NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Highly Specialised Technologies Evaluation

Volanesorsen for treating familial chylomicronaemia syndrome

Draft scope (pre-referral)

Draft remit/evaluation objective

To evaluate the benefits and costs of volanesorsen within its licensed indication for treating adults with familial chylomicronaemia syndrome for national commissioning by NHS England.

Background

Familial chylomicronaemia syndrome (FCS) also known as familial lipoprotein lipase deficiency, is an inherited metabolic disorder of lipid metabolism. It is caused by the absence or low activity of the enzyme lipoprotein lipase (LPL), due to mutations in the *LPL* gene. Lipoprotein lipase is responsible for uptake of triglycerides from the circulating chylomicrons into the tissues.[1] FCS is 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.[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 restriction of dietary fat intake to no more than 20 g/day 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
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: • reduction in chylomicron levels after meals • incidence of acute pancreatitis, chronic pancreatitis and diabetes • 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; including symptoms such as pain and fatigue).
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.
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

1. Burnett JR, Hooper AJ, Hegele RA. (2017) Familial Lipoprotein Lipase Deficiency, GeneReviews [accessed October 2017].
2. Dixon JB (2010) Mechanisms of chylomicron uptake into lacteals. Annals of the New York Academy of Sciences 1207(Suppl 1): E52–E57.
3. National Organisation for Rare Disorders (2016) Familial Lipoprotein Lipase Deficiency [accessed October 2017].
4. Heart UK (2017) Lipoprotein Lipase Deficiency (LPLD) [accessed October 2017].
5. European Medicines Agency (2013) Public summary of opinion on orphan designation: Adeno-associated viral vector expressing lipoprotein lipase for the treatment of lipoprotein lipase deficiency [accessed October 2017].
6. Office for National Statistics (2017) Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016 [accessed October 2017].
7. Heart UK (2012) LPLD04 Fact Sheet – Treatment options [accessed October 2017].

Questions for consultation

Will volanesorsen be used on its own, or will it be combined with other treatments? Will it be used as an adjunct to a low-fat diet?

How many people would be expected to have treatment with volanesorsen in the NHS in England?

How is familial chylomicronaemia syndrome managed in the NHS in England?

- Which treatments are considered to be established clinical practice in the NHS for familial chylomicronaemia syndrome?
- In what settings would this condition be managed in the NHS?
- Have all relevant comparators for volanesorsen been included in the scope?

Are both molecular genetic testing and measurement of lipoprotein lipase enzyme activity required to confirm a diagnosis of familial chylomicronaemia syndrome? Are these tests routinely performed in the NHS?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom volanesorsen is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the

proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which volanesorsen will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

NICE intends to evaluate this technology through its Highly Specialised Technologies Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on the Institute's Highly Specialised Technologies interim methods and evaluation processes is available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf.

