National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: November 2017

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

LAY SUMMARY

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.

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.[4, 5] It is caused by mutations in the mitochondrial DNA (mtDNA) with most occurring at nucleotide positions 11778, 3460 or 14484.[6] The most common genetic mutation is the 11778 mutation which accounts for approximately 50% of all LHON reported cases.[7] Whilst patients inherit the mutated gene from their affected mother not all are affected by the disease.[8] Other genetic and epigenetic factors are thought to have an effect on the development of the disease.[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.[4] Although this condition usually begins in adolescence and early adulthood, rare cases may appear either in early childhood or late adulthood.[5] LHON vision loss primarily affects men aged 15 to 25 years; women tend to be affected later in life when oestrogen levels fall.[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.[4,9] Visual recovery rates associated with the 11788 genetic mutation vary between 4%-25%.[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.[10,11] These abnormalities, when in conjunction with LHON, comprise a condition referred to as "Leber plus disease."[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.[12] However, global prevalence estimates are largely variable (1 in 15,000-50,000).[6]

The prognosis for LHON is far more favourable for younger patients.[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.[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.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE evidence summary. Mitochondrial disorders in children: Co-enzyme Q10 (ES11). March 2017

NHS ENGLAND and POLICY GUIDANCE

None identified.

OTHER GUIDANCE

Newcastle Mitochondrial Disease Guidelines (2012). *Ocular Involvement in Adult Mitochondrial Disease: Screening and Initial Management.* Wellcome Centre Mitochondrial Research. Available at: http://www.newcastle-mitochondria.com/wp-content/uploads/2016/03/Ophthalmology-Guidelines.pdf [Accessed 31 Oct. 2017]

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).[14]

EFFICACY and SAFETY

Trial	RESCUE; NCT02652767; GS-010 vs sham comparator; phase III
Sponsor	GenSight Biologics
Status	Ongoing
Source of Information	GlobalData[1] and trial registry[2]
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 or less
Schedule	Randomised to receive intravitreal lenadogene nolparvovec (rAAV2/2-ND4) or intravitreal placebo
Follow-up	The active treatment period was 48 weeks, and a three year long-term follow-up is to be conducted
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 fibre 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

	Adverse Events and Serious Adverse Events Immune Responses Blood Bio-dissemination of AAV2 Vector DNA
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as September 2019

Trial	REVERSE; NCT02652780; GS-010 vs sham comparator; phase III
Sponsor	GenSight Biologics
Status	Ongoing
Source of Information	GlobalData[1] and trial registry[3]
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 Adverse Events and Serious Adverse Events Immune Responses Blood Bio-dissemination of AAV2 Vector DNA
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Study completion date reported as January 2019

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

[1]GlobalData. *GS-010*. Available from: https://pharma.globaldata.com/ProductsView.aspx?id=Preview&ProductId=276496&ProductType=0,1 [Accessed 01 November 2017; Log-in required]

[2]ClinicalTrials.gov. *Efficacy Study of GS010 for the Treatment of Vision Loss up to 6 Months From Onset in LHON Due to the ND4 Mutation (RESCUE).* Available from: https://clinicaltrials.gov/ct2/show/NCT02652767 [Accessed 01 November 2017]

[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]

[4]Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. *Progress in retinal and eye research*. 2004 Jan 31;23(1):53-89.

[5]Meyerson C, Van Stavern G, McClelland C. Leber hereditary optic neuropathy: current perspectives. *Clinical ophthalmology.* 2015;9:1165.

[6]Orphanet. *Leber's hereditary optic neuropathy.* Available from: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=167&Disease_Disease_Search_diseaseGroup=leber&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Leber-hereditary-optic-neuropathy&title=Leber-hereditary-optic-neuropathy&search=Disease_Search_Simple [Accessed 01 November 2017]

[7]LHON Society. *Leber's hereditary optic neuropathy*. http://www.lhonsociety.org/about-lhon/ [Accessed 01 November 2017]

[8]European Medicines Agency. *Adeno-associated viral vector containing the human NADH dehydrogenase 4 gene for the treatment of Leber's hereditary optic.* Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2011/05/WC500106744.pdf [Accessed 01 November 2017]

[9]Wai-Man Y, Chinnery PF. Leber Hereditary Optic Neuropathy. In: Adam MP et al. (eds.) *Gene Reviews.* University of Washington, Seattle; 2016.

[10]McFarland R, Chinnery PF, Blakely EL, Schaefer AM, Morris AA, Foster SM, Tuppen HA, Ramesh V, Dorman PJ, Turnbull DM, Taylor RW. Homoplasmy, heteroplasmy, and mitochondrial dystonia. *Neurology*. 2007 Aug 28;69(9):911-6.

[11]Martikainen MH, Ng YS, Gorman GS, Alston CL, Blakely EL, Schaefer AM, Chinnery PF, Burn DJ, Taylor RW, McFarland R, Turnbull DM. Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease. *JAMA neurology*. 2016 Jun 1;73(6):668-74.

[12]Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, Feeney C, Horvath R, Yu-Wai-Man P, Chinnery PF, Taylor RW. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Annals of neurology*. 2015 May 1;77(5):753-9.

[13]Health & Social Care Information Centre. Hospital Episode Statistics for England. Admitted Patient Care statistics, 2016-17. Available from: www.hscic.gov.uk [Accessed 01 November 2017]
[14]Electronic Medicines Compendium. *Raxone Santhera Pharmaceuticals.* Available from: https://www.medicines.org.uk/emc/medicine/32655 [Accessed 01 November 2017]