesorsen at the licensed dose: the licensed dose was not used in trials. What is the committee's view on volanesorsen's effect, at the licensed dose, on:

- Change in TG levels and response to the treatment in long term?
- Clinical outcomes such as AP, CP, pain and type 2 diabetes, in which only very limited evidence of low quality from trials was reported *(no subgroup analysis by SmPC dosing conducted either)?*
- Safety outcomes (such as thrombocytopaenia)?
- Discontinuation?

TG levels as the surrogate outcome and the dose-response relationship between it and AP:

- What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Equality:

- Volanesorsen is indicated for FCS patients who are genetically diagnosed, however some patients may have unknown mutations and could not be genetically diagnosed. Does this raise a potential equality issue?

Disease background

Familial chylomicronaemia syndrome (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**: 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)

Diagnosis

- Historically, FCS has been **diagnosed by clinical criteria**, including ***recurrent raised TG levels*** refractory to current lipid-lowering therapies and not due to other causes (e.g. type 2 diabetes, hypothyroidism), plus a ***history of recurrent AP*** and ***abdominal pain***
- Genetic diagnosis (*a condition of the license*) is becoming more usual
  - Not all patients with FCS have a known mutation, may not receive genetic confirmation if tested

Prevalence

- Estimated to be **1 to 2 per million people** which equates to approximately 55 to 110 people in England
- It is expected that between **80 and 100 people in England** are likely to be eligible for treatment with volanesorsen¤

¤ estimated by Akcea

Current treatment options

No standard clinical pathway or licensed treatment available

- Management consists of: severe restriction of dietary fat intake (10 to 20g/day), and no alcohol intake (to keep plasma triglyceride levels low)
  - Even severely restricted low-fat diet not sufficient to reduce the risk of a potentially fatal episode of AP for most patients
  - Fibrates and statins (lipid lowering agents) may be prescribed but have limited value
- Patients may be on a cocktail of drugs to control pain and other symptoms of FCS, including steroids, analgesics, anxiolytics, antidepressants, diabetes treatments and antithrombotic
- Essential fatty acids and fat soluble vitamin supplements are required for patients on a fat restricted diet

Related NICE guidance

- None

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

Decision problem I.

	Final scope issued by NICE	Company deviations	ERG comments
Population	Adults with FCS	***Narrower than scope***: adult patients with ***genetically confirmed FCS and at high risk for pancreatitis*** in whom response to diet and triglyceride-lowering therapy has been inadequate	Population change ***matches final MA***; • ***License does not define "high risk" for pancreatitis***; • Any patient with high TG level is clinically considered to be at high risk of pancreatitis; • Clinicians may have widely ***differing interpretations of the license*** → uncertainty about how patients will be selected for treatment • Some people with FCS may have unknown gene mutations and ***may not be diagnosed genetically*** →such patients ***may have entered the trial*** • ***Population in trials is likely to be generalisable to UK clinical practice***
Intervention	Volanesorsen in combination with established clinical management (incl. dietary fat restrictions)		The licensed dosing was not used in clinical trials, leading to ***uncertainty on the licensed dose's efficacy and safety*** outcomes, consequently on ***discontinuation rates***
Comparator	Established clinical management without volanesorsen (incl. dietary fat restrictions)		***Reflects established clinical practice in England*** Use of fibrates and statins not routinely recommended in patients

MA: Marketing authorisation, TG: triglyceride; FCS: Familial chylomicronaemia syndrome

How would "high risk for pancreatitis" be defined in clinical practice?
Some patients could not be genetically diagnosed. Does this raise a potential equality issue?

Decision problem II.

	Final scope issued by NICE	Company deviations	ERG comments
Outcomes	• Chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease • incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications • hospitalisation • mortality (including all-cause and pancreatitis related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers)	***Data gaps and limitations***, and concerns regarding double counting mean that some outcomes are not explicitly considered in the model Cardiovascular disease (CVD) is not in the economic model as there is no clinical consensus regarding the impact of FCS on CVD outcomes	***Outcomes not reported in trials:*** • ***Neurological and psychological impacts*** (depression, cognitive ability) • Hospitalisation - ***proportion of patients requiring hospitalisation was estimated for use within the health economic model*** ***Additional analyses relating to hard clinical outcomes submitted***, including rate of APs in APPROACH and APPROACH OLE patients for the 5 years prior to study enrolment versus on treatment ***Fatigue, diabetes and mortality measured as adverse events only***

[redacted]

Clinical effectiveness evidence

Completed clinical trials

Trial	Intervention	Population	Treatment duration	Outcomes	Used in clinical effectiveness	Used in cost-effectiveness
APPROACH Phase III, double-blinded RCT**	Volanesorsen (285 mg) by SC injection, once weekly Placebo by SC injection	***N=66*** , adult patients with FCS with fasting triglycerides >=8.4 mmol/L (>=750 mg/dL)	52 weeks +13 weeks follow-up or *entry to APPROACH OLE open-label extension*	***Primary***: % change in TG level at Month 3 and over time ***Secondary***: • Abdominal pain; • AP; • Response rate ¥ , • Absolute change in TG level from baseline to month 3	YES	YES
COMPASS Phase III, double-blinded RCT	Volanesorsen (285 mg) by SC injection, once weekly Placebo by SC injection	Patients with hypertriglyceridemia including FCS ***(N=7)*** with fasting triglycerides +/- 500 mg/dL	26 weeks +13 weeks follow-up or *entry to APPROACH OLE open-label extension*	% change in TG level at Month 3*	YES	NO

AP: acute pancreatitis; *average of 12-13 week assessments; ⁺ baseline to 6, 12 months; ¥ (defined as 40% reduction in fasting TG between baseline and month 3; attaining levels <750 mg/dL in fasting TG between baseline and month 3), **RCT – randomised controlled trial; SC: subcutaneous; FCS: Familial chylomicronemia syndrome

[redacted] Are the study populations representative to people with FCS seen in the UK practice?

Ongoing clinical trials

Trial	Intervention	Population	Treatment duration	Outcomes	Used in clinical effectiveness	Used in cost-effectiveness
APPROACH OLE Phase III	Volanesorsen (285 mg) by SC injection, once weekly	***N*=XX**, Adult patients with FCS, rolled over from: • APPROACH volanesorsen XXXX • COMPASS volanesoresen XXXX • Treatment naiive XXXX	Ongoing	• % change and absolute change from baseline in fasting TG level† ; • Frequency and severity of patient-reported abdominal pain during the treatment period; • % change from baseline in other fasting lipid measures at Months 3, 6 and 12	YES	YES – except results from the subgroup which used SmPC dosing during the trial (due to AE related dose adjustment)

AP – acute pancreatitis; † no formal designation of outcomes as 'primary' or 'secondary'; SC: subcutaneous; FCS: Familial chylomicronemia syndrome

ERG comment

- **APPROACH OLE**: characterised as a before-after study design → descriptive and of poor quality for the assessment of intervention efficacy
- Subject to risk of bias, including open label design; unclear if all eligible patients were enrolled; high level of withdrawals XXXX missing data were not factored in the main analysis (e.g., % change in TG levels), no *p* values reported for results on changes from baseline

Other sources of evidence used in clinical and cost-effectiveness evidence

Information	Interventions	Population	Treatment duration	Outcome	Used in clinical effectiveness	Used in cost-effectiveness
ReFOCUS, single-arm, retrospective web-based survey	Volanesorsen (285 mg) by SC injection, once weekly	***N=22***, patients from OLE who received at least 3 months of treatment with volanesorsen	NA	HRQoL/burden of the disease 3 months prior to enrolment vs. the latest 3 months on treatment	YES	NO
EAMS Early Access to Medicines Scheme	Volanesorsen (285 mg) by SC injection, bi-weekly dosing from inception	***N=20*** on treatment (25 eligible), including patients who have received treatment in APPROACH and OLE previously	Ongoing*	Not reported	NO	No data used, but basis for a scenario analysis
CALIBER Retrospective registry study	Data collected for ~1.8million patients with at least 1 TG record between 1997-2016 Contains linked electronic health records in England between the Clinical Practice Research Datalink, Hospital Episode Statistics and Office for National Statistics				NO	Yes

HRQoL: health-related quality of life; SC: subcutaneous; NA: not applicable, TG: triglycerides

[redacted]

*EAMS started in July 2018, mean follow-up time 7 months; no stopping rule in EAMS

Baseline characteristics

	APPROACH				[redacted]			COMPASS	
	Volanesorsen (n = 33)		Placebo (n = 33)		[redacted]			Volanesorsen (n = 5)	Placebo (n = 2)
Age, mean (range) years	47	(22 – 75)	46	(20 – 68)	[redacted]			47 (33 – 54)	51 (43 – 58)
Gender, % Male	48.5		42.4		[redacted]			40	0
Fasting TG, mean (range) mg/dL	2267 (347 – 5660)		2152 (631 – 5475)		[redacted]			2134 (1074 – 3998)	2644 (2422 – 2867)
History of acute pancreatitis, n (%)	24	(72.7)	26	(78.8)	[redacted]			NR	NR
Abdominal pain*	7	(21.2)	10	(30.3)	[redacted]			NR	NR
Platelet aggregation inhibitors	8	(24.2)	5	(15.2)	[redacted]			NR	NR

ERG comment

- Levels of abdominal pain in APPROACH high in comparison to the English population (although TG levels lower than average)
- In/exclusion criteria of APPROACH set a cap on patients with no history of pancreatitis at ***28%*** → ***24% of patients recruited had no prior history of AP***
- 11% in APPROACH received alipogene tiparvovec → may have lower baseline levels of pancreatitis than patients in England
- 25% of patients recruited to APPROACH with no known mutation (in keeping with levels in England)
- APPROACH OLE recruited [redacted] than APPROACH study – [redacted]
- [redacted]
- [redacted]

Impact of imbalances in baseline characteristics on the treatment effect is unclear

Clinical effectiveness results

[redacted]

Patient flow across trials - *APPROACH, COMPASS and APPROACH OLE*

[redacted]

Source: Figure 1 ERG report

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Discontinuation I.

Relatively high discontinuation rates observed across studies

APPROACH (N=66)

- **Volanesorsen arm** (n=33): ***42% (14/32) discontinued before Month 12***
  - 2 patients (6%) discontinued before week 13; 7 patients (21%) discontinued between weeks 13 and 26; and 5 (15%) discontinued after week 26;
    - Most common reason for discontinuation was adverse event
- **Placebo arm** (n=33): 1 patient voluntarily withdrew from the study, 1 lost to follow-up and 1 withdrew for other reason

APPROACH OLE ([redacted]) †

- **APPROACH volanesorsen group** [redacted]
- **Treatment naïve (at roll-over) group*** [redacted]
- **COMPASS volanesorsen group** [redacted]
- **SMPC dosing subgroup in APPROACH OLE** [redacted]

Discontinuation after the first 12 months of treatment in trials (APPROACH vs. APPROACH OLE) :

- At 12 months/52 weeks: 42% in APPROACH vs. [redacted] in APPROACH OLE
- At 104 weeks: 79% in APPROACH vs. [redacted] in APPROACH OLE
- *Note: (monitoring schedule was in place in APPROACH OLE due to protocol adjustment)*

† Exact duration of treatment for patients in APPROACH OLE is unclear as they have rolled over from APPROACH or COMPASS; ¥ 52 weeks of enrolment into APPROACH OLE

** Volanesorsen treatment naïve at roll-over from APPROACH or recruitment, all patients received treatment in APPROACH OLE*

Discontinuation II.

Relatively high discontinuation rates observed across studies

Mixed dose subgroup *(defined as people who changed to bi-weekly dosing any time after 3 months across trials, n=36);*

- 39% (14/36) discontinued *(exact discontinuation times unknown)*

ERG summary on discontinuation

- Discontinuation rate in clinical practice is currently unknown, unlikely to be zero
- Likely discontinuations in clinical practice between ***10% per annum and 20% in total***
- Main reasons are burden of monitoring and adverse events including injection site reactions and thrombocytopaenia

[redacted]

Clinical effectiveness: % change in fasting TG (mg/dL) levels from baseline - *Substantial reduction in % TG levels observed*

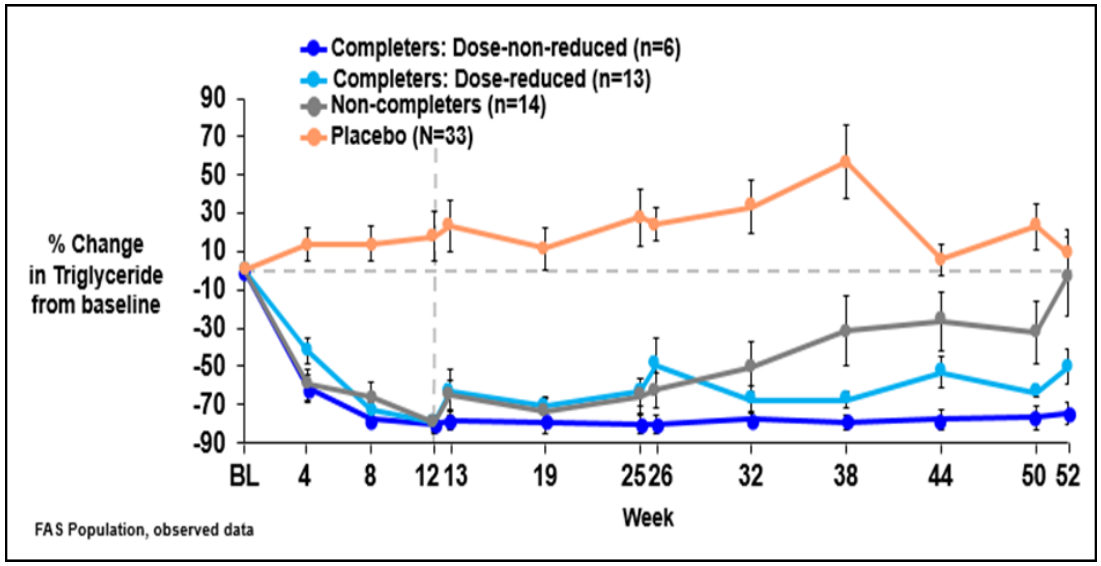
	APPROACH		APPROACH OLE						
			Whole trial population			Subgroup of patients with licensed dose	Subgroup of patient with history of pancreatitis	
Timepoint	Volanesorsen (n=33)	Placebo (n=33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	-76.5	17.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	-52.5	25.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	<0.0001 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	-40.2	8.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value or SD	0.0347 (ANCOVA)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	See Month 6 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	See Month 12 APPROACH-vol	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source, Table 10, ERG report

* Treatment naïve at the enrolment of OLE; all patients received volanesorsen in OLE; SD: standard deviation

Clinical effectiveness: % change in fasting TG (mg/dL) levels from baseline

APPROACH (n=66)



- Volanesorsen once-weekly treatment: consistent, sustained response
- Mean percent reduction clinically meaningful regardless of dose adjustments
- For patients with dose adjustments and non-completers: dose pauses led to a lower reduction in TG level

[redacted]

*Source: Figure 12, ERG report; TG levels over time in **APPROACH,** including dose adjustments and non-completers*

Clinical effectiveness: % change in fasting TG (mg/dL) levels over time

*APPROACH and COMPASS through to APPROACH OLE**

Source: revised figure 20, company clarification, 2019; CS 6= APPROACH; CS16=COMPASS;

*

-
-
-

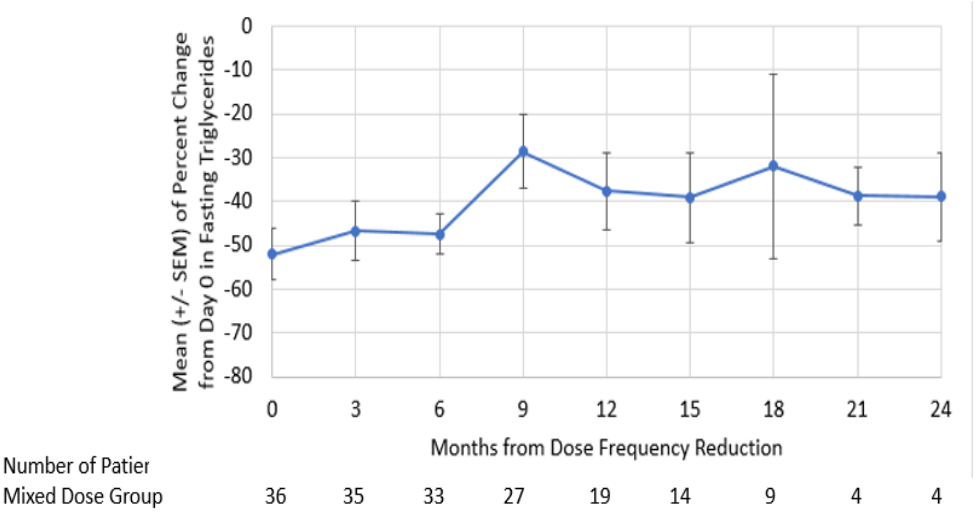
Clinical effectiveness: % change in TG levels (mg/dL) from baseline

Subgroup of people conforming to SmPC dosing (from APPROACH OLE, [redacted])

[redacted]

Source: Figure 5 ERG report

Mixed dose subgroup across APPROACH and APPROACH OLE, (n=36)



Source: Figure 11, Appendix, ERG report

ERG comment

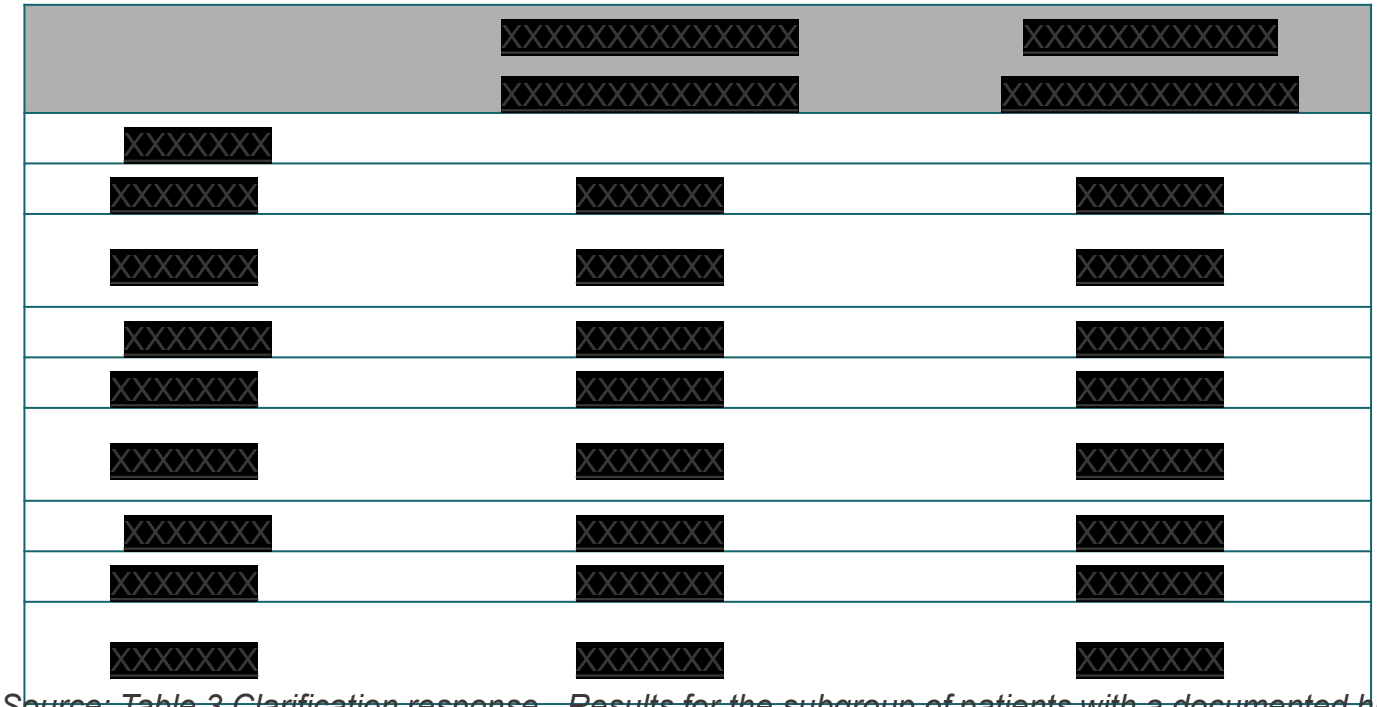
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

ERG comment

- Larger patient numbers than SmPC subgroup but patients could adjust dosing at any time after month 3, unclear when the switch occurred
- TG levels remained stable from Month 12 to 24, -40% change from baseline
- May be an overestimate of treatment effect as patients were on treatment for longer (exact length unknown), may still be washing out from full dose up to 6 months after treatment cessation

Clinical effectiveness: % change in TG levels (mg/dL) from baseline - *Subgroup of patients who had a history of pancreatitis (from APPROACH OLE, [redacted])*



ERG comment

- [redacted]
- [redacted]

Source: Table 3 Clarification response - Results for the subgroup of patients with a documented history of AP

SD: standard deviation

ERG comment

- [redacted]
- Clinical advisor: ***did not expect to see a greater effect in patients with a prior history of pancreatitis***, *or* ***by any other definition of "high risk"***

[redacted]

ERG summary on: % change in TG levels (mg/dL) from baseline - *responses seemed generally lower in later months*

- Responses across studies seemed generally lower in later months with a few exceptions
  - Possible waning effect of volanesorsen is probably small
    - Follow-up and clinical experience with the treatment do not appear to go beyond around 3 to 4 years, there is some uncertainty about long terms effects
- [redacted]
- [redacted]
- [redacted]
- [redacted]

What is the committee's view on volanesorsen's effect, at the licensed dose, on % change in TG levels in long term?

[redacted]

Clinical effectiveness: absolute change in fasting TG (mg/dL) levels from baseline – *Similar results and trend seen as for % change in TG levels*

APPROACH (n=66)

- Mean absolute reduction in the volanesorsen group (n=33) of 1712 mg/dL, compared with a mean absolute increase of 92 mg/dL (in the placebo group (n=33) at Month 3)
  - Least squares mean difference was -1804 mg/dL (95% CI: -2306, -1302), the difference was statistically significant

APPROACH OLE ([redacted])

- TG levels for Months 3, 6, 12, weeks 76 and 104 were [redacted]
  - [redacted]
  - [redacted] *(p values not reported)*
  - [redacted]

ERG:

- Substantial mean absolute change in TG levels on volanesorsen treatment
- Standard deviations indicate a great deal of variation → may reflect the very variable baseline TG values of patients, or may be due to dose pauses and reductions meaning treatment effect varies
- Clinical advisors to ERG indicated that nearly all patients have a substantial TG response to treatment

[redacted]

Clinical effectiveness: Responder analysis at month 3

APPROACH (n=66), more patients on volanesorsen meeting the end point vs. those on placebo

Responder analysis (endpoint fasting TG <750 mg/dL at Month 3)		
	Volanesorsen	**Placebo**
n (%) of patients	23 (76.7)	3 (9.7)
Odds ratio	186.16 (95% CI: 12.86, N/A)	
p value	0.0001 (logistic regression model)	

Responder analysis (≥40% reduction in fasting TG at Month 3)		
	Volanesorsen	**Placebo**
n (%) of patients	29 (87.9)	3 (9.1)
Odds ratio	99.69 (95% CI: 15.75, 631.06)	
p value	<0.0001 (logistic regression model)	

ERG comment

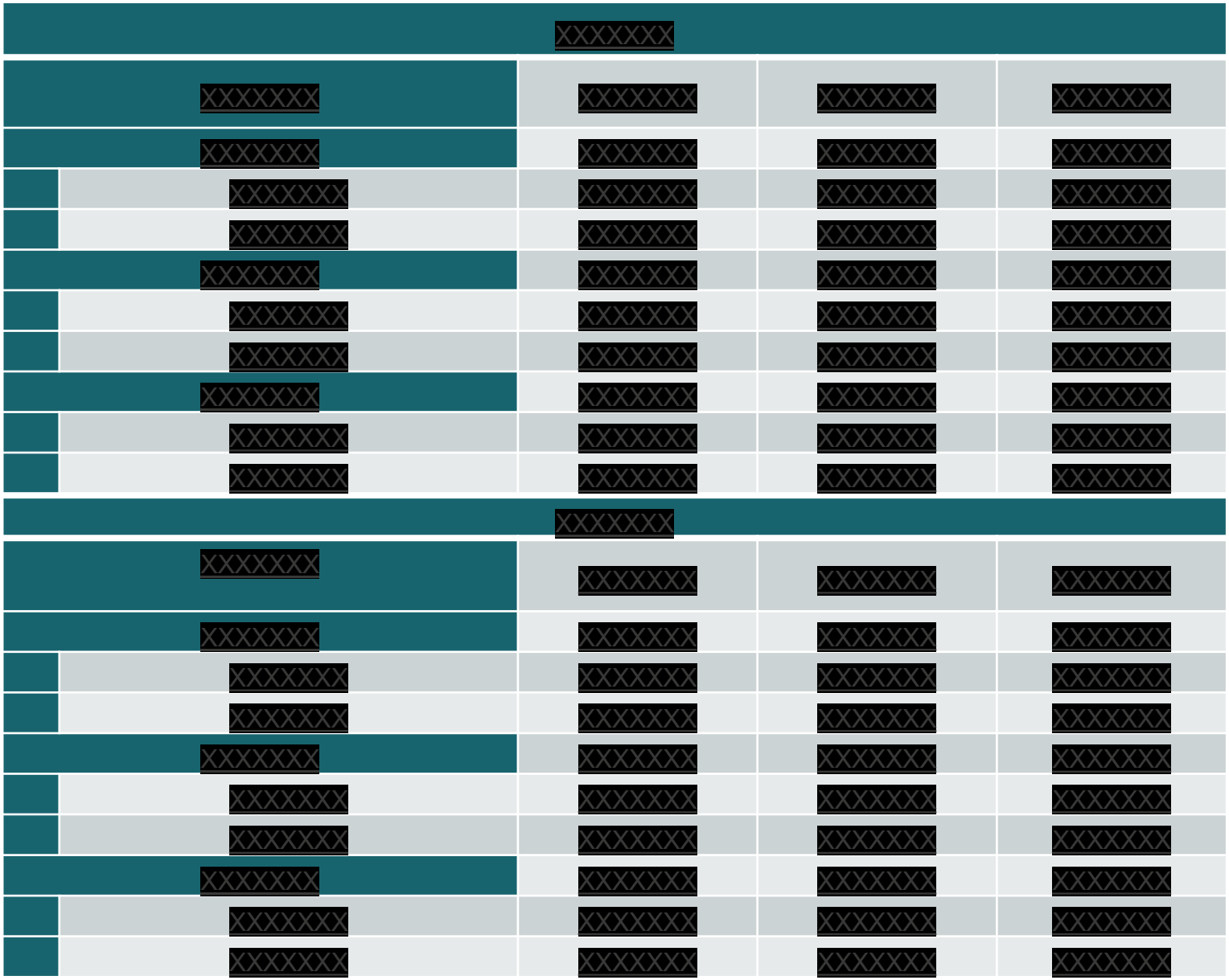
- The outcome was met, 76% of volanesorsen patients vs. 9.7% of placebo patients meeting the end point
- *12-month data from APPROACH not reported*

[redacted]

Source: Table C15, company submission

Clinical effectiveness: Responder analysis over time

APPROACH OLE ([redacted])



ERG comment

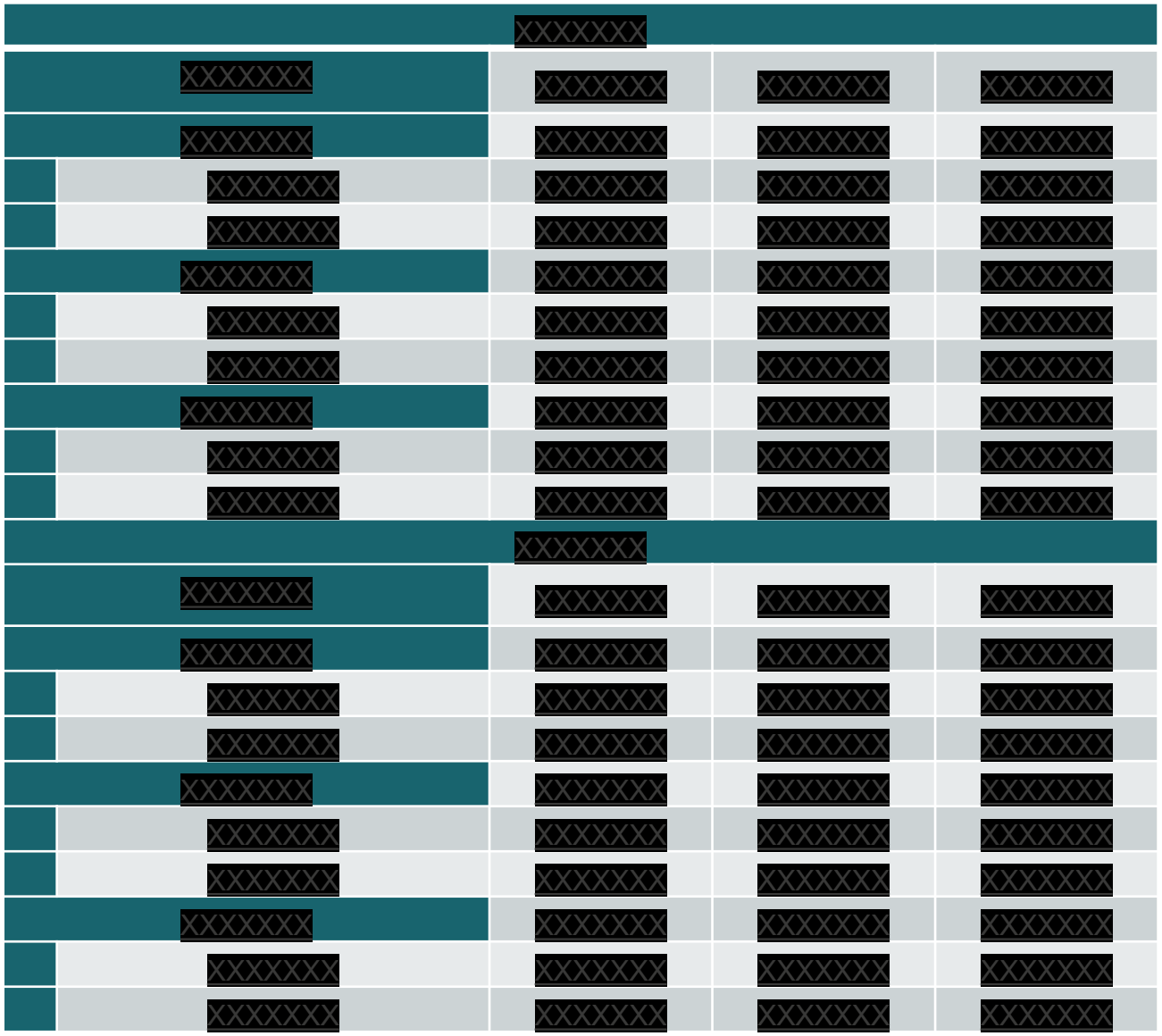
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Source: Table C19, company submission

** patients have received volansorsen in APPROACH and COMPASS before rolling over to APPROACH OLE, exact treatment time on volanesorsen is unclear*

Clinical effectiveness: Responder analysis over time

APPROACH OLE ([redacted])



ERG comment

- [redacted]
- [redacted]

*Source: **Table C19**, company submission*

p values not reported in APPROACH OLE: could not conclude whether significant difference does exist between groups or from baseline for each group;

** patients have received volansorsen in APPROACH and COMPASS before rolling over to APPROACH OLE, exact treatment time on volanesorsen is unclear*

ERG summary on: responder analysis over time

- Most patients appear to achieve a reduction in TG levels at month 3 and/or a moderate-to-high relative reduction in TG levels
- Indicates that a good proportion of patients are likely to continue on the treatment after the assessment of stopping rule in the license
  - Stopping rule: TG levels <22.6mmol/L (around 2000mg/dL) or at least a 25% reduction in TG levels
- Response rates wanes over time → may reflect the very variable baseline TG values of patients, or may be due to dose pauses and reductions meaning treatment effect varies
- No data provided on licensed dose patients → 3 month data is the most relevant to the licence
- Unclear how many patients would maintain TG levels <750 mg/dL (8.5mmol/L) or less than 22.6mmol/L at the SmPC dose, as used in the model

What is the committee's view on volanesorsen's effect, at the licensed dose, on discontinuation over time?

[redacted]

Clinical effectiveness: abdominal pain - *average maximum intensity or abdominal pain during on-treatment period: APPROACH, OLE, subgroup of licensed dose + exploratory analysis of subgroup of people who had abdominal pain at baseline*

	APPROACH		APPROACH OLE			Subgroup of patients with licensed dose
Outcome	Volanesorsen (N=33)	Placebo (N=33)	[redacted]	[redacted]	[redacted]	[redacted]
Average maximum intensity of abdominal pain during on-treatment period**	[redacted]					
Mean (SD)	0.38 (0.83)	0.36 (0.79)	[redacted]	[redacted]	[redacted]	[redacted]
p value	0.8959 (two-sample t-test)					

Source: Table 11, ERG report

Pre-explained exploratory analysis: people with abdominal pain at baseline in APPROACH (n= 17; 7 on volanesorsen vs. 10 on placebo)

Statistically significant difference in reduction in the average maximum intensity of abdominal pain between volanesorsen treated group and placebo group (P**=** ***0.0227***)

ERG comments on the exploratory analysis

Baseline characteristics are unlikely to predict response to treatment

Result does not reflect a more responsive subgroup of patients but may be due to higher baseline events therefore an effect could be detected → ***effect of volanesorsen on abdominal pain is uncertain***

Clinical effectiveness: AP

Pancreatitis events (pre-planned safety analysis) - APPROACH

Outcome	Volanesorsen (n=33)	Placebo (n=33)
Patients (events)	1 (1)**	3 (4)
p-value	P = 0.6132	

Ad/post hoc analysis of AP rate: 5-year history of AP prior to study enrolment versus on-volanesoresen treatment

	APPROACH		APPROACH OLE
	Volanesorsen (n = 33)	Placebo (n = 33)	[redacted]
Patients in analysis	7	4	[redacted]
Events prior 5 years	24 events =0.69 per patient year	17 events =0.85 per patient year	[redacted]
Events on treatment	0 events	4 events	[redacted]
p-value	0.0242		[redacted]

NR: not reported

ERG comment

APPROACH

- Analysis restricted to patients with at least 2 APs in the 5 years prior to treatment (n=11); did not account for time on treatment → there may be some bias as discontinuation rates were high

APPROACH OLE

- [redacted]
- [redacted]

Source: Table 11, ERG report

ERG summary on: AP

Volanesorsen's effect on AP is uncertain

- Treatment may reduce AP events → it remains uncertain, effect size is unclear, especially at the reduced dose indicated by the license
- [redacted]
- ***In the model*** AP rates are predicted by TG levels as well as using the rate ratio calculated from the APPROACH OLE analysis of AP rates 5 years before treatment and whilst on treatment

What is the committee's view on volanesorsen's effect, at the licensed dose, on clinical outcomes - AP and pain?

[redacted]

Clinical effectiveness: diabetes and mortality

APPROACH and APPROACH OLE

Diabetes rates were only reported for APPROACH (n=66)

- Volanesorsen arm: [redacted]
- Placebo: [redacted], p value not reported

No deaths in APPROACH or APPROACH OLE

[redacted]

Clinical effectiveness: health related quality of life measured by EQ-5D and SF-36

APPROACH (n=66)

Patients who have been on treatment for 3 months, HRQoL assessed along with other outcomes at month 3, 6, and 12

- Baseline values were high (utility >0.97 in both arms: [redacted] volanesorsen vs. [redacted] placebo)
- No significant change from baseline for the SF-36 or EQ-5D-5L at:
  - Month 3 (p = 0.6627 and p = 0.2920, respectively)
  - Month 6 (p = 0.9226 and p = 0.5923, respectively)
  - and Month 12 (P = 0.7912 and P = 0.4079, respectively)

APPROACH OLE ([redacted])

- [redacted]
  - [redacted]

ERG

- Baseline values seem high for the patient group
  - Although FCS has a considerable impact on patients' HRQoL
- Very little room for improvement → ceiling effect

Clinical effectiveness: health related quality of life

Retrospective web-based survey **ReFOCUS** conducted among APPROACH OLE patients (n=22)

- Entry to survey: patients on volanesorsen treatment for 3 months and were asked about the 3 months prior to enrolment and the latest 3 months on treatment
- % of patients who believe:
  - FCS was more effectively managed with volanesorsen (40% vs. 19% before treatment)
  - Symptoms controlled with adherence to diet (90% vs. 55% before treatment)
    - *No p values reported*

ERG comment

- ReFOCUS was a single-arm, retrospective design study asking patients to recall symptoms, subject to risk of recall bias → the period of recall would be over a year before
- Not clear how many patients were approached or were eligible
- The study is open-label → high risk of detection bias, may interact with recall bias
- No baseline characteristics presented; unclear how representative the enrolled patients were of the wider trial of patients in England → ***low quality and at high risk of bias to answer a question of efficacy***

[redacted]

Adverse events - Most frequent (≥1/10 patients) treatment-emergent AEs are injection site reaction, fatigue, headache and thrombocytopaenia

APPROACH

Most frequent (≥1/10) treatment-emergent AEs	Volanesorsen arm (n=33)	Placebo arm (n=33)
Type of AE: n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

APPROACH OLE

Most frequent (≥1/10) treatment-emergent AEs	[redacted]	[redacted]	[redacted]
Type of AE: n (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Table C 22 and section 9.7 company submission; page 53 ERG report

[redacted]

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Adverse events II.

APPROACH

Severe treatment emergent AEs

- Volanesorsen arm (n=33): 5 severe TEAEs - 4 related to study drug (severe thrombocytopaenia (n=2), fatigue (n=1) and musculoskeletal pain (n=1))
- Placebo arm (n=33): 3 patients had severe TEAEs, none considered potentially related to treatment

Serious AEs:

- Volanesorsen arm (n=33): 8 events experienced by 7 patients (21%, 7/33)
- Placebo arm (n=33): 6 events experienced by 5 patients (15%, 5/33)

SmPC dosing subgroup in APPROACH OLE [redacted]:

- Results showed that [redacted]

ERG comment

- Clinical advisors concerned about injections site reactions and platelet counts/thrombocytopaenia
- Revised dosing schedule and monitoring could reduce the events
  - Unclear to what extent the licensed dosing schedule and monitoring prevent the most serious and significant adverse events
- Impact of using the ***licensed dose on safety outcomes and discontinuation generally uncertain*** → long-term treatment and tolerance of treatment with volanesorsen is uncertain

[redacted]

What is the committee's view on volanesorsen's effect, at the licensed dose, on safety outcomes?

ERG's comments on treatment effectiveness and dose-response relationship between TG levels and AP

Treatment effectiveness	• Treatment statistically significantly (p<0.05) reduced TGs levels • However, not all patients achieved TG levels below 8.4mmol/L • Results relating to AP, abdominal pain and HRQoL were less certain • High rates of discontinuations in the clinical studies, mostly due to AEs **Long-term response and tolerance to the treatment is uncertain** **Uncertainty relating to clinical effectiveness, treatment discontinuation and safety of the treatment at the licensed dose in clinical practice**
Dose response relationship between TG levels and AP; **Cut-offs for TG band levels**	Clinical studies measured a surrogate outcome (TG levels) **Dose response relationship:** • Evidence suggested that the general linear relationship between TG levels and the risk of AP is acceptable at population level • However, uncertainties remain regarding whether this evidence is generalisable to people with FCS, as FCS patients may experience AP at lower TG levels than patients with raised TG levels by other causes **TG level cut-offs at which AP risk appears increased in FCS patients:** • The cut-off of ≥10mmol/L and further increased at >22.6m mmol/L is appropriate according to the evidence available, however **Uncertainties remains in cut-offs of TG levels** at which **more severe consequences of AP arise in FCS patients**; so are the uncertainties **in magnitude of the differences** associated with those cut-offs

AP: acute pancreatitis, AE: adverse event; SmPc: Summary of product characteristics; TG: triglycerides; FCS: Familial chylomicronemia syndrome; HRQoL: health-related quality of life

[redacted]

ERG's comments on surrogate outcomes and clinical effectiveness

Surrogate outcomes and uncertainties	• **Uncertainties remain regarding whether the dose-response relationship between TG levels and the risk of AP is generalisable to FCS patients** • Clinical evidence on volanesorsen's effect on hard clinical outcomes such as AP at the trial's dose, is of low quality and uncertain • Clinicians: chylomicron TG levels is considered a better clinical indicator of risk of AP → directly responsible for causing AP
Summary on Outcomes	• **TG level bands and selected cut-offs:** used as surrogate for clinical outcomes such as AP, CP, type 2 diabetes, and death → uncertainties about its clinical significance and cut-offs in people with FCS • **AP:** volanesorsen's effect on AP was uncertain, no analyses was presented at the bi-weekly nor the licensed dosing • **Subgroup analyses for AP (by AP 5 years prior to study enrolment versus AP on treatment)** were subject to limitations such as underpowered, exploratory, singled-armed, and post-hoc in nature • **Subgroup analysis by SmPC dosing is only available for:** TG levels, response, average maximum intensity of pain, and the composite of AP and pain • Long-term response and tolerance to the treatment is uncertain • Uncertainty relating to **clinical effectiveness**, **treatment discontinuation** and **safety of the treatment** at the licensed dose in clinical practice

AP: acute pancreatitis, CP: chronic pancreatitis; SmPc: Summary of product characteristics; TG: triglycerides; FCS: Familial chylomicronemia syndrome

What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Key issues for consideration

Clinical effectiveness

Population: volanesorsen is indicated for adult patients with genetically confirmed FCS at high risk for pancreatitis. Not all patients in company's trials (APPROACH, APPROACH OLE, COMPASS) were genetically diagnosed (89.13%, 82/92):

- How would "high risk for pancreatitis" be defined in clinical practice?
- Are the study populations representative to people with FCS seen in the UK practice?

Clinical effectiveness and safety of volanesorsen at the licensed dose: the licensed dose was not used in trials. What is the committee's view on volanesorsen's effect, at the licensed dose, on:

- Change in TG levels and response to the treatment in long term?
- Clinical outcomes such as AP, CP, pain and type 2 diabetes, in which only very limited evidence of low quality from trials was reported *(no subgroup analysis by SmPC dosing conducted either)?*
- Safety outcomes (such as thrombocytopaenia)?
- Discontinuation?

TG levels as the surrogate outcome and the dose-response relationship between it and AP:

- What is the committee's consideration on the surrogate outcome? Is it an appropriate proxy for clinical outcomes such as AP for people with FCS?

Equality:

- Volanesorsen is indicated for FCS patients who are genetically diagnosed, however some patients may have unknown mutations and could not be genetically diagnosed. Does this raise a potential equality issue?

Information about Early Access to Medicines Scheme (EAMS)

- Volanesorsen has been available to eligible patients via the EAMS since March 2018
- From 25 eligible patients, 20 were on treatment as of 31 July 2019 (at the time of submission)
- EAMS uses a similar platelet monitoring and dose adjustment schedule as that in the SmPC
  - But no stopping rule at 3 months, and bi-weekly dosing administered from inception, lower than SmPC dosing
- No EAMS patient has had a platelet level < 50 x 10^9/L with the monitoring and dosing programme in place
- Patients initiate on every 2 weeks dosing, 1 patient has increased dosing frequency
- 1 person discontinuation in the programme (due to cancer recurrence)

[redacted]

Authors

Orsolya Balogh
Technical Lead

Yelan Guo
Technical Adviser

with input from the Lead Team

- **Paul Arundel** (clinical)
- **Linn Phipps** (lay)
- **Sarah Davis** (cost)

Slides for public – redacted

Lead team presentation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

1st Evaluation Committee Meeting
Highly Specialised Technology, 28 November 2019
Economic effectiveness

Lead team member: Sarah Davis
Company: Akcea Therapeutics
Chair: Peter Jackson
Evidence review group: School of Health and Related Research (ScHARR)
NICE team: Orsolya Balogh, Yelan Guo, Melinda Goodall

[redacted]

Key issues for consideration

Cost-effectiveness

- What is the committee's view on the model in general? Does the model structure capture disease progression of people with FCS and aspects important for them?
- Clinical evidence on volansorsen's effect on AP, at the licensed dose, is lacking from the trials. What is the committee's considerations on TG levels as surrogate outcome for AP and the assumptions related to it in the model, including:
  - The risk of AP was conditional on TG-risk band in FCS patients; and
  - Volanesorsen has a direct protective effect on clinical outcomes, such as AP and mortality, independent of/not mediated through TG levels?
- What is the committee's view on the underlying utilities associated with TG level bands, which utility values does the committee prefer?
- Should the utility benefits to carers be included in the analysis?
- Is the company's assumption on patient discontinuation in the model, at the licensed dosing, appropriate?
- Are there any equality issues to consider?

[redacted]

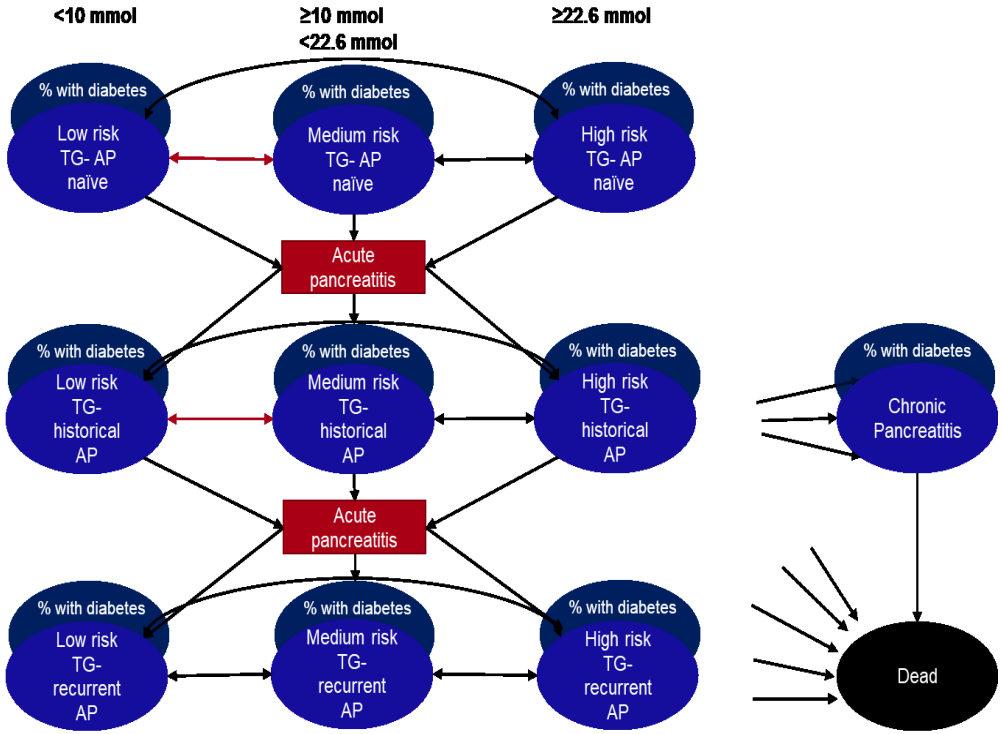
Company model structure

Three-month decision tree model

Continuation criteria applied in volanesorsen arm

[redacted]

Longer-term Markov model



QALYs half-cycle corrected

Cost and QALYs half-cycle corrected

Source: Figure 28 Company submission

[redacted]

What is the committee's view on the model in general? Does the model structure capture disease progression of people with FCS and aspects important for them?

Economic model

Model structure	2 components: 1) A decision tree model for the initial 3-month; and 2) Markov model for the long-term beyond 3 months;
Health states	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
Population	Patients with genetically confirmed FCS who are at high-risk of pancreatitis Hypothetical cohort of patients assumed to be 41 years old and are comprised of 54.5% females High-risk of pancreatitis defined as having had a previous AP event → population in the base case model have a history of AP (***different from APPROACH trial data***) Otherwise patients have characteristics in terms of AP history and baseline TG bands as patients in APPROACH
Dosing	Weekly for the initial 3 months and bi-weekly thereafter in the long-term Markov model until discontinuation or death
Benefits associated with treatment	Mainly come from it reducing patients' TG band level (to medium-risk) compared with SoC, with additional benefits on hard clinical outcomes assumed.
Discounting	3.5%
Perspective	NHS / PSS
Cycle length	3-month model cycle
Time horizon	59-year time horizon Assumed to represent the maximum remaining lifetime of a patient

TG: triglycerides; AP: acute pancreatitis; CP: chronic pancreatitis; SoC: standard of care; PSS: personal social services

Population: population split at model entry

- Patients with genetically confirmed FCS who are at high-risk of pancreatitis
  - High-risk of pancreatitis defined as having had a previous AP event
- Hypothetical cohort of patients assumed to be 41 years old and comprised of 54.5% females
- Patients assumed to have characteristics in terms of AP history and baseline TG bands as patients in APPROACH: (low risk: <10 mmol/L; medium risk: ≥10 and <22.6 mmol/L; and high risk: ≥22.6 mmol/L)
- The split of patients on model entry by risk of TG band:
  - low-risk: 4%; medium-risk: 42%; high-risk: 54%

ERG comment

- No patients have CP at the start of the model
- Contrast to [redacted]
- [redacted]
- It was assumed that the TG levels post-volanesorsen are not affected by CP status

[redacted]

Transition in the model: *treatment effectiveness on TG levels*

Treatment effectiveness up to month 3

- Actual reduction in TG levels and absolute TG level at 3-month based on APPROACH trial used to determine whether a patient met the continuation criteria (fixed at deterministic values in PSA)
  - APPROACH OLE subgroup of patients who conformed to the licensed dose not incorporated in model → small numbers "would likely have resulted in highly unstable ICER estimates"

Beyond month 3

- TG levels for all patients were predicted using generalised linear mixed model (GLMM) techniques
- The analysis included 1,508 unique TG observations collected from 90 patients from both APPROACH and APPRAOCH OLE
- GLMM included 9 dosage regimens → the principle of maximum likelihood was used to guide the selection of duration for kick-in and washout period
  - Change in the length of kick-in or washout period had little impact on the estimates of the coefficients

ERG comment
Within the company's model the benefit associated with treatment was mainly due to moving patients to medium-risk TG band compared with SoC (high-risk band) with additional benefits assumed.

[redacted]

Model assumptions

Treatment safety

Adverse Event	Number per three-month cycle in the base case	Assumed associated cost per event	Assumed associated QALY decrement per event
Fatigue	Zero	Zero	0.004
Injection site reaction	0.130	Zero	0.00002
Thrombocytopaenia Grade 1	0.070	£70	Zero
Thrombocytopaenia Grade 2	0.017	£70	Zero
	Probability per three-month cycle in the base case (scenario analyses)	Assumed associated cost per event	Assumed associated QALY decrement per event
Thrombocytopaenia Grade 3	0.004	£70	0.004
Thrombocytopaenia Grade 4	0.004	£581	0.038

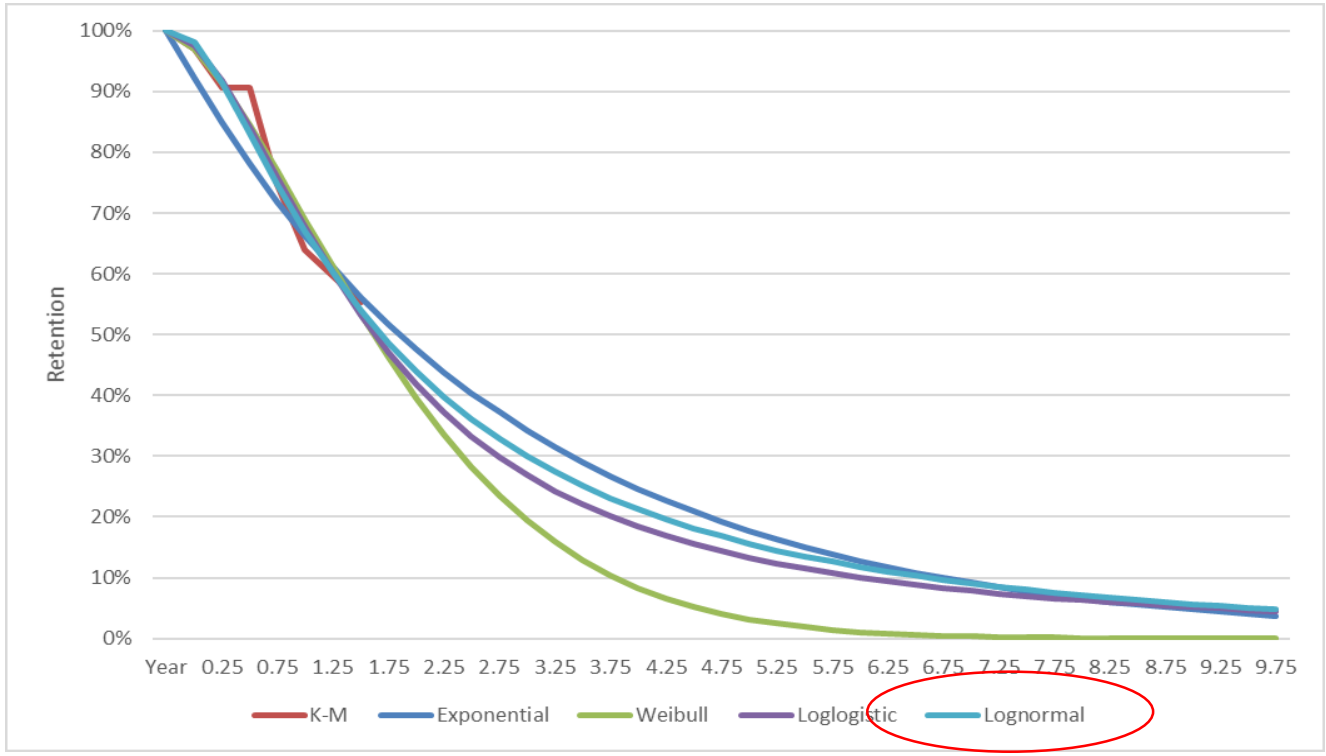
- Estimating rate of AEs with volanesorsen compared with SoC difficult → no RCT with licensed posology of volanesorsen
- AEs used from APPROACH OLE
  - Entire study population, including AEs experienced by patients on long-term weekly dosing → may overestimate AE frequency
- Only AEs affecting 10% or more of patients included in model
  - No AEs assumed for the comparator arm

[redacted]

Source:Table 13 ERG report

Model assumptions

Treatment duration



Source: Figure 32 of company submission

The parametric survival functions of time on treatment

- Discontinuation can be a consequence of 1 of 3 factors: not meeting the continuation criteria; the patient died, or the patient discontinued due to lack of adherence
- Parametric survival functions fitted to time on treatment data for 32 patients within the APPROACH OLE study (fortnightly treatment) → curve with a long tail that best represents a proportion of patients remaining on treatment over the long - term – **lognormal function-** as only 1 out of 20 patients in EAMS discontinued treatment due to recurrent cancer

[redacted]

Is the company's assumption on patient discontinuation in the model, at the licensed dosing, appropriate?

Model assumptions: benefits associated with treatment

Volanesorsen

- Historical AP: Treatment with volanesorsen would reduce the probability of experiencing APs, not only through the lower TG band, but also due to volanesorsen treatment itself independent of TG levels
  - Rate ratio: 0.13, which is derived from the post hoc analysis comparing the rate of AP in the 5 years prior to APPROACH OLE enrolment and when on treatment in APPROACH OLE
- Recurrent AP: Treatment with volanesorsen would reduce the risk of APs, with the same rate ratio of 0.13

SOC

- Historical AP: absolute AP rate calculated from CALIBER
  - CALIBER used to predict AP rates by TG band; patients in CALIBER could have [redacted]
- Recurrent AP: AP event rate of patients in APPROACH who had an AP within the previous 5 years was used to estimate the probability of an AP in a 3-month period

ERG comment

- Factor of 0.13 has been calculated from a population who have already had a potential reduction in TG levels then this represents double-counting of the benefits
- ***ERG applied a multiplication factor related to the rate of APs within a specific TG-risk band of 0.50 through the use of volanesorsen***

Assumed risk of AP per three-month cycle for patients in base case

TG band	Historical AP		Recurrent AP	
	SoC	Volanesorsen	SoC	Volanesorsen
Low	0.88%	0.12%	11.52%	1.51%
Medium	2.13%	0.28%	11.52%	1.51%
High	5.20%	0.70%	11.52%	1.51%

[redacted]

Source: Table 14 ERG report

Volanesorsen has both a direct and indirect effect on clinical outcomes such as AP in the model. What is the committee's consideration on that?

Model assumptions: CP and diabetes in the model

Relationship between AP events and developing CP

- Frequency of CP is conditional on the incidence of AP
- Rates of CP for those with historical and recurrent AP taken from literature (Yadav et al)
- Rate was then calibrated in the model (increased) so that the maximum prevalence was ~60%, representing the peak prevalence of CP in FCS estimated by the experts

ERG: **assumed in its base case that a multiplication factor of 28, which would be aligned with a lifetime CP prevalence of approximately 40%, may be more reasonable**

Relationship between TG bands, AP events, CP events and developing type 2 diabetes

- AFT models fitted to the CALIBER data to estimate type 2 diabetes risk
- Risk of diabetes by TG band estimated from CALIBER; then was capped as CALIBER data over predicted prevalence of diabetes in FCS
  - For those without CP, cap differentiated based on TG band and type of AP, historical or recurrent

	With historical AP	With recurrent AP
Low risk TG band	5.2%	5.2%
Medium risk TG band	14.6%	14.6%
High-risk TG band	23%	72%

Source: Based on company submission, page 193

  - For patients with CP a cap of 80% was set

[redacted]

Is it appropriate to adjust/cap observed rate of type 2 diabetes? And if so, how much?

Model assumptions: *Relationship between TG bands, AP events, CP events and mortality*

Rate of death	Estimate (source)	Assumptions
Patients with an historic AP and no subsequent event	From England and Wales life tables (2014-2016)	--
Patients who have subsequent APs	**4.78%** in patients with FCS (Gaudet et al. 2016)	Risk of death was assumed independent of the number of previous APs
Impact of volanesorsen on the mortality rate following AP	**0.17** on volanesorsen compared with SoC (Wang et al. 2016)	Risk of death would be reduced by volanesorsen treatment: use of volanesorsen would both reduce the number of APs, and the risk of the AP resulting in death All SoC patients would have high TG levels, people on volanesorsen have low TG levels
Relative risk of death following a CP	**5.83** (Nojgaard et al. 2011)	--
Relative risk of mortality for patients with type 2 diabetes	**1.28** (based on data from NHS Digital, 2017)	--

Health-related quality of life - *Utility associated with health states*

- EQ-5D data collected in APPROACH study → provided implausible values = higher than average UK index value
  - Items of the EQ-5D may not be adequately sensitive to the wide range of symptoms of FCS
- Vignette study in order to collect [redacted]
- Study conducted with [redacted]

Patients receiving:	Utility value used by the company	Utility value preferred by the ERG
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Source: Table 19 ERG report

ERG comments on limitations

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

What is the committee's view on the ***utilities associated with TG level bands***, ***which utility values does the committee prefer***?

Health-related quality of life

QALY and utility decrements used in the model

*Decrements are assumed **additive***

Type of decrement	Method of calculation
QALY decrement of the AP [redacted]	Average decrement between the value for those in AP-naïve vignette health states and those in recurrent AP vignette health states; multiplied by duration of AP event in APPROACH; multiplied by two on the assumption that patients only went to hospital on 50% of AP episodes
QALY decrement of CP	Utility in the AP state minus the disutility of monthly AP flares
QALY decrement of type 2 diabetes = 0.225	Associated with uncomplicated diabetes (0.0621 - Sullivan et al) plus 50% of the additive decrements of complication of diabetes
Utility decrement for carers = 0.1	Values from 'Metreleptin for treating lipodystrophy' [ID861] Lipodystrophy is another metabolic disease sharing similar outcomes in scope with FCS and has similar challenges in daily dietary management
Utility decrement with AEs	Please see slide 9

Source: Based on company submission, section 10

ERG comment

- Unclear whether the CS met NICE reference case → participants of the vignette study [redacted]
- [redacted]
- [redacted]
- [redacted]

ERG used its own preferred utilities in its base-case

ERG prefers excluding utility gain for carers to represent no net change in carer utility between diseases –used in its base case

Should the utility benefits to carers be included in the analysis?

Resources and costs

- Health state costs - *no specific NHS reference costs or HRG codes applicable to management of FCS patients*
  - Lack of published data on healthcare resource use for UK FCS
  - Systematic literature review and clinical expert opinion sought

- Costs per three-month period

Variable used in model	Value
Quarterly cost of volanesorsen adjusted for dose pauses	XXXXXX- includes a pricing scheme that has not been finalised
Costs of hospital admissions	Ranging from £717 for a person with a low-risk TG band to £1070 for a person with a medium- or high-risk TG band
Specialist visits	ranging from £308 (low-risk TG band) to £316 (medium- and high-risk TG bands) and CP (£12,668)
Cost per annum of background treatment for FCS	£372 for all patients in all health states
Costs associated with each AE	Please see slide 9

Costs provided for all health-states (depending on risk, AP involvement and for CP)

- *ICER is insensitive to source of resource use*

[redacted]

Cost-effectiveness results

[redacted]

Cost-effectiveness results (including PAS)

Company's deterministic results

Description	Incremental Discounted QALY	Cost per QALY gained
Dosing schedule - 285 mg weekly for three months followed by every 2 weeks maintenance dosing	XXX	£260,587

QALY, Quality-adjusted life year

Company base-case and majority of scenario analyses include an additional commercial arrangement which has not been formally agreed

Cost-effectiveness analysis results, including that associated with the additional arrangement, will be presented in Part2

[redacted]

Source: Table D26 clarification response letter

Limitations identified by the ERG in the company's modelling I.

Acquisition price of volanesorsen used in the model	• Company base case presented with results incorporating additional reduction in price • ***ERG has produced results which do not include this additional price reduction as it has not been formally agreed***
Method for estimating the distribution of patients entering the model in terms of AP history and TG-risk	• ***ERG used absolute counts as it preserved the integrity of the data and ensured that the numbers were integers***
HRQoL – Data incorporated from vignette study	• Utility for a patient within a health state should not depend on whether a patient is on treatment as assumed in company's base case • Prefers utilities more aligned to the vignette results (not distinguishing patients on or not on treatment), assuming that values for patients with an historical AP lie halfway between those with no prior AP and those with an AP with lingering effects • ***Used ERG preferred utilities in base-case (see slide 14)***
Company's assumption on treatment discontinuation	• Assumption of no discontinuation is not plausible, having noted that 6 of 14 (43%) of patients conforming to SmPc dosing in APPROACH OLE had discontinued at 2 years. • ***ERG deemed that 10% per year, would not be an unreasonable estimate of the discontinuation rate***
Half-cycle correction used in long-term Markov model	• It is not appropriate when doses are given at fixed intervals • ***ERG added the costs of half a dose in the discontinuation cycle for each patient who discontinues treatment in that cycle***

What is the committee's view on how utility values obtained from the vignette study were applied in the model?

Limitations identified by the ERG in the company's modelling II.

Assumed reduction in APs associated with volanesorsen additional to that related to TG level reduction	• Factor has been calculated from a population who have already had a potential reduction in TG levels → double-counting of the benefits • Maybe an overestimate of the impact of patients enrolling in an open label study, by regression to the mean or through a higher dose of volanesorsen administered in the trial; • ***Regarding the multiplication factor related to the rate of APs within a specific TG-risk band through the use of vaolanesorsen, ERG believes that 0.50 would be more appropriate than the 0.13***
Assumed level of CP in the model	• ***ERG assumed that a multiplication factor of 28, which would be aligned with a lifetime CP prevalence of approximately 40%, may be more reasonable as a base case compared with 60% presented by the company***
Disutility with uncomplicated diabetes	• Company added 50% of the disutility associated with four major conditions and five concomitant conditions • ***ERG assumed that 50% of patients had congestive heart failure, which was the most impactful condition with a decrement of 0.1034. The ERG prefers a disutility value of 0.114 rather than the estimate of 0.225 used in the company base case***
Carer's disutility	• ***ERG prefers excluding utility gain for carers to represent no net change in carer utility between diseases***
Cost of CP	• £50,671 per year in company's model • ***ERG has arbitrarily used £30,000 per annum for CP patients***

[redacted]

Exploratory analyses undertaken by the ERG

Scenario description	Cost per QALY gained
Using the currently agreed price of volanesorsen	£244,522
Amending the proportions in each TG-risk band	£216,260
Using the ERG's preferred utility values	£277,720
Assuming 10% discontinue treatment per year	£207,876
Amending half-cycle correction of volanesorsen drug costs	£218,400
Assuming a relative risk of 0.50 for AP due to volanesorsen treatment instead of 0.13	£240,595
Calibrating the lifetime probability of CP to 40%	£226,926
Amending the disutility associated with type 2 diabetes	£231,030
Excluding the utility benefit to carers	£261,999
Changing the cost of CP care to £30,000 per year	£232,876
ERG-preferred deterministic ICER, incorporating all changes	£483,814
ERG-preferred probabilistic ICER, incorporating all changes	£492,364

Source: Table 20 ERG report

[redacted]

There was no single factor that caused the increase in the ICER

ERG summary

A number of limitations within the company's base case analysis

- After correcting these the ICER increased to £490,000 per QALY
- There was no single factor that caused the increase. Assumptions having the greatest impact in one way sensitivity analyses from the company's deterministic base case were:
  - **Using the ERG-preferred utility** (£60,000)
  - **Excluding the utility benefit to carers** (£45,000)
  - Assuming that the **reduction in AP through volanesorsen independent of TG-level was not as large as assumed by the company** (0.13 vs. 0.50 assumed by ERG) (£25,000)
  - Assuming **volanesorsen's protective effect on mortality following an AP was removed**, with the relative risk changed from 0.17 to 1.00 → increased the deterministic ICER to £525,440 per QALY gained (an increase of £ 40,000);
- Substantial uncertainty remained in the utility associated with each TG-risk band
  - If a flat rate utility of 0.7 across all TG states is assumed, it further increases ICER by approximately £100,000
- Substantial uncertainty related to the robustness of the clinical evidence

[redacted]

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

Lifetime incremental QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr.)
Greater than or equal to 30	3

- Undiscounted incremental QALYs across all scenarios are <10

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

Equality

- Prevalence of FCS is higher in South Asian communities
- Consideration should also be given to women with FCS who may wish to become pregnant
  - In the IN-FOCUS study, 44% of respondents reported that having FCS impacted their decision on whether to have children, or how many children to have
  - No data available regarding the use of volanesorsen in pregnant women, it is not contra-indicated and the biochemistry suggests that it doesn't cross the blood placenta barrier
- FCS more likely to be found in people with distinct cultural/religious/ethnic background

Innovation

The company considers volanesorsen an innovative treatment because:

- It represent a 'step-change' in the management of FCS
- Demonstrates significant and sustainable TG lowering effect and reduction in pancreatitis events
  - Alleviating the broad and negative impact that FCS has physical, psychosocial, cognitive and economic aspects of patients' lives

[redacted]

Key issues for consideration

Cost-effectiveness

- What is the committee's view on the model in general? Does the model structure capture disease progression of people with FCS and aspects important for them?
- Clinical evidence on volansorsen's effect on AP, at the licensed dose, is lacking from the trials. What is the committee's considerations on TG levels as surrogate outcome for AP and the assumptions related to it in the model, including:
  - The risk of AP was conditional on TG-risk band in FCS patients; and
  - Volanesorsen has a direct protective effect on clinical outcomes, such as AP and mortality, independent of/not mediated through TG levels?
- What is the committee's view on the underlying utilities associated with TG level bands, which utility values does the committee prefer?
- Should the utility benefits to carers be included in the analysis?
- Is the company's assumption on patient discontinuation in the model, at the licensed dosing, appropriate?
- Are there any equality issues to consider?

[redacted]

Authors

Orsolya Balogh
Technical Lead

Yelan Guo
Technical Adviser

with input from the Lead Team

- **Paul Arundel** (clinical)
- **Linn Phipps** (lay)
- **Sarah Davis** (cost)

Slides for committee, projector and public – noACIC

Lead team presentation

Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]

1st Evaluation Committee Meeting

Highly Specialised Technology, 28 November 2019

Lay slides

Lead team member: Linn Phipps

Company: Akcea Therapeutics

Chair: Peter Jackson

Evidence review group: School of Health and Related Research (ScHARR)

NICE team: Orsolya Balogh, Yelan Guo, Melinda Goodall

[redacted]

Patient experience of FCS - expert and support group comments (I)

- ***Based on*** written patient expert and patient support group submissions and telephone interviews using NICE patient and professional group template
- Participants: 20 patients (18 England/Wales; 10 have taken volanesorsen) and 8 caregivers, plus evidence collected from patient meetings, Facebook support group and a webinar

Patients experience with FCS :

- The disease is ***poorly recognised*** with little dietetic support
- ***Lack of understanding, guidance and support*** amongst healthcare professionals

- **Delay in diagnosis, inappropriate treatment provided**
  - ***Misdiagnosis***: '*I had my gall bladder removed on recommendation of my consultant who thought it might reduce the number of episodes of pancreatitis*'
  - ***Unprofessional treatment***: '…*One doctor told me it's in the mind and I thought well you live in my body for one day and you see what chronic pain is like. I even moved doctors because of it. That's how you get treated. The ignorance of someone who doesn't know anything about it.*'
  - ***Range of different medications***:
    - Fibrate, statin: '*I've been on every fibrate going and any statin going and they haven't really done anything. Medication never worked*'
    - Fish oil: '*I was given fish oils but they made me bloated and repeated on me*'

[redacted]

Patient experience of FCS - expert and support group comments (II)

Impact of the disease on patients:

- **Frequent and severe abdominal pains** necessitate the need for frequent self medication of pain relief
- **Recurrent hospital admissions** are frustrating and depressing for patients and worrisome for family; also have a severe impact on work/study
  - ***Constant fear of a life threatening attack of acute pancreatitis***
    - *'Abdominal pain and pancreatitis and the fear of the onset of both has been ever-present'*
    - '*I woke up one Saturday morning and collapsed and two weeks later I woke up in intensive care, they nearly lost me twice, it was that severe.*'
    - '*I was out of hospital every 10-15 days then three days in hospital. I feel tired and felt the effects for at least two days, get eventually better and then go to back to hospital again. Not a normal life*.'
- **Fatigue**: impacts on ability to live lives fully
- **Burden of dietary restrictions**
  - Keeping a strict diet is challenging → means not eating enough calories to maintain normal energy levels and nutrients for overall wellbeing
  - ***There is a fear of eating food that have not been prepared by the individual***
    - 'It's always there – every time you eat, you're thinking about how much fat there is in it and what you've already had that day.'
  - ***Eating out is difficult and often impossible***
    - '*My life has been completely shaped by having FCS. It has hugely restricted the choices I have been able to make, made me fearful of attacks of pain and pancreatitis and made me really suspicious of food and what it contains*'

Patient experience of FCS - expert and support group comments (III)

- **Diabetes associated with FCS**
  - ***Some can develop diabetes as a result of FCS due to decreased insulin production***
    - 'For years my triglycerides were very low - under five – until I developed diabetes. Since then they're creeping up and I don't seem to be able to do anything about it, despite being on two diabetes medications. … For the first time in years I'm scared I'll have pancreatitis.'
- **Emotional wellbeing/depression**
  - ***Patient felt depressed and was taking anti-depressants; had suicidal thoughts***
    - 'I've spent most of my life watching others get on with their lives while I felt completely restricted in the choices I can make and worrying about or being in pain. I have periods of depression where I feel I have nothing to offer anyone and can't see why people would want to have anything to do with me.'
    - 'My attempts to be 'normal' would always lead to periods of pain, fatigue and self-hatred'

Patient experience of FCS - expert and support group comments (IV)

- **Pregnancy**
  - Pregnancy can be difficult as triglycerides rise naturally in the third trimester (> 60mmol/L)
    - ***Most women were unaware that there might be complications due to pregnancy; for some the pregnancy was highly medicalised***
      - *'My trigs were about 70… I would have plasmapheresis every Monday and my trigs would drop to about 20. I would have a blood test on the Friday and they would be rising and then I'd be back in again on the Monday – this was from 16/17 weeks.'*
    - While women from some religions do not access health services and seek out treatment (equity concern)
- **Impact on work life**
  - Recurrent pain has an impact on the ability of patients to work, the choices about which jobs to do, and the number of manageable hours
  - ***Choice of job was limited to a role that did not involve much travel or attending social events***
    - *'I always had a job, I shied away from jobs with any responsibility because I was concerned about having time off with pain, and not being able to think clearly because of the brain fog due to high triglyceride levels'*
  - ***Lack of understanding from employers***
    - *'Your health isn't my problem. Your wellbeing isn't my problem. You're here to do a job". ….It was difficult going back knowing people didn't want you there.'*

Impact on carers/family and friends - Patient expert and support group comments

- **Impact on carers/partners' ability to work**:
  - '*My mother gave up her work to look after me…So little was known about FCS that it would have been impossible to try and manage my condition safely without her being able to devote her full attention on how to manage the condition and how to accommodate and meet my dietary requirements*'
  - '…*Couldn't get paid. For the second baby he had to take time off…. Held him back a little, things he didn't go to, when I was in hospital*.'
- **Impact on children**: seeing their parents in pain or in hospital can be deeply distressing and prompt the child taking on the role of a carer:
  - '…*I [child of a patient living with FCS] will often take her and pick up from school, she will stay at mine if Mum is in hospital because Dad will need to get up early – we have to try and keep things normal for everyone because life still goes on and school and work still has to happen'*
- **Guilty feeling towards family members:**
  - '*I feel bad because I'm imposing my lifestyle on them… it makes me feel bad that they can't eat, or they can't have stuff in the house because I will want to eat it. It puts restrictions on quite a few things*.'

Benefits of the technology – Patient expert and support group comments

Positive impact on every aspect of life, mainly include:

- **Reduction of pain and fear of pain**
- **Incidence of pancreatitis reduced** to almost zero

- **Engage more fully in lives**, avoiding visits to A&E and hospital stays; and retreating from daily routine to manage attacks of abdominal pain and pancreatitis
- **Improved ability to work, to study and to manage friendships → reduced the stress and anxiety**
- Benefits would allow carers and families the opportunity to live their lives in a manner that **enables forward planning**
  - *'I'll be able to have a full life. Everything I do - work, mentally physically, family, workwise, it's going to make my life a lot better, and if the lipids are down, make my life last a lot longer.'*
  - *'the treatment has made me feel so very, very much better. My triglycerides have reduced by about 60% and with that reduction I have felt much more alert, do not feel fatigued, have not had any pain at all which. I am therefore no longer feeling paranoid about the onset of pancreatitis'*
  - *'My diabetes is also looking better controlled and I feel in control, rather than out-of-control and anticipating the next 'off day' or period of abdominal pain'*
  - *'I have not any abdominal pain since starting this treatment in December 2015 and zero days off work'*
  - *'Now that I am not getting pancreatitis every 2 months or so I feel well in myself, and can consider starting my own family'*

[redacted]

Disadvantages of the technology – patient expert and support group comments

Possible platelet reduction, need for monitoring and difficulties with the injection site

- ***Side effects: bloating, pain around the injection site,*** and ***reduction in platelets*** flagged by blurred vision and headaches
  - *'The main problem I suffered with when taking the drug was that I had blurred vision and headaches…. The following day my bloods were done, by the afternoon the hospital contacted me and said that my platelets were low and I shouldn't inject that week. I had to wait three weeks for my platelets level to come up and then I was told to inject every two weeks. My platelets level is checked every week and they have been normal….. I still feel nervous when I inject'.*
  - 1 patient in the trial was asked to stop taking the therapy after experiencing symptoms attributable to the drug
- Patients ***who have not taken the therapy had different opinion on side effects and frequent monitoring*** (some might have opted for not taking the drug – with less severe form of the disease)
  - *'I think I'd at least like to be able to have a full discussion with my consultant about whether, on balance it would be suitable for me. My triglycerides keep rising and I'm struggling to manage them. It's giving me a lot of stress thinking I might suddenly have an episode of pain and if I did have pain, I worry about the impact that might have on me both in the immediate and in the long term…. It's not an easy decision to make.'*
- Some who have taken the drug felt that the ***platelet monitoring was a small price to pay for the benefits*** that the drug had brought them
  - *'Notionally, the disadvantages are that there is regular monitoring and injection site reactions, however these are insignificant compared to the regular abdominal pains, pancreatitis and hospital admissions I was experiencing prior to my participation in the trial.'*

Comments from clinical experts

Condition and current treatment options

- FSC is a recessive disorder caused by rare gene variants
- There is a huge unmet need for people living with FCS
- Current treatment management varies considerably
- Low fat diet (difficult to follow and often unsuccessful); fibrates and statins (minimally effective); medication to treat complications of pancreatitis (analgesia, digestive enzymes, insulin)

New technology

- It has a potential for life-changing improvement for people living with FCS
- Easy to adhere to, but does require intense monitoring
- Innovative in reducing morbidity and mortality associated with pancreatiti***s***

Outcomes

- The ***most important outcome*** is ***reduction in frequency of pancreatitis events***
- Substantial reduction in plasma triglycerides in patients
- Reduction in hospital admissions for AP and in complications of acute and chronic pancreatitis (pain, requirement for analgesia, development of pancreatic insufficiency and diabetes)
- Improved quality of life, increased freedom with dietary choices, fewer days 'lost' to illness
- A ***clinically significant reduction of incidence of pancreatitis and its complications in the long term***

Service delivery

- There is a ***significant uncertainty about the diagnosis*** of the FCS
- The disease is best defined by genetics, although there is currently no testing centre available
- In the future it would be reasonable to concentrate the treatment into a few specialist centres

NHS England comments

Pathway of care

- No specific treatment pathway, NHSE service specification or clinical commissioning exist
- Patients are managed via a strict fat restricting diet and restriction of alcohol alongside treatments for hypercholesteraemia

Commissioning

- Volanesorsen is likely to be a high cost drug
- Prescriptions expected to be initiated and monitored by a small number of expert lipid centres
  - Likely those centres already offering lipid apheresis and participated in the Early Access to medicines Scheme (EAMS)
- After initial dosing administration of the medicine is expected via home care
  - No difficulties expected in administration
- **Use of technology**
- Volanesorsen received a positive Scientific Opinion from the MHRA as part of the EAMS
- To date 29 patients* have accessed the treatment under this scheme
- Likely the 7 trusts accessed volanesorsen through the EAMS → will be commissioned if the treatment is approved

[redacted]

*Company reported that 20 patients received treatment in EMAs (25 eligible)

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