NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome

Final scope

Remit

To evaluate the benefits and costs of volanesorsen within its marketing authorisation for treating familial chylomicronaemia syndrome in adults for national commissioning by NHS England.

Background

Familial chylomicronaemia syndrome (FCS) is an inherited metabolic disorder of lipid metabolism, characterised by extremely high levels of chylomicrons in the blood. Chylomicrons are triglyceride-rich lipoprotein particles that transport dietary fat absorbed from the intestine to the organs like skeletal muscle, adipose tissue and cardiac muscle for energy production and storage.[1] It is caused by the absence or low activity of enzymes that control lipids in the blood. It is most commonly due to mutations in the *LPL* gene causing deficiency in the enzyme lipoprotein lipase (LPL), responsible for the uptake of triglycerides from the circulating chylomicrons into the tissues.[2] Other causes of FCS include apolipoprotein C-II deficiency and mutations in *APOA5*, *GP1HBP1* and *LMF1* genes.[2]

FCS may present in infancy or childhood, although diagnosis (including genetic testing and/or measurement of enzyme activity) is sometimes not confirmed until adolescence or adulthood. Symptoms include repetitive episodes of severe abdominal pain, repeated episodes of pancreatitis (inflammation of the pancreas), enlargement of the liver and spleen and fatigue. The severity of the symptoms depends on the levels of chylomicrons in the blood. Acute pancreatitis is a life-threatening condition which may require intensive care and repeated attacks of pancreatitis may lead to chronic pancreatitis. FCS is associated with diabetes, which can develop as a result of pancreatitis and often makes FCS more difficult to manage. FCS can be particularly difficult to manage during pregnancy, as triglyceride levels rise and the risks of pancreatitis and diabetes increase.[3]

The prevalence of FCS is estimated to be 1 to 2 per million people[4,5] which equates to approximately 55 to 110 people in England.[6]

Currently, the management of FCS in England consists of severe restriction of dietary fat intake, usually to between 10 and 20 g/day, and no alcohol intake, in order to keep plasma triglyceride levels low.[1] Essential fatty acids (linoleic and alpha linolenic acids) and fat soluble vitamins (vitamins A, D, E and K) supplements are required for patients on a fat restricted diet. In addition,

treatments for hypercholesterolaemia (such as fibrates, nicotinic acids and statins) may be prescribed but have limited value.[7] The strict dietary regimen is highly restrictive and often challenging for patients and their families, and even when the diet is closely followed people often still have high triglyceride levels.

The technology

Volanesorsen (brand name unknown, Akcea Therapeutics) is an antisense oligonucleotide drug that aims to reduce the production of apolipoprotein C-III (APOC-III), a key regulator of lipoprotein metabolism and plasma triglyceride levels. It is administered subcutaneously.

Volanesorsen does not currently have a marketing authorisation in the UK for FCS. It has been studied in clinical trials compared with placebo in adults with FCS.

Intervention(s)	Volanesorsen in combination with established clinical management (including dietary fat restrictions)
Population(s)	Adults with familial chylomicronaemia syndrome
Comparators	Established clinical management without volanesorsen (including dietary fat restrictions)
Outcomes	The outcome measures to be considered include: • chylomicron and triglyceride levels • abdominal pain • fatigue • neurological and psychological impact of disease (including depression and cognitive ability) • incidence of acute pancreatitis, chronic pancreatitis, diabetes and other complications (including pancreatic necrosis, fatty liver disease and cardiovascular disease) • hospitalisation (including admissions to intensive care units; all-cause and pancreatitis-related admissions) • mortality (including all-cause and pancreatitis-related mortality) • adverse effects of treatment • health-related quality of life (for patients and carers).

Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	• Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements • The evaluation will include consideration of the costs and implications of genetic testing and measurement of enzyme level, but will not make recommendations on specific diagnostic tests. • Consideration should be given to the precise definition and clinical diagnosis of familial chylomicronaemia syndrome. • If evidence allows, consideration will be given to the subgroup of patients with comorbid diabetes. • If appropriate, consideration may be given to the impact of the disease on people who are or wish to become pregnant; any such consideration will take into account any relevant equality issues. • If appropriate, consideration may be given to whether factors contributing to, or exacerbating hypertriglyceridemia are associated with characteristics that are protected under equality legislation (for example, but not limited to, women using oral contraceptives).
Related NICE recommendations and NICE Pathways	None
Related National Policy	Department of Health (2016) NHS outcomes framework 2016 to 2017: Domains 1–5. NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 62. NHS England (2013) NHS standard contract for metabolic disorders (adults) E06/s/a. NHS England (2013) NHS standard contract for metabolic disorders (laboratory services) E06/s/c.

References

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6. Office for National Statistics (2017) Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016 [accessed April 2018].
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