Volanesorsen for familial chylomicronaemia syndrome – first line

LAY SUMMARY

Familial chylomicronaemia syndrome is a rare genetic disease in which there are too many fat particles, called chylomicrons, in the blood. Depending on how many chylomicrons there are in the blood, the symptoms experienced can be mild or more serious. Patients can experience repeated episodes of severe abdominal pain which may affect the pancreas. People with this disease often have to keep to a diet with little fat and no alcohol to control the levels of fat particles in their blood.

Volanesorsen is currently in phase III trials to see if it is effective and safe to use for reduction of fat particles in the blood. The drug is injected under the skin once a week. If volanesorsen is licensed for use in the UK, it will be a new treatment option for people with familial chylomicronaemia syndrome, who have few effective treatments available, and one that could improve their quality of life.

NIHR HSRIC ID: 9640
TARGET GROUP

- Familial chylomicronaemia syndrome – first line.

TECHNOLOGY

DESCRIPTION

Volanesorsen (ISIS APOCIII; IONIS-304801) is an antisense phosphorothioate oligonucleotide that inhibits the production of apolipoprotein C-III (APOC-III). APOC-III is a key regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma triglyceride levels. It is synthesized principally in the liver and is a component of triglyceride-rich lipoproteins. APOC-III is known to inhibit lipoprotein lipase-mediated hydrolysis of triglyceride-rich lipoproteins and to adversely affect receptor-mediated hepatic uptake of remnants of triglyceride-rich lipoproteins. In phase III clinical trials, participants receive volanesorsen 300mg administered subcutaneously (SC) once weekly for 52 weeks.

Volanesorsen does not currently have Marketing Authorisation in the EU for any indication.

Volanesorsen is currently in phase III clinical trials for familial partial lipodystrophy.

INNOVATION and/or ADVANTAGES

If licensed, volanesorsen will offer an additional treatment option for patients with familial chylomicronaemia syndrome, who currently have few effective therapeutic options.

DEVELOPER

Ionis Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

Volanesorsen is a designated orphan drug in the EU and USA.

Phase III trials.

PATIENT GROUP

BACKGROUND

Familial chylomicronaemia syndrome (FCS), also referred to as familial lipoprotein lipase (LPL) deficiency and hyperlipoproteinaemia type 1, is a rare autosomal recessive disorder characterised by a deficiency in LPL (an enzyme responsible for the breakdown of triglycerides) and a build-up of lipoprotein particles called chylomicrons in the blood. FCS is caused by mutations in the gene encoding LPL or less frequently, by mutations in genes encoding other proteins necessary for LPL function. Deficiency of LPL function prevents individuals from processing and clearing triglycerides from the blood and results in a

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* Company provided information.
massive accumulation of chylomicrons in the circulation and an increase in the plasma concentration of triglycerides.

The clinical significance and severity of FCS depends on the degree of chylomicronaemia and varies with the amount of fat in an individual’s diet, in addition to other factors. Patients with this syndrome have plasma triglyceride levels ranging from 10 to 100 times the normal value, which has a number of important clinical consequences. Patients may experience eruptive xanthomas, arthralgias, neurological symptoms, lipaemia retinalis, and hepatosplenomegaly. Nearly all individuals have recurrent episodes of severe abdominal pain, with or without acute pancreatitis, that interfere with normal life and result in frequent hospitalisations. The related pain and associated morbidity can be incapacitating, affecting the ability to work and conduct activities of daily living. Episodes of acute pancreatitis can result in chronic pancreatitis, exocrine or endocrine insufficiency including diabetes and, in severe cases, multi-organ failure, pancreatic necrosis, and death.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


CLINICAL NEED and BURDEN OF DISEASE

The genetic mutation for FCS is inherited as an autosomal recessive trait. Nearly one hundred mutations associated with FCS have been identified and about 1 in 500 people are thought to carry one of the defective genes. The condition is estimated to affect less than 0.1 in 10,000 people in the European Union. FCS affects both males and females and has been described in individuals of all races. The prevalence is, however, much higher in certain populations such as in Quebec which is thought to be due to a founder effect. Patients with severe familial chylomicronaemia are susceptible to attacks of acute pancreatitis which has mortality rates of up to 20% in adults and 6.5% in children.

The population likely to be eligible to receive volanesorsen could not be estimated from available published sources. Whilst the exact prevalence in the UK is unknown, the company expect that fewer than 1000 individuals in the UK would be eligible for treatment.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- No relevant guidance identified.

Other Guidance


b Company provided information.
CURRENT TREATMENT OPTIONS

Because of the mechanism of disease, patients with FCS are generally under-responsive or non-responsive to conventional triglyceride-lowering medications such as fibrates, which are dependent upon LPL activity.\(^\text{8,c}\)

As a result of the limitations of standard pharmacological therapy, a highly restrictive diet is the mainstay of treatment for all forms of FCS. By restricting the amount of fat in the diet, an individual can reduce their chylomicron and triglyceride levels, reducing symptoms and risk of pancreatitis. Doctors recommend reducing fat intake to 10-15% of total caloric intake, and less than 10-20g per day.\(^\text{5,7}\) Alcohol increases chylomicron formation and should be avoided. Medications that increase triglyceride production should also be avoided such as some oral contraceptives, diuretics and beta-adrenergic blocking agents. In addition, hormonal changes, such as those seen during pregnancy, can significantly impact triglyceride levels. Some individuals are recommended a diet rich in medium chain fatty acids which, because they are absorbed directly into the portal vein of the liver, are not integrated into chylomicrons.\(^\text{9}\) Fish oil supplements, effective in disorders of excessive hepatic lipase production, are ineffective and contraindicated in FCS due to their potential to increase chylomicron levels.\(^\text{9}\)

Glybera is a gene therapy approved in the EU for adults with LPL deficiency who have severe or multiple attacks of pancreatitis despite maintaining a low-fat diet.\(^\text{5,12}\) In order to be eligible for the drug, the patient must have detectable levels of LPL enzyme in their blood and have a genetic confirmation of their disease.\(^\text{12,c}\) Glybera is administered by multiple injections into the muscles of the upper and lower legs. Patients are given immunosuppressive treatment for three days before and for twelve weeks after Glybera treatment to reduce the reaction of the body’s immune system. Due to the multiple injections required, it is advisable to give it with a spinal or regional anaesthetic.

A clinical expert has stated that they do not use Glybera and treatments currently rely on dietary modification, which can be difficult at times.\(^\text{d}\)

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**EFFICACY and SAFETY**

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<th>Trial</th>
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<th>NCT02658175, ISIS 304801-CS7, volanesorsen, phase III extension.</th>
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<td>Location</td>
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\(^{\text{c}}\) Company provided information.

\(^{\text{d}}\) Expert personal communication.
## Horizon Scanning Research & Intelligence Centre

### Participants
- n=50 (planned); aged 18 yrs and older; diagnosis of familial chylomicronaemia syndrome; fasting triglycerides ≥750mg/dL at screening; no diabetes mellitus or HbA1c ≥9.0%; no other type of severe hypertriglyceridaemia; no active pancreatitis within 4 wks of screening; no acute coronary syndrome within 6 mths of screening; no major surgery within 3 mths of screening; no treatment with Glybera therapy within 2 yrs of screening; no previous treatment with volanesorsen.
- n=60 (planned); aged 18 yrs and older; completion of ISIS 304801-CS6 (index study); no new condition or worsening of existing condition.

### Schedule
- Randomised to volanesorsen 300mg administered SC once weekly; or placebo SC once weekly.
- Participants receive volanesorsen 300mg administered SC once weekly.

### Follow-up
- Active treatment for 52 wks, follow-up 13 wks.
- Active treatment for 52 wks, follow-up 13 wks.

### Primary outcome/s
- Efficacy of volanesorsen as measured by the percent change in fasting triglycerides from baseline.
- Efficacy of extended dosing of volanesorsen as measured by the percent change in fasting triglycerides from baseline.

### Secondary outcome/s
- Measurement of abdominal pain and pancreatitis; patient reported quality of life outcomes EuroQol (EQ) 5D and Short Form Health Survey (SF) 36.
- Measurement of abdominal pain and pancreatitis; patient reported quality of life outcomes EQ5D and SF36.

### Key results
- -

### Adverse effects (AEs)
- -

### Expected reporting date
- The trial data is expected to be reported in the first half of 2017.
- Primary completion date reported as Jan 2017.

### ESTIMATED COST and IMPACT

#### COST

The cost of volanesorsen is not yet known.

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability: A clinical expert has stated there would be a definite place for volanesorsen in the management of the disorder particularly in patients that suffer with recurrent pancreatitis and decreased quality of life.

- Other
- No impact identified

* Expert personal communication.
Impact on Health and Social Care Services

☑ Increased use of existing services: weekly SC injections, unless indicated that this may be self-administered.
☐ Decreased use of existing services

☐ Re-organisation of existing services
☐ Need for new services

☐ Other
☐ None identified

Impact on Costs and Other Resource Use

☑ Increased drug treatment costs
☐ Reduced drug treatment costs

☐ Other increase in costs
☐ Other reduction in costs

☐ Other
☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified: a clinical expert stated there would be further research questions regarding the potential impact of this treatment on incidence of pancreatitis, to what degree the diet can be relaxed on a patient with this treatment and whether the drug would be used throughout pregnancy.

☐ None identified

REFERENCES


1 Expert personal communication.
