NHS National Institute for Health Research

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Lenti-D for adrenoleukodystrophy in boys

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LAY SUMMARY

Adrenoleukodystrophy (ALD), otherwise known as Lorenzo's oil disease, is a rare genetic disorder linked to the X chromosome (i.e. mainly affecting boys and men, although female carriers can exhibit symptoms). Mutations in a gene called ABCD1 initiate a set of problems which result in the destruction of the protective sheath around nerve cells, and lead to progressive neurologic deterioration. The form of the disease most commonly found in children is called cerebral adrenoleukodystrophy (CALD) and is the most severe; if untreated it progresses rapidly and causes brain damage and eventually death in most patients.

The only treatment currently available is allogeneic haematopoietic stem cell transplant (HCT). The proposed treatment involves harvesting stem cells from the patient's bone marrow and inserting a healthy version of the ABCD1 gene using Lenti-D. Defective cells are destroyed with chemotherapy, and the healthy cells are grown in culture and re-injected into the patient.

TARGET GROUP

- Males up to 17 years with adrenoleukodystrophy (Lorenzo's oil disease).

TECHNOLOGY

DESCRIPTION

Lenti-D (ALD 102; ALD-102; ALD102) is used in gene therapy, which involves harvesting CD34+ haematopoietic stem cells from the patient's bone marrow and inserting a healthy version of the disease-causing gene (ABCD1). The cells are then grown in culture and administered back to the patient after myeloablative treatment. Lenti-D is the lentiviral vector used to deliver the gene, which is self inactivating and incorporates safety elements to prevent creation of replication-competent viruses and unwanted gene activation. This gene addition should result in the production of functional adrenoleukodystrophy protein (ALDP), a protein critical for the breakdown of very-long chain fatty acids (VLCFAs). Build up of VLCFAs in the central nervous system contributes to neurodegeneration in adrenoleukodystrophy (ALD).[1]

The only effective existing treatment option is allogeneic haematopoietic stem cell transplant (HCT) which can be life-saving, provided it is conducted early in the course of cerebral disease.
Lenti-D does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Lenti-D has the potential to improve safety compared to current allogenic haematopoietic stem cell transplant treatment because it is autologous, so the risk of graft versus host reaction is eliminated.

DEVELOPER

bluebird bio Inc., development partners Institut Pasteur and Clayton Biotechnologies Inc.

Licensed from Inserm Transfert SA.

AVAILABILITY, LAUNCH or MARKETING

Lenti-D is a designated orphan drug in the EU and USA for adrenoleukodystrophy.

PATIENT GROUP

BACKGROUND

Adrenoleukodystrophy (ALD) is a rare, X-linked genetic disorder, characterised by progressive neurologic deterioration due to demyelination of the cerebral white matter. Mutations in the ABCD1 gene lead to loss of function of adrenoleukodystrophy protein, which in turn causes toxic

accumulation of very-long chain fatty acids (VLCFAs) in blood and all tissues, but primarily the adrenal glands and nervous system.[2]

In children, early symptoms include hyperactivity, difficulty at school, difficulty understanding spoken material, deterioration of handwriting, crossed eyes (strabismus), and possibly seizures. As the disease progresses, further signs of damage to the white matter of the brain appear; they include changes in muscle tone, stiffness and contracture deformities, swallowing difficulties, and coma. Early symptoms usually develop between 4 and 10 years of age with rapid progression to total dependence and death within 6 to 24 months of the onset of symptoms.[3]

A severe form of ALD where the damage is restricted to the brain, known as cerebral adrenoleukodystrophy (CALD), develops in approximately 40% of males with ALD. Symptoms of CALD usually occur in early childhood and progress rapidly if untreated, leading to severe loss of brain function and eventual death in most patients.

The adult form of the disease is called adrenomyeloneuropathy (AMN), which typically presents as muscle stiffness, paraparesis and sexual dysfunction. It progresses similarly to the childhood form with dementia and behavioural disturbances.

Approximately half of all females who carry the gene will develop some symptoms of ALD.

CLINICAL NEED and BURDEN OF DISEASE

The estimated birth incidence of ALD is 1 in 20,000 worldwide, and neither ethnicity nor country of birth is thought to have any impact on this. The global prevalence is 1 to 9 in 100,000.[4] Incidence and prevalence figures for the UK are unavailable at the time of writing.
In 2015, there were 268 admissions for ALD in England, resulting in 952 bed days and 310 finished consultant episodes (FCEs).[5]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance was identified.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for metabolic disorders (laboratory services). E06/S/e.
- NHS England. 2013/14 NHS Standard Contract for metabolic disorders (children). E06/S/b.
- NHS England. 2013/14 NHS Standard Contract for metabolic disorders (adult). E06/S/a.
- NHS Commissioning, Specialised Services, National Programmes of Care and Clinical Reference Groups: Blood and Infection - F01. Blood and Marrow Transplantation.

OTHER GUIDANCE

Engelen M, Kemp S, de Visser M, van Geel, Björn M, Wanders RJA, Aubourg, P et al. X-linked adrenoleukodystrophy (x-ald): Clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet Journal of Rare Diseases* 2012;7(1):51.

CURRENT TREATMENT OPTIONS

There are two treatments available for childhood CALD:

- Allogeneic haematopoietic stem cell transplantation (HCT) – uses umbilical cord cells or bone marrow cells from a related or unrelated individual to replace the malfunctioning cells.
- Lorenzo's oil – a combination of two fats extracted from olive oil and rapeseed oil have been shown to reduce the levels of very long chain fatty acids in the body, but not to treat the demyelation[3].

There appear to be no treatments for the adult onset form of the disease.

EFFICACY and SAFETY

Trial	**NCT02698579, EudraCT-2015-002805-13, GDCT0259685, LTF-304, IRAS-129575, UKCRN-20304 CHIL 5109, 2015-002805-13; phase III.**
Sponsor	bluebird bio Inc.
Status	Ongoing.
Source of Information	Trial registry,[6] manufacturer.[7]
Location	Argentina, Australia, UK, USA.
Design	Prospective observational study.
Participants	N=17 (planned); subjects with cerebral adrenoleukodystrophy (CALD) who have received Lenti-D Drug Product in Study ALD-102.
Schedule	Receive one dose of Lenti-D intravenously.
Follow-up	Follow-up 17 yrs.
Primary Outcomes	Overall survival; drug-related adverse effects; Neurological Function Score (NFS); clinical signs of oncogenesis; brain MRI (with and without gadolinium enhancement; archiving samples and potentially monitoring for the presence of vector-derived replication competent lentivirus (RCL) in archived samples using RCL detection assay; monitoring for clonal dominance using integration site analysis.
Secondary Outcomes	Assessment of adrenoleukodystrophy protein (ALDP) expression in peripheral blood; assessment of vector copy number (VCN) in peripheral blood; assessment of changes from baseline in very long chain fatty acids (VLCFA) levels in fasting serum; assessment of changes from baseline in IQ using the age-appropriate test from the Wechsler panel; health related quality of life assessment (PedsQL).
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	November 2033.

Trial	**Starbeam, NCT01896102, ALD-102, 2011-001953-10, EudraCT-2011-001953-10, GDCT0195906, MCRN3045, UKCRN -16192, 091388; phase II/III.**
Sponsor	bluebird bio Inc.

Status	Ongoing.
Source of Information	Abstract,[8] trial registry,[9] manufacturer.[7]
Location	France, USA, UK.
Design	Interventional, non randomised, single group assignment.
Participants	N=25 (planned); aged up to 17 years; male; active cerebral ALD as defined by elevated VLCFA values, and Loes score between 0.5 and 9 (inclusive) on 34 point scale, and Gadolinium enhancement on MRI of demyelinating lesions, and Neurological Function Score (NFS) ≤ 1, and Gad positive.
Schedule	Receive one dose of Lenti-D intravenously.
Follow-up	Follow-up at least 6 mths; 8 subjects 12-24 mths.
Primary Outcomes	Proportion of subjects who are alive and have no Major Functional Disabilities (MFDs) as determined by key measures in the Neurological Function Score (NFS) - 24 months (±1 months) post-transplant; proportion of subjects who experience either acute (≥Grade II) or chronic GVHD at Month 24 - 24 months (±1 months) post-transplant.
Secondary Outcomes	Incidence of resolution of gadolinium positivity on MRI (i.e., GdE-); time to resolution of gadolinium positivity on MRI (i.e., GdE-); change in total NFS from baseline; MFD-free survival over time; overall survival.
Key Results	As of October 2015, 17 subjects with CALD have been treated with Lenti-D drug product with median follow-up time of nine months. ALDP expression was observed in leukocytes of all subjects; integration site analyses have demonstrated polyclonal reconstitution in all subjects without evidence of clonal dominance. In the 12 subjects with at least six months of follow-up: no major functional disabilities and no NFS worsening were reported; median change in Loes score was 1 (range 0-6); all subjects experienced resolution of gadolinium enhancement.
Adverse effects (AEs)	Reported adverse events were consistent with myeloablative conditioning, one serious adverse event with possible relation to drug product was reported (BK virus cystitis) and resolved with supportive care.
Expected reporting date	August 2019.

ESTIMATED COST and IMPACT

COST

The cost of Lenti-D 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

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs: *specify, e.g. reduced use of secondary care/specialist services, reduced need for interventional procedures, reduced social care costs, etc.*

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*

☒ None identified

INFORMATION FROM

bluebird bio 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 HSRIC 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 bluebird bio. *Our focus: severe diseases*. Available from: https://www.bluebirdbio.com/our-focus/severe-diseases/ [Accessed 09-05-2017].

2 bluebird bio. *Patients and families: adrenoleukodystrophy* Available from: https://www.bluebirdbio.com/patients-families/adrenoleukodystrophy/ [Accessed 09-05-2017].

3 Stop ALD Foundation. *What is ALD?* Available from: http://www.stopald.org/what-is-ald/ [Accessed 09-05-2017].
4 Orphanet. *X-linked adrenoleukodystrophy*. Available from: http://bit.ly/2qOjgpS [Accessed 09-05-2017].
5 NHS Digital. *Hospital episode statistics for England. Admitted patient care statistics, 2015-16* Report 2015.
6 ClinicalTrials.gov. *Long-term follow-up of subjects with cerebral adrenoleukodystrophy who were treated with Lenti-D drug product*. Available from: https://clinicaltrials.gov/ct2/show/NCT02698579 [Accessed 05-05-2017].
7 bluebird bio. *bluebird bio to present clinical data on Lenti-D in CALD in plenary session at AAN 2016 annual meeting*. Available from: http://bit.ly/2pYDA6U [Accessed 09-05-2017].
8 Eichler FS. PL02.002 - Interim results from a phase 2/3 study of the efficacy and safety of ex vivo gene therapy with Lentiviral Vector (Lenti-D) for childhood cerebral adrenoleukodystrophy. *American Academy of Neurology 2016 Annual Meeting*, Vancouver; 2016.
9 ClinicalTrials.gov. *A phase 2/3 study of the efficacy and safety of hematopoietic stem cells transduced with Lenti-D Lentiviral Vector for the treatment of cerebral adrenoleukodystrophy (CALD)*. Available from: https://clinicaltrials.gov/ct2/show/NCT01896102?term=NCT01896102&rank=1 [Accessed 05-05-2017].