Early Access to Medicines Scheme Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

1. NAME OF THE MEDICINAL PRODUCT

Volanesorsen 300 mg Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose prefilled syringe contains 300 mg of volanesorsen sodium in 1.5 mL clear, colourless to slightly yellow solution.

This medicinal product contains less than 1 mmol sodium (23 mg) per 300 mg, i.e., essentially sodium- free.

Excipient(s) with known effect:
None of the excipients have a known effect. For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in prefilled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Volanesorsen is indicated as an adjunct to diet for the treatment of adult patients with familial chylomicronemia syndrome (FCS).

4.2 Posology and method of administration

Posology

The recommended starting dose of volanesorsen for all patients is 300 mg in 1.5 mL injected subcutaneously once every two weeks (150 mg weekly dose equivalent). After six months, a re-evaluation of therapy is recommended. In patients weighing 70kg or more (see Section 4.4) the dose may be increased to a maximum of 300 mg once weekly, depending on triglyceride levels, the goal of therapy, and platelet count.

Patients should be instructed to give the injection on the same day of the week, according to medically determined frequency of administration.

If a dose is missed, the patient should be directed to give the missed dose as soon as possible. If the next scheduled dose is within 48 hours, then the missed dose should be skipped, and the next planned injection given.

Platelet monitoring and dose adjustments:

Before initiation of treatment with volanesorsen, platelet count should be measured. At least two separate measurements are recommended. Volanesorsen should not be initiated in patients with a baseline platelet count below 140 x 10^9/L .

After commencing treatment patients should have platelet levels monitored every two weeks.

Dosing should be adjusted according to laboratory values in line with table 1.

Table 1. Volanesorsen ; Platelet (PLT) Monitoring and Treatment Recommendations

PLT Level (count x 10^9/L**)**	**Dose schedule**			**PLT Monitoring**
	Body Weight < 70 kg	**Body Weight ≧ 70 kg**		
Normal (≥140)	Every 2 weeks	Every 2 weeks	Weekly[+]	Every 2 weeks
100-140	Every 2 weeks	Every 2 weeks	Weekly[+]	Weekly until stable
75-100	Pause, resume every 2 weeks when ≥100 x 10^9/L		Every 2 weeks[+]	Weekly
50-75	Pause, resume every 2 weeks when ≥100 x 10^9/L			Twice per week until stable
<50	Discontinue volanesorsen**			Every other day until stable*

[+]For patients up-titrated to a dose of 300 mg once weekly

**Daily if PLT <25 x 10^9/L/mm^3; if platelet count <25 x 10^9/L steroid therapy should be considered

**For any patient dose paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment should be carefully considered. For discontinued patients, a haematologist should be consulted prior to resuming treatment

Elderly population

No starting dose adjustment is recommended for elderly patients. There are limited clinical data in patients aged 65 and over.

Patients with renal impairment

No starting dose adjustment is necessary in patients with mild to moderate renal impairment. No data are available in patients with severe renal impairment.

Paediatric population

The safety and efficacy of volanesorsen in children and adolescents below 18 years of age have not yet been established.

Patients with hepatic impairment

Volanesorsen has not been studied and should be used with caution in patients with hepatic impairment.

Method of administration

Volanesorsen is intended for subcutaneous use only. Do not administer intramuscularly or intravenously.

The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the administration of volanesorsen in accordance with the Patient Information Leaflet.

Volanesorsen prefilled syringe should be allowed to reach room temperature prior to injection. It should be removed from refrigerated storage (2° to 8°C) at least 30 minutes before use. Other warming methods should not be used.

It is important to rotate sites for injection. Sites for injection include the abdomen, upper thigh region, or outer area of the upper arm. If injected in the upper arm, the injection should be administered by another person. Injection should be avoided at the waistline and other sites where pressure or rubbing may occur from clothing. Volanesorsen should not be injected into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed.

For guidance on product handling and disposal, see Section 6.6.

4.3 Contraindications

Volanesorsen is contraindicated in patients with known hypersensitivity to the active substance(s) or to any of the excipients listed in Section 6.1.

Volanesorsen should not be initiated in patients with thrombocytopenia (platelet count <140 x 10^9/L).

4.4 Special warnings and precautions for use

Volanesorsen is not indicated to treat patients with severe hypertriglyceridemia due to causes other than FCS.

Thrombocytopenia

Volanesorsen is associated with reductions in platelet count in patients with FCS, which may result in thrombocytopenia. Patients with FCS have also been described to have intermittent thrombocytopenia. Patients with lower body weight (less than 70 kg) may be more prone to

thrombocytopenia while on volanesorsen Careful monitoring for thrombocytopenia is important during treatment with volanesorsen in patients with FCS (see Section 4.2).

Volanesorsen should be used with caution in patients treated with medications that may affect platelet count or function and in patients treated with antithrombotic agents. For patients with persistent, consistent platelet levels <100x 10^9/L, follow recommended platelet monitoring and dose frequency (see Section 4.2).

Patients should be instructed to report to their physician immediately if they experience any signs of bleeding, which can include petechiae, spontaneous bruising, subconjunctival bleeding, or other unusual bleeding (including nosebleeds, bleeding from gum, stools, or unusually heavy menstrual bleeding), neck stiffness, atypical severe headache, or any prolonged bleeding.

4.5 Interaction with other medicinal products and other forms of interaction

No formal clinical drug interaction studies have been conducted.

In vitro studies indicate that volanesorsen is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 or inducer of CYP1A2, CYP2B6, or CYP3A4.

In vitro studies show that volanesorsen is not a substrate or inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP1B1, OATP1B3), bile salt export pump (BSEP), organic cation transporters (OCT1, OCT2), or organic anion transporters (OAT1, OAT3).

Clinically relevant pharmacokinetic interactions are not expected between volanesorsen and substrates, inducers or inhibitors of cytochrome P450 (CYP) enzymes, and drug transporters. In clinical studies, volanesorsen has been used in combination with fibrates and fish oils with no impact on volanesorsen pharmacodynamics or pharmacokinetics. There were no adverse events related to drug-drug interactions reported during the clinical program with volanesorsen.

Antithrombotic Agents and Medications That May Lower Platelet Count

It is not known whether the risk of bleeding is increased by concomitant use of volanesorsen and antithrombotic agents or medications that may lower platelet count or affect platelet function. Caution should be used with antithrombotic agents, platelet function antagonists, and medications that may lower platelet count (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data from the use of volanesorsen in pregnant women is available.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3).

As a precautionary measure, it is preferable to avoid the use of volanesorsen during pregnancy.

Breastfeeding

There is no information regarding the presence of volanesorsen in human milk, the effects on the breastfed infant, or the effects on milk production. In nonclinical studies, levels of volanesorsen in milk were very low in pregnant mice (≤ 0.7 µg/mL at subcutaneous doses up to 87.5 mg/kg/wk).

Due to the poor oral bioavailability of volanesorsen, it is considered unlikely that these low milk concentrations would result in systemic exposure from nursing.

Fertility

No clinical data on the effect of volanesorsen on human fertility are available. Volanesorsen had no effect on fertility or fetal development in mice at doses up to 87.5 mg/kg/wk or in rabbits at doses up to 52.5 mg/kg/wk.

4.7 Effects on ability to drive and use machines

Volanesorsen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In clinical studies in patients with FCS, the most commonly reported adverse reactions during treatment were

- Thrombocytopenia (see Section 4.4)
- Injection site reactions (see Section 4.8)

The safety of volanesorsen was evaluated in a clinical program that included 283 patients and subjects treated with at least one dose of volanesorsen, of which 62 patients were exposed for more than 3 months and 26 patients for more than 6 months. The mean age of the population was 50 years, 37.8% of the population were women, 90.2% were White, 0.8% were Black, 6.1% were Asian, and 2.8% were of other races.

The clinical program included 66 patients from the Phase 3, randomized, placebo-controlled trial in FCS (APPROACH). The APPROACH Open Label Study includes 29 FCS patients that were treated with volanesorsen for up to over 2 years.

Table 2 presents common and very common adverse reactions from the APPROACH study in which patients received volanesorsen 300 mg subcutaneously (n=33).

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 2: Summary of Adverse Reactions in APPROACH Study in Patients with FCS

System Organ Class	Very Common	Common
General disorders and administration site conditions	Administration-related reactions[a] Injection site reactions[b] Asthenia Fatigue	Chills Malaise Feeling hot Influenza-like illness Oedema
Investigations	Platelet count decreased	Blood creatinine increased Blood urea increased Creatinine renal clearance decreased

		Transaminases increased White blood cell count decreased
Skin and subcutaneous tissue disorders		Erythema Pruritus Urticaria Hyperhidrosis Rash Petechiae
Musculoskeletal and connective tissue disorders	Myalgia	Pain in extremity Arthralgia Arthritis Back pain Muscle spasms Musculoskeletal pain
Nervous system disorders	Headache	Hypoaesthesia Presyncope Retinal migraine Syncope
Blood and lymphatic system disorders	Thrombocytopenia	Eosinophilia Immune thrombocytopenic purpura Spontaneous haematoma
Gastrointestinal disorders		Nausea Diarrhoea Dry mouth Gingival bleeding Mouth haemorrhage Parotid gland enlargement Vomiting
Respiratory, thoracic and mediastinal disorders		Epistaxis Cough Dyspnoea Nasal congestion Pharyngeal oedema Wheezing
Vascular disorders		Haematoma Hypertension
Eye disorders		Conjunctival haemorrhage
Injury, poisoning and procedural complications		Contusion
Metabolism and nutrition disorders		Diabetes mellitus

[a] An administration-related reaction is defined as any treatment-emergent local cutaneous reaction of one day duration.

[b] An injection site reaction is defined as any treatment-emergent local cutaneous reaction which occurred from the first dose of the study drug through 28 days post the last dose of study drug and include erythema, swelling, pruritus, pain, or tenderness that started on the day of injection and persisted for at least 2 days.

Thrombocytopenia

In the pivotal Phase 3 study of volanesorsen in patients with FCS (the APPROACH study), confirmed reductions in platelet counts to below normal (140 x 10^9/L) were observed in 75% of FCS patients treated with volanesorsen and 24% of placebo patients; confirmed reductions to below 100 x 10^9/L were observed in 47% of patients treated with volanesorsen compared with no placebo patients. In APPROACH and its open-label extension, 3 patients had platelet counts <25 x 10^9/L, which led to study treatment discontinuation. None of these patients had any major bleeding events and all recovered to normal platelet count following drug discontinuation and administration of corticosteroids.

Immunogenicity

In the Phase 3 clinical trials (COMPASS and APPROACH), 16% and 30% of volanesorsen-treated patients tested positive for anti-drug antibodies during 6-month and 12-month treatment, respectively. Efficacy results in these trials in patients who tested positive for anti-drug antibodies were similar to those for patients who were negative for these antibodies. The incidence of adverse events and drug discontinuations were similar in antibody-positive and antibody-negative patients.

Injection site reactions

Injection site reactions defined as any local cutaneous reaction at the injection site persisting more than 2 days occurred following 12% of injections in volanesorsen-treated patients and were not seen in placebo patients in the APPROACH study in FCS patients. Overall, 61% of volanesorsen-treated patients experienced at least 1 injection site reaction during the study, compared to none in the placebo arm. These local reactions were mostly mild and typically consisted of 1 or more of the following: erythema, pain, pruritus, or local swelling. Injection site reactions do not occur with all injections and resulted in discontinuation for 1 patient in the APPROACH study.

To minimise the potential for injection site reactions, patients should be advised to follow proper technique for subcutaneous administration, including ensuring the drug has reached room temperature prior to administration, rotating areas of the body for each injection, icing the proposed site prior to and after injection, injecting slowly, and pausing before removing the needle to ensure dispersion of drug.

Monitoring and Laboratory Tests

In the APPROACH study in patients with FCS, volanesorsen reduced fasting triglycerides, total cholesterol, non-high-density lipoprotein cholesterol (HDL-C), apolipoprotein (apo)C-III, apoB-48, and chylomicron triglyceride levels and increased low-density lipoprotein cholesterosl (LDL-C), HDL-C, and apoB. Patients with untreated FCS have very low LDL-C values; with treatment with volanesorsen, LDL-C levels may rise but will usually remain with the normal range (see Table 3). Laboratory studies should be performed prior to initial treatment and periodically to measure the patient's triglyceride and other lipid levels during therapy with volanesorsen.

4.9 Overdose

There is no clinical experience with overdose of volanesorsen. In the case of over dosage, patients should be carefully observed and supportive care administered, as appropriate.

Haemodialysis is unlikely to be beneficial given that volanesorsen is rapidly distributed into cells.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10AX

Mechanism of action

FCS is a serious, rare disorder characterised by extremely high plasma triglycerides, lipemic plasma, and increased risk of pancreatitis, which can be accompanied by recurrent abdominal pain.

FCS is caused by inherited mutations that inhibit the activity of lipoprotein lipase (LPL), the enzyme required to break down triglycerides carried by lipoproteins, including chylomicrons. The mutations that result in FCS may encode for LPL or other proteins necessary for LPL function. ApoC-III is elevated in FCS patients and acts as an inhibitor of triglyceride metabolism through both LPL-dependent and LPL-independent pathways.

Volanesorsen sodium is an antisense oligonucleotide designed to inhibit the formation of apoC-III. The selective binding of volanesorsen sodium to the apoC-III messenger ribonucleic acid (mRNA) within the 3′ untranslated region at base position 489-508 causes the degradation of the mRNA.

This binding prevents translation of the protein apoC-III, thus removing an inhibitor of triglyceride clearance and enabling metabolism through an LPL-independent pathway, believed to be through enhanced hepatic clearance.

Pharmacodynamic effects

Effects of Volanesorsen on lipid parameters

In APPROACH, the Phase 3 clinical study of volanesorsen in patients with FCS, volanesorsen reduced fasting triglycerides, total cholesterol, non-HDL cholesterol, apoC-III, apoB-48, and chylomicron triglyceride levels and increased LDL-C, HDL-C, and apoB (see Table 3).

Table 3: Mean Baseline and Percent Change in Lipid Parameters from Baseline to Primary Endpoint (Month 3)

Lipid Parameter (g/L for apoC-III, apoB, apoB-48; mmol/L for cholesterol, triglycerides)	**Placebo (N=33)**		**Volanesorsen 300 mg (N=33)**	
	Baseline	% Change	Baseline	% Change
Triglycerides	24.3	+24%	25.6	-72%
Total Cholesterol	7.3	+13%	7.6	-39%
LDL-C	0.72	+7%	0.73	+139%
HDL-C	0.43	+5%	0.44	+45%
Non-HDL-C	6.9	+14%	7.1	-45%
ApoC-III	0.29	+6%	0.31	-84%
ApoB	0.69	+2%	0.65	+20%
ApoB-48	0.09	+16%	0.11	-75%
Chylomicron Triglycerides	20	+38%	22	-77%

Cardiac Electrophysiology

At a drug concentration 4.1 times the peak drug plasma concentrations (C_{max}) of the maximum recommended dose (300 mg subcutaneous injection), volanesorsen did not prolong the heart-rate corrected QT (QTc) interval.

Clinical efficacy and safety

Three Phase 3 clinical trials are being conducted: a randomized, double-blind placebo-controlled 52-week multicenter clinical trial in patients with FCS (APPROACH); a randomized, double-blind placebo-controlled 26-week multicenter clinical trial in patients with severe hypertriglyceridemia, including patients with FCS (COMPASS); and a 52-week multicenter open-label study for patients with FCS (APPROACH open-label study).

APPROACH study in patients with FCS

The APPROACH study comprised 66 patients with FCS and evaluated volanesorsen 300 mg administered as a subcutaneous injection (33 treated with volanesorsen and 33 on placebo).

Mean age was 46 years (range 20-75 years), with 7.6% of patients ≥65 years old; 45% were men; 80% were White, 17% were Asian, and 3% were of other races. Mean body mass index was 25 kg/m^2. A history of documented acute pancreatitis was reported for 76% of patients and a history of diabetes was reported for 15% of patients; 21% of patients had a recorded history of lipaemia retinalis and 23% of patients had a recorded history of eruptive xanthomas. The median age at diagnosis was 27 years, with 24% of patients lacking a known FCS genetic mutation.

At study entry, 55% of patients were on lipid lowering therapies (48% on fibrates, 29% on fish oils, 20% HMG-CoA reductase inhibitors), 27% were on pain medications, 20% were on platelet aggregation inhibitors, and 14% were on nutritional supplements. Background lipid-lowering therapies remained consistent throughout the study. Patients were prohibited from receiving plasma apheresis within 4 weeks prior to screening or during the study; 11% of patients had previously received gene therapy for lipoprotein lipase deficiency (i.e., Glybera treatment), on average 8 years prior to starting this study. After a 6-week diet run-in period, the mean fasting triglyceride level at baseline was 2,209 mg/dL (25.0 mmol/L). Compliance with diet and alcohol restriction was reinforced through periodic counselling sessions during the study.

Volanesorsen led to a statistically significant reduction in triglyceride levels as compared to placebo at the primary efficacy endpoint, defined as percent change from baseline to Month 3 in fasting triglyceride, in addition to a lower incidence of pancreatitis over the 52-week treatment period in a post-hoc analysis (Table 6).

At the primary efficacy endpoint, the treatment difference between volanesorsen and placebo in mean fasting triglyceride percent change was -94% (95% CI: -122, -67; p<0.0001, with a decrease of -77% (95% CI: -97, -56) in patients receiving volanesorsen and an increase of 18% (95% CI: -4, 39) in patients receiving placebo (Table 4).

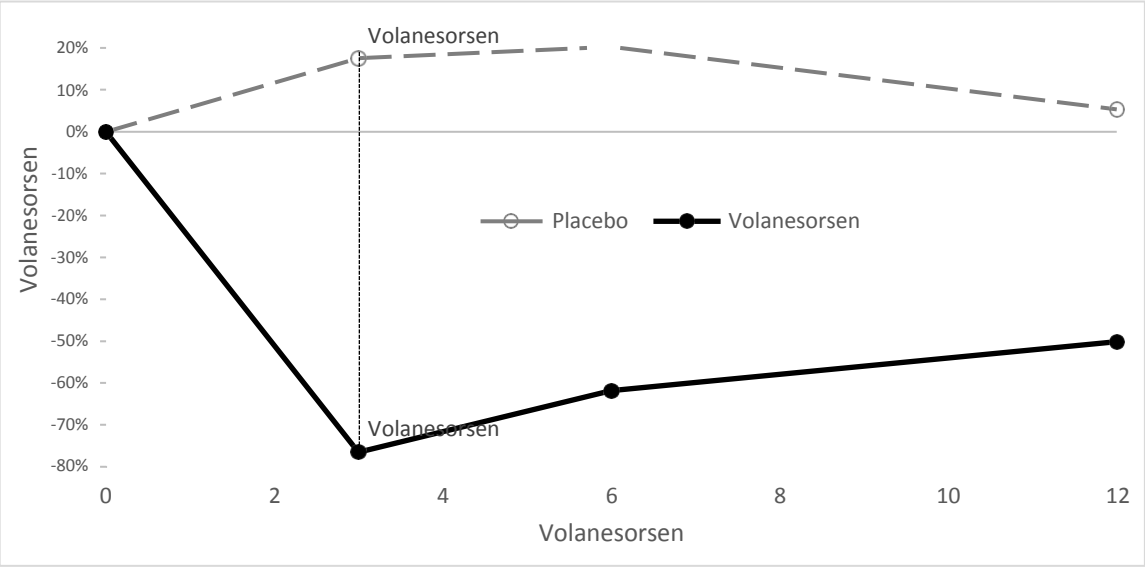
Table 4: Mean Change from Baseline in Fasting Triglycerides in the Phase 3 Placebo-Controlled Trial in Patients with FCS at Month 3 (APPROACH)

	Placebo (N=33)	**Volanesorsen 300 mg (N = 33)**	**Relative Difference in Change vs Placebo**
LS Mean Percent Change (95% CI)	+18% (-4, 39)	-77% (-97, -56)	-94%* (-122, -67)
LS Mean Absolute Change (95% CI) mg/dL or mmol/L	+92 (-301, +486) mg/dL +1 (-3, +5) mmol/L	-1,712 (-2,094, -1,330) mg/dL -19 (-24, -15) mmol/L	-1,804 (-2,306, -1,302) mg/dL -20 (-26, -15) mmol/L

*p-value < 0.0001 (primary efficacy endpoint)
Difference= LS Mean of [Volanesorsen % Change – Placebo % Change] (ANCOVA model)

Onset of the reduction was rapid with separation from placebo seen as early as 4 weeks and maximum response seen at 12 weeks, with clinically and statistically significant triglyceride reduction maintained over 52 weeks (Figure 1). The mean fasting triglyceride percent change was significantly different between volanesorsen and placebo arms at 3, 6, and 12 months; the volanesorsen arm included patients who did not complete dosing but who returned for assessments over the 52-week study. There were no significant differences in treatment effect across the stratification factors of presence or absence of concurrent omega-3 fatty acids or fibrates. Twelve of the 33 volanesorsen-treated patients had treatment pause. Ten of the 33 volanesorsen-treated patients had treatment adjustment with frequency reduced from once weekly (QW) to Q2W with their last QW dose taken on Week 26 to Week 46 before switching to Q2W. In all, 17 volanesorsen-treated patients had treatment pause and/or adjustment. Five patients had both treatment pause and adjustment, 7 patients had treatment pause only and 5 had treatment adjustment only. Two of the patients with both treatment pause and adjustment discontinued treatment as did 2 of the patients with only treatment pause.

Figure 1: LS Mean Percent Change in Fasting Triglycerides in Phase 3 Trial in Patients with FCS (APPROACH)



Difference= LS Mean of [Volanesorsen % Change – Placebo % Change] (ANACOVA model)
p-value from Shapiro-Wilk normality test
p-value < 0.0001 at Month 3 (primary efficacy endpoint), 0.0002 at Month 6 and p-value =0.0034 at Month 12

Additional efficacy results for changes in triglyceride are presented in Table 5. Most patients receiving volanesorsen experienced a clinically significant reduction in triglycerides. Of the patients receiving volanesorsen, 77% had fasting plasma triglyceride < 750 mg/dL (8.5 mmol/L) and of the patients receiving placebo, 10% had fasting plasma triglyceride < 750 mg/dL (8.5 mmol/L) (Table 5). Of the patients receiving volanesorsen, 88% achieved ≥ 40% reduction in fasting triglycerides from baseline at the primary endpoint, compared to 9% of patients on placebo.

Table 5: Additional Results for Changes in triglycerides in the APPROACH study

Parameter at Month 3[a]	**Placebo (N=31)**	**Volanesorsen 300 mg (N=30)**
Percent of patients[b] with fasting plasma triglyceride < 750 mg/dL (8.5 mmol/L)*	10%	77%
Percent of patients[c] with ≥ 40% reduction in fasting triglycerides**	9%	88%

[a] The Month 3 endpoint was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments. If 1 visit was missing, then the other visit was used as the endpoint.
[b] The denominator for percentage calculation was the total number of patients in FAS with baseline fasting triglyceride ≥ 750 mg/dL (or 8.5 mmol/L) in each treatment group.
[c] The denominator for percentage calculation was the total number of patients in each treatment group.
* p-value =0.0001
**p-value <0.0001
P-values from logistic regression model with treatment, presence of pancreatitis and presence of concurrent omega-3 fatty acids and/or fibrates as factors, and logarithm-transformed baseline fasting triglycerides as a covariate.

In patients treated with volanesorsen there was a lower incidence of pancreatitis compared to those treated with placebo (Table 6).

Table 6: Incidence of Pancreatitis in 2 Phase 3 Placebo-Controlled Trials, in Patients with either FCS or Hypertriglyceridemia

	Placebo			**Volanesorsen 300 mg**		
Incidence of Pancreatitis	Total Patients	Patients n (%)	Events	Total Patients	Patients n (%)	Events
APPROACH[a*]	33	3 (9%)	4	33	1 (3%)	1
COMPASS[b**]	38	3 (8%)	5	75	0 (0%)	0
Total*** (APPROACH + COMPASS)	71	6 (8%)	9	108	1 (1%)	1

* p-value = not statistically significant
**p-value = 0.036
***p-value = 0.0185
[a] Data includes results from 52-week treatment period and 28 days after treatment.
[b] Data includes results from 26-week treatment period and 28 days after treatment.

In a pre-specified analysis conducted using next observation carried back (NOCB) imputation on patients who reported any abdominal pain during the screening period and Week 1, volanesrosen-treated patients had higher percent reduction in pain compared with placebo-treated patients, although these results were not statistically signficant (p=0.0774). In a further analysis, in which missing data were imputed as zero, a statistically significant reduction in the average of maximum

intensity of abdominal pain was observed in volanesorsen-treated patients who had baseline abdominal pain, compared with the same subset of placebo-treated patients (p=0.02).

Nineteen (58%) of the 33 patients in the volanesorsen group and 32 (94%) of the 34 randomized patients in the placebo group completed the study treatment. Of the 14 patients who discontinued treatment with volanesorsen, 2 (6%) discontinued prior to Week 13, 7 (21%) discontinued on or after Week 13 and prior to Week 26, and 5 (15%) discontinued after Week 26. The most common reason for discontinuation of volanesorsen treatment was AE (9 patients, 27%). In the placebo group, 1 patient discontinued treatment due to voluntary withdrawal.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with volanesorsen in the treatment of paediatric FCS patients from birth to less than 2 years of age (see Section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with volanesorsen in the treatment of paediatric population from 2 years to less than 18 years of age (see Section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Single- and multiple-dose pharmacokinetics of volanesorsen in healthy volunteers and patients with hypertriglyceridemia have shown that volanesorsen plasma exposure (C_{max} and AUC) increases approximately proportionally with increasing subcutaneous doses in the range of 50 mg to 400 mg. Steady-state was reached approximately 3 months after starting volanesorsen and the estimated accumulation at steady-state based on plasma trough concentration (C_{trough}) was 7-fold. Accumulation based on C_{max} and AUC was negligible. Following a dose of 300 mg once weekly in patients with FCS, the estimated geometric mean steady-state C_{max} is 8.92 μg/mL, AUC_{0-168h} is 136 μg*h/mL, and C_{trough} is 127 ng/mL.

Absorption

Following subcutaneous injection, peak plasma concentrations of volanesorsen are typically reached in 2 to 4 hours. The absolute bioavailability of volanesorsen following a single subcutaneous administration is 78.7%.

Distribution

The estimated apparent steady-state volume of distribution (V_{ss}/F) is 436 L. Volanesorsen is highly bound to human plasma proteins (>98%) and the binding is concentration independent.

Biotransformation

Volanesorsen is not a substrate for CYP metabolism, and is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. Unchanged volanesorsen is the predominant circulating component.

Elimination

Elimination involves both metabolism in tissues and excretion in urine. Urinary recovery of the parent drug was limited in humans with < 3% of administered subcutaneous dose recovered within 24 hours post dose. Following subcutaneous administration, terminal elimination half-life is approximately 2 to 5 weeks.

Special Populations

Renal impairment

A population pharmacokinetic analysis suggests that mild and moderate renal impairment has no clinically relevant effect on the systemic exposure of volanesorsen. No data are available in patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of volanesrosen in patients with hepatic impairment is unknown.

Age, sex, weight, and race

Based on the population pharmacokinetic analysis, age, body weight, sex, or race has no clinically relevant effect on volanesorsen exposure.

Anti-volanesorsen antibody formation affecting pharmacokinetics

The formation of binding antibodies to volanerosen appeared to increase total C_{trough} without impact on efficacy (triglyceride lowering) or safety.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In a carcinogenicity study in mice, volanesorsen was administered subcutaneously for up to 104 weeks at doses of 6, 25, and 40 mg/kg/week. There were increased incidences of a number of tumours common to mice including hepatocellular adenomas, pituitary gland adenomas, hemangiosarcomas, and/or histiocytic sarcomas.

In a subcutaneous carcinogenicity study in rats, volanesorsen was administered for up to 104 weeks at doses of 0.2, 1, and 5 mg/kg/wk. Malignant fibrous histiocytoma was increased at 1 and 5 mg/kg/wk. The rodent is known to be particularly susceptible to development of sarcomas in the subcutaneous tissue in the presence of chronic tissue irritation and inflammation (as occurred at the injection sites in this study).

Volanesorsen did not exhibit genotoxic potential in a battery of studies, including the *in vitro* Bacterial Reverse Mutation (Ames) assay, an *in vitro* cytogenetics assay using a mouse lymphoma cell line, and an *in vivo* micronucleus assay in mice.

In animal reproduction studies in mice and rabbits, at doses that exceeded the maximum recommended human equivalent dose, there were no effects seen on pregnancy and neonatal development at the highest doses studied. There were no effects on organogenesis. The placental barrier is impermeable to antisense oligonucleotides, such as volanesorsen, because of their size, molecular charge, water solubility and high plasma protein binding. Thus, there was no detectable volanesorsen in fetal tissues in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store refrigerated at 2° to 8°C in the original carton to protect from light.

In addition, volanesorsen can be moved from refrigeration to be kept at room temperature in the original carton for 6 weeks; if not used within the 6 weeks, discard Volanesorsen.

6.5 Nature and contents of container

Volanesorsen (volanesorsen sodium injection) is a clear, colourless to slightly yellow solution supplied in a single-dose, 2.25 mL, clear prefilled syringe made of Type I, clear glass. Each single-dose prefilled syringe of volanesorsen is filled to deliver 300 mg of volanesorsen sodium in 1.5 mL of solution.

Volanesorsen is available in a single carton or in a 4-pack of cartons contained in an outer box.

6.6 Special precautions for disposal and other handling

Volanesorsen should be inspected visually prior to administration. The solution should be clear and colourless to slightly yellow. If the solution is cloudy or contains visible particulate matter, the contents must not be injected and the product should be returned to the pharmacy. Volanesorsen must not be injected if the expiration date on the carton has passed.

Use each prefilled syringe only once and then place in a sharps disposal container for disposal according to community guidelines.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Akcea Therapeutics UK Ltd.
First Floor West, Davidson House,
Forbury Square,
Reading
RG1 3EU

8. EAMS NUMBER

47857/0001

9. DATE OF SCIENTIFIC OPINION

Additional information:
Prescribing physician will be provided with a primary physician pack containing all the relevant documents needed to manage patients receiving volanesorsen under EAMS. This can be requested by sending an email to EAMS@caligorrx.com.

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm eligibility within the scheme once the patient has signed the informed consent form.

If the patient is considered eligible for EAMS, prescribing physicians will be provided with training and guidance documents on the safety reporting requirements and processes. The training must be completed before volanesorsen supply and patient treatment

Contact information

Contact details for reporting Adverse Events/Special Situations/Pregnancies:

Email: drugsafety@pharsafer.com

Tel number: +44 1483 212150

Fax number: +44 1483 212178

Contact email for the EAMS programme (excluding AE reporting):

EAMS@caligorrx.com