LCQ908 (Pradigastat) for familial chylomicronaemia syndrome – first line

SUMMARY **NIHR HSC ID: 7444**

LCQ908 (Pradigastat) is intended to be used as first line therapy for the treatment of familial chylomicronaemia syndrome (FCS). If licensed, it would offer a treatment option for people with FCS, for whom there are currently few licensed therapies available. LCQ908 is a diacylglycerol acyltransferase-1 (DGAT-1) inhibitor. DGAT-1 catalyses the final committed step in processing dietary fatty acids into triglycerides carried on chylomicrons for transport around the body.

Homozygous lipoprotein lipase deficiency (LPLD)/FCS is rare, affecting 1 in 1,000,000 individuals. Severe hypertriglyceridaemia affects approximately 1 in 20,000 people in the EU, equivalent to around 3,000 people in England and Wales; most cases are found in heterozygous LPLD/FCS. The onset of homozygous FCS is usually around the age of ten, however 25% of cases occur during infancy, and the primary presentation can occur as late as early adulthood. Children with FCS present with recurrent abdominal pain or pancreatitis Secondary complications include diabetes mellitus, steatorrhoea, and pancreatic calcification, which can develop by middle age. Prognosis is thought to be relatively good for FCS when a very low fat (<20g/day) diet is maintained, with early mortality and morbidity mainly due to recurrent pancreatitis.

The primary objective of treating FCS is to reduce pancreatitis by reducing triglyceride levels preventing chylomicronaemia. Therapies recommended for the treatment of LPL deficiency include fibrates, omega-3 fatty acids, and niacin (nicotinic acid). Alipogene tiparvovec (Glybera) is a lipoprotein lipase gene therapy that has recently been approved by the EMA for the treatment of homozygous LPLD/FCS. LCQ908 is currently in a phase III clinical trial comparing its effect on fasting triglycerides against treatment with placebo. This trial is expected to complete in February 2014.

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TARGET GROUP

- Familial chylomicronaemia syndrome (FCS) – first line; in addition to a low fat diet.

TECHNOLOGY

DESCRIPTION

LCQ908 (Pradigastat) is a diacylglycerol acyltransferase-1 (DGAT-1) inhibitor. DGAT-1 is one of the two DGAT enzymes that catalyse the formation of triglycerides from diacylglycerol and acyl- coenzyme A. DGAT-1 catalyses the final committed step in processing dietary fatty acids into triglycerides carried on chylomicrons for transport around the body. LCQ908 may decrease the level of triglycerides in the blood[1] and is intended for the first line treatment of FCS. It is administered orally at 10-40mg daily in addition to a low fat diet.

LCQ908 is also in phase II clinical trials for type 2 diabetes and severe hypertriglyceridaemia (familial hyperchylomicronaemia phenotypes I and V).

INNOVATION and/or ADVANTAGES

If licensed, LCQ908 will offer a treatment option for people with FCS, for whom there are currently few licensed therapies available.

DEVELOPER

Novartis General Medicines.

AVAILABILITY, LAUNCH OR MARKETING

LCQ908 is a designated orphan drug in the EU. In a phase III clinical trial.

PATIENT GROUP

BACKGROUND

FCS (also known as lipoprotein lipase deficiency [LPLD] or type I hyperlipoproteinaemia [HLP type 1]) is a rare autosomal recessive disorder of lipoprotein metabolism that usually presents in childhood. In adults, chylomicronaemia syndrome is primarily caused by familial hyperlipoproteinaemia; however, excessive alcohol intake, uncontrolled type 1 or 2 diabetes mellitus, pregnancy or a number of medications such as oestrogens and retinoids can also trigger acute hypertriglyceridaemic pancreatitis[2].

FCS results from LPL deficiency; deficiency of the lipase activating protein, apolipoprotein C-II; deficiency in the LPL synthesis controller apolipoprotein A-V; deficiency in the LPL receptor glycosylphosphatidyl inositol anchored HDL binding protein (GPIHBP-1) or the presence of LPL inhibitors[3]. LPL hydrolyses the triglyceride component of circulating chylomicrons, very low density lipoproteins (VLDL) and other triglyceride-rich lipoproteins[4]. When LPL activity is significantly reduced, chylomicrons and VLDL accumulate within the bloodstream[3]. Chylomicronaemia occurs when plasma triglyceride

(TG) levels exceed 10mmol/L (900mg/dL)[a]. Levels of triglyceride >20mmol/L (or >1,800mg/dL) are a medical emergency and form part of Royal College of Pathology notification emergency guidelines for clinicians from laboratories[b].

FCS is characterized by severe hypertriglyceridaemia (>2,000mgdL)[b] and fasting chylomicronaemia[5]. FCS is defined as chylomicronaemia accompanied by one or more of the following[6]:

- Eruptive xanthoma
- Lipaemia retinalis
- abdominal pain, acute pancreatitis, and/or hepatosplenomegaly.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to the National Framework for Long-term Conditions (2005).

CLINICAL NEED and BURDEN OF DISEASE

Severe hypertriglyceridaemia affects approximately 1 in 20,000 people in the EU, equivalent to around 3,000 people in England and Wales[b]. Most cases are found in those who are heterozygous for LPLD and present in middle age with eruptive xanthomata and/or pancreatitis. Homozygous LPLD is rare, affecting 1 in 1,000,000 individuals and has a far earlier and more severe initial presentation with a worse prognosis[b]. The onset of homozygous FCS is usually around the age of ten, however 25% of cases occur during infancy[3], and the primary presentation can occur as late as early adulthood[7].

Children with FCS present with recurrent abdominal pain or pancreatitis that often becomes worse after fatty meals[8]. Secondary complications include diabetes mellitus, steatorrhoea, and pancreatic calcification, which can develop by middle age[2]. Prognosis is thought to be relatively good for FCS when a very low fat (<20g/day)[b] diet is maintained, with early mortality and morbidity mainly due to recurrent pancreatitis[1]. Patients with recurrent pancreatitis are at risk of developing diabetes mellitus[3] secondary to pancreatic destruction[b]. In heterozygous LPLD, a number of acquired conditions including diabetes mellitus, kidney disease, liver disease and alcoholism may also raise triglyceride levels and precipitate initial presentation[3,b]. There is debate about how closely LPLD is also associated with accelerated atherosclerosis and increased cardiovascular risk independent of diabetes[3]. Homozygous LPLD is rarely associated with atherosclerosis. In heterozygous disease atherosclerosis is far commoner and often relates to the presence of type 2 diabetes and its complications[b].

The burden of disease to the NHS is related to recurrent admissions with pancreatitis which occur approximately every month for those with homozygous LPLD and about two to four times per year with heterozygous disease[b]. Additional morbidity and mortality is associated with LPLD in pregnancy where physiological hypertriglyceridaemia of the third trimester exacerbates the underlying condition. Admissions with pancreatitis can involve stays on intensive care units, the use of plasmapheresis or haemofiltration to reduce lipid levels, and may be associated with fatal complications[b]. Patients progress to diabetes through recurrent symptomatic and asymptomatic bouts of pancreatic destruction which exacerbates the underlying hyperlipidaemia and can also result in malabsorption syndromes[b]. Hugely elevated triglycerides (>50mmol/L; 4,500mg/dL) can be associated with a 'hyper-viscosity' type of blood rheology and associated manifestations including symptoms similar to transient

[a] Expert personal communication.

ischaemic attacks[c]. FCS in pregnancy is an obstetric emergency requiring specialised management[c].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- No NICE guidance.

Other Guidance

- The Endocrine Society. Evaluation and Treatment of Hypertriglyceridaemia: An Endocrine Society Clinical Practice Guideline. 2012[9].
- European Society of Cardiology and the European Atherosclerosis Society. ESC/EAS Guidelines for the management of dyslipidaemias. 2011[10].

EXISTING COMPARATORS and TREATMENTS

The primary objective of treating FCS is to reduce the occurrence of pancreatitis by reducing triglyceride levels[b]. Therapies recommended for the treatment of LPL deficiency include fibrates, omega-3 fatty acids, and niacin (nicotinic acid) which all act primarily to reduce triglycerides[c]. Other treatments include essential fatty acids; medium chain triglyceride oils (in acute admissions)[c]; statins (HMG-CoA reductase inhibitors), in combination with other drugs such as fibrates, to enhance clearance of triglyceride-rich lipoproteins[c]; heparin (in combination with other drugs only); orlistat, to reduce gut chylomicron production[c] and insulin and insulin-sensitising therapies[3,11,12,13]. Apheresis and plasmapheresis can also be used to rapidly lower plasma triglyceride levels and may be required on a daily basis in the initial acute management of LPL deficiency[14,c].

However, lipid-lowering drugs may show reduced or sometimes no activity in homozygous LPLD[c]. Alipogene tiparvovec (Glybera) is a lipoprotein lipase gene therapy that has recently been approved by the EMA for the treatment of homozygous LPLD/FCS[14]. It is available for patients with a proven homozygous genetic defect in the LPL gene, but not for other genetic causes of LPLD or for heterozygous LPLD[15,c]. Most cases of heterozygous LPL deficiency respond well to current therapies but 10% have significant residual hypertriglyceridaemia and suffer recurrent episodes of pancreatitis[c].

Patients with homozygous LPLD/FCS must follow a lifetime diet with extremely low fat intake at less than 20g per day (<10% of total daily intake in calories)[3]. A 20g to 40g per day medium-chain triglyceride diet may be used to supplement calorie intake[3]. Patients are also advised to avoid the use of substances known to increase the level of triglycerides in the blood, such as alcohol, triglyceride-inducing drugs e.g. diuretics systemic steroids[c] or oestrogens[1]. Fat soluble vitamins A, D, E and K and mineral supplements are recommended in patients with recurrent pancreatitis[3,12,c].

[b] Expert personal communication.

EFFICACY and SAFETY

Trial	NCT01514461, CLCQ908B2302, 2011-005535-68; LCQ908 vs placebo, both in addition to a low fat diet; phase III.	NCT01146522, CLCQ908A2212; LCQ908 vs placebo, both in addition to a low fat diet; phase I/II.	NCT01589237, CLCQ908B2305, 2012-000802-32; LCQ908; phase III extension.
Sponsor	Novartis Pharmaceuticals.	Novartis Pharmaceuticals.	Novartis Pharmaceuticals.
Status	Ongoing.	Complete but unpublished.	Ongoing.
Source of information	Trial registry[16], manufacturer.	Trial registry[17], manufacturer.	Trial registry[18], manufacturer.
Location	EU (incl UK), USA, Canada, and South Africa.	Canada.	EU (incl UK), USA, Canada, and South Africa.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.	Non-randomised, single arm.
Participants	n=42 (planned); aged ≥18 years; FCS; history of pancreatitis; excluding subjects with type 1 diabetes mellitus or type 2 diabetes mellitus if HbA1C ≥8.5%.	n= company confidential information; aged 18-75 years; severe hypertriglyceridemia and chylomicronaemia (phenotypes I and V); excluding subjects with uncontrolled type 1 or type 2 diabetes mellitus; excluding subjects with active pancreatitis.	n=42 (planned); completed or discontinued prematurely trial NCT01514461 or completed trial NCT01146522.
Schedule	Randomised to LCQ908 20mg once daily for weeks 0-12, reduced (without dose titration) to LCQ908 10mg for weeks 12-52; or LCQ908 40mg once daily for weeks 0-12, reduced (without dose titration) to LCQ908 20mg for weeks 12-52; or placebo for weeks 0-52. All given in addition to a low fat diet.	Company confidential information.	LCQ908 10mg once daily. After ≥8 weeks, optional up-titration to the next possible dose allowed. One down titration allowed from the highest dose attained.
Follow-up	Active treatment for 52 weeks, follow-up at week 56.	Company confidential information.	Active treatment for 52 weeks, no follow-up.
Primary outcome	Change in fasting triglycerides.	Fasting and postprandial plasma triglycerides.	Adverse and serious AEs.
Secondary outcomes	≥40% relative reduction in fasting TG or final fasting TG <8.4mmol/L (750mg/dL); proportion of subjects achieving fasting TG target thresholds <1,000mg/dL (11.4mmol/L) or <2,000mg/dL (22.8mmol/L).	LCQ908 kinetics and blood lipid biomarkers.	Change in lipid and lipoprotein profiles; change in triglyceride levels.
Key results	-	Not reported.	-
Adverse effects (AEs)	-	Not reported.	-

Expected reporting date	Study completion date reported as Feb 2014.	Previously reported as Oct 2011.	Study completion date reported as Mar 2014.

ESTIMATED COST and IMPACT

COST

The cost of LCQ908 is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☑ Reduced mortality/increased length of survival
- ☐ Other:
- ☑ Reduced symptoms or disability
- ☐ No impact identified

Impact on Services

- ☐ Increased use of existing services
- ☐ Re-organisation of existing services
- ☐ Other:
- ☑ Decreased use of existing services
- ☐ Need for new services
- ☐ None identified

Impact on Costs

- ☑ Increased drug treatment costs
- ☐ Other increase in costs:
- ☐ Other:
- ☐ Reduced drug treatment costs
- ☐ Other reduction in costs:
- ☐ None identified

Other Issues

- ☑ Clinical uncertainty or other research question identified: *the efficacy of the drug in genetically defined heterozygous as opposed to homozygous LPLD, and on long-term clinical outcomes including effects on atherosclerosis or pancreatitis-related endpoints*[c].
- ☐ None identified

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