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HEALTH TECHNOLOGY BRIEFING
SEPTEMBER 2020

Lonafarnib for Hutchinson-Gilford Progeria syndrome and progeroid laminopathies

NIHRIO ID	5095	**NICE ID**	10409
Developer/Company	Eiger BioPharmaceuticals Inc	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Lonafarnib is in clinical development for the treatment of Hutchinson-Gilford Progeria syndrome (HGPS) and other progeroid laminopathies (PL). Progeroid laminopathies are characterised by the premature appearance of certain signs of physiological ageing in a subset of tissues, and the most prevalent of these rare diseases is HGPS. HGPS is caused by genetic abnormalities in a gene, which produces a protein called lamin A that helps to keep cells of the body strong and stable. HGPS is a severe and life-threatening condition which leads to premature death, primarily due to cardiovascular morbidities, such as heart attacks and strokes. The mean life expectancy in progeria is 14.5 years of age.

Lonafarnib, administered orally, works by preventing the formation of abnormal lamin A. An abnormal quantity of lamin A causes overproduction of a defective protein called progerin, which is believed to cause premature ageing in children. If licensed, lonafarnib will provide the first and only approved treatment option for patients with HGPS and PL.

PROPOSED INDICATION

Treatment of patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and progeroid laminopathies (PL).[1-4]

TECHNOLOGY

DESCRIPTION

Lonafarnib (SCH 66336) is a farnesyltransferase inhibitor (FTI) which reversibly binds to the farnesyltransferase CAAX binding site, thereby inhibiting progerin farnesylation and intercalation into the nuclear membrane.[5] This prevents the mutant protein from absorbing into the cellular wall where it causes much of its damage, reversing instability of the nuclear structure.[6]

Lonafarnib is in clinical development for the treatment of HGPS and PL. Lonafarnib is evaluated in several single-arm studies, which enrolled a global study population of 84 distinct patients. The individuals, from 34 countries across five continents comprised more than half of all identified progeria patients worldwide.[a] In the phase II and I/II clinical trials (NCT00425607, NCT00879034, NCT00916747, NCT02579044), patients received various doses of lonafarnib.[1-4] Details of the dosing regimens and administration schedule are detailed in the clinical trial tables of this briefing.

INNOVATION AND/OR ADVANTAGES

HGPS and PL are extremely rare and fatal diseases with no currently approved treatment. If licensed, lonafarnib would become the first and only approved treatment for this condition.[7] Patients who completed at least two years receiving lonafarnib have demonstrated prolonged survival along with one or more benefits, including weight gain, improved bone structure and hearing ability, as well as a reduction in vascular stiffness.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lonafarnib currently does not have Marketing Authorisation in the EU/UK for any indication.

Lonafarnib has received the following regulatory designation:[9]

- Orphan drug designation in the EU in December 2018 for the treatment of HGPS.

Lonafarnib is in phase III clinical development for the treatment of hepatitis delta virus.[10]

[a] Information provided by Eiger Biopharmaceutical Inc

PATIENT GROUP

DISEASE BACKGROUND

PL which includes HGPS, is characterized by an accumulation of unprocessed prelamin A or variants.[11] HGPS or progeria is a rare, fatal, genetic condition of childhood with striking features resembling premature ageing.[12] Affected children typically look normal at birth and in early infancy, but then grow more slowly than other children and do not gain weight at the expected rate.[13] It is caused by a mutation of the gene LMNA, or lamin A. The lamin A protein holds the nucleus of a cell together and the defective lamin A protein, makes the nucleus unstable. This cellular instability appears to lead to the process of premature ageing.[12] Children with progeroid laminopathies are either processing proficient or deficient category and have a mutation in the Lamin pathway that may produce progeroid-like proteins.[b]

Children with progeria show symptoms around 18-24 months and are typically born looking healthy.[14] At approximately 9 to 24 months, affected children begin to experience growth delays, resulting in short stature and low weight. They also develop a distinctive facial appearance characterized by a disproportionately small face in comparison to the head; an underdeveloped jaw, malformation and crowding of the teeth, a small nose, prominent eyes and a subtle blueness around the mouth. In addition, by the second year of life, the scalp hair, eyebrows, and eyelashes are lost, and the scalp hair may be replaced by small, downy, white or blond hairs.[12] Children born with this condition live for around 14.5 years.[15]

Unlike many genetic mutations, HGPS is rarely passed down in families. There are no known risk factors, such as lifestyle or environmental issues, which increase the risk of having progeria or of giving birth to a child with progeria. For parents who have had one child with progeria, the chances of having a second child with progeria are about 2 to 3 percent. The gene mutation is a rare, chance occurrence in the majority of cases.[16]

CLINICAL NEED AND BURDEN OF DISEASE

HGPS is extremely rare, with an estimated incidence of 1 per 4 million births and a prevalence of 1 in 18-20 million living individuals.[17,18] As of 1st June 2020, the Progeria Research Foundation estimates 176 known children with progeria currently living worldwide. Of these 129 children have HGPS and a further 47 have progeroid laminopathy.[19] According to estimates HGPS affects less than 0.01 in 10,000 people in the European Union.[9] Based on known cases of PL the prevalence is approximately 1 in 36.4 million.[a]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently, there is no approved curative treatment for these diseases.[20] With as many organ systems and cellular processes that are affected in HGPS, a combination of therapies are required to treat HGPS and PL.[21] Management of this condition generally focuses on the signs and symptoms.[22] Certain therapies may ease or delay some of the signs and symptoms.[20]

[b] Information provided by Eiger BioPharmaceuticals Inc

These include low-dose aspirin which may help to prevent atherothrombotic events, including transient ischemic attacks stroke and heart attacks, by inhibiting platelet aggregation.[23] Statins, drugs to lower blood pressure, and anticoagulants and other medications to treat headaches and seizures.[20] Management for progeria also includes physical and occupational therapy to help maintain range of motion in large and small joints.[22]

CURRENT TREATMENT OPTIONS

There are currently no pharmacological treatment options for HGPS and PL.

PLACE OF TECHNOLOGY

If licensed, lonafarnib will provide the first and only approved treatment option for patients with HGPS and PL.

CLINICAL TRIAL INFORMATION

Trial	NCT00425607; An Open Label Dose Adjusted Phase II Trial of the Oral Farnesyltransferase Inhibitor (FTI) Lonafarnib (SCH66336) for Patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies **Phase II** - Completed **Location(s):** USA **Primary completion date**: October 2009
Trial design	Single group assignment, open-label
Population	N=29; G608G mutation in the lamin A gene; progeroid laminopathies, showing clinical signs of progeria; APC (ANC + bands + monocytes = APC) > 1,000/ml, platelets > 75,000/ml (transfusion independent); haemoglobin >9g/dl; aged 1 year and older.
Intervention(s)	Oral lonafarnib twice daily at a dose of 115mg/m^2 and escalated to 150 mg/m^2.
Comparator(s)	No comparator
Outcome(s)	Proportion of participants with successful rate of weight gain (Time frame: assessed at weeks 16, 32, 52, 68, 84 and 104).
Results (efficacy)	Lonafarnib demonstrated a statistically significant improvement in mean survival time of 2.773 years (mean 8.097 vs. 5.324 year) compared to untreated controls at last follow-up, where median age of 11.14 years (range: 2.5 to 21.8 years). HR: 0.23 (95% CI 0.118,0.451); p⩽0.0001.[c] • Results consistently favored lonafarnib regardless of analysis method utilized for incidence of all-cause mortality.

[c] Information provided by Eiger Biopharmaceutical Inc

	• Odds ratios (OR) for mortality using the Cochran-Mantel Haenszel test adjusted for sex and continent Censored at 3 years: 0.16 (95% CI 0.056, 0.464), p=0.0002; Censored at last follow-up: 0.18 (95% CI 0.079,0.426), p<0.0001. • Adjusted by patient-time of observation - Relative risk (RR) using the poisson regression model stratified on sex and continent showed ≥30% reduction in mortality rates. Censored at 3 years: 0.24 (95% CI 0.090, 0.635), p=0.0041; Censored at last follow-up: 0.44 (0.256,0.740), p=0.0021.[d]
Results (safety)	Total serious adverse events were 10/28 (35.71%). See trial record for further details.[1]

Trial	**NCT00879034,** An open label, study of Zoledronic Acid, Pravastatin, and Lonafarnib (SCH66336) for Patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies **Phase II**- Completed **Location (s):** USA **Primary completion date**: April 2009
Trial design	Single group assignment, open-label
Population	N=5; all patients must have confirmatory mutational analysis showing mutation in the lamin A gene; must display clinical signs of progeria as per the clinical trial team and patient must have adequate organ and marrow function as defined by study parameters.
Intervention(s)	**Lonafarnib** • Oral lonafarnib capsules twice per day approximately every 12 hours. Lonafarnib dosing will begin at 150 mg/m^2 by mouth twice daily. Dose levels are 150, 115, 90 and 70 mg/m^2. **Zoledronic acid** • Intravenous zoledronic acid for 1 week of this treatment trial. Which will consist of 1 infusion (30-minute period) per 0.0125 mg/kg body weight. **Pravastatin** • Oral administration once per day 5mg of pravastatin for children weighing less than 10 kg, and 10 mg for children weighing 10 kg or greater.
Comparator(s)	No comparator
Outcome(s)	The primary objective of this study is to evaluate the feasibility of administering intravenous zoledronic acid, oral pravastatin and oral lonafarnib, to patients with progeria for a minimum of 4 weeks (Time frame: 4 weeks).

[d] Information provided by Eiger Biopharmaceutical Inc

	See trial record for full list of other outcomes.
Results (efficacy)	Primary outcome success was predefined by improved per-patient rate of weight gain or carotid artery echodensity; 71.0% of participants succeeded (P<0.0001). Key cardiovascular and skeletal secondary variables were predefined. Secondary improvements included increased areal (P=0.001) and volumetric (P<0.001-0.006) bone mineral density and 1.5- to 1.8-fold increases in radial bone structure (P<0.001). Median carotid artery wall echodensity and carotid-femoral pulse wave velocity demonstrated no significant changes. Percentages of participants with carotid (5% to 50%; P=0.001) and femoral (0% to 12%; P=0.13) artery plaques and extraskeletal calcifications (34.4% to 65.6%; P=0.006) increased. Other than increased bone mineral density, no improvement rates exceeded those of the prior lonafarnib monotherapy treatment trial.[24]
Results (safety)	No participants withdrew because of side effects.[e]

Trial	**NCT00916747**; Open label trial of Zoledronic acid, Pravastatin, and Lonafarnib for patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies **Phase II -** Enrolling by invitation **Location (s):** USA **Primary completion date**: July 2020
Trial design	Single group assignment, open label
Population	N=85 (planned); lamin A gene; display clinical Progeria signs; adequate organ and marrow function; blood: APC (ANC + bands + monocytes = APC) > 1,000/microliters, platelets > 75,000/microliters (transfusion independent); haemoglobin >9g/dl; renal: creatinine less than or equal 1.5 times normal for age or GFR > 70 ml/min/1.73m2; hepatic: bilirubin less than or equal to 1.5 x upper limit of normal for age; SGPT (ALT) < and SGOT (AST) < 5 x normal range for age, PT/PTT: PT/PTT < 120% upper limit of normal OR PI approval; 25-hydroxyvitamin D ⩾ 20 ng/ml within 4 weeks of bisphosphonate infusion; no overt renal, hepatic, pulmonary disease or immune dysfunction.
Intervention(s)	**Lonafarnib** • Lonafarnib dosing will begin at 150 mg/m^2 by mouth twice daily. Lonafarnib will be orally administered without planned breaks, approximately every 12 hours, for a period of 24 months. **Zolendronic acid**

[e] Information provided by Eiger Biopharmaceutical Inc

	• Zoledronic acid will be administered intravenously at week one, and months 6, 12, 18 and 24. One infusion over a 30-minute period. **Pravastatin** • Pravastatin will be orally administered once daily without planned breaks, approximately every 24 hours, for a period of 24 months. Patients <10 kg will receive 5 mg orally, once daily. Patients >10 kg or greater will receive 10 mg daily.
Comparator(s)	No comparator
Outcome(s)	To evaluate the therapeutic effects of the combination of zoledronic acid, pravastatin and lonafarnib in patients with HGPS.
Results (efficacy)	Primary outcome success was predefined by improved per-patient rate of weight gain or carotid artery echodensity; 71.0% of participants succeeded (P<0.0001). Key cardiovascular and skeletal secondary variables were predefined. Secondary improvements included increased areal (P=0.001) and volumetric (P<0.001-0.006) bone mineral density and 1.5- to 1.8-fold increases in radial bone structure (P<0.001). Median carotid artery wall echodensity and carotid-femoral pulse wave velocity demonstrated no significant changes. Percentages of participants with carotid (5% to 50%; P=0.001) and femoral (0% to 12%; P=0.13) artery plaques and extraskeletal calcifications (34.4% to 65.6%; P=0.006) increased. Other than increased bone mineral density, no improvement rates exceeded those of the prior lonafarnib monotherapy treatment trial.[24]
Results (safety)	-

Trial	**NCT02579044;** Phase I/II trial of Everolimus in combination with Lonafarnib in Progeria **Phase I/II-** Enrolling by invitation **Location(s): USA** **Primary completion date:** December 2020
Trial design	Single group assignment, open label
Population	N=80 (planned); 18 months – 25 year olds; genetically-confirmed progeria; display clinical signs of Progeria; currently receiving lonafarnib; not experienced a grade 3 or 4 toxicity within two months preceding enrolment; within 4 week no recent fractures or major surgery; absolute poly count (absolute neutrophil count + bands + monocytes) >1,000/uL; platelets >75,000/uL (transfusion independent); haemoglobin >9 g/dL; creatinine ⩽ 1.5 times upper limit of normal (ULN) for age or glomerular filtration rate (GFR) >70 mL/min/1.73m2; bilirubin ⩽ 1.5x upper limit of normal for age; SGPT (ALT) < and SGOT (AST) ⩽ 2.5x normal range for

	age; serum albumin greater than or equal to 2 g/dL; PT/PTT: INR <1.3 (or <3 on anticoagulants); fasting LDL cholesterol within 1.5x ULN per institutional guidelines (ie, <195 mg/dL for 2 - 18 years of age, <240 mg/dL for subjects >18 years old)* and fasting serum cholesterol <300 mg/dL (<7.75 mmol/L)* and fasting triglycerides <2.5 ULN (<325 mg/dL for ages 2 - 18, <400 for ages >18)* *may be re-evaluated for eligibility after initiation of lipid-lowering therapy
Intervention(s)	**Phase I:** Lonafarnib with escalating doses of everolimus to determine maximum-tolerated dose (MTD) **Phase II:** Lonafarnib plus everolimus at MTD (efficacy assessment)
Comparator(s)	Everolimus
Outcome(s)	• MTD of everolimus when administered orally in combination with lonafarnib in subjects with progeria (Time frame: 12 months). • Number and type of dose-limiting toxicities when everolimus and lonafarnib are administered in combination to children with progeria (Time frame: 12 months). • Annual increase in weight gain (Time frame: 24 months). • Change in pulse wave velocity (PWV) (Time frame: 24 months).
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of lonafarnib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

- No relevant guidance identified.

ADDITIONAL INFORMATION

Eiger BioPharmaceuticals Inc 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.

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