Lenadogene nolparvovec (GS-010) for vision loss from Leber's hereditary optic neuropathy due to mutation of the ND4 gene

NIHRIO (HSRIC) ID: 12235
NICE ID: 9139

Leber’s hereditary optic neuropathy (LHON) is a genetic condition inherited from the mother, which causes rapid loss in vision. It is caused by an alteration in DNA of the mitochondria (structures in the cells that convert energy from food into a form that the cells can use). The vision loss caused by LHON is associated with disruptions in the functioning of these mitochondria. LHON is primarily associated with men. LHON usually begins with the blurred vision of one eye, with the other eye usually affected within two to three months. Significant improvements in vision are rare.

There are currently very few treatment options for LHON. Most treatment methods are used to support the patient rather than cure them. Lenadogene nolparvovec is a new gene-targeted treatment intended for vision loss caused by LHON due to an alteration in a specific gene. As a genetic medicine, lenadogene nolparvovec could be a promising option to treat LHON and if licensed, could provide a new treatment option for those with LHON.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP
Vision loss in Leber’s hereditary optic neuropathy (due to mutation of the ND4 gene) in adults.

TECHNOLOGY
DESCRIPTION
Lenadogene nolparvovec (GS-010) is a gene therapy currently in development for the treatment of Leber’s hereditary optic neuropathy (LHON) due to mutation of the ND4 gene. Lenadogene nolparvovec is a recombinant AAV vector serotype 2 containing the human wild-type mitochondrial ND4 gene (rAAV2-ND4 vector). It is based on a mitochondrial targeting sequence technology platform that enables efficient expression of a mitochondrial gene by nuclear deoxyribonucleic acid and delivery of messenger ribonucleic acid to polysomes located at the mitochondrial surface.¹

Lenadogene nolparvovec delivers the nicotinamide adenine dinucleotide dehydrogenase subunit 4 (ND4) gene directly to the mitochondrial membrane of the retinal ganglion cells. Retinal ganglion cells (RGC) communicate visual information to the brain through fibres forming the optic nerve. Mutation in the mitochondrial complex of the RGC induce a decrease in ATP synthesis while increasing oxidative stress. Lenadogene nolparvovec shows allotropic expression and proteins involved in the respiratory chain can be directly integrated in the mitochondrial membrane during the translation process, thus checking the progression of disease.¹

Lenadogene nolparvovec is currently in phase III clinical trial development for the treatment of LHON due to the mutation of the G11778A ND4 gene.²,³ It is administered as an intravitreal injection containing 9E10 viral genomes in 90μL balanced salt solution (BSS) plus 0.001% Pluronic F68® in a randomly selected eye.

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

INNOVATION and/or ADVANTAGES
As there is only one marketed treatment option in Europe available for LHON, lenadogene nolparvovec will offer an additional treatment option to address a significant unmet medical need. Furthermore as a gene therapy, lenadogene nolparvovec could be considered an appealing option as the RGC layer in the retina is accessed easier.⁴

DEVELOPER
GenSight Biologics SA

AVAILABILITY, LAUNCH or MARKETING
Lenadogene nolparvovec was designated Orphan Drug Status for Leber’s hereditary optics neuropathy in the EU in 2011 and in the USA in 2013.¹

The company’s regulatory submission and marketing plans were not available at the time of writing this briefing.
PATIENT GROUP

BACKGROUND

LHON is a maternally inherited genetic disorder that results in the rapid loss of bilateral central vision.\textsuperscript{4, 5} It is caused by mutations in the mitochondrial DNA (mtDNA) with most occurring at nucleotide positions 11778, 3460 or 14484.\textsuperscript{6} The most common genetic mutation is the 11778 mutation which accounts for approximately 50% of all LHON reported cases.\textsuperscript{7} Whilst patients inherit the mutated gene from their affected mother not all are affected by the disease.\textsuperscript{8} Other genetic and epigenetic factors are thought to have an effect on the development of the disease.\textsuperscript{7} However, the primary symptom, vision loss, is caused by the degeneration of the retinal ganglion cells (RGC), which are highly sensitive to dysfunctions in the mitochondria.\textsuperscript{4} Although this condition usually begins in adolescence and early adulthood, rare cases may appear either in early childhood or late adulthood.\textsuperscript{5} LHON vision loss primarily affects men aged 15 to 25 years; women tend to be affected later in life when oestrogen levels fall.\textsuperscript{7}

In general, LHON initially presents with blurred vision in one eye while, on average, the second eye is affected two to three months later. Significant improvements in visual acuity are rare and most patients become legally blind with visual acuity values at ≤20/200 within a few months. Additionally, visual field testing illustrates that an enlarged dense central or centrocecal scotoma is present in many cases.\textsuperscript{4, 9} Visual recovery rates associated with the 11788 genetic mutation vary between 4%-25%.\textsuperscript{9} Certain neurological abnormalities (such as postural tremor) and movement disorders (such as dystonia) are reported frequently in patients with LHON, indicating a susceptibility caused by mitochondrial dysfunction.\textsuperscript{10, 11} These abnormalities, when in conjunction with LHON, comprise a condition referred to as “Leber plus disease.”\textsuperscript{6}

CLINICAL NEED and BURDEN OF DISEASE

For the North East of England, the minimum prevalence rate of 1 in 5000 was reported for those with mutations in mtDNA, similar to the type seen in LHON patients.\textsuperscript{12} However, global prevalence estimates are largely variable (1 in 15,000-50,000).\textsuperscript{6}

The prognosis for LHON is far more favourable for younger patients.\textsuperscript{6} Additionally a better prognosis is associated with those who develop a subacute time course of vision loss, in those who develop LHON before the age of 20 years, and those with a larger optic disc.\textsuperscript{5}

In 2016, there were 49 admissions for optic atrophy (ICD-10 H47.2) in England, resulting in 47 bed days, 50 finished consultant episodes and 39 day cases.\textsuperscript{13}

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE


NHS ENGLAND and POLICY GUIDANCE
OTHER GUIDANCE


CURRENT TREATMENT OPTIONS

The treatment of mitochondrial disorders is still in its infancy. Whilst promising research is being conducted, the majority of clinical treatment for LHON remains supportive rather than curative.4

Currently, there is only one marketed medicine in the EU for LHON. Idebenone is formulated as 150 mg film-coated tablets and is recommended at a dose of 900 mg/day (300 mg, 3 times a day).34

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<th>Trial</th>
<th>RESCUE; NCT02652767; GS-010 vs sham comparator; phase III</th>
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<td>Design</td>
<td>Randomised, double-masked, sham-controlled study</td>
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<td>Participants</td>
<td>n=36 (planned); aged ≥18 years; patients with LHON due to the G11778A ND4 mitochondrial mutation when vision loss is present for six months or less</td>
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<td>Follow-up</td>
<td>The active treatment period was 48 weeks, and a three year long-term follow-up is to be conducted</td>
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<td>Primary Outcomes</td>
<td>ETDRS visual acuity, utilizing derived LogMAR acuity</td>
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### Key Results

**Adverse effects (AEs)**
- -

**Expected reporting date**
- Study completion date reported as September 2019

### Trial
**Trial**
REVERSE; NCT02652780; GS-010 vs sham comparator; phase III

**Sponsor**
GenSight Biologics

**Status**
Ongoing

**Source of Information**
GlobalData¹ and trial registry³

**Location**
EU (incl UK) and USA

**Design**
Randomised, double-masked, sham-controlled study

**Participants**
n=36 (planned); aged ≥18 years; patients with LHON due to the G11778A ND4 mitochondrial mutation when vision loss is present for six months up to one year

**Schedule**
Randomised to receive intravitreal lenadogene nolparvovec (rAAV2/2-ND4) or intravitreal placebo

**Follow-up**
The active treatment period was 48 weeks

**Primary Outcomes**
ETDRS visual acuity, utilizing derived LogMAR acuity

**Secondary Outcomes**
ETDRS visual acuity, utilizing derived LogMAR acuity

- Responder Analysis: Improvement from Baseline by 15 ETDRS letters or having Visual Acuity >20/200 at 48 and 96 weeks

- High Resolution Spectral Domain Optical Coherence Tomography to measure the optic nerve retinal nerve fiber layer (RNFL) thickness and the thickness/volume of the retinal layers of the macula

- Humphrey Visual Field 30-2

- Pelli-Robson Contrast Sensitivity

- Farnsworth-Munsell Color 100 Hue Vision Test

### Key Results

**Adverse Events and Serious Adverse Events**

**Immune Responses**

**Blood Bio-dissemination of AAV2 Vector DNA**

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<th>Expected reporting date</th>
<th>Study completion date reported as January 2019</th>
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## ESTIMATED COST and IMPACT

### COST

The cost of lenadogene nolparvovec is not yet known.

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

- [☐] Reduced mortality/increased length of survival
- [☒] Reduced symptoms or disability
- [□] Other
- [□] No impact identified

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- [□] Increased use of existing services
- [☑] Decreased use of existing services
- [☑] Re-organisation of existing services
- [□] Need for new services
- [☑] Other: new staff training requirements
- [□] None identified

## IMPACT ON COSTS and OTHER RESOURCE USE

- [☑] Increased drug treatment costs
- [□] Reduced drug treatment costs
- [☑] Other increase in costs: new specialist clinics required
- [□] Other reduction in costs
- [□] Other
- [□] None identified

## OTHER ISSUES
Clinical uncertainty or other research question identified

☐ None identified

INFORMATION FROM

No information was received from GenSight Biologics SA

GenSight Biologics SA did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

3 ClinicalTrials.gov. Efficacy Study of GS010 for Treatment of Vision Loss From 7 Months to 1 Year From Onset in LHON Due to the ND4 Mutation (REVERSE). Available from: https://clinicaltrials.gov/ct2/show/NCT02652780 [Accessed 01 November 2017]