19 May 2022
EMA/656670/2022 Rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zokinvy

International non-proprietary name: lonafarnib

Procedure No. EMEA/H/C/005271/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAG	Alpha-1-acid glycoprotein
ABI	Ankle-brachial index
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve beginning from the first dose until the last quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
CHE	Current health expenditure
CI	Confidence interval
CITT	contemporaneous intention-to-treat
CMH	Cochran-Mantel-Haenszel
CPP	Critical process paramater
CQA	Critical quality attribute
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECM	Extracellular matrix
GC	Gas chromatography
GDP	Gross domestic product
HGPS	Hutchinson-Gilford Progeria Syndrome
HLM	Human liver microsome
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HPLC	High performance liquid chromatography
HR	Hazard ratio
HAS	Human serum albumin
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control
IR	Infrared spectroscopy
ITT	intention-to-treat
LC-MS	Liquid chromatography – mass spectrometry
LMNA	Lamin A/C gene
MO	Major objection
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
OATP	Organic anion transporting polypeptide
OC	Other comment
OR	Odds ratio
PACMP	Post approval change management protocol
P-gp	Permeability-glycoprotein
PK	Pharmacokinetic
PL	Progeroid laminopathies
PP	Process parameter
PPQ	Process performance qualification
PRF	Progeria Research Foundation
PWV	Pulse wave velocity
PWV_{cf}	Corrected carotid-femoral pulse wave velocity
QTc	Corrected QT interval
QTcB	Bazett's QTc
QTcF	Fridericia's QTc

QTPP	Quality target product profile
RH	Relative humidity
RR	Relative risk
RTV	Ritonavir
SAE	Serious adverse event
SDD	Spray dried dispersion
SM	Starting material
$T_{1/2}$	Terminal beta elimination half-life
TEAE	Treatment-emergent adverse event
TGA	Thermal gravimetric analysis
T_{max}	Time to maximum concentration
TRAE	Treatment-related adverse event
UV	Ultraviolet spectroscopy
Vd/F	Volume of distribution
VSMC	Vascular smooth muscle cell
XRPD	X Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant EigerBio Europe Limited submitted on 9 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Zokinvy, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

Zokinvy was designated as an orphan medicinal product EU/3/18/2118 on 14 December 2018 in the following condition:

'Treatment of Hutchinson-Gilford progeria syndrome'

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zokinvy as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/zokinvy

The applicant applied for the following indication:

'Zokinvy is indicated:

- to reduce the risk of mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome;

- for the treatment of Progeroid Laminopathies in patients 12 months of age or older with a processing-deficient mutation in LMNA or ZMPSTE24 (e.g., ZMPSTE24 mutations that cause mandibuloacral dysplasia type B).'

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0258/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0258/2019 was completed.

The PDCO issued an opinion on compliance for the PIP P/0258/2019.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance lonafarnib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
31 January 2019	EMEA/H/SA/3967/1/2018/PED/SME/III

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The proposed stability package to support registration; the approach to define the start of shelf life.
- The adequacy of the non-clinical package to support a MAA; the need for a post-approval carcinogenicity study.
- The adequacy of the mechanistic studies to support an indication for treatment of progeroid laminopathies.
- The scientific rationale behind the proposed clinical programme as the basis for paediatric development; the proposed primary, secondary and sensitivity analysis/methodology; the proposed mechanistic supportive data for the primary endpoint; sufficiency of the clinical pharmacology package to support a MAA; the proposed efficacy and safety database for MAA.

- The appropriateness of a MAA under Exceptional Circumstances.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kirstine Moll Harboe

The application was received by the EMA on	9 March 2020
Accelerated Assessment procedure was agreed-upon by CHMP on	27 March 2020
The procedure started on	23 April 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 June 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 June 2020
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 July 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 December 2020
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a 1st list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP 1st List of Outstanding Issues on	16 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 September 2021
The CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	16 September 2021

The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	16 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	03 December 2021
The CHMP agreed on a 3rd list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on	18 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 3rd List of Outstanding Issues to all CHMP and PRAC members on	07 April 2022
The CHMP agreed on a 4th list of outstanding issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	22 April 2022
The applicant submitted the responses to the CHMP 4th List of Outstanding Issues on	26 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 4th List of Outstanding Issues to all CHMP and PRAC members on	04 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zokinvy on	19 May 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Following the CHMP assessment of all data provided, the agreed indication for Zokinvy is:

'ZOKINVY is indicated for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford Progeria Syndrome or a processing-deficient Progeroid Laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.'

Related conditions

Classic and non-classic progeria

Classical HGPS is usually caused by a sporadic autosomal dominant mutation (except unique inheritable variety such as Werner's syndrome). The bi-allelic mutation results in an accumulation of progerin.

Non-classical HGPS follows an autosomal recessive pattern of inheritance (Hennekam, 2006). Non-classic HPGS overlap with patients with mandibuloacral dysostosis (MAD). Other LMNA-dominant mutations have been associated with the production of progerin or other deleted prelamin A isoforms (e.g. prelamin AΔ35 and prelamin AΔ90) (Barthelemy *et al.*, 2015).

Progeroid laminopathies (PL) are genetically related to HGPS and have clinical features that overlap with HGPS, including severe cardiovascular disease.

Figure 1 displays different mutations for classic, non-classic HGPS, and progeroid laminopathy.

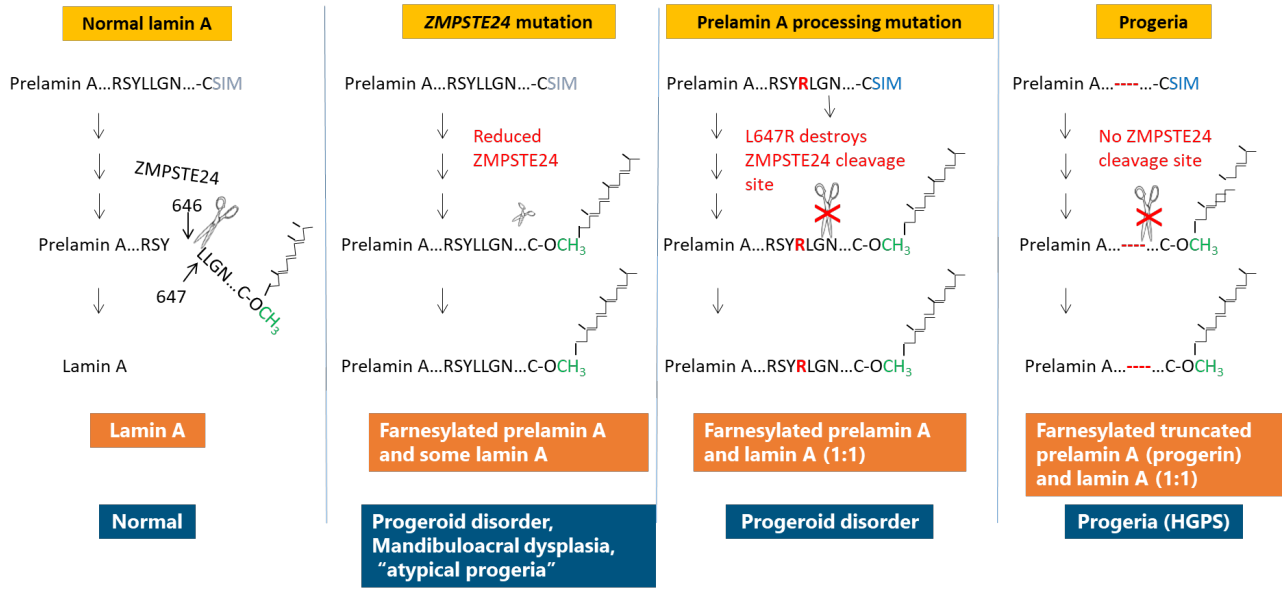


Figure 1: examples of genetic variants of Lamin A in HGPS and progeroid laminopathies.

2.1.2. Epidemiology

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare multi-systemic "premature aging" disease in which most children die of the complications of severe atherosclerosis at an average age of 14.5 years (Gordon *et al.*, 2018). Hennekam (2006) reported mean survival of classic HGPS is 12.4 (1.5 – 27) years while deBusk (1972) reported a median age of death at 13.4 (7 – 27.5 years).

The incidence of HGPS is approximately 1 in 4 million births (Hennekam, 2006) with a prevalence of 1 in 20 million living individuals (Gordon *et al.*, 2018). Progeroid laminopathies, which are rarer than HGPS, are genetically related to HGPS and have clinical features that overlap with HGPS including severe cardiovascular disease. As of October 2021, 133 children with the classic HPGS phenotype and 63 children with progeroid laminopathies (who have a mutation in the Lamin pathway but do not produce progerin) are known to be alive[1].

2.1.3. Aetiology and pathogenesis

Patients affected with typical or classic HGPS carry a heterozygous, recurrent *de novo* mutation in exon 11 (c.1824C4T; p.Gly608Gly) of chromosome 1 (q21-q23), leading to the activation of a cryptic splice site and the in-frame deletion of its last 150 bp in pre-mRNAs specifically encoding prelamin A. Due to the in-frame deletion, the Zmpste24 cleavage site is completely absent. The truncated transcript is translated into a 50 amino acid-deleted prelamin A precursor, also called progerin or lamin AΔ50, which cannot undergo all the physiological post-translational processing steps leading to mature lamin A and accumulates in cell nuclei in a permanently farnesylated state (Barthelemy *et al.*, 2015). Lamin A plays a critical role in nuclear envelope integrity, chromosome organisation, DNA replication and gene transcription. Thus, unlike lamin A, progerin retains the farnesyl group, which is key to its ability to associate with the inner nuclear membrane and cause cellular damage via structural instability (Goldman *et al.*, 2004; Cao *et al.*, 2007). This accumulation of progerin is thought to be responsible for the clinical manifestations of the disease (Kieran *et al.*, 2014).

The current knowledge of HGPS is highly empirical and consists of numerous observations without a clear conjunctive theory. Progerin is particularly toxic to vascular smooth muscle cells and results in the accelerated arteriosclerosis characteristic of HGPS. In HGPS, cardiovascular complications due to atherosclerosis lead to early death in HGPS patients.

Progeroid laminopathies are caused by mutations in LMNA or proteins affecting the post-translational pathway of *LMNA* such as Zmpste24 cleavage site that result in progerin-like proteins (Gordon *et al.*, 2019). These farnesylated abnormal progerin-like proteins cause cellular damage as described above. These diseases are rarer than HGPS and more heterogeneous making them even more challenging to study the effects of pharmacological interventions.

PLs can be grouped into two classes: 1) processing-deficient in which a farnesylated prelamin A protein accumulates, as it does in HGPS; and 2) processing-proficient (sometimes called "atypical" progerias) resulting from mutations that do not lead to accumulation of farnesylated prelamin A proteins. Retention of the farnesyl group allows these abnormal proteins to associate with the inner nuclear membrane and cause cellular damage *via* structural instability and functional abnormalities (Cao, Capell, Erdos, Djabali, & Collins, 2007; Goldman *et al.*, 2004).

[1] https://www.progeriaresearch.org/meet-the-kids/

2.1.4. Clinical presentation, diagnosis and prognosis

Besides genetic diagnosis, diagnosis of HGPS is based on recognition of a consistent pattern of clinical features, including severe failure to thrive, characteristic facial features (receding mandible, narrow nasal bridge and pointed nasal tip), total alopecia, global lipodystrophy, joint contractures, skeletal dysplasia, sclerodermatous skin, dental abnormalities, low-frequency conductive hearing loss, and premature progressive atherosclerosis; see Figure 1 (Gordon, Brown, & Collins, 2019; Merideth *et al.*, 2008). Death in children with HGPS occurs as a result of complications of severe atherosclerosis.

As in other forms of progressive cardiovascular disease, hypertension, stroke, angina, cardiomegaly, and congestive heart failure are often end-stage events. Impaired vascular compliance has been postulated to comprise a major component of the vascular pathology in HGPS, based on observations in both mouse models (Capell *et al.*, 2008; Osorio *et al.*, 2011) and isolated human studies (Baker *et al.*, 1981; Stehbens *et al.*, 2001; Stehbens *et al.*, 1999; Gerhard-Herman *et al.*, 2012). The above normal echodensity observed in patients with HGPS is related to the loss of vascular smooth muscle cells (VSMC) that are replaced with extracellular matrix (ECM), resulting in fibrosis (Gerhard-Herman *et al.*, 2012; Gordon *et al.*, 2012). This phenomenon of replacing VSMC with ECM can be induced by progerin, along with progerin-related accelerated atherosclerosis and increased plaque vulnerability in mouse models (Hamczyk *et al.*, 2018). Furthermore, the severity of atherosclerosis in progeria correlates with increased ECM in the human condition (Olive *et al.*, 2010). There are a few atypical forms of progeria, also called non-classical progeria in which growth is less retarded, scalp hair fall off slowly, progression of lipodystrophy is delayed, osteolysis is more visible with exception in face and survival is observed mostly till adulthood (Table 1).

Table 1: Differences Between Classical Hutchinson–Gilford Progeria Syndrome and Non-Classical Progeria (Hennekam, 2006).

Feature	HGPS	Non-classical Progeria
Growth deficiency		
Prenatal	Mild	Mild
Postnatal	Severe	Mild
Lipodystrophy	Expressed	Slower but in the end expressed everywhere except cheeks, submandibular, and suprapubic region
Hair loss	Expressed	Variable: minimal to severe[a]
Scleroderma	Moderate	Moderate
Osteolysis		
Acra	Moderate	Expressed
Clavicles	Mild	Expressed
Mandible	Moderate	Expressed
Viscerocranium	Moderate/severe	Mild, slowly progressive
Neurocranium	Mild	Expressed
Fractures	Late; head	Early; humeri, ribs
Vascular problems	Early; expressed	Often late, but sometimes early

a) Some scalp hair usually remains present.

HGPS negatively impacts day-to-day function. Once symptoms develop, progression of the disease is inexorable and universally fatal due to accelerated atherosclerosis and premature death, usually from myocardial infarction, stroke or congestive heart failure. Despite advances in modern medicine, there have been no changes in the life expectancy of children with HGPS (pre/post-1991).

2.1.5. Management

There are no drugs approved for the treatment of children with Hutchinson Gilford Progeria Syndrome (HGPS) or progeroid laminopathies (PLs). Additionally, there are no evidence-based guidelines that provide clinicians with effective, safe and standardised treatment regimens. It is for these reasons there is no broadly recognised and commercially available standard of care.

Other medications used to treat HGPS include low-dose aspirin, statins to lower cholesterol, antihypertensives to lower blood pressure, anticoagulants to help prevent blood clots, and various medications to treat headaches and seizures.

Examples of supportive care include hearing aids as clinically needed; ocular lubrication for exposure keratopathy; tooth extractions for dental crowding; physical and occupational therapy for skeletal abnormalities and joint contractures; annual screening with ECG, echocardiogram, carotid ultrasound, MRI/MRA of head and neck, bone density/structure imaging, hip x-ray (Gordon *et al.*, 2019).

While these measures may provide some comfort for patients with HGPS and PLs, they are only supportive and are limited to symptom management to reduce the risk of secondary complications.

For the above reasons, lonafarnib may be a welcomed treatment modality.

2.2. About the product

Lonafarnib (4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[1,2]cyclohepta[2,4-b]pyridin-11-yl]piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide) is a potent and specific inhibitor of farnesyltransferase (FTI).

Lamin A and progerin are both farnesylated. However, farnesylated-progerin cannot be cleaved, resulting in tight association with the nuclear envelope, resulting in changes in nuclear envelope morphology and subsequent cellular damage. Lonafarnib blocks the farnesylation of progerin.

Posology

The recommended starting dosage of ZOKINVY capsules is 115 mg/m^2 twice daily. Clinical trials used the Du Bois formula for calculating BSA. The complete dosing schedule can be found in the SmPC. Each dose is to be taken with food and a sufficient amount of water. After 4 months of treatment with ZOKINVY, increase to the maintenance dose of 150 mg/m^2 twice daily (morning and evening).

2.3. Type of Application and aspects on development

Accelerated assessment

The CHMP agreed to the Applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that "*to date, there is no effective disease-modifying treatment available besides the standard of care and interventions for symptomatic treatment of HGPS and PLs. Therefore, the CHMP agrees with the applicant that there is an unmet medical need for new medicinal products which can modify the disease course of HGPS and PLs. Lonafarnib may be a potential candidate to fill in the gap. The data shows encouraging results and the overall data package to be submitted seems sufficient to make a benefit/risk assessment. The data points to a clinical benefit for the patient, which seems to translate in a lower mortality rate compared in the lonafarnib group compared to the untreated group. In addition, there is a plausible mechanistic effect in reducing cardiovascular risk based on Corrected carotid-femoral pulse wave velocity (PWVcf)*

and Carotid Artery Ultrasonography (echodensity) analysis. Therefore, lonafarnib can be considered disease-modifying. Further, it is believed that lonafarnib may contribute to clinical practice and the patient's quality of life. Taking into account all data, it is concluded that at this point, an accelerated assessment is recommended."

However, during the assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as among others, major objections were raised regarding the definition of the starting materials and GCP, which required more time to solve than possible within the accelerated assessment timetable.

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence;

- it would be contrary to generally accepted principles of medical ethics to collect such information.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules, containing 50 mg or 75 mg of lonafarnib as active substance.

Other ingredients are:

Capsule contents: povidone, poloxamer, croscarmellose sodium, silica colloidal anhydrous, and magnesium stearate.

Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172), sunflower lecithin (E322) and for the 75-mg capsules also red iron oxide (E 172).

Printing ink: shellac, iron oxide black (E172), propylene glycol, ammonia solution, and potassium hydroxide.

The product is available in HDPE bottle, containing desiccant in a cannister and capsules, with induction seal and polypropylene cap, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of lonafarnib is 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[1,2]cyclohepta [2,4-b]pyridin-11-yl]piperidin-1-yl]-2- oxoethyl]piperidine-1-carboxamide corresponding to the molecular formula $C_{27}H_{31}Br_2ClN_4O_2$. It has a relative molecular mass of 638.8 and the following structure:

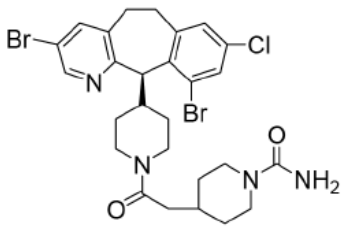


Figure 2: Active substance structure

The chemical structure of lonafarnib was elucidated by a combination of elemental analysis, nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), infrared spectroscopy (IR), ultraviolet spectroscopy (UV), and single crystal X-ray crystallography. The solid state properties of the active substance were measured by X Ray powder diffraction (XRPD), thermal gravimetric analysis (TGA) and water sorption.

The active substance is a non-hygroscopic white to off-white powder practically insoluble in water (<0.1 mg/mL), and sparingly soluble in ethyl acetate (0.9 mg/mL) and tetrahydrofuran (1 mg/mL), these solvents are used in the final crystallization of the active substance.

Information on particle size distribution was not provided since the particle size was not identified as a critical material attribute. The active substance is dissolved, along with povidone K30, prior the spray drying step and fixated as an amorphous co-precipitate in the spray dried dispersion (SDD) intermediate. A 80:20 w/w mixture of dichloromethane: methanol is used for the spray-drying step, in which the active substance is freely soluble (10.6 % w/w).

Lonafarnib exhibits stereoisomerism due to the presence of one chiral centre. The active substance is the R-enantiomer. The chiral centre is formed in stage I of the synthesis, the S-Enantiomer impurity is purged when the salt of the desired R-isomer is selectively crystallized. This salt formation with L-N-Boc-Asparagine is a major purification procedure. The stereochemical purity is routinely controlled by chiral HPLC in the stage 1 Intermediate, as well as in the active substance.

2.4.2.2. Manufacture, characterisation and process controls

Lonafarnib is synthesized using well defined starting materials (SMs) in 3 main stages.

One of the SMs was not considered acceptable and redefinition to an earlier stage was requested as Major Objection (MO). The applicant responded satisfactorily to this MO by submission of a post approval change management protocol (PACMP) containing a commitment to redefine this SM, and submit this via a post-approval variation. The applicant acknowledged that only the active substance batches already currently used for manufacture of finished product batches are accepted for proposed marketing of finished product batches, and updated the dossier to include all information on these batches. No additional batches will be used for commercial distribution until new active substance manufactured with the redefined starting material will be available.

Critical steps of the synthetic process have been identified and described in detail. And appropriate in process controls have been put in place. For the defined intermediates acceptable specifications have been presented.

Information on genotoxic and potential genotoxic impurities has been provided and is sufficient. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The identity, origin, fate, purge, carryover and control of the of the lonafarnib active substance, and starting material impurities were discussed. The discussion is divided into non-genotoxic and genotoxic impurities related to either the active substance or starting materials. The impurity control strategy is based on ICH M7 and ICH Q3A. The Stage 1 and Stage 2 intermediate impurity acceptance criteria were tightened to limit carryover of the impurities. Available spiking results were provided during the procedure and considered acceptable to support adequacy of the proposed control strategy, especially after redefinition of one of the starting materials.

The applicant adopts limits for elemental impurities in the specification of the active substance. None of these elements is added to the process with the exception of one element. The applicant has explained that the elemental impurities are controlled in line with ICH Q3D, which is acceptable, however, routine testing is not required if it can be demonstrated that the elemental impurities are consistently below 30% of the ICH Q3D limits. During the procedure, the applicant has provided the commitment to evaluate whether the elemental impurities can be omitted from the specifications, and remove them from the specification, if possible; which is acceptable as well (through submission of a variation).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

No process validation data was included in the original application. Process validation will be executed concurrent to the commercial manufacturing. Given the ultrarare nature of the disease and thus limited commercial demand, a concurrent validation approach is acceptable (see recommendation). During the procedure, the applicant provided batch results of one commercial size process validation batch.

The container closure system for lonafarnib active substance consists of double-lined low-density polyethylene bags. Relevant information, i.e. specification, compliance with relevant legislation (EU 10/2011, Ph.Eur. 3.1.5), and details on the composition of the materials were provided and considered acceptable.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual), identity (IR, HPLC), assay (HPLC), impurities (HPLC), chiral impurity (chiral HPLC), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), moisture (Ph. Eur.), residual solvents (GC), genotoxic impurities (LC-MS), and microbial purity (Ph. Eur.).

Test and limits with respect to appearance, identity, assay, residue on ignition, moisture, and microbiological limits are set as per general (European) guidance and considered acceptable. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Residual solvents likely to be present in the active substance were limited to the levels per Option 1 criteria defined in ICH Guideline Q3C with the exception of tetrahydrofuran (THF), which is controlled at the level of the spray-dried intermediate, and ethylbenzene, which is not specified in ICHQ3C, but for which adequate justification of the limit was provided.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided: three registration batches produced at the commercial site, and ten supportive batches produced either at the commercial site or at a development site. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three batches of active substance from the proposed manufacturer (one commercial-scale process validation batch and two smaller-scale registration batches) stored in the intended commercial package for 3 to 9 months under long term conditions (25 ºC/60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability data from five supportive batches of active substance stored for 12-36 months under long term conditions (25 ºC/60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

All tested parameters under long term and accelerated conditions were within the specifications.

For one development batch, a solid state stress study (thermal stress at 60°C-4weeks, and 60°C/80%RH-4weeks), and photostability stress study following the ICH guideline Q1B was performed, as well as polymorphic stability testing after storage for up to 36 months under long term conditions (25 ºC/60% RH) and up to 6 months under accelerated conditions (40 ºC / 75% RH).

There was no significant degradation of the solid samples stressed under thermal and ICH light conditions. Photostability studies demonstrated no significant change in the assay or related compounds, and no change to physical appearance, moisture, crystalline form and IR spectrum.

No polymorphic conversion was observed in the polymorphic stability testing study.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container, without any special temperature storage conditions.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as immediate-release hard gelatin capsules for oral administration. The 50 mg strength is a size '4' opaque yellow hard gelatin capsule with a black "50" imprint on the body and "LNF" imprint on the cap. The 75 mg strength is a size '3' opaque light orange hard gelatin capsule with a black "75" imprint on the body and "LNF" imprint on the cap. The same blend is filled into the capsule.

The quality target product profile (QTPP) was defined as an immediate release dosage form, which has adequate bioavailability, that meets compendial and other relevant quality standards for uniformity of dosage units and dissolution, and would be sufficiently stable to ensure an adequate shelf-life given the ultra-rare indication.

The crystalline lonafarnib is practically insoluble in aqueous media (<0.2 mg/ml). The finished product contains amorphous lonafarnib stabilized in a povidone matrix, which is produced by dissolving

lonafarnib and povidone in methylene chloride and methanol (80:20 W/W) and spray drying the solution. This amorphous lonafarnib coprecipitate has a higher solubility (~30X) than the crystalline form, and in preclinical animal PK studies, has shown enhanced bioavailability than that of the crystalline form. Therefore, the amorphous coprecipitate (further called spray-dried dispersion (SDD) Intermediate) was deemed to be the more desirable form to develop formulations with acceptable bioavailability.

The SDD intermediate is further processed into a granulate by roller compaction, followed by manufacturing a blend which is encapsulated into hard gelatin capsules.

The encapsulation blend composition is identical for both the 50 and the 75mg strength and the different strengths are achieved by different filling volume within differently sized capsule shells.

A hard gelatin capsule formulation was chosen as final finished product as they offer immediate release drug and flexibility of the formulated product.

The critical quality attributes (CQAs) identified were related substances/impurities/degradation products, crystallinity, uniformity of dosage units and dissolution.

The relationship between CQAs and Critical Process Parameters (CPPs) was further explored by conducting risk assessments and experimental studies to understand any interactions. Likewise, material attributes whose variability has a significant impact on a finished product CQA were also evaluated.

The crystalline solid-state form of the active substance was not identified as a critical material attribute since the active substance is dissolved in solvents and fixated as an amorphous co-precipitate with Povidone K30 during the spray-drying step in the SDD Intermediate. Absence of crystalline active substance is controlled upon release and stability of the SDD Intermediate.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Excipient compatibility studies were conducted. Compatibility of the active substance with the formulation components is further supported by extensive stability studies.

An assessment was conducted to identify potential CPPs and input/in-process material attributes, which impact the quality of the finished product. These variables were then investigated during process development to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch. Ultimately, the control strategy for the commercial finished product manufacturing process was developed by a combination of process characterization studies, clinical manufacturing experience and risk assessment.

There were no major changes to the SDD Intermediate or finished product manufacturing process over the product history. Minor process adjustments for the purpose of improving process robustness, scale-up and equipment availability were implemented. Clinical batches produced at different production sites are considered equivalent to each other and are representative as development batches for the proposed commercial process.

The spray drying process is performed to rapidly remove solvents from the atomized droplets, forming the amorphous solid dispersion. Any residual solvents are further reduced during the secondary drying process. The final drying step also decreases any residual water. The process is adequately controlled by monitoring selected process parameters and performing testing on the SDD Intermediate.

A residual solvent risk assessment for the finished product was performed in accordance with applicable standards, which demonstrates that residual solvents in the finished product are consistently

below ICH control thresholds, and thus, no testing of the finished product for residual solvents needs be considered.

For the residual solvents, acceptance criteria meet ICH Q3C.

Sufficient information has been provided to justify the present formulation is suitable for the paediatric population which might use the current finished product. The capsule sizes used are the smallest sizes available, furthermore, the capsules may be opened and the content can be added to a suitable vehicle. Compatibility studies were conducted with diluents such as orange juice. A relative bioequivalence study demonstrated that administration of lonafarnib suspension in orange juice and as an intact capsule resulted in a similar concentration versus time profile. Detailed directions for mixing and administering lonafarnib in a suspension in orange juice are included in the SmPC.

The selection of the dissolution method (basket apparatus, surfactant type, rotation speed, medium volume, temperature) was sufficiently justified, and the discriminatory power of the dissolution method towards various formulations and process parameters, has been demonstrated. The applicant also demonstrated that the dissolution method is able to discriminate levels of crystalline active substance in the finished product if present above the specification limit. During the procedure the applicant lowered the concentration of surfactant, at request of the CHMP. The updated method was validated, and method and validation data incorporated in the dossier. The updated method will be used for release testing and stability testing of future commercial batches, whereas the previous method will continue to be used for batches that are currently on stability, as to allow direct comparison of stability data to release data and facilitate evaluation of any potential stability trends.

The principles of the CHMP Guideline on The Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) have been used to support the conclusion that 50 mg batches and 75 mg batches manufactured at the same manufacturing site, according to the same process, are bioequivalent. The bioequivalence claim was substantiated by an f2 similarity comparison of in vitro dissolution data (3 batches per strength). Based on this, in-vivo bioequivalence study was waived.

During the procedure, a MO was raised on lacking pharmaceutical development information and consequent inadequate link between the clinical batches and the commercial finished product. In the response to this MO, the applicant has provided sufficient data to show that the batches used in the clinical studies had the same composition and were made by similar processes as the commercial batches, and that all batches are of comparable quality and have similar dissolution profiles, and are therefore expected to behave similar in vivo as well.

Stress studies conducted for both the SDD intermediate and the finished product demonstrated the products to be sensitive to moisture. Water content was found to promote formation of a hydrolysis degradant. Thus, the container closure systems for both the SDD Intermediate and the commercial finished product were chosen based on the need for moisture barrier packaging.

The container closure for the SDD intermediate is a double Low Density Polyethylene (LDPE) bag in a heat-sealed foil bag. In addition, a desiccant is added between interior and exterior LDPE bags.

The primary packaging of the finished product is a HDPE bottle, containing desiccant in a cannister and capsules, with induction seal and polypropylene cap. The material complies with Ph.Eur. and EC requirements.

The choice of the container closure system for the SDD intermediate and the finished product has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The SDD intermediate is manufactured by one manufacturing site.

The manufacturing process of the SDD intermediate consists of five main steps:

- Solids Dispensing
- Solution Preparation
- Spray Drying
- Secondary Drying
- Packaging

The manufacturing process for the SDD Intermediate consists of a non-sterile spray-drying operation using standard industry equipment, followed by a secondary tray drying operation.

The capsules are manufactured by one manufacturing site.

The manufacturing process of the capsules consists of four main steps:

- Granulation by roller-compacting a blend of SDD Intermediate with excipients
- Blending of the granulate with excipients
- Encapsulation
- Primary packaging, labeling and secondary packaging

The manufacturing process of the capsules is a standard non-sterile manufacturing process.

Process parameters and attributes were evaluated for inclusion in the process controls program and criticality based on assessment of risk to the Critical Quality Attributes (CQAs). For each critical manufacturing step, process parameters (PPs) and in-process controls (IPCs) have been classified and acceptance criteria defined.

The SDD Intermediate undergoes full testing according to appropriate specifications including tests for: appearance (visual), identity (HPLC), assay (HPLC), related substances (HPLC), water content (Ph. Eur.), residual solvents (GC-HS), crystallinity (XPRD), microbial content (Ph. Eur.), specified micro-organisms (Ph. Eur.).

A holding time of 24 months is adopted for the SDD intermediate, based on stability data (see below under 'Stability of the SDD intermediate').

No process validation data is provided in the original application. Process validation will be executed concurrent to the commercial finished product distribution. Given the ultrarare nature of the disease to be treated and thus, a limited commercial demand, a concurrent validation approach is acceptable (see recommendation): prior to distribution of each dosage strength, the applicant intends to complete production and concurrently assess one commercial scale process performance qualification (PPQ) batch of: lonafarnib, lonafarnib SDD intermediate, lonafarnib capsules, 50mg, and lonafarnib capsules, 75mg. Each batch will be concurrently assessed against the PPQ protocol and released if it meets the acceptance criteria., i.e., PPQ product will be released concurrently to commercial distribution. In addition, all batches manufactured in the concurrent release program (Lonafarnib, SDD Intermediate and Lonafarnib Capsules) will be placed into a stability program at long-term and accelerated conditions. Process validation scheme/protocols for the SDD intermediate and for the capsule manufacturing processes were provided.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (HPLC, HPLC-UV), assay (HPLC), related substances (HPLC), dissolution (HPLC/Ph. Eur.), disintegration (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), crystallinity (XPRD), microbial content (Ph. Eur.), specified micro-organisms (Ph. Eur.).

The proposed specification tests and limits are considered acceptable and have been sufficiently justified and/or revised during the procedure as requested. Batch data showed compliance to the specification.

During the procedure, the CHMP requested the applicant, via a MO, to tighten the proposed limit for dissolution in the finished product specification. In order to respond, the Applicant tightened the dissolution specification. The applicant also tightened the specification for dichloromethane. The CHMP recommended to validate an assay to measure residual carbon tetrachloride content in methylene chloride raw material at levels below compendial requirements, this to control carbon tetrachloride in dichloromethane before manufacturing of any additional SDD intermediate batches. The latter will be submitted through a post-approval variation (see recommendation).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

In order to respond to a MO on lack of nitrosamine risk assessment, the Applicant performed a risk evaluation concerning the presence of nitrosamine impurities in the finished product considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, the applicant was further requested to discuss the risk for formation of Diisopropylnitrosamine (NDIPA) / DIPNA), perform confirmatory testing, and – as appropriate - implement a control strategy. Based on the results of three batches of active substance and three batches of finished product, in which the level of NDIPA is below 10% of the limit, omission of a specification is justified. Carry-over of nitrite is not considered a potential risk. The applicant has explained how nitrite, if present, will be removed from the process supported by information on nitrite purge factors and confirmatory testing of nitrite level for three batches of starting material and on process water. As nitrite is not carried over in the synthesis, there is no risk for nitrosamine formation. Based on this, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three batches per strength (3 small-scale batches for the 50-mg strength, 2 small-scale and 1 commercial scale batch for the 75-mg strength) manufactured at the proposed commercial manufacturing site, as well as supportive (clinical) batches (three for 50-mg strength and two for the 75-mg strength) manufactured at development sites according to a manufacturing process representative for the proposed commercial process. The data package confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the SDD intermediate

Stability data from one development batch, two registration batches and one PPQ batch of SDD intermediate, stored for up to 24 months under long term conditions (25°C/60% RH) and up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Stability study results showed little or no changes in appearance, water content, assay and crystallinity at both long-term (25°C/60% RH) and accelerated (40°C/75% RH) conditions for all investigated batches throughout the testing period. The level of one degradant increased slightly under long-term conditions and more significantly under accelerated conditions, resulting at an out-of-specification result at 6 months 40°C/75% RH for the development batch. However, the level of the degradant remained within the specification limit over the entire tested period at the long-term storage condition for all the tested batches.

These data support a retest period of 24 months, when stored at 25°C/60% RH.

2.4.3.5. Stability of the finished product

Stability data from six batches of the 50-mg strength, and five batches of the 75-mg strength, stored for up to 36 months under long term conditions (25°C / 60% RH) and up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. For each strength, 3 batches were manufactured at the commercial manufacturing site, with batch size of at least 10% of the commercial batch size packed in the primary packaging proposed for marketing. The other (supportive) batches are representative to those proposed for marketing and were packed in representative primary packaging.

Samples were tested for appearance, assay, related substances, dissolution, water content, crystallinity, and microbial content. The analytical procedures used are stability indicating. They are identical to the ones used for release of these batches. The new dissolution method, which utilizes a lower concentration of SDS as a surfactant, will be used for release testing and stability on future commercial batches.

In all studies, the product met specifications throughout shelf-life for all investigated stability conditions. There were no significant changes in appearance, assay, and dissolution. One degradant and water content increased gradually over time but remained within specifications. This increase was more pronounced under the accelerated storage conditions. Trending of Water Content results from stability studies of both formulations indicates that the proposed release and shelf-life specifications assure that the primary degradation product will remain within specification at 36 months at recommended storage condition.

Crystallinity remained unchanged over shelf-life and microbial specifications were met under all investigated conditions.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability data show that light has no significant effect on the physical and chemical characteristics of the capsules.

In-use (in opened bottles) stability studies were performed for both finished product strengths at 25°C/60%RH for up to 30 days. The test results after 30 days complied with specifications and all tested parameters were well within limits. The applicant has not included a separate in-use shelf life for the finished product in the SmPC; this is acceptable based on the results of the in-use study.

Based on available stability data, the proposed shelf-life of 3 years and storage conditions 'Store in the original package. Keep the bottle tightly closed to protect from moisture. This medicinal product does not require any special temperature storage conditions.' as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.6. Adventitious agents

Gelatine obtained from bovine source is used for the capsules. Valid TSE CEPs from the suppliers of all sources of the gelatine is provided.

No excipients derived from animal or human origin have been used. The magnesium stearate is confirmed to be of vegetable origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

A number of issues were raised by CHMP as Major Objections (MO) related to acceptability of one of the starting materials, incomplete pharmaceutical development section / inadequate link between clinical and commercial batches, acceptability of the dissolution method and specifications, and lacking nitrosamine risk assessment. The issues were resolved satisfactorily by the applicant, with provision of additional information and justifications. With regard to the redefinition of the starting material the CHMP accepted that the applicant would implement the redefinition to the new starting material post-approval– as committed by the applicant through a post-approval change management protocol.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the benefit/risk ratio of the product, which pertain to concurrent validation approach for active substance, SDD intermediate and finished product and the need to develop and validate an assay to measure carbon tetrachloride in methylene chloride raw material. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. To execute process validation concurrent to the commercial finished product distribution. Prior to distribution of each dosage strength, during production, one commercial scale process performance qualification (PPQ) batch of: Lonafarnib active substance, Lonafarnib SDD intermediate, Lonafarnib Capsules, 50mg, and Lonafarnib Capsules, 75mg should be concurrently assessed against the PPQ protocol that was submitted during the MAA procedure, and released if it meets the acceptance criteria., i.e., PPQ product will be released concurrently to commercial distribution. In addition, all batches manufactured in the concurrent release program (Lonafarnib active substance, SDD Intermediate and Lonafarnib Capsules) should be placed into a stability program at long-term and accelerated conditions.
2. To submit the analytical procedure to measure carbon tetrachloride in methylene chloride, including full validation data. A variation application should be submitted using the variation classification of type IB, B.II.c.1.f.

2.5. Non-clinical aspects

2.5.1. Pharmacology

2.5.1.1. Primary pharmacodynamic studies

Mechanism of action

HGPS is caused by genetic mutations in the lamin A/C (LMNA) gene, coding for the nuclear lamina proteins lamin A and lamin C. The lamina, located inside the inner nuclear membrane, have been shown to have significant roles in DNA replication, transcription, chromatin organisation, nuclear shape, and cell division. Normal prelamin A undergoes a farnesylation of a CaaX motif at its C-terminal, which locates the prelamin protein to the nuclear membrane, where it is defarnesylated before becoming functional lamin A in the lamina. In contrast, the mutant protein retains the farnesyl group resulting in an accumulation of this farnesylated abnormal lamin A protein (progerin) in the nuclear membrane.

Progeroid laminopathies (PLs) are caused by mutations in LMNA or mutations in proteins affecting the post-translational pathway of LMNA. The LM variants that result from processing-deficient mutations can progress to clinical features that overlap with HGPS.

By inhibiting farnesyltransferase, Lonafarnib targets a step believed to be a pathophysiological hallmark, preventing farnesylation and subsequent accumulation in the inner nuclear membrane of progerin or progerin-like proteins. In HGPS, the progerin accumulation typically leads to a disturbed nuclear architecture that appear as a nuclear blebbing. The accumulation of progerin or progerin-like proteins is thought to be responsible for the clinical manifestations of HGPS and certain forms of PL.

Primary pharmacodynamics in vitro

The potency of lonafarnib (SCH 66336) was determined in a biochemical assay, where its ability to inhibit farnesylation of H-Ras, on its C-terminal CVLS, was investigated in comparison to inhibitory activity towards the related enzyme geranylgeranyl protein transferase-1 (GGPT-1) (Njorge *et al.* 1998). Lonafarnib inhibited human farnesyl protein transferase with an IC50 of 1.9 nM and was only

weakly active against the rat brain GGPT-1 (IC50>50 μM), claimed to be closely related to farnesyl protein transferase.

Inhibition of farnesylation of progerin by treatment with lonafarnib at the cellular level, blocked the nuclear blebbing in HeLa cells transfected with wild type lamin A or progerin, and in cultured dermal fibroblasts from HGPS patients (Capell *et al.*, 2005). Lonafarnib at all tested doses (0.5 - 2 μM) significantly reduced nuclear blebbing in progerin-transfected HeLa cells ($p<0.001$) and HGPS dermal fibroblasts ($p<0.001$) in dose-dependent fashion (see also clinical reports from John Hopkins and Wuxi, where Lonafarnib showed a blebbing reducing effect in both HGPS and PL derived cultured fibroblasts, however without a clear dose-response). Moreover, by transfecting an SSIM motif that could not be farnesylated into HeLa cells, the critical involvement of prenylation/farnesylation of progerin for the appearance of nuclear blebbing was demonstrated. Without prenylation/farnesylation, there was no progerin-induced nuclear blebbing, as demonstrated by confocal microscopy imaging. (Similar results were noted in HEK 293 cells and NIH 3T3 cells with other FTIs). In addition, it was found that progerin is not alternatively geranylgeranylated when farnesylation is inhibited. This is in contrast to K- and N-Ras, some other substrates of farnesyl transferase, that upon treatment with FTIs are alternatively prenylated by geranylgeranyl transferase-1 (Basso et al, 2005).

In addition, data from a supportive *in vitro* pharmacodynamic study with Lonafarnib in a non-progeria related cellular model was presented. A pharmacodynamic effect by Lonafarnib on a farnesylation dependent process in a hepatitis D virus (HDV) cellular model was investigated. *In vitro*, HDV virion assembly critically depends on prenylation/farnesylation of its nucleocapsid-like protein large delta antigen (LHDAg). Lonafarnib blocked the release of LHDAg from the cells with an EC50 of 35 pM (2.4 ng/mL).

Primary pharmacodynamics in vivo

During the procedure, the Applicant provided additional results from a prepublication by Yale university, which shows how lonafarnib in a mouse model of Hutchinson-Gilford Progeria Syndrome (homozygous LmnaG609G/G609G mice) prolonged survival (100% survival of the treated progeria mice to the study end-point (time of 50% survival of untreated mice)). Furthermore, an improvement in cardiovascular function, a modest improvement in arterial structure and function, translated into a significantly reduced pulse wave velocity and improvement left ventricular diastolic function. The study design included untreated wild-type littermate controls, untreated progeria mice, and progeria mice given lonafarnib daily in the chow from postnatal day P21 to P168. All 6 lonafarnib-treated progeria mice survived to the intended end-point, P168, while 10 of the 19 untreated mice (~53%) died. A formal report on these data was requested, but this was not presented since the Applicant does not own the data. However, the study described in the paper appears to have been well pursued. Sufficient non-clinical support for the hypothesized MoA is provided, although a full understanding of the lonafarnib induced effects on the set of complex mechanisms potentially affected is not possible to reach at this point. As expected, a considerable uncertainty is difficult to avoid due to the translational distance between animal models and clinical use. Since no formal report is possible to access, the request for a formal report is not further pursued.

Before these results became available, as described above, a non-clinical proof of concept study with lonafarnib treatment in a progeria animal model had not been carried out. Instead of bridging the *in vitro* findings, *in vivo* pharmacodynamic studies with Lonafarnib in a non-progeria animal model in a Ras-dependent oncology model (Njoroge *et al.*, 1998) were carried out. Farnesylation of Ras matures it into its biologically active form in oncogenesis. Consequently, FPT has been of considerable interest as a potential therapeutic target in oncology. In the actual study, xeno- and syngeneic tumour models in nude mice were transplanted with human or murine carcinoma cell lines, respectively, containing a mutated K- or H-ras isoform. Lonafarnib was administered PO, QID at 2.5, 10 and 40 mpk or at 10 and

50 mpk (DLD-1 model). In the DLD-1 model, lonafarnib treatment resulted in a 76% tumour growth inhibition at 50 mpk and 40% at 10 mpk, indicating a dose-dependent response. In the MIA PaCa-2, HCT-116 and NIH3T3-CVLS models, lonafarnib also resulted in a dose-dependent tumour growth inhibition ranging from approximately 15 – 50% at 2.5 mpk; 50-70% at 10 mpk to 75-100% at 40 mpk. In conclusion, Lonafarnib demonstrated anti-tumour activity in these animal models in a dose-dependent manner.

Supporting bridging studies in progeria animal models were provided as studies of treatments with other Farnesyl transfer inhibitors (FTIs). ZMPSTE24-deficient mice, which have an impaired ability to defarnesylate farnesylated lamin A and thus accumulate progerin in the nuclear membrane, shows increased mortality, reduced body weight, grip strength and bone integrity (Fong *et al.* 2006). The FTI, ABT-100 was orally administered via drinking water beginning at 5 weeks of age (n=6-9/ group) at a dose of 39 mg/kg/day. Immunoblots of HDJ-2, a biomarker of FTI activity, demonstrated that protein farnesylation was inhibited by FTI *in vivo*. Between 20 and 50% of HDJ-2 in extracts of tail biopsies was nonfarnesylated, and nonfarnesylated prelamin A was detected in the tail extracts from FTI-treated, but not from untreated, wild-type mice. Treatment with ABT-100 resulted in body weight gain ($p<0.0001$), delayed grip abnormalities ($p<0.05$), reduced the median number of rib abnormalities ($p=0.0002$), and reduced mortality (FTI-vs. vehicle-treated mice: 1/13 and 6/14 deaths respectively, $p<0.05$). In contrast to the body weight gain observed in the FTI-treated ZMPSTE24-deficient mice, wild-type mice treated with FTI showed reduced body weights relative to vehicle-treated wild-type mice, with significant reductions observed in females ($p=0.022$). However, no direct association between improved nuclear morphology and phenotype improvement could be confirmed. However, the ZMPSTE24-deficient mice treated with FTI did not display a complete elimination of diseased phenotype. The Applicant suggests this can play a role in the absence of a direct association between improved nuclear morphology and phenotype improvements.

Another supporting study with a different FTI, tipifarnib, was carried out in the C608G LMNA transgenic mouse, a progeria mouse model mimicking the cardiovascular disease of progeria. The C608G LMNA mouse model shows progressive loss of vascular smooth muscle cells in the media of the large arteries, in a pattern similar to the cardio-vascular disease seen in patients with HGPS.

Tipifarnib was orally administered via the diet starting at: I) 1 month of age until 9 to 12 months of age (n=13-15/group); II) 9 months of age, continuing for a 6-months period. Treatment with tipifarnib with a start at 1 month of age resulted in decreased total cholesterol ($p=0.00032$), total protein ($p=0.0027$), and creatinine ($p=0.0027$), while significantly increasing alkaline phosphatase ($p=0.016$). Moreover, a reduced cardiovascular disease progression was demonstrated, manifesting as an increased abundance of vascular smooth muscle cells affecting the descending aorta ($p= 0.0014$) and ascending aorta ($p=0.0090$). Improvement in vascular smooth muscle cell integrity was also noted following tipifarnib treatment and a decrease in proteoglycan deposition in the descending aorta. Treatment with tipifarnib starting at 9 months of age resulted in reduced progression of vascular smooth muscle cell loss relative to vehicle-treated controls ($p<0.01$). The observed reduction in cardiovascular disease progression affected all vessels, including the descending aorta, ascending aorta, carotid artery, and abdominal aorta.

The Applicant also provided a supportive *in vivo* pharmacodynamic study with FTIs in another non-progeria farnesylation dependent animal model. In this Hepatitis D Virus (HDV) infection mouse model, HDV virion assembly critically depends on prenylation/farnesylation of its nucleocapsid-like protein large delta antigen, as has been determined *in vitro*. HDV-encoding plasmids were co-injected with the full-length HBV genome IV into HBV-transgenic FVB mice (HDV depends on HBV envelope protein to become infective). The prenylation inhibitors FTI-277 and FTI-2153 or vehicle were administrated by IP injections QD for one week (n= not provided) at a dose of 50 mg/kg/d. HDV viremia was readily detectable in mice receiving vehicle controls but not in the serum of parallel cohorts of FTI-treated

mice (for both compounds). HDV RNA levels were comparable in the livers of mice in all treatment groups. The Applicant concludes that although not examined in this study, it is expected that Lonafarnib would show similar effects as other prenylation inhibitors based on a common mechanism of action. The Applicant's reasoning can be followed.

2.5.1.2. Secondary pharmacodynamic studies

Four secondary pharmacodynamic studies were carried out with Lonafarnib and the HM21 metabolite including a broad off-target receptor screen with Lonafarnib and the main metabolite HM21. Lonafarnib showed antagonist activity with an IC50 < 10 µM at four molecular targets: B1 adrenoceptors (ADRB1) (IC50 = 2.1 µM), cannabinoid-1 (CNR1) (IC50 = 1.2 µM), cannabinoid 2 (CNR2) (IC50 = 2.0 µM), and OX1 (IC50 = 7.1 µM). The HM21 metabolite showed antagonist activity with an IC50 < 10 µM at three molecular targets, including ADRB1 (IC50 = 3.5 µM), CNR2 (IC50 = 4.4 µM), and mu-1 opioid receptor (OPRM1) (IC50 = 3.6 µM), and agonist activity at one molecular target (5-hydroxtryptamine 1b [HTR1B]; EC50 = 2.2 µM). The calculation of safety margins indicate that secondary pharmacology is not considered a concern for lonafarnib.

An additional metabolite, HM17, was also present at concentrations at least 10% of the parent drug; however, HM17 cannot be stably synthesised. Therefore, evaluation of the secondary pharmacodynamics of this metabolite was not possible. In addition, in study P-6339 it is referred to a radioligand binding study performed by Panlab. It is stated that inhibition of muscarinic M2 and M3 by SCH66336 was observed. However, dating some twenty years back, the study report could not be retrieved. Therefore, the metabolite HM21 was clarified as being the same designated as M33.

2.5.1.3. Safety pharmacology programme

Lonafarnib was evaluated for the core battery of safety pharmacological parameters in the central nervous, cardiovascular, and respiratory systems. In addition, effects on gastrointestinal, renal, and hepatic systems were also evaluated. Several safety pharmacology parameters were investigated in two separate non-GLP studies in rats.

Voltage clamp studies were conducted in mouse L-929 cells transfected with hERG, in a non-GLP compliant study. The hERG IC50 was 1.3 µM (0.83 µg/mL), which is approximately 3 times below the clinical Cmax (2.64 µg/mL). A commonly used pragmatic approach in drug development is to set an absolute hERG potency cut-off value at 10 µM, since test substances with IC50 values below 10 µM are considered to have an increased risk of causing a QTc prolongation in the clinic (Pollard *et al.*, 2017). However, when considering the plasma protein binding of lonafarnib, which was very high (>99%), the free fraction concentration in the patient (0.01 x 2.64 µg/mL = 0.026 µg/mL) is 32 times lower than the hERG IC50.

In the *in vitro* study in isolated dog cardiac Purkinje fibres, no significant effects of lonafarnib were observed.

In the *in vivo* study, cannulated rats administered lonafarnib (≥30 mg/kg) showed significant prolongation of the QT interval compared to control. Repolarisation through Ikr (such as hERG) does not contribute significantly to repolarisation in rodents. The effect of lonafarnib on other ion channels in rat can thus not be excluded. No alteration by lonafarnib was observed in the male guinea pigs at the QTc interval.

ECG was analysed in the repeat dose toxicity studies in monkeys. No effects by lonafarnib were observed.

Increase in QTc was measured in the patients in the ProLon 1 and ProLon 2 studies in which prolongation of the QTc values were observed.

Taken together, there is no clear signal of QTc prolongation from the non-clinical studies while in the clinic, QTc prolongation has been observed.

The effect of lonafarnib on the gastrointestinal system regarding *in vivo* transit time and damage to gastric mucosa was studied in rats. Lonafarnib at 100 mg/kg inhibited gastric emptying and intestinal transit. In a second study, higher doses were administered repeatedly, and 500 mg/kg caused a significant inhibition of gastric emptying. No exposure was measured in the animals, but a Cmax value of 29.8 µM was measured in animals administered 100 mg/kg. This corresponds to x7 times the Cmax observed in patients administered the intended clinical dose of 150 mg/m^2 (mean Cmax 2.64 µg/mL/ 4µM).

Safety pharmacology studies on renal and liver function were performed, but the data were only briefly assessed since the parameters are also discussed in the toxicology section.

Effects on behavioural, neurological and autonomic changes related to lonafarnib were investigated in male rats in a non-GLP study. There were no indications of lonafarnib induced effects on CNS in this safety pharmacology study or in any of the repeat dose toxicity studies. The animals were administered a single dose of lonafarnib (10, 30, and 100 mg/kg). No exposure was measured in the animals, a Cmax value of 29.8 µM was measured in animals administered 100 mg/kg. This corresponds to x7 times the Cmax observed in patients administered the intended clinical dose of 150 mg/m2 (mean Cmax 2.64 µg/mL/ 4µM).

No stand-alone respiratory safety pharmacology studies were conducted for lonafarnib. There was no treatment-related effect on respiratory rate in monkeys treated with daily doses of 15, 30, 60 /10, 20, 40 mg/kg lonafarnib for 13 weeks or 52 weeks, respectively, as evaluated in the repeat dose toxicity studies. The Cmax in animals administered 40 mg/kg on day 1 was 12.8 µg/mL in males and 16.6 µg/mL in females. This corresponds to x4.8-6.3 times the Cmax observed in patients administered the intended clinical dose of 150 mg/m^2 (mean Cmax 2.64 µg/mL).

2.5.2. Pharmacokinetics

Bioanalytical methods

The bioanalytical HPLC-UV and LC/MS/MS methods used to quantify Lonafarnib in plasma in the toxicity studies of rats, rabbits, and monkeys appear to have been validated according to GLP standard in most cases. However, no validated GLP compliant bioanalytical methods were developed for plasma exposure measurement of Lonafarnib in the definitive rat embryofoetal development (EFD) study (SN02292) and in the definite rat pre- and postnatal development toxicity (PPND) study (SN96047).

Absorption

The absorption of Lonafarnib was studied *in vitro* in Cacao cells and *in vivo* after single oral and intravenous dosing to rats and cynomolgus monkeys, where oral dosing is the intended route of administration in patients. The *in vitro* transepithelial permeability of Lonafarnib was high, and [^{14}C]-Lonafarnib was rapidly absorbed in rats following oral dosing (T_{max} ~ 2-4 hours), whereas the absorption of Lonafarnib in monkeys was slower after oral administration (T_{max} ~ 6-8 hours). The half-life ranged from 1 to 2 hours in rats and 2 to 3.75 hours in monkeys, respectively. The absolute bioavailability following oral administration was high in both species (F = 66-91 %), which may be attributable to the high permeability of Lonafarnib across cell membranes.

Plasma concentrations following repeat oral administration of Lonafarnib in rats, rabbits and monkeys are presented in the TK analysis in the toxicology section.

Distribution

The *in vitro* plasma protein binding of Lonafarnib has been studied in rat monkeys and humans with an ultrafiltration method. Plasma protein binding of [14C]-Lonafarnib at concentrations between 0.5 and 40 µg/mL was high (99.0 (rat) to 99.7% (human)) and similar across species for rat, monkey, and human plasma. Binding of [14C]-Lonafarnib (0.4 and 2 µg/mL) to human plasma proteins alpha1-acid glycoprotein (AAG) and human serum albumin (HSA) and HAS/AAG combinations was also assessed *in vitro*. Binding was high for both proteins (>92.5%) and depended on Lonafarnib concentration for AAG and HSA concentrations for HSA. When Lonafarnib was incubated in both HSA and AAG, binding was consistent across all concentrations of HSA (95.1 to 98.4%), and the applicant concluded that the total binding of Lonafarnib to human plasma proteins might not be affected in pathophysiological conditions with low HSA concentrations.

The tissue distribution of Lonafarnib in pigmented rats (n=2-3) and cynomolgus monkeys (n=1/sex) was determined following oral administration of [^{14}C]-Lonafarnib (15, 30 mg/kg) in 0.4% (w/v) MC) by oral gavage using both radioactivity analysis and whole-body autoradiography. In rats, all tissues evaluated reached maximum concentrations by 4 hours post-dose, except for perirenal fat, spinal cord (1-hour post-dose), and Harderian gland (12 hours post-dose; females only). The liver, adrenal glands, pancreas, bile duct, and kidneys displayed the highest concentrations of radioactivity for both sexes in rats (excluding the GI tract). At 4 hours post-dose, 5 to 8% of the administered dose was present in the liver of the remaining tissues; only the skeletal muscle and non-pigmented skin contained greater than 1% of the administered dose. There was no apparent binding to pigmented tissue. Similarly, in monkeys, the distribution of Lonafarnib-derived radioactivity was highest in the liver, small intestine, and eye. Distribution was low for both sexes in the lung and skeletal muscle.

The brain: plasma ratio of Lonafarnib (30, 60, 90 mg/kg, BID for 8 days) following repeat oral administration in rats was evaluated *in vivo*. The AUC ratio of brain to plasma was about 6.5% at each dose level, indicating a low to moderate brain penetration of Lonafarnib.

In a placental transfer study in pregnant rats, the radioactivity of Lonafarnib was detected in foetal blood following oral dosing, with exposure to drug-derived radioactivity in the foetus of approximately 10% of that seen in dams. Thus, the results of the placental transfer study indicate that Lonafarnib-related material was transferred to the foetus via the placenta following oral administration to pregnant rats. The applicant did not report any milk excretion studies.

Metabolism

The metabolite profile of Lonafarnib was determined in mouse (CD-1), rat (Sprague Dawley), monkey (male cynomolgus), and human hepatocytes. The *in vitro* metabolic profiling indicates that Lonafarnib was extensively metabolized by rat and monkey hepatocytes and to some lesser extent by mice and human hepatocytes. A total of 32 metabolites were characterized following incubation of [14C]-Lonafarnib with mouse, rat, monkey, and human hepatocytes. The most common metabolic pathways included oxidation, dehydrogenation, and/or a combination of these two processes, and the majority of metabolites across all species were associated with changes in the region of the pendant piperidine ring. No human specific metabolite appears to have been detected in the *in vitro* studies.

The *in vivo* metabolic profile of Lonafarnib was characterized in Sprague Dawley rats and in cynomolgus monkeys administered a single oral dose of [^{14}C]-Lonafarnib (15, 30 mg/kg in 0.4% methylcellulose) or 5 mg/kg IV (in DMSO in 20% (w/v) HPβCD in a 2:3 (v/v) ratio). The single-dose metabolite profiling studies following oral or intravenous administration indicate that Lonafarnib was extensively metabolized in both rats and monkeys. A total of 30 metabolites were identified in plasma,

urine (rats only; radioactivity in the urine of monkeys was <1.62% of the dose), and faeces. The metabolites appear to have been primarily generated as a result of structural changes of the pendant piperidine ring of Lonafarnib, and the predominant metabolic conversions were considered to be oxidations and dehydrogenations. In monkeys, the metabolic profiles in both plasma and faeces were similar across sexes and dosing routes. In contrast, some metabolites were observed in the rat only in male faeces (RM2a and RM3), and RM2b was only detected in female faeces. In the human metabolism study (Study P00260), there were no human-specific metabolites detected that were not also detected in the rat and monkey following a single oral dose of [14C]-Lonafarnib (104 mg) to healthy subjects. Similar to the studies in animals, the common metabolic pathways in humans included oxidation, dehydrogenation and combinations of these two processes and the majority of metabolites in man resulted from structural changes in the region of the pendant piperidine ring of Lonafarnib.

Excretion

Mass balance studies were conducted in rats and cynomolgus monkeys to determine [^{14}C]-Lonafarnib excretion following oral or IV administration. The excretion data in rats and monkeys indicate that faecal elimination is the dominant route (> 99% in rats and > 85% in monkeys after IV dosing), whereas urinary excretion was limited (< 0.5 to 1.6% in rats and monkeys, respectively). After oral and IV administration, the excretion was rapid, and most of the radioactivity was excreted within 48 hours in intact rats and within 72 hours in fed monkeys. The presence of large amounts of radioactivity in the faeces of both species following both oral and IV administration suggests that biliary excretion and/or secretion by the gut contribute to eliminating Lonafarnib and its metabolites. In humans, Lonafarnib is primarily excreted via faeces (98% of the radioactive administered dose) with minimal excretion in urine (<1% unchanged parent).

Pharmacokinetic drug interactions

Please see the Clinical pharmacokinetics section for the assessment of pharmacokinetic drug interactions studies.

2.5.3. Toxicology

The toxicological profile of lonafarnib has been evaluated in non-clinical studies in agreement with relevant guidelines. Overall, the toxicity profile of lonafarnib has been characterized via single-dose toxicity studies in mice and rats, repeat-dose toxicity studies (up to 6 months in Sprague Dawley rats and 12 months in cynomolgus monkeys), genotoxicity and impurity studies, reproductive and developmental studies (in Sprague Dawley rats and New Zealand White rabbits) and mechanistic studies (nephrotoxicity, myelotoxicity and electroretinography). No studies on juvenile toxicology or carcinogenicity have been conducted.

The oral route of administration was utilized in all pivotal toxicity studies to match the intended clinical administration route.

Lonafarnib is intended for patients with genetic disorders Hutchinson-Gilford Progeria Syndrome (HGPS) and progeria laminopathies (PL), and treatment is intended to be given to children (from 12 months) and adolescents. Therefore, it needs to be mentioned that the general toxicity studies have been conducted in rats with a corresponding human age of 12.5 years or 18 years at the end of the studies and in pre-adult or adult cynomolgus monkeys and therefore does not cover totally the age-stages of this young patient population.

The recommended clinical maximal dose of lonafarnib is an oral dose of 150 mg/m^2 BID and the applicant propose that this dose results in an $AUC_{0\text{-}12}$ mean value of 20.6 µg•h/mL and a Cmax value

of 2.64 µg/mL. Throughout this assessment, these values have been adopted when calculating marginals between exposure in animals with that at the maximal clinical dose.

The Sprague Dawley rat and cynomolgus monkey were selected as the main rodent and non-rodent species in the general toxicity studies. Sprague Dawley rat and New Zeeland White rabbits were selected for reproduction and developmental studies.

2.5.3.1. Single dose toxicity

A number of GLP compliant single-dose toxicity studies were conducted with oral gavage and IP administration in mice (two oral gavage studies and two IP studies) and rats (one oral gavage and one IP study), respectively.

In mice oral gavage studies, mortality was noted at doses of 2000 mg/kg and 1500 mg/kg and occurred 24h and 3 days post-dose. In addition to the common clinical signs prior to death, observations of soft or scant faeces were noted at high and intermediate doses, indicating an adverse effect on the GI tract. Lower body weight gain without an obvious dose-response relation were observed despite no changes in food consumption. NOAELs were 300 mg/kg (males) and 1000 mg/kg (females) in the first study (SN960277) and 1500 mg/kg (males) and 300 mg/kg (females) in the second study (SN97266). The two IP single-dose toxicity mice studies were conducted with a few months apart. In the first study (SN96028), dose groups of 0, 100, 200, 400, 600, or 1000 mg/kg were tested, whereas the 200 mg/kg dose group was excluded from the second study (SN97267), which was otherwise identical to the first study. In both studies, high mortality was seen in the 1000 mg/kg and 600 mg/kg dose groups. Additionally, mortality was also observed in the 400 mg/kg dose group, especially in the second study SN97267. NOAELs were 200 mg/kg for males and females in the first study (SN96028) but could not be established in the second study (SN97267). Likewise, LD50 values were lower in the second study SN97267, compared to the first study SN96028 (489 mg/kg and 375 mg/kg compared to 716 mg/kg and 772 mg/kg in males and females, respectively).

In the rat oral gavage single-dose toxicity study, mortality was low (one animal died in the 2000 mg/kg group), indicating that rats were less sensitive to lornafarnib administered PO compared to mice. However, soft and scant faeces was still noted as the most common adverse effect in the high dose groups, and NOAELs were 1000 mg/kg and 300 mg/kg for males and females, respectively. In rats given lonafarnib IP, mortality was observed in the 600 mg/kg (6/10) and in the 400 mg/kg dose group (2/10). In this study, soft and scant faeces was also noted in the high dose groups. Hypoactivity, ataxia, and decreased BW gain were observed at a lower dose and NOAELs were set to 30 mg/kg and <30 mg/kg for males and females, respectively.

2.5.3.2. Repeat dose toxicity

In repeat-dose toxicity studies, the main organs and tissues affected were primarily liver, male reproductive organs (testes and epididymides), lymphoid organs/tissues, haematopoietic system (bone marrow) and immune system. Effects were also observed in female reproductive organs, gastrointestinal system, eye, adrenal glands, and parathyroid. No NOAELs were established in any of the conducted repeat-dose toxicity studies. As discussed below, for most of the treatment-related toxicity, there were no (or very low) exposure marginals compared to that in the clinic with the intended dosing at 150 mg/m^2 BID.

Treatment-related mortality occurred in the 3-months rat and monkey toxicity studies, while no deaths occurred in the longer-term studies. Two female rats died after treatment of 180 mg/kg/day lonafarnib. One of the females, who died week 12, displayed liver toxicity (centrilobular hepatocellular

necrosis and pigmentation and increase of mitoses) indicative of anaemia and hypoxia in the liver, and the other female, died week 3; there was no apparent cause of death. The deaths in the female rats occurred at an AUC exposure marginal of 21 times to the intended clinical highest dose (150 mg/m2). Notably, for the 13-weeks rat study, the exposure of females was 2-3 times higher than male rats. The mortalities in cynomolgus monkeys occurred in two males dosed at 60 mg/kg/day at weeks 3 and 9 in the 13-weeks study. This dose corresponds to 3.3 -fold higher exposure than the intended clinical dose of 150 mg/m2. Both animals were dehydrated with up to severe atrophic changes of lymphoid organs (spleen, thymus, and lymph nodes), and the cause of death was attributed to a loss of blood due to haemorrhages in multiple organs (severe thrombocytopenia), and hypervolemia and stress. To summarize, mortality occurred in two monkeys and two rats after treatment with lonafarnib at doses corresponding to 3.3 and 21-fold higher exposure, respectively, compared to the intended clinical dose of 150 mg/m^2.

Treatment-related toxicity in the liver was observed in both rat and cynomolgus monkeys and was characterised by hepatic dysfunction and a pathologic response to increased metabolic stress. In rats, toxicity was observed in both 3- and 6-months studies, which included liver enzyme induction (CYP1A1, 1A2, and 2B, CYP2B, CYP3A; only analysed in the 3-months study), increased liver weights, and microscopic findings such as centrilobular hypertrophy and vacuolation which was mainly graded as minimal in severity. Enzyme induction was observed in males ≥30 mg/kg/day while a potential inhibition was observed in female rats at 30 and 90 mg/kg/day, and microscopic findings were observed at 60 mg/kg/day in both sexes after 6 months of lonafarnib treatment. No liver enzyme induction or inhibition was observed after 5 weeks of recovery in the 3 months study. There were no exposure marginals (x 0.11 to 0.68) at the NOAEL for liver findings (enzyme induction, increased weight and microscopic changes) in rats compared to that at the intended clinical dose of 150 mg/m^2. In monkeys, enzyme induction occurred at ≥ 15 mg/kg/day (only analysed in the 3-months study) and increased liver weight was observed in both studies. However, no microscopic changes were observed in monkeys that were dosed up to 40 and 60 mg/kg/day in the 3-months and 1-year study, respectively. In monkeys, the NOAEL for liver findings (enzyme induction, increased weight) occurred at no exposure marginals (x 0.63 to 1.22) to the intended clinical dose. To summarize, there were no exposure marginals for the observed liver findings (based on increased liver weight and enzyme induction). However, the microscopic changes were mild up to 90 mg/kg/day (corresponding to 10- to 40-fold higher exposure than in the clinic), occurred only in rats, and all liver findings were reversible. Therefore, it is considered that the microscopic liver changes may pose only a small risk in the clinic. However, the liver enzyme induction occurred at no exposure marginal compared to that in the clinic. It should be mentioned that altered liver enzymes have been monitored after lonafarnib treatment in the clinic.

Male reproductive organs were affected after administration with lonafarnib in rats and cynomolgus monkeys. In monkeys, effects were observed in the 52 weeks study, with effects observed as an approximately 40% decrease of testes weight at the low dose (10 mg/kg/day), which was followed by 60% and 80% weight decrease at the intermediate dose (20 mg/kg/day) and high dose (40 mg/kg/day), respectively. Notably, no correlating microscopic testes changes were reported at the low dose, while up to severe atrophy of the testicular seminiferous tubules was reported in 3 out of 4 animals at 20 mg/kg/day, and in all 4 animals at 40 mg/kg. This mismatch between 40% weight loss with no corresponding atrophy seems odd. Furthermore, in epididymides, no sperms were observed in 3 out of 4 animals at 20 mg/kg/day and in all 4 animals at 40 mg/kg/day, and weight loss was reported with approximately 30%, 40%, and 60% abs. weight loss at 10, 20 and 40 mg/kg/day, respectively. The applicant reports a NOAEL at 10mg/kg/day for monkey male reproductions organ, which corresponds to x 1.22 exposure marginal to that in the clinic with the intended dose of 150 mg/m^2. This NOAEL is considered not fully justified based on the apparent weight loss observed at this dose level. In rats, effects in male reproductive organs occurred in the 3-months study only. In main

animals, reduced testicular and epididymal weight loss was observed at the high dose (180 mg/kg/day) without any corresponding microscopic findings. However, in the recovery group (180 mg/kg/day; 5 weeks recovery) testicular aspermia and spermatogonial debris and epididymal oligospermia and spermatic debris in 1 or 2 males out of 5. In the male fertility study in rats, profound effects on fertility, -30% and –90% was observed at 30 and 60 mg/kg/day, respectively.

Toxicity in lymphoid organs and tissues was observed in rats and cynomolgus monkeys. In rats, toxicity was seen after 3-months administration of lonafarnib and were attributed as lymphoid hypocellularity and with corresponding weight loss and the affected organs/tissues included spleen, thymus and mesenteric lymph node, and occurred at 30 mg/kg/day but only in few animals (2F) and with minimal severity. However, in the intermediate dose group (90 mg/kg/day) the number of affected animals increased and the severity grades (up to severe grades). Partial recovery was observed after 5 weeks of recovery and included 2 out of 5 females with minimal lymphoid hypocellularity. Hypocellularity (decreased erythroids and myeloids) and increased megakaryocytes were observed in bone marrow with related haematology findings (for example, dose-related decrease of WBCs) indicative of bone marrow suppression was observed. In the long-term rat study, lymphoid hypocellularity was limited to thymus with grades of severity up to moderate. In cynomolgus monkeys, hypocellularity was limited to the thymus in single or few animals, mild in the bone marrow. The NOAELs were at no or low exposure marginals (x 0.68 to 1.87 in rats and 0.63 to 1.22 in cynomolgus monkeys) for lymphoid organ/tissue toxicity compared to that at the intended clinical dose of 150 mg/m^2. For bone marrow suppression, the NOAELs were at exposure marginals of x1.87- to 6.60 in rat and of x7 in cynomolgus monkeys. The follow-up *in vitro* myelotoxicity studies revealed a dose-related growth inhibition in both monkey and human progenitor cells, suggesting similar levels of myelosuppression in the different cell types.

Ocular findings were observed in monkeys, but not rats, and included single-cell necrosis of the retinal photoreceptors in the layer of the rods and cones at 60 mg/kg/day (3-month toxicity study) and in two 40 mg/kg/day animals (1-year toxicity study). However, in a follow-up ERG study, changes in terms of minimal decreases in the scotopic amplitudes were noted at 15 mg/kg/day followed with substantial decreases at 60 mg/kg/day. The effect on retinal conductivity was considered to represent potential perturbation of the function of the rod cells that would influence on night vision. The applicant proposes that as there was an only minimal influence on rod cell function at 15 mg/kg/day, the NOAEL for ocular toxicity be based on the findings observed in the 1-year study that is considered to be at 20 mg/kg/day corresponding to an exposure marginal of x 1.67 to 4.0 compared that in the clinic at the intended dose of 150 mg/m^2 BID.

Treatment-related effects in the kidney occurred in rats but not in cynomolgus monkeys. Microscopic findings included minimal or slight tubular mineralization and basophilia at ≥90 mg/kg/day in females in the 3-months study and interstitial mineralization and basophilia at ≥30 mg/kg/day in both genders. Treatment-related effects on urinalysis included, among others, altered calcium/phosphorous/ potassium/sodium/chloride excretion. The exploratory nephrotoxicity study in female rats confirmed the observed microscopic findings and additional necrosis and vacuolisation findings and the altered calcium excretion at 180 mg/kg/day.

Gastro-intestinal effects were observed only in cynomolgus monkeys and were consistent with diarrhoea (soft/water faeces) and loose stools in the 3-months study and microscopical changes (increased histiocytes in lamina propria) in the 1-year study. The NOAEL for the gastrointestinal effects were at low marginals (x1.22-to 1.67) compared to that at the intended clinical dose 150 mg/m^2 BID. Notably, diarrhoea and loose stools were frequently reported in clinical studies. However, in safety pharmacology studies, gastric emptying and intestinal transit were inhibited by lonafarnib (see pharmacology section).

Toxicity in adrenal glands was observed in male cynomolgus monkeys in the 1-year study and was consistent with increased organ weights and minimal/slight vacuolation in the zona fasciculata at 40 mg/kg/day. The NOAEL for toxicity in adrenal glands were 4-fold higher AUC exposure marginal compared to human exposure at 150 mg/m^2 BID.

Effects on the parathyroid were seen in female rats, which included cytoplasmic vacuolation at ≥90 mg/kg/day in the 3-months study, which was not reversible after 5 weeks of recovery vacuolisation in chief cells at ≥30 mg/kg/day in the 6-months study. Furthermore, cytoplasmic vacuolation and/or single-cell necrosis in chief cells of the parathyroid were observed at 180 mg/kg/day in the 1-month exploratory nephrotoxicity study in female rats. There were no exposure marginals (x 0.68) at NOAEL for parathyroid toxicity compared to human exposure at 150 mg/m^2 BID.

Toxicokinetic analyses were undertaken in all repeat-dose toxicology studies. Notably, in rats, plasma exposure was consistently higher in females than in males. In the 13-weeks study, the difference was 2- to 3- fold, and in the longer-term study, there was a 2- to 8-fold difference. There were no significant differences between the genders in cynomolgus monkeys. Notably, sex-related differences in some Lonafarnib PK parameters, including bioavailability and exposure, were observed in both rats, monkeys and humans (see pharmacokinetic section). In the 13-weeks studies, no Cmax values were provided, and no AUC values were presented at the end of the studies, e.g. day 91 (AUC exposure values from day 57 was presented instead). In the rat 13-weeks study, plasma AUC exposure was approximately 2-fold higher at day 57 compared to day 1, while the opposite was seen in the 13-weeks monkey study at the high-dose (60 mg/kg/day) with an approximately 3-fold decrease in plasma AUC exposure at day 57 compared to day 1. Generally, in the repeat-dose toxicity studies (except males in the 1-year monkey study) there was a tendency of over proportional exposure with increasing doses.

Two major metabolites (M26 and M33) have been identified in human plasma. As major metabolites may imply, a safety concern qualification of these metabolites should be assessed in toxicological studies. However, the applicant provides no information regarding the identification of any metabolites in toxicological studies.

2.5.3.3. Genotoxicity

A complete package of genotoxicity studies in agreement with the ICH S2(R1) guideline, including tests for gene mutations in bacteria, chromosomal aberrations in human lymphocytes, and micronuclei *in vivo* (mouse), has been conducted with lonafarnib. All tests were negative. Based on the results of the conducted genotoxicity studies, the overall conclusion is that lonafarnib does not have any genotoxic potential.

Five different experiments on lonafarnib in the bacterial reverse-mutation assay were conducted. Lonafarnib did not increase the number of revertants in any of the studies; the outcome was negative. It is not understood why the experiment was repeated 5 times. It is noted that different batches of lonafarnib were investigated.

Exposure in the *in vivo* test was not measured. No other study on the pharmacokinetic profile of mice was provided. Observations on marrow toxicity was observed in the study, indicating that the bone marrow was exposed. However, a weakness of the study is the lack of exposure measurements, which can be considered acceptable given the product charactereistics.

2.5.3.4. Carcinogenicity

Long-term carcinogenicity studies have not been conducted. The Applicant has stated that other regulatory authorities have requested a carcinogenicity study to be submitted post-approval. No further discussion was provided.

2.5.3.5. Reproductive and developmental toxicity

Studies were conducted to evaluate the standard reproductive and developmental toxicity profile of lonafarnib: a segment I 'fertility' in male and female rats, one segment II 'EFD' study in rats and one in rabbits, and one segment III 'prenatal/postnatal study in rats. The studies were stated to be GLP compliant, and the program is in accordance with ICH M3. In general, the studies are considered adequate and relevant for the evaluation of potential risk for humans.

Male and female fertility

The Applicant performed separate fertility studies in male and female rats. A pilot dose-finding combined male and female fertility study was conducted prior to the definitive studies.

In the pilot study, animals were administered lonafarnib at 30, 90, 120, 180 mg/kg/day. These doses were not tolerated by the female animals and animals were found dead or euthanized in moribund condition in the 90 and 180 mg/kg dose groups. No NOAEL could be established in the females, and the dose levels were reduced to 10, 30 and 60 mg/kg/day in the definitive study. For the male study, the same high dose level as in the pilot study was used in the definitive study; dose levels 30, 90, and 180 mg/kg/day.

In female rats, the administration started 2 weeks prior to mating through gestational day 7. Administration of lonafarnib in female rats caused resorptions and an increase in post-implantation loss. There were no effects on the mating performance or fertility parameters in female animals at the highest tested dose of 60 mg/kg. This was also concluded in the pilot study with doses up to 180 mg/kg/day. The NOAEL for maternal toxicity and F1 litters was considered 10 mg/kg/day, this was agreed. Exposure of lonafarnib was not measured in the study. In the 6-month repeat-dose toxicity study, a dose of 15 mg/kg/day in female rats corresponded to 0.7 times the exposure observed in patients, based on AUC.

Lonafarnib was administered 10 weeks prior to mating and through the cohabitation period in male rats. The administration of lonafarnib cause a dose-dependent decrease in fertility index and increase in both pre- and post-implantation loss. The NOAEL for the paternal toxicity and the F1 litters was 30 mg/kg/day. Exposure of lonafarnib was not measured in the study. In the 3-months repeat dose toxicity study, 30 mg/kg/day in male rats corresponded to 0.8 times the exposure observed in patients, based on AUC.

Embryo-foetal development

Embryo-foetal development was investigated in GLP studies in rats and rabbits. A pilot, dose-range finding study in each species was also conducted before the definitive studies.

In the definitive EFD-study in rats, the dose levels were reduced from 10, 30, 60, and 120 mg/kg/day in the pilot study to 5, 15, and 30 mg/kg/day due to 100 % early resorptions in the animals administered 60 and 120 mg/kg/day. Lonafarnib was administered during the period of organogenesis (GD6-17). Increased post-implantation loss was observed in the definitive study at the highest dose administered (30 mg/kg).

In the high dose group (30 mg/kg), administration of lonafarnib was related to uncommon findings such as red/black tab around the placenta, dark and/or swollen placenta, two of the foetuses had tissue connected to adjacent placenta, or an enlarged placenta were observed.

An increased number of visceral malformations was observed in the high dose group (30 mg/kg). The findings consisted of a convoluted ureter and dilated ureter. The applicant considered both findings as non-related to the treatment since the number of observations was high also in the control group and that the number in the treated group was close to the historical control. This is not agreed upon. While historical controls are important, the main control is within the study where animals, handling of the animals, and the environment are the same. Since the incidence of a convoluted ureter and dilated ureter is higher in the high dose group compared with both the study control group and the historical control group, it is not possible to exclude that these effects are related to treatment.

A supernumerary rib was observed in one foetus in the 15 mg/kg group and one in the 30 mg/kg group. In the control group, one foetus was observed with an absent rib. No other skeletal malformations were observed. Of the reported skeletal variations, an increased number of variations in the lumbar rib was observed in the high dose group. The finding was considered unrelated to the test item by the Applicant. It is, however not possible to exclude that this is a treatment-related effect, although the historical control data shows a higher number of affected litters.

The historical control data was collected between 1999 and 2004; the EFD study was conducted in 2004; the historical data could thus be considered representative.

The NOAEL was set at 15 mg/kg/day. Exposure of lonafarnib was not measured in the study. In the 6-month repeat-dose toxicity study, a dose of 15 mg/kg/day in female rats corresponded to 0.7 times the exposure observed in patients, based on AUC.

In the definitive EFD-study in rabbits, the dose levels were slightly reduced from 30, 90, and 180 mg/kg/day in the pilot study to 10, 40, and 120 mg/kg/day due to maternal toxicity at 180 mg/kg and increase in post-implantation losses at all doses. Lonafarnib was administered through the period of organogenesis (GD7-19).

In the high dose group (120 mg/kg) four animals were euthanized before the scheduled sacrifice. It is stated that it was due to observation of hairball in the stomach and that it was unrelated to the test item. There was no pathological report stating that the presence of a hairball was the cause of the assumed moribund status. It cannot be excluded that the moribund status was test-article related, also as inhibition of gastric emptying by lonafarnib was observed in a safety pharmacology study.

Increased post-implantation loss was observed in the definitive study at the highest dose administered (120 mg/k) but also at the lower dose levels, including the lowest level (10 mg/kg).

The placental findings observed in the rat study was not observed in the rabbit study.

There were no foetal external or foetal visceral findings that could be related to the exposure of lonafarnib. Skeletal malformations and variations were observed in all treated groups. Findings were observed in the cranium, thoracic and lumbar vertebra and hyoid wing.

The historical control data was collected between 1998 and 2003, the EFD study was conducted in 2003; the historical data could thus be considered representative.

No NOAEL could be established. The exposure following the lowest administered dose, 10 mg/kg, corresponds to 0.6 times the exposure observed in patients, based on AUC.

Prenatal and postnatal development

Lonafarnib was administered orally to pregnant rats during organogenesis, parturition, and lactation at doses up to 20 mg/kg/day. A decrease in body weight was observed in the F0 animals in the high dose group (20 mg/kg). There were no treatment-related effects noted in the F1 and F2 generations. The proposed maternal NOAEL of 10 mg/kg/day and ≥20 mg/kg/day for the F1 pups are accepted. The exposure or transfer to milk was not measured in the study. 14C-SCH-66336-derived radioactivity was transferred into the milk following a single oral dose of 30 mg 14C-SCH 66336/kg suspension. Compared to dam rats, nursing pups were exposed to low amounts of drug-derived radioactivity with a plasma AUC of 1.76%.

In the reproductive performance of the F1 generation, it was noted that the animals in the 20 mg/kg group had 4.0 days prior to mating, vs 2.6 in the control group. The applicant considers this not test article related since no effects on other parameters were observed (mating, fertility and conception indices). In historical control data, the mean number of days prior to mating has been between 1.8 and 4.7.

Juvenile toxicity

No juvenile toxicity studies were conducted, although lonafarnib is intended for children. The lack of juvenile toxicity studies has previously been agreed upon. In addition, the age of the animals in the toxicological studies corresponded to human ages from approximately 12 years and older and did not cover the ages of the intended paediatric patients (from 12 months and older).

2.5.3.6. Other toxicity studies

No studies have been conducted with lonafarnib regarding local tolerance, antigenicity, immunotoxicity, dependence, and metabolites. This is considered acceptable.

Impurities

Compound W is a manufacturing intermediate and also a degradation product of the lonafarnib drug substance and is observed in stability studies of the drug product. The potential genotoxicity of Compound W was investigated in a micronucleus assay in mice.

Compound W was together with two other impurities of Lonafarnib drug substance investigated in a repeat dose toxicity study in rats. The impurities with proposed specification limits were compound W (≤1.4 %), Des-10-bromo (≤0.30 %), and chiral impurity (≤2.0 %).

Ethylbenzene is used in stage 1 of the lonafarnib drug substance manufacturing procedure. A toxicological evaluation to justify the set threshold of 273 ppm was provided.

Five genotoxic impurities have been identified (Compound II, JJ-4a, JJ-4b, JJ-5a, and JJ-5b). Specifications are adopted at 20 ppm, based on TTC value of 30 µg/day intake for >1 to 10 years.

Phototoxicity

Lonafarnib gives a UV spectrum with a peak maximum at approximately 295 nm. Although the molar extinction coefficient at the peak at 295 nm is not specified, it does not seem likely that it would exceed 1000 L mol^{-1} cm^{-1}, and can thus be considered not sufficiently photoreactive to result in direct phototoxicity.

2.5.4. Ecotoxicity/environmental risk assessment

Lonafarnib PEC surface-water value is below the action limit of 0.01 µg/L.

The log Kow is >4.5, and further assessment of persistence, bioaccumulation, and toxicity is necessary. The tests outlined in Phase II Tier A should be performed in the order persistence-bioaccumulation-toxicity.

The Applicant has provided an assessment that was not based on eco toxicological data. Instead, the assessment relies on QSAR data and discussion on the toxicological studies. The Applicant concludes that lonafarnib should be treated as a PBT substance and that further definitive testing is not required due to the ultra-rare indication with potentially very few patients in the EU. This is not acceptable. Due to the persistence, bioaccumulation, and ecotoxicity of a PBT substance, an accumulation in the environment and in biota with possible long-term effects cannot be excluded, regardless of the predicted environmental concentration. The Applicant is asked to perform an experimentally PBT assessment for lonafarnib in a step-wise procedure for persistence (OECD 308) - bioaccumulation (OECD 305) – toxicity. The Applicant has committed to conduct the requested studies. The results will be submitted post-approval as soon as possible but no later than the end of 2025.

2.5.5. Discussion on non-clinical aspects

Pharmacology

Most of the documentation in the non-clinical file originate from previous development for oncology indications, which were not conducted by the Applicant. As a result the data are quite old and descriptions very brief in parts. This is especially true in the section on non-clinical pharmacology, where in the initial application, no studies on *in vivo* models of progeria had been conducted with Lonafarnib. Instead, data on progeria models with other farnesyltransferase inhibitors were presented and supplemented with data from *in vivo* studies with lonafarnib in an oncology model. However, during the procedure, the Applicant provided additional results from a prepublication by Yale university, deriving from a study with lonafarnib in a mouse model of Hutchinson-Gilford Progeria Syndrome.

Primary pharmacodynamics

The IC50 of 1.9 nM, obtained from the biochemical inhibition test of human farnesyl protein transferase (FPT) with farnesylation of H-Ras-CVLS, was sufficient in order to progress further into cellular and *in vivo* studies. However, *in vitro* studies have not been conducted to compare the potency of lonafarnib for farnesyl protein transferases across species. The lack of *in vitro* potency comparison between species was justified by referring to data showing that the amino acid sequence was highly conserved between humans and the relevant nonclinical species rat, mouse, rabbit and monkey. Given the high degree of high amino acid sequence identity, the Applicant anticipated a low likelihood of marked differences in potency. This is considered acceptable.

The ability of lonafarnib to dose-dependently reduce nuclear blebbing in a cellular assay with progerin transfected HeLa cells or HGPS dermal fibroblasts is encouraging since the progerin accumulation in HGPS typically is associated with such a disturbing nuclear architecture thought to be involved in the cause of the clinical manifestations of HGPS and the related forms of PL. In addition, it was found that progerin is not alternatively geranylgeranylated when farnesylation is inhibited. This was in contrast to some other substrates of farnesyl transferase, K- and N-Ras, that, upon treatment with FTIs, are alternatively prenylated by geranylgeranyl transferase-1. The importance of this finding is agreed. Supportive data on additional patient-derived fibroblast cultures from HGPS and PL is also presented in reports (John Hopkins and Wuxi) in the clinical documentation. In response to a question, it was substantiated that the cellular materials used in the study by Capell *et al.* (2005) and the John Hopkins and the Wuxi studies were not obtained from HGPS patients in clinical study Prolon1 or Pronlon2. However, cellular material from two patients with processing mutations, 4371 (PSADFN318) and 4729

(PSADFN317), deriving from the 09-06-0298 study (Group 1), was included in both the Johns Hopkins and Wuxi studies. Mutation details, participation in clinical studies and outcome were provided for these two patients.

During the procedure, the Applicant provided additional results by Yale university, which shows non-clinical proof of concept, i.e. how lonafarnib in a mouse model of Hutchinson-Gilford Progeria Syndrome prolonged survival and improved cardiovascular function. Before these results were provided, no studies on *in vivo* models of progeria had been conducted with Lonafarnib. Instead, data from *in vivo* studies with lonafarnib in an oncology model was presented. Lonafarnib demonstrated anti-tumour activity in a dose-dependent manner in the xeno- and syngeneic tumour models in nude mice that were transplanted with human carcinoma cell lines containing mutated K- or H-ras isoforms. The value of these studies in bridging lonafarnib from *in vitro* to *in vivo* efficacy is agreed. However, it should be noted that the value of mouse tumour models with long-term cultured cell lines is of limited value when estimating the effect within the oncology field. In other words, human cell lines that have been through several passages and cultured for a long-term may have changed over time, including in the pathway of interest.

In light of the sparse clinical data due to the extremely rare disease (HGPS and PL), there is encouraging *in vivo* pharmacology data (Fong *et al.*, 2005) on the FTI ABT-100. The use of ABT-100 to support the *in vivo* proof of concept was justified by its similarity to lonafarnib. The pharmacokinetics of lonafarnib and ABT-100 appear to be comparable as determined from exposure after a similar oral dose; however, the ABT-100 is 20 times more potent (0.05 vs 1.9 nM). Therefore, the relevance of the data based on treatment with ABT-100 as initial non-clinical proof of concept for the less potent lonafarnib was questioned. Thus, before the study with lonafarnib on LmnaG609G/G609G mice was provided, non-clinical *in vivo* proof of concept of the efficacy of lonafarnib itself was considered missing. However, with the additional data showing prolonged survival and improved cardiovascular function in a mouse model of progeria, the clinical efficacy of lonafarnib is considered supported by non-clinical data.

In ZMPSTE24-deficient mice, in the study by Fong *et al.* 2005, the ZMPSTE24-deficiency should lead to the inability to cleave off the farnesylated end from lamin A, leading to accumulation of progerin in the nuclear lamina. The progerin accumulation results in disturbed nuclear morphology (blebbing). By treating with FTI (ABT-100), the production of farnesylated lamin A should be reduced, leading to a reduction of progerin accumulation in the nuclear membrane and thus, less blebbing. If it is true, the disturbed nuclear membrane is linked to the other phenotypic changes observed in this mouse model; it is surprising that the observed normalizations of, e.g. grip strength, bone abnormalities and mortality, were not directly associated with the observed degree of disturbed nuclear morphology. However, the ZMPSTE24-deficient mice treated with FTI did not display a complete elimination of diseased phenotype, which the Applicant suggests can play a role in the absence of direct association between improved nuclear morphology and phenotype improvements. The Applicant also clarifies it is not claiming that treatment with lonafarnib produces a direct and measurable relationship between the degree of reduction in misshapen nuclei and the magnitude of improvement in the signs and/or symptoms of Progeria. Due to the complexity provided by the broad and diverse roles lamin A plays in cellular functions, there are challenges associated with linking the degree of nuclear deformity and phenotype severity. It is also possible that phenotype severity is influenced by more than the deleterious effects of prelamin A or mutant variants on nuclear shape, potentially explaining why mutations affecting the same pathway result in different clinical phenotypes. Additionally, nuclear morphology in fibroblasts does not necessarily represent precisely what is going on in tissues. Furthermore, the Applicant put forward that in their Progeroid Laminopathy White Paper, there is clearly a correlation between phenotypic improvement with lonafarnib treatment in humans and decreased numbers of fibroblasts with abnormal nuclear morphology. Similar observations are made in

previously published studies of other fanesyltransferase inhibitors in ZMPSTE24-deficient mice and cultured fibroblasts from the same animals. The Applicant suggests that improved nuclear morphology is a proven marker for FTI's beneficial effects on animals, including humans.

From the study of the cardiovascular disease in a transgenic C608G LMNA mouse model of progeria the Applicant concluded, these data indicate that tipifarnib can improve the cardiovascular phenotype when treatment is initiated at weaning; the significantly improved cardiovascular parameters are suggestive of disease regression in this HGPS mouse model that mimics human vascular disease; and the nearly normal phenotype is indicative of the fact that FTIs may induce disease regression in mice that already manifest phenotypic changes with early treatment. It is agreed, that these data generated with tipifarnib are encouraging, supporting a pharmacodynamic FTI effect on a progerin accumulation induced cardiovascular damage similar to what is observed in HGPS.

From the study on the Hepatitis D Virus (HDV) model, carried out with two prenylation inhibitors FTI-277 and FTI-2153, the Applicant concludes that it is expected although not examined in this study that Lonafarnib would show similar effects as other prenylation inhibitors based on a common mechanism of action. It is agreed that this may not be an unlikely scenario, considering the demonstrated anti-viral effect by Lonafarnib *in vitro*. However, it is acknowledged, an *in vivo* effect by treatment with lonafarnib in this model has not yet been shown.

Secondary pharmacodynamics

Inhibition of farnesyltransferase by lonafarnib could potentially impact other farnesylated proteins. In general, these proteins tend to be involved in the promotion of cell growth and division, except for the HDJ proteins, which serve as co-chaperones and stimulate the ATPase activity of Hsp70; RRP22, which inhibits cell growth; and the prostacyclin receptor, which plays a negative role in platelet aggregation and vasodilation. Given the functions of farnesylated proteins in cell growth and division, potentially clinically relevant effects would be on proliferating cells, such as those in the bone marrow (a known effect for this class of compounds). In addition, there are local effects on the gastrointestinal system. The most frequent adverse events observed with lonafarnib, as mild diarrhoea, fatigue, nausea, vomiting, and depressed serum haemoglobin, may be related to the bone marrow or gastrointestinal tract. Therefore, some of the most frequently seen adverse events may theoretically result from the inhibition of cell proliferation in these tissues.

Safety pharmacology

The safety pharmacology of lonafarnib was evaluated by targeting a range of endpoints, which is appreciated. However, only the dog Purkinje fibre study (Quintiles, SN 02160) appeared to be conducted under GLP compliance. The CNS and hERG assays were not conducted under GLP compliance as required in current guidelines since these studies were performed at the time prior to ICH S7A finalization, and therefore, GLP compliance cannot be expected.

Regarding safety pharmacology, there is no clear signal of QTc prolongation for the cardiovascular system from the non-clinical studies, while in the clinic, QTc prolongation has been observed. It is not known if lonafarnib affects other cardiac ion channels (e.g. NaV 1.5) that could explain the findings in patients. There were no lonafarnib related effects of concern on the nervous system observed in safety pharmacology experimental models.

No stand-alone safety pharmacology study was performed regarding respiratory function, which is not according to the current guideline since lonafarnib is not a highly selective biotechnology product. However, the assessment of respiratory safety pharmacology for lonafarnib was also conducted prior to the finalization of ICH S7A (2000) [CPMP/ICH/539/00]. Therefore, when this study was conducted, it was considered an appropriate option to evaluate this endpoint by including an assessment of respiratory function through the measurement of respiratory rate in the design of the GLP repeat-dose

toxicity studies in monkeys. This is acknowledged. Moreover, no abnormalities were observed in respiratory function in patients over the treatment period.

A pharmacokinetic evaluation was not performed in any of the *in vivo* safety pharmacology studies conducted with lonafarnib. This is a clear weakness for the interpretation of data and e.g. establishing exposure margins. However, based on measurements from the toxicity studies, the calculated margins to clinical exposure was x7 for the gastrointestinal effects, with the same dose (and calculated margin), no effect on the nervous system was observed. No effect on respiration rate was observed at 5-6 times the clinical Cmax.

It should also be noted that there is a question regarding two major human metabolites (M26 and M33) in the pharmacokinetic section. It is currently not known whether these metabolites are of relevance regarding safety pharmacological considerations.

Non-clinical pharmacodynamic drug interaction studies have not been conducted and were not warranted since off-target screening did not reveal any concern for pharmacodynamic interactions.

Pharmacokinetics

Relevant non-clinical studies to characterise the absorption, distribution, metabolism and excretion of Lonafarnib and its major metabolites were performed in non-clinical species. The bioanalytical methods used for quantification of Lonafarnib in plasma in the pivotal toxicity studies of rats, rabbits and monkeys were stated to have been validated according to GLP requirements. The bioanalytical HPLC-UV methods used for quantification of Lonafarnib in plasma in the pivotal toxicity studies of rats, rabbits and monkeys (i.e. Studies SN02160, SN96030, SN96612, SN96034, SN96036, SN94046) are claimed to have been validated according to GLP standard. However, it is unclear if the method validations included in these study reports were formally performed under GLP. The Applicant was asked to provide information on the GLP aspects in the above-mentioned studies and discuss the potential impact on the TK analysis of the samples collected from these GLP studies. The applicant confirmed in the response that all plasma sample bioanalyses across all pivotal toxicity studies were conducted according to GLP regulations using validated methods. Thus, there was no potential impact on the TK analysis of samples collected in the GLP studies.

Furthermore, no validated GLP compliant bioanalytical methods were developed for plasma exposure measurement of Lonafarnib in the definitive rat embryofoetal development (EFD) study (SN02292) and in the definite rat pre- and postnatal development toxicity (PPND) study (SN96047). This is understandable since no samples for analysis were obtained in the studies. Thus, no TK analysis has been performed in these two pivotal toxicity studies. The Applicant was asked to justify the absence of TK assessment in these pivotal toxicity studies and discuss the possible consequences for the non-clinical safety evaluation of Lonafarnib. The Applicant responded that although exposure data in pregnant rats were not obtained in the pivotal rat reproductive toxicity studies for lonafarnib (SN02292, SN96047), exposure data are available from the GLP, 6-month toxicity study in rats at the same or similar dose levels as tested in the rat reproductive toxicity studies (see exposure data in the table below). As surrogate TK data are available to provide a comparative assessment of exposure, the lack of TK data in pregnant animals has a limited impact on the overall non-clinical safety evaluation of lonafarnib.

Table 3: Supporting TK Data for Pivotal Rat Reproductive Toxicity Studies

Study Type (Study No.)	Doses Tested (mg/kg/day)	Maternal NOAEL (mg/kg/day)	Exposure (AUC_{0-24}) Data from 6-Month Rat Toxicity Study (Day 176; SN96034)	
			15 mg/kg/day	30 mg/kg/day
EFD (SN02292)	5, 15, or 30	≥30		M:19.0 µg•h/mL F:46.1 µg•h/mL
PPND (SN96047)	5, 10, or 20	10	M:2.31 µg•h/mL F:14.1 µg•h/mL	

AUC=area under the plasma-concentration time curve; EFD=embryo-fetal development; NOAEL=No-Observed-Adverse-Effect Level; PPND=pre- and postnatal development; TK=toxicokinetic.

Absorption, distribution, metabolism and excretion

The absorption of Lonafarnib was studied *in vitro* in Cacao cells and *in vivo* after single oral and intravenous dosing to rats and cynomolgus monkeys. Oral dosing is the intended route of administration in patients. There were clear sex-related differences in some PK parameters, including bioavailability and exposure in both rats and monkeys. For example, the mean plasma concentration and exposure were 3.3- and 5.5-fold greater in female than male rats following oral dosing of [14C]-Lonafarnib (30 mg/kg). Following IV administration of [14C]-Lonafarnib (5 mg/kg), the clearance was 2.66-fold faster in males, and the half-life was longer in female rats than in male rats (2.38 and 1.54 hours, respectively), and exposure (AUC) was 2.6-fold higher in female rats. In addition, following repeat oral dosing in rats, the exposure was noticeably higher in females than males after 3- and 6-months of daily administration (see TK data in toxicology section). The effect of gender on the Lonafarnib PK profile following oral administration in men was also assessed in healthy subjects in a clinical study (Study P02673). The AUC0-inf of lonafarnib was significantly higher (44%) in females as compared with males, whereas Cmax values were approximately 26% higher in females. The Applicant states that this difference is likely due to the faster clearance rate and the shorter half-life in male animals.

The tissue distribution of Lonafarnib in pigmented rats and cynomolgus monkeys was determined following oral administration of [^{14}C]-Lonafarnib. In the monkey WBA study, one animal was sacrificed at 4 hours and another after 28 days (SN00039). On Day 28, moderate levels of drug-derived radioactivity remained in the retina and liver, and low levels were detected in the adrenal gland, bone marrow, gall bladder, harderian gland, myocardium, GI wall, kidney, lymph node, salivary gland, skin, spleen, and stomach wall, indicating prolonged retention of ^{14}C-Lonafarnib in these tissues. Moreover, only 78% of the administered dose was recovered at this time point. The Applicant was asked to discuss the possible mechanism of retention of radioactivity in these tissues and potential clinical relevance since the human AME study (P00260) also showed low recovery. The Applicant explained that the low recovery in the exploratory WBA study (SN00039, N=1) could be attributed to a more qualitative method of analysis as compared to the main WBA study (SN96559) in which >90% recovery was obtained. Therefore, this is considered a plausible explanation.

In a phototoxicity study, Lonafarnib did not absorb light within the range of natural sunlight (290-700 nm), indicating that Lonafarnib has a low potential for phototoxicity (see toxicology section). However, ocular toxicity findings were observed in the monkey following repeat oral dosing of Lonafarnib, yielding low exposure margins to the clinical exposure of Lonafarnib at the proposed human dose (see toxicology section).

The Applicant states that Lonafarnib is secreted into the milk of lactating rats. However, no such data can be located. The Applicant was asked to submit the study report describing the Lonafarnib concentrations in milk. The Applicant submitted data concerning the transfer of drug-related activity

into milk in rats to support the wording in section 4.6 of the SmPC. The data indicate that 14C-SCH 66336-derived radioactivity was transferred into the milk of lactating, 12-day postpartum (dam) rats following a single oral dose of 30 mg 14C-SCH 66336/kg suspension. Nursing pups were exposed to low amounts of drug-derived radioactivity with a plasma AUC of 1.76% compared to dam rats.

The metabolite profile of Lonafarnib was determined in mouse, rat, monkey, and human hepatocytes *in vitro* and in rats and monkeys following oral dosing *in vivo*. The most common metabolic pathways across species, including humans, included oxidation, dehydrogenation, and/or a combination of these two processes, and the majority of metabolites across all species were associated with changes in the region of the pendant piperidine ring. However, there are no data on *in vitro* metabolism of Lonafarnib in the rabbit. Since the rabbit is used in embryo-foetal developmental (EFD) studies, these data may be of importance. The Applicant was initially asked to justify why no metabolism data in the rabbit had been presented. Whereas the Applicant acknowledged that *in vitro* metabolism data in rabbits is potentially supportive, such data are not considered critical for evaluation of the results obtained with rabbits in the non-clinical toxicity program. Lonafarnib has been shown to be pharmacologically active in rabbits, and the TK profile was similar across species, including rabbits, rats and monkeys. Therefore, the justification for the lack of metabolism data in rabbits is acceptable.

No human specific metabolite appears to have been detected *in vitro* or *in vivo* studies. Two major metabolites, M26 (MM33; RM25; SCH 629153) and M33 (MM38; RM30; SCH 441746), were identified in human plasma. M26 was formed by adding oxygen to the pendant piperidine ring, and M33, was formed by dehydrogenation, representing 15.1% and 13.9% of total plasma radioactivity detected 8 hours post-dose in humans, respectively. As major metabolites may imply, a safety concern qualification of these metabolites should be assessed in toxicological studies. However, the Applicant initially provided no data regarding identifying any metabolites in the toxicity studies. In response to this question, the Applicant provided estimated exposure data for Lonafarnib and the two major human metabolites, M26 and M33 in rats and monkeys. The calculated exposure margins were lower in rats than in humans, with margins of 0.43 to 0.50 and approximately 0.19 for M26 and M33, respectively. In monkeys, on the other hand, exposure to major human metabolites was slightly higher than that in humans, with exposure margins of 1.11 to 1.18 and 1.33 to 1.47 for M26 and M33, respectively. The two major human metabolites, M26 and M33, have been sufficiently qualified in the pivotal repeat-dose toxicity studies, including monkeys. In the rat toxicity studies, mainly the M33 is lower than 50% of the human exposure. Since monkeys were not used in the pivotal EFD studies, the low exposure of M33 in rats is uncertain which may impact the results and conclusion of the reproductive toxicity studies. However, since Lonafarnib has shown reproductive toxicity in animals, demonstrating teratogenic potential at clinically relevant exposures, the current recommendation in section 4.6 of the SmPC is considered sufficient.

In summary, the overall non-clinical pharmacokinetic characterisation of Lonafarnib is considered acceptable.

Toxicology

The Sprague Dawley rat and cynomolgus monkey were selected as the main rodent and non-rodent species in the general toxicity studies. Sprague Dawley rat and New Zeeland White rabbits were selected for reproduction and developmental studies. The Applicant has not provided a detailed justification of the selected species but shortly commented that the selection was based on the pharmacological relevance of the target and the pharmacokinetic profile. Therefore, the Applicant was in the first round of the procedure, asked to provide a thorough discussion to further justify the selection of the chosen species for the toxicological program. The Applicant described that farnesyl protein transferases are highly conserved across species and anticipate that the same is true for the pharmacological activity. While this is possible, no supporting data was presented. The observations in

the toxicological studies have not been described as pharmacological effects. The Applicant further claims that the pharmacokinetic profile supports the selected species as relevant. However, no comparison to the pharmacokinetic profile in humans was made. The issue is not further pursued.

The Applicant has provided a comparison of animal and human systemic exposure. Human AUC values used for the interspecies comparison are based on AUC0-12h from an article by Gordon *et al.* 2012, whereas the animal AUC values from the repeat-dose studies are based on AUC0-24h. When comparing animal AUC0-24h values with human AUC0-12 values, it provides an incorrect picture of the real ratio of animal to human exposure. Therefore, the Applicant was asked to recalculate the interspecies comparison using human AUC0-24 values and discuss the new animal to human exposure ratios, especially regarding the adequacy of the exposure margins or provide an acceptable justification for the current strategy. The Applicant has provided recalculations of the previously presented exposure margins. Generally, the recalculation reduces the exposure margins of 40%, and it should be clearly stated that ratio values < 1 represent a lack of exposure margins to human clinical exposure.

Single-dose toxicity

Both the single-dose oral gavage studies and the IP injection studies in mice was conducted twice. The two oral gavage single-dose studies in mice (SN97266 and SN96027) appear to be identical, and the two IP single-dose studies (SN96028 and SN97267) only appear to differ by the exclusion of the 200 mg/kg dose group in the second IP study conducted (SN97267). In the first single-dose IP study (SN96028), extremely high mortality was observed in the 1000 mg/kg and 600 mg/kg dose groups (10/10 and 8/10, respectively); however, these doses were still included in the second repeated IP study (SN97267), whereas, the 200 mg/kg dose determined as the NOAEL was excluded. Additionally, no discussion comparing the results from the different studies were provided, even though discrepancies in the reproducibility of the study results concerning NOAELs in the oral gavage studies and NOAELs, MTDs and LD50s in the IP studies were noted. During the procedure, the Applicant was asked, from a 3R perspective, to justify a) the reason for repeating the oral gavage study and b) the choice of IP route for administration when the intended clinical route is PO and the selection of doses for the second IP study conducted.

Additionally, a discussion of the potential reasons for the differences in NOAELs, LD50s and MTDs values in the studies should be included**.** The Applicant emphasised that the single-dose studies were conducted by Merck (Schering), and Eiger, therefore, has limited information regarding study design and conduct. The Applicant has, therefore, only sparsely addressed the issues. The repetition of the oral gavage study in mice was assumed to be related to GLP issues, whether the repetition of the IP study was more unclear. The choice of IP as the route of administration in two studies was suggested to support the mouse micronucleus assay (Study SN 96049) and potential efficacy models, which is considered a plausible explanation. The requested discussions on the difference in NOAEL, LD50 and MTD values were brief. However, as single-dose toxicity studies are not pivotal for approval of the MAA and the Applicant only seems to have limited information regarded these studies, there does not seem to be any point in further pursuing these issues.

Repeat-dose toxicity

In repeat-dose toxicity studies, multiple organs/tissues were affected. Primarily, these included liver, male reproductive organs (testes and epididymides), lymphoid organs/tissues, haematopoietic system (bone marrow) and immune organs but also female reproductive organs, gastrointestinal system, eye, adrenal glands and parathyroid. No NOAEL could be established in any of the studies. Most of the toxicity occurred at no or very low exposure marginals compared to that in the clinic, with the intended dosing at 150 mg/m^2 BID.

In the 3-months oral gavage study in rats, findings suggestive of renal toxicity and/or altered calcium/phosphorus metabolism, reabsorption, and/or excretion were observed. The Applicant was asked to discuss further the consequence and clinical relevance of these findings, especially the altered calcium/phosphorus homeostasis.

Evidence of renal toxicity and altered calcium/phosphorus metabolism were seen at doses ≥30 mg/kg/day in the 6-month rat study. The NOAEL for kidney toxicity in rats were therefore 15 mg/kg/day in both sexes, with the end of study AUC_{0-24} of 2.31 µg•h/mL in males and 14.1 µg•h/mL in females. This should be compared to a mean human AUC_{0-24} of 36 µg•h/mL, corresponding to exposures of ~ 0.06-to 0.39-fold, respectively, concluding that renal toxicity in rats was detected at exposures much lower than clinically relevant exposure. Even though nephrotoxic changes were not seen in the monkeys, the rat findings could potentially indicate a clinically relevant effect on kidney and bones in humans. This was, however, according to the Applicant, sufficiently addressed in the clinical studies (ProLon1 and ProLon2 combined group) where no clear or consistent pattern of changes in clinical chemistry measures from baseline to the end of therapy suggested an adverse drug effect on kidney function or bone. However, low alkaline phosphatase was detected in two patients (3.2%), and two patients (3.2%) showed high calcium.

Mortality occurred in two monkeys and two rats after treatment with lonafarnib at doses corresponding to 3.3 and 21-fold higher exposure, respectively, compared to the intended clinical dose of 150 mg/m^2. In the first round of the procedure, the Applicant was asked to further discuss the mortality in cynomolgus monkeys in relation to the low exposure marginals and potential consequences for the clinic. In response, the Applicant described that the acute morbidity of these two monkeys given 60 mg/kg/day (720 mg/m2/day) was caused by loss of blood (haemorrhages in multiple organs attributed to severe thrombocytopenia), hypovolemia, and stress. Clinical pathology and necropsy findings in these moribund monkeys were generally consistent with those expected with dehydration, diarrhoea, blood loss, exudative loss, and stress. The Applicant argued that the mortalities observed in monkeys are of low consequence for humans since preventive measures are available to preclude the development of consequences for GI-related effects. This part is acceptable. The Applicant did not further discuss the mortality in cynomolgus monkeys in relation to the low exposure marginals and potential consequences for the clinic but points out that haemorrhage in multiple organs was observed in the deceased monkeys. This finding has been included in the SmPC.

In both rats and cynomolgus monkeys, toxicity occurred in the liver characterised by hepatic dysfunction and a pathologic response to increased metabolic stress through enzyme induction, increased weight, hypertrophy and vacuolation with no exposure marginals at NOAEL. Notably, altered liver enzymes levels have been monitored after lonafarnib treatment in the clinic.

Male reproductive organs (testes and epididymides) were affected in both rats and cynomolgus monkeys after administration with lonafarnib for 3 months or 1 year, respectively. Generally, the toxicity included decreased testes weight and atrophy, aspermia or oligospermia and spermatogonial debris with apparently profound effects on fertility as observed in the rat FEED study. No specific studies regarding the potential mechanism behind the observed toxicity in male reproduction organs have been conducted. The Applicant has, however, provided a discussion regarding the potential mechanisms behind the toxicity. In the scientific literature, studies suggest that the inhibition of farnesyl protein transferase and subsequent farnesylation of proteins at the C-terminal CaaX box are likely to have downstream effects on male reproductive health. Also, the inhibition of pathways studied in cancer cells, namely that lonafarnib prevents the farnesylation of ras proteins and other farnesyl transferase substrates, such as the nuclear centromere-associated proteins CENP-E and CENP-F, the nuclear lamin prelamin A, the co-chaperone protein HDJ-2, may also have implications for male reproductive health. Thus, at least two pathways have been discussed as mechanisms behind the toxicity observed in male reproductive organs. It is possible that both pathways can be involved. The

clinical implications were only very briefly discussed. At present, it is not known if treatment with lonafarnib has any impact on pubertal development or fertility in humans.

Ocular findings of single-cell necrosis of rods and cones in the retina were observed in the monkeys but not in the rats. A mechanistic electroretinography (ERG) study in monkeys concluded that the extent of the changes corresponded to an impairment of night vision. Furthermore, clinical signs of GI disturbances were noted in both species but especially pronounced in the monkeys.

Toxicokinetic analyses were undertaken in all repeat-dose toxicology studies. In both the 3-months and 6-months repeat-dose study in rats, a difference in systemic exposure between males and females, with a consistently higher systemic exposure in females, were observed. The difference in exposure corresponded to sex-dependent metabolic differences observed in rats related to the expression of hepatic enzymes with approximately a 10-fold greater level of expression of sex-specific cytochrome P450s such as CYP2C11, CYP2C13, and CYP3A2. As lonafarnib is primarily metabolized by CYP3A, it is likely that the differences seen in exposure in rats for lonafarnib could be attributed to hepatic enzyme expression. According to the Applicant, a similar picture was also seen in humans, where a higher exposure was detected in females compared to male patients.

In the rat and monkey 13-week-studies, no exposure was presented at the end of the studies (day 91). Exposure data were presented on days 1 and 57. The Applicant argues that a steady-state was achieved, and the potential effects on CYP enzymes would be similar. Since the exposure margins to clinical exposure in most of the studies were below 1, the representativeness of the day 57 data is considered acceptable.

In humans, two major metabolites (H17/M26 and HM21/M33) have been identified. The metabolites were tested for farnesyl transferase inhibition, and HM21/M33 was found to have pharmacological activity similar to that of the parent drug (lonafarnib). No secondary pharmacodynamics studies have been conducted for the H17/M26 metabolite since it cannot be stably synthesized. However, the Applicant provided initially no information whether plasma exposure of the two human major metabolites has been assessed in pivotal toxicological studies. In response to this question, the Applicant submitted estimated exposure data for Lonafarnib and the two major human metabolites, M26 and M33, in rats and monkeys (see details in the Pharmacokinetics section above).

Genotoxicity and carcinogenicity

Regarding genotoxicity, the *in vivo* study (Mouse micronucleus test), was performed at dose levels corresponding to doses lower than the clinically relevant doses.

Following the Scientific Advice (EMA/CHMP/SAWP/25263/2019), no carcinogenicity studies are considered needed before marketing authorisation approval. Based on the available data, lonafarnib is not considered genotoxic, and no preneoplastic lesions were observed in repeated dose toxicity studies within the tested dose regimen. Furthermore, the 26-week rat study findings indicate that exposures around or below the intended clinical exposure would be suitable in a study of longer duration. Given the lack of apparent concerns and based on the limited life expectancy of the patients and the feasibility of conducting a long-term animal study, carcinogenicity studies are also not considered needed post-approval. The Applicant has however accepted the request from other regulatory authorities to conduct a carcinogenicity study and will submit the results of the CARC studies no later than the first quarter of 2024.

Reproductive and developmental toxicity

In the embryo-foetal development study in rats in the high dose group (30 mg/kg), administration of lonafarnib was related to uncommon findings such as red/black tab around the placenta, dark and/or swollen placenta, two of the foetuses had tissue connected to adjacent placenta, or an enlarged

placenta were observed. There is no explanation for these findings. The placental findings were not observed in the rabbit study. In the first round of the procedure, the Applicant was asked to discuss possible mechanisms for these findings. The Applicant has presented possible explanations for the placental findings in the rat as reviewed by Furukawa *et al.* No discussion on a possible mechanism based on the pharmacological effect of lonafarnib was provided. At the same dose at which these placental findings were observed, the increased post-implantation loss was observed. Furthermore, an increased number of visceral variations were observed. The Applicant's conclusion that there was no correlation with foetal development is thus not agreed upon. Although no clarification of the placental findings can be expected at this stage, the totality of data remains to support the recommendation that lonafarnib is not recommended in pregnancy and in women of childbearing potential not using effective contraception.

In section 4.6 of the SmPC, upon request by the CHMP, the Applicant has included a recommendation and justification regarding how long after the final dose effective contraception should be used. The Applicant initially proposed that effective methods of contraception should be used 3 months after cessation of treatment in females of childbearing potential and sexually active males. The justification was based on data from male studies only. The proposed time for effective contraception for males is acceptable. For women, a shorter period should be recommended. There were no effects on the mating performance or fertility parameters in female animals in the fertility studies in rats. Furthermore, in healthy adult volunteers, the t1/2 was 5.6 h after 75 mg of lonafarnib, twice daily for 5 days. The PK appears similar in healthy volunteers and the patient population although the predictive performance of the model is poor. Despite the uncertainties, the t1/2 of 5.6 h could be used to estimate a relevant time period after dosing during which effective contraceptives are recommended. Thus, one week is deemed a sufficiently safe margin to ensure no remaining lonafarnib residues at the time of a potential conception.

No juvenile toxicity studies were conducted, although lonafarnib is in this application intended for children. The lack of juvenile toxicity studies has previously been agreed upon. In addition, the age of the animals in the toxicological studies corresponded to human ages from approximately 12 years and older and did not cover the ages of the intended paediatric patients (from 12 months and older). As requested by PDCO and in a previous scientific advice the Applicant has discussed the target organs of particular relevance to children, the liver, kidney testicles and retina. Further discussion provided upon request in the first round of the procedure did not include any specific discussion regarding developing organs. Since farnesylated proteins are involved in cell growth and division, potentially clinically relevant effects would be on proliferating cells.

Impurities

Lonafarnib with 1% of compound W was investigated in the *in vivo* micronucleus assay in mice. An increase in micronucleated polychromatic erythrocytes was observed in female animals. The Applicant considers these findings not likely to be test article-related. The conclusion that the study outcome was negative is acceptable since the results were not reproducible in independent scoring of replicate slides. It is, however, not agreed that, based on the provided information, Compound W could be considered non-genotoxic. In the conducted study, Compound W was only 1% of the administered test item. To better investigate the genotoxic potential of Compound W, the substance itself should have been tested and preferably in a bacterial reverse mutation assay. The quality section of the file states that Compound W is non-mutagenic according to ICH M7 compliant QSAR test. The QSAR analysis report was submitted upon request in the first round of the procedure. The assessment included a statistical and an expert-rule based methodology. It is agreed that Compound W can be considered non-mutagenic.

The repeat-dose toxicity study in rats investigated a mixture of the drug substance impurities Compound W, Des-10-bromo and chiral impurity for daily oral gavage dose for 28 days. The high-dose mixture was considered the NOAEL, which is accepted.

The high-dose group received the following amounts of the impurities:

Compound W, 0.613 mg/kg/day

Des-10-bromo, 0.131 mg/kg/day

Chiral impurity, 1.758 mg/kg/day

The Applicant has provided a clarification on how the investigated doses in the toxicity study correlate with the proposed qualification levels of Compound W, Des-10-bromo, and chiral impurity. From these calculations, based on the calculations and the maximum daily dose of 200 mg, compound W can be considered qualified up to 0.9 %. The proposed drug substance specification limit of ≤0.30 % can thus be acceptable from a toxicological point of view. The proposed limits in the drug product is 0.5% (release) and 0.6% (stability) are also acceptable from a toxicological viewpoint.

Regarding the des-10-bromo impurity and based on the calculations and the maximum daily dose of 200 mg, the des-10-bromo impurity can be considered qualified up to 0.2 %. The proposed drug substance specification limit of ≤0.30 % can thus not be considered qualified from a non-clinical aspect. Also, with the more liberal way of calculating with the 150 mg daily dose, the qualified level (0.26%) does not reach the proposed specification limits.

Based on the calculations and the maximum daily dose of 200 mg, the chiral impurity can be considered qualified up to 1.30%. The proposed drug substance specification limit of ≤2.0 % can thus not be considered qualified from a non-clinical perspective. When calculating with the more common daily dose of 150 mg the qualified level is 1.70 % and does not reach the proposed specification limits.

Thus, according to the calculations the specification limits for Des-10-Bromo and the chiral impurity could be considered qualified up to 0.2% and 1.3%. However, it is acknowledged that there is a high structural similarity between lonafarnib and the impurities of concern. The specified minor differences do not indicate any major toxicological concern not already observed with lonafarnib itself. It is also acknowledged that the NOAEL used in the calculations is the highest tested dose in the 28-days repeat dose toxicity study. It is thus likely that the actual NOAEL is higher for all three impurities.

The Applicant has provided a toxicological justification for the maximum levels of ethylbenzene in the quality section. The conservative approach to using the NOAEL from the studies in which ethylbenzene was inhaled is acknowledged. The selection of factors for the PDE calculation is also agreed. The actual calculation of the PDE was, however, not clear. The Applicant provided clarification of the calculated residual threshold and adjusted the threshold from 273 ppm to 373 ppm. The PDE of 3.725 mg/day and the following threshold of 373 ppm are acceptable.

The Applicant has identified five genotoxic impurities. No data on the identification of the compounds as mutagenic was provided. A QSAR analysis was referred to, but the report could however not be located. The reports were submitted upon request. According to the dates, the reports were in fact not in place during the application. The conclusion is that the impurities were either positive or inclusive and therefore handled as potentially genotoxic remains.

The Applicant was asked to justify the approach of a TTC value of 30 µg/day intake for >1 to 10 years according to the ICH M7, considering lonafarnib is for chronic life-long treatment. In the response, the Applicant has described actions to enable testing of the lower limits and also proposed a lowered limit to 14 ppm (from 20 ppm) of total genotoxic impurities. The Applicant also presented a plan to include a more sensitive approach and tighten the limits further in the future.

The 14 ppm limit and a maximum dose of 300 mg would allow 4.2 µg total daily intake of multiple impurities. This is below the ICH M7 level of 5 µg and thus acceptable.

2.5.6. Conclusion on the non-clinical aspects

The review of the non-clinical data available for lonafarnib indicates no major issues for concern. The application is acceptable from a non-clinical viewpoint.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The development programme

Lonafarnib was previously developed for treatment in oncology. The lonafarnib oncology program was eventually terminated for reasons not related to safety.

Lonafarnib as monotherapy or combination treatment has been studied in a few studies in 84 distinct patients; the primary endpoint in these studies was the change in the rate of weight gain compared to baseline (table 4).

In order to evaluate the efficacy of lonafarnib monotherapy on the survival of patients with classic and non-classic HGPS, an observational cohort study survival analysis was conducted comparing all-cause mortality in patients treated with lonafarnib monotherapy with contemporaneous untreated patients from a large natural history cohort. The survival cohort study is considered the pivotal study.

In addition, two single-arm, single-centre, open-label studies were submitted. Prolon1 was a Phase 2, open-label, single-arm, dose-escalation study to evaluate the therapeutic effect of lonafarnib monotherapy in children (≥ 3 years of age) with HGPS or PL. The Triple Therapy study (Study 09-06-0298) was a Phase 2, open-label, single-arm study to evaluate the therapeutic effect of the prenylation inhibitors pravastatin and zoledronic acid in combination with lonafarnib for children (≥ 1 year of age) with HGPS or PL. The triple therapy patient cohort (Group 1) was treated with lonafarnib, pravastatin, and zoledronic acid. Patients previously on lonafarnib monotherapy could roll over to this study; an additional 23 treatment naïve patients were added to group 1. Based on results from the 40 to 52-month visit, no additional benefit to triple-drug therapy was observed compared to lonafarnib monotherapy. As a result, treatment with pravastatin and zoledronic acid was discontinued, and patients were permitted to enter a lonafarnib monotherapy extension. Within study 09-06-0298 the Lonafarnib monotherapy treatment was expanded to include treatment-naïve patients (Prolon2 or Group 2).

Prolon1 and Prolon2 are considered supportive studies as the data from these studies pertains to the proposed posology and indication.

- **Tabular overview of clinical studies**

Table 4 provides an overview of the clinical studies conducted for lonafarnib in the requested indications (see further below).

Note: the 18 contemporaneous patients from a clinical trial that did not involve lonafarnib therapy are the 18 treatment naïve patients enrolled in group1 study 09-06-0298 (triple therapy).

Figure 3 provides an overview of the clinical program and the flow of patients through the different study parts.

Table 4: Description of Clinical Efficacy Studies in the lonafarnib clinical development program.

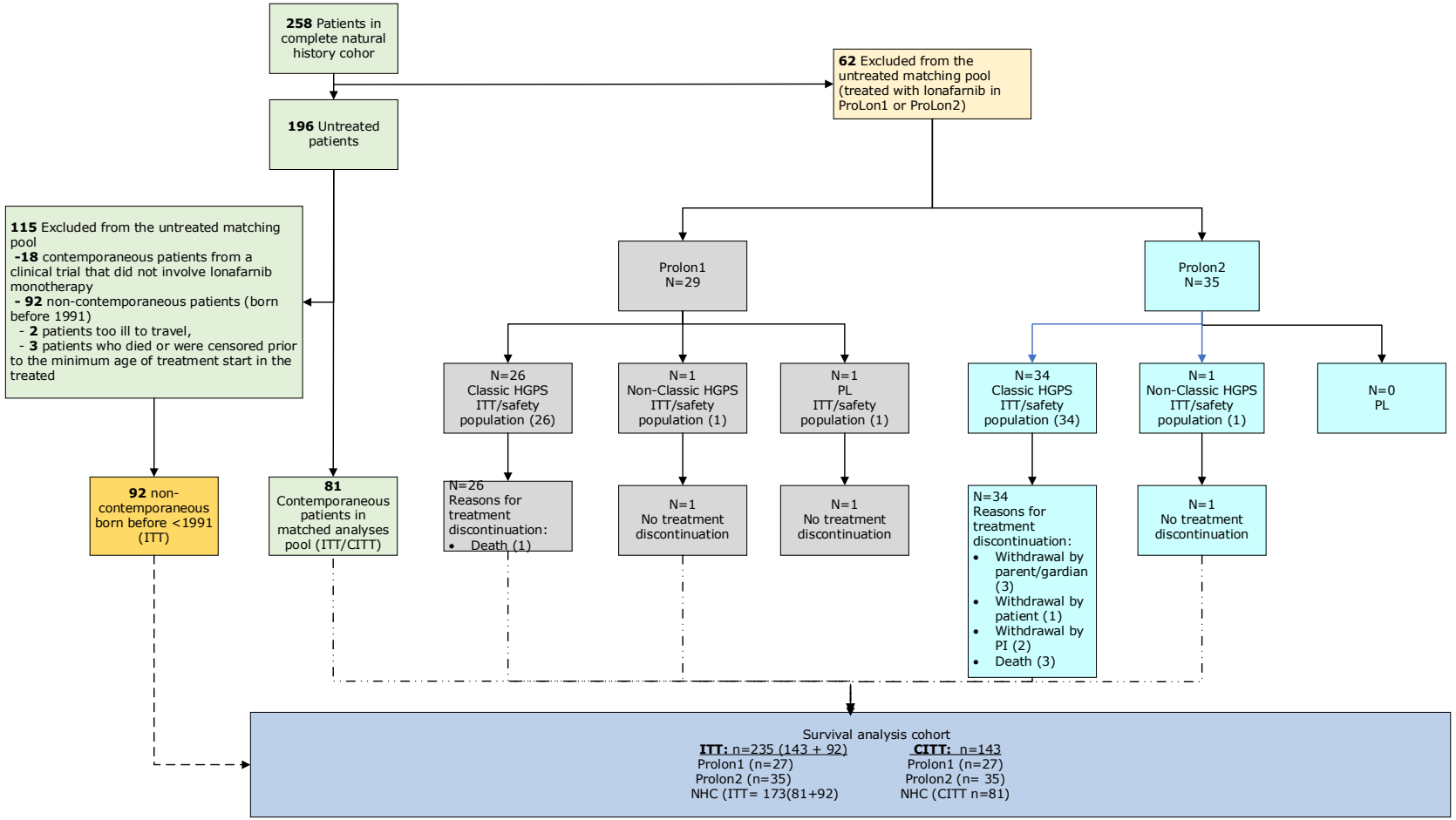
Study ID	No. Centers/ Location (Start–Completion)	Total Enrolment (Planned / Actual)	Design / Control	Route and Regimen	Population	No. of Patients by Treatment (Entered / Treated)	Duration	Number of Treated Patients by Gender Median Age (Range)	Primary Endpoint	Secondary Endpoints[a]
Observational cohort survival analyse		Actual: 81 patients from NHC Actual: 27 patients from Prolon1 Actual: 35 patients from PRolon2	Pooled analysis of lonafarnib treatment in patients with HGPS, compared with untreated patients from the natural history cohort	Natural history cohort (NHC) untreated patients Patients in Prolon1 and Prolon2 received treatment in the original trial	Patients with classic and non-classic HGPS		Data censored at 3 years	81 patients from NHC[@] 42M / 39F 38 Classic HGPS/ 9 non-classic HGPS/ 24 unknown mutation 27 patients from Prolon1[#] 11M / 16F 26 Classic HGPS/ 1 non-classic HGPS 35 patients from PRolon2[#] 22M / 13F 34 Classic HGPS/ 1 non-classic HGPS	Difference in survival (years)	

Study ID	No. Centers/ Location (Start–Completion)	Total Enrolment (Planned / Actual)	Design / Control	Route and Regimen	Population	No. of Patients by Treatment (Entered / Treated)	Duration	Number of Treated Patients by Gender Median Age (Range)	Primary Endpoint	Secondary Endpoints[a]
								Prolon1 + Prolon2 6.69 years (2.1 - 17.5 years)		
07-01-0007 (**Prolon1**®)	Single center/ Dana-Farber Cancer Institute and Boston Children's Hospital (2007-2009)	Planned: 25-30 patients Actual: 29 patients	Open label, single arm	Lonafarnib, oral, initiated at 115 mg/m^2 BID and increased to 150 mg/m² BID after an adjustment period of ≥4 months Single-step dose reductions (in case of drug-related Grade 3-4 toxicity) to 115 mg/m^2 (or from 115 to 90 mg/m^2, from 90 to 70 mg/m^2), and subsequent single-step increases (e.g., from 115 to 150 mg/m^2) were allowed.	Patients with HGPS (classic and non-classic) and PL	29/28	24 to 30 months	11M / 17F 7.5 years (3-16 years)	Change in rate of weight gain over baseline	Carotid artery echodensity Corrected carotid-femoral pulse wave velocity Skeletal bone structure and strength
09-06-0298 (Group 1; Triple Therapy)	Single center/ Boston Children's Hospital (2009-2013)	Planned: 39-45 patients Actual: 47 patients	Open label, single triple therapy treatment arm	Lonafarnib, oral, 150 mg/m² BID Single-step dose reductions (in case of drug-related Grade 3-4 toxicity) to 115 mg/m^2 (or	Patients with HGPS (classic and non-classic) and PL	47/47 26 from Prolon1; 21 newly naïve patients	24 to 60 months	20M / 27F 6.0 years (1 - 18 years) ProLon1 Triple	Change in rate of weight gain over baseline	Carotid artery echodensity Corrected carotid-femoral

Study ID	No. Centers/ Location (Start–Completion)	Total Enrolment (Planned / Actual)	Design / Control	Route and Regimen	Population	No. of Patients by Treatment (Entered / Treated)	Duration	Number of Treated Patients by Gender Median Age (Range)	Primary Endpoint	Secondary Endpoints[a]
		26 patients from Prolon1		from 115 to 90 mg/m^2, from 90 to 70 mg/m^2), and subsequent single-step increases were allowed. Pravastatin, oral 5-10 mg QD Zoledronic acid, IV, 0.0125 – 0.05 mg/kg at baseline; and at months 6, 12, and 18; and at the end of therapy.				Therapy: 11M / 15F 7.0 years (3-16 years) Triple Therapy: 9M / 12F 3.0 years (1-17years)		pulse wave velocity Skeletal bone structure and strength
09-06-0298 (Group 1 Mono-therapy Extension)	Single center/ Boston Children's Hospital (2014-2018)	Planned: 36 patients Actual: 36 patients	Open label mono-therapy study including: Patients from the triple therapy study (18 patients ProLon1 Mono-therapy; 18 patients Triple Therapy Mono-therapy)	Lonafarnib, oral, 150 mg/m² BID	Patients with HGPS (classic and non-classic) and PL	ProLon1 Triple Therapy Monotherapy Extension: 18/18 Triple Therapy Monotherapy Extension: 18/18	24 to 36 months	13M / 23F 10.0 years (2- 19 years) **ProLon1**[@] Triple Therapy Mono-therapy Extension: 6M / 12F 7.0 years (3-12 years) Triple Therapy Mono-therapy Extension	Change in rate of weight gain over baseline	Carotid artery echodensity Corrected carotid-femoral pulse wave velocity Skeletal bone structure and strength

Study ID	No. Centers/ Location (Start–Completion)	Total Enrolment (Planned / Actual)	Design / Control	Route and Regimen	Population	No. of Patients by Treatment (Entered / Treated)	Duration	Number of Treated Patients by Gender Median Age (Range)	Primary Endpoint	Secondary Endpoints[a]
								7M / 11F 3.0 years (1-10 years)		
09-06-0298 (Group 2: Mono-therapy) (**Prolon2**[@])	Single center/ Boston Children's Hospital (2014-ongoing)	Planned: 40 drug naïve patients Actual: 35 drug naïve patients	Open label monotherapy	Lonafarnib, oral, 150 mg/m² BID	Patients with HGPS (classic and non-classic) and PL	35/35	24 to 36 months	22M / 13F 6.0 years (2-17 years)	Change in rate of weight gain over baseline	Carotid artery echodensity Corrected carotid-femoral pulse wave velocity Skeletal bone structure and strength

BID = twice daily; F = female; HGPS = Hutchinson-Gilford Progeria Syndrome; IV = intravenous; M = male; PL = progeroid laminopathies; QD = once daily.
@) All patients (treated and untreated) and their associated data were identified using the Progeria Research Foundation International Registry http://www.progeriaresearch.org/patient_registry.html, published scientific and news articles, and publicly available databases.
#) patients from the natural history cohort (NHC) are untreated; Prolon1 and Prolon2 patients received lonafarnib monotherapy in the respective studies, no additional treatment in the survival study was administered.



HGPS: Hutchinson-Gilford Progeria Syndrome; PL: progeroid laminopathies; ITT: intent-to-treat

Note: the 18 contemporaneous patients from a clinical trial that did not involve lonafarnib therapy are the 18 treatment naïve patients enrolled in group1 study 09-06-0298 (triple therapy).

Figure 3: Flowchart of the natural history cohort and the clinical studies Prolon1 and Prolon2 and subsequently their inclusion into the survival cohort study.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Lonafarnib is a farnesyltransferase inhibitor that is developed for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and progeroid laminopathies (PL). For patients with HGPS and PL, the recommended starting dose is 115 mg/m^2 twice daily. This dose is administered in the morning and the evening during meals. After 4 months of treatment, the dose should be increased to 150 mg/m^2 twice daily, with a maximum dose of 150 mg per administration.

The clinical pharmacology of lonafarnib was assessed in healthy volunteers, patients with advanced cancer and patients with HGPS and PL. Clinical studies were performed to investigate the absorption, metabolism and elimination of lonafarnib and the effect of food, the effect of opening the capsule, the effect of intrinsic factors (age, sex, renal and hepatic impairment), and several drug-drug interactions (DDI). In addition, *in vitro* studies were performed investigating the permeability, plasma protein binding, metabolism, transport and potentially clinically relevant DDIs. The studies in patients with advanced cancer could not be assessed and only provided as supportive, since it was unclear if the analytical methods used were sufficiently validated.

Table 5. Summary of studies supporting the clinical pharmacology of lonafarnib

Study number	Study type	Lonafarnib dose	Population	PK sampling scheme
Healthy volunteers				
EIG-LNF-015	Phase 1 DDI Study, loperamide (LPM)	LNF 50 mg + RTV 100 mg BID × 5 Days	Healthy Volunteers (N=15)	Intensive
EIG-LNF-016	Phase 1 DDI Study, midazolam (CYP3A4) and fexofenadine (P-gp)	LNF 100 mg BID × 5 Days	Healthy Volunteers (N=36)	Intensive
EIG-LNF-017	Phase 1 DDI Study, omeprazole (CYP2C19) and Food Effect Study	LNF 75 mg BID × 5 Days	Healthy Volunteers (N=36)	Intensive
EIG-LNF-008	Phase 1 DDI Study, LNF + RTV, fexofenadine, (P-gp), rosuvastatin (BCRP)	LNF 50 mg + RTV 100 mg multiple dose + fexofenadine 180 mg single dose or rosuvastatin 10 mg single dose	Healthy Volunteers (N=36)	Intensive
EIG-LNF-009	Phase 1 DDI Study, midazolam (CYP3A4), pitavastatin (OATP1B1)	LNF 50 mg + RTV 100 mg BID + midazolam 1.5 mL single dose or pitavastatin 2 mg single dose	Healthy Volunteers (N=36)	Intensive
EIG-LNF-007	Phase I DDI Study, rifampin (CYP3A) and food-effect	LNF 50 mg single dose +RTV 100 mg single dose	Healthy Volunteers (N=36)	Intensive
EIG-LNF-010	Phase 1, multiple-dose LNF + RTV, QTc study	LNF 50 mg + RTV 100 mg BID × 5 days then LNF 100 mg + RTV 100 mg × 4 days	Healthy Volunteers (N=65)	Intensive
P00393	Phase 1 DDI Study, Ketoconazole (CYP3A4)	LNF 50 mg single-dose + placebo/ketoconazole for 5 doses	Healthy Volunteers (N=16)	Intensive
P00260	Phase 1, [14C], Absorption, Metabolism, Excretion	LNF 104 mg (107 µCi) single dose oral suspension	Healthy Volunteers (N=9)	Intensive
P02673	Phase 1, Intrinsic Factors: Age and Sex	LNF 100 mg single dose	Healthy Volunteers (N=48)	Intensive
P00042	Phase 1, Food-Effect	LNF 100 mg single dose	Healthy Volunteers (N=12)	Intensive
Special populations				
EIG-LNF-003	Phase 1, effect of hepatic impairment (mild and moderate)	LNF 50 mg single dose + RTV 100 mg single dose	Patients with Hepatic Impairment (N=27), mild hepatic function (N=9), moderate hepatic function (N=7), normal hepatic function (N=11)	Intensive
EIG-LNF-006	Phase 1, effect of renal impairment (moderate and severe)	LNF 50 mg single dose + RTV 100 mg single dose	Patients with Renal Impairment (N=18), severe renal impairment (n =4), moderate renal impairment (n = 5), healthy volunteers (n = 9)	Intensive
Patients with advanced cancer				

I97-211	Phase 1, multiple-dose, MTD, DLT	LNF 25 to 300 mg BID x 28 days or LNF 300 to 400 mg QD x 28 days	Adults with advanced cancer (N=36)	Intensive
C97-258	Phase 1, dose escalation, safety, tolerability, MTD, DLT	LNF 25 to 400 mg BID x 7 days	Adults with advanced cancer (N=22)	Intensive
C97-262	Phase 1, multiple-dose, dose-escalation, safety, tolerability, MTD, DLT	LNF 25 to 300 mg BID x 14 days	Adults with advanced cancer (N=21)	Intensive
P00394	Phase 1, multiple-dose, dose-escalation, safety, tolerability, MTD	LNF 150, 200, 250 mg BID x 28 days	Adults with advanced cancer (N=34)	Intensive
Kieran *et al.*	Phase 1, multiple-dose, dose-escalation, safety, MTD	LNF 70 to 200 mg/m^2 BID × 28 day cycles	Paediatric patients with advanced CNS tumours (N=53)	Sparse
Patients with HGPS and PL				
ProLon1 (07-01-0007)	Phase 2, open-label, dose-adjusted, single-arm study	LNF initiated at 115 mg/m2 BID and increased to 150 mg/m² BID after an adjustment period of ≥4 months	Patients with HGPS and PL (N=28)	Sparse

BCRP = breast cancer resistance protein; BID = twice daily; CNS = central nervous system; CYP = cytochrome P450; DDI = drug-drug interaction; DLT = dose-limiting toxicity; HGPS = Hutchinson-Gilford Progeria Syndrome; LNF = lonafarnib; MTD = maximum tolerated dose; OATP = organic anion transporting polypeptide; P-gp = p-glycoprotein; PK = pharmacokinetic; PL = progeroid laminopathies; QD = once daily; RTV = ritonavir

Physical-chemical properties

Lonafarnib has one chiral centre and is administered as R-lonafarnib. No *in vivo* conversion to S-lonafarnib is expected to occur. Lonafarnib is considered a high permeable but low solubility substance. The fraction absorbed *in vivo* has not been determined.

Analytical methods

Several bioanalytical methods have been used throughout the clinical development programme of lonafarnib to determine lonafarnib concentrations in plasma. These bioanalytical methods have individually been sufficiently validated. However, the bioanalytical methods used in studies EIG-LNF-015, EIG-LNF-017 and ProLon1 have not been cross-validated. The population pharmacokinetic model, however, estimated the residual error of the individual studies to be in the same order of magnitude. Therefore, no clinically relevant differences are to be expected due to the use of different analytical methods.

Population pharmacokinetic analysis

Data was used from patients included in the ProLon1, and healthy volunteers included in EIG-LNF-015 (Group 2) and EIG-LNF-017 (Group 1 and 2). No studies were included in which patients received lonafarnib boosted with ritonavir. A non-linear mixed effect model was developed using NONMEM 7.4 (ADVAN2 and TRANS2). First-order conditional estimation with interaction was used to obtain model parameters. The final model was a 1-compartment model with first-order absorption and first-order elimination, weight allometrically scaled with estimated exponents, sex as a covariate on CL and formulation as a covariate on bioavailability. The stochastic component of the model was best described with inter-individual variability on CL, V, KA and F1 and a proportional residual error model.

The predictive performance of the model was considered to be quite poor due to bias in the prediction-corrected visual predictive checks (Figure 4) and high estimate for the proportional error model (estimate = 0.43, which corresponds to a CV of approximately 70%). Therefore, the model cannot be

used for simulations but will provide some guidance in the estimation of pharmacokinetic parameters of patients included in the ProLon 1 trial.

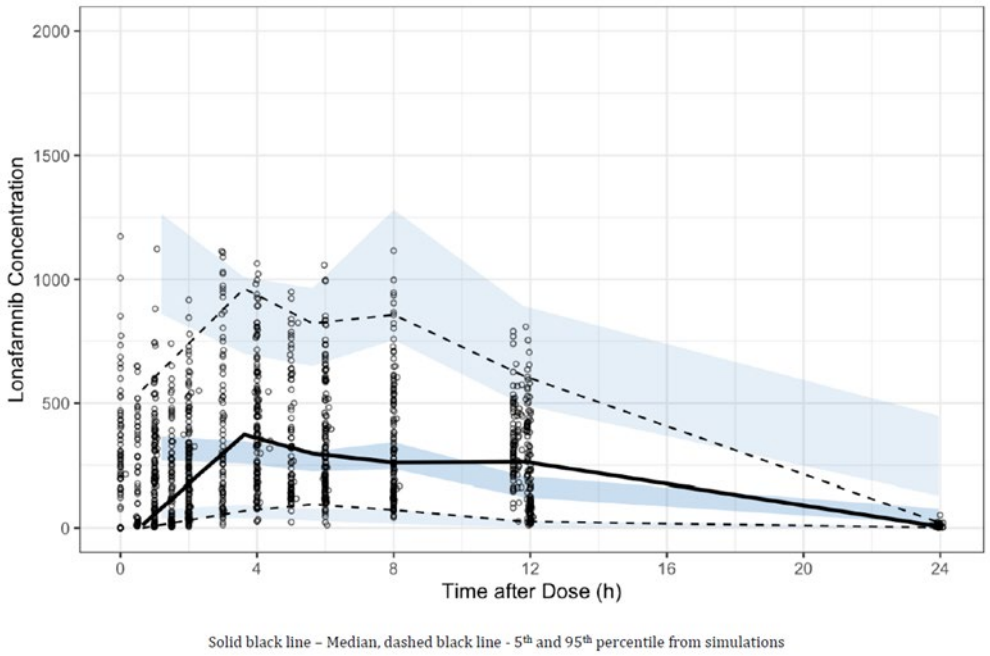
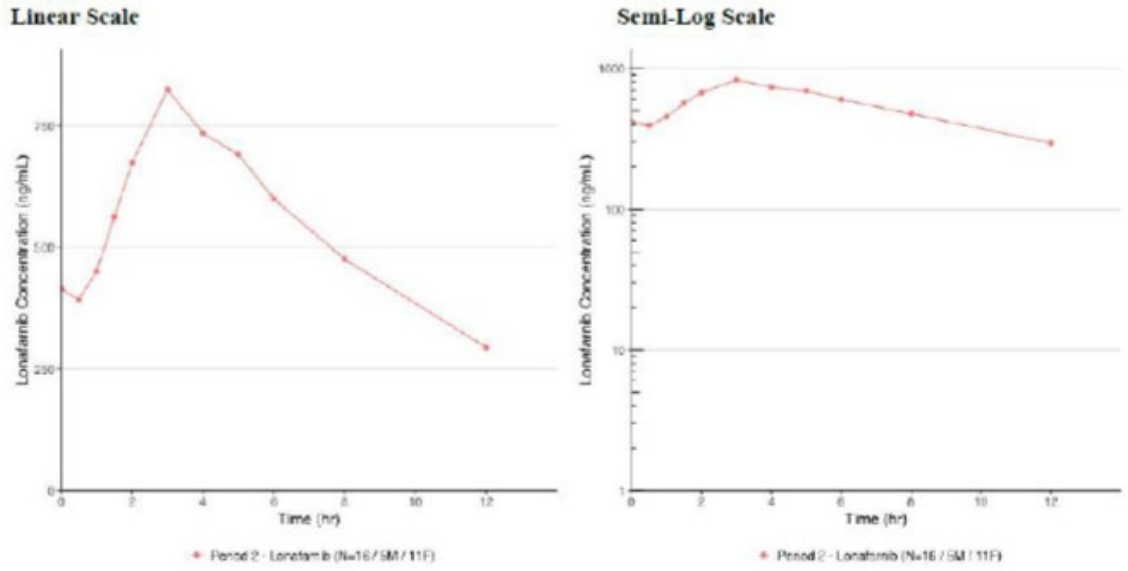


Figure 4. prediction-corrected visual predictive check

Absorption

The pharmacokinetic profile of lonafarnib alone was characterised in 3 single-dose studies in healthy volunteers (lonafarnib dose of 50 to 104 mg) and in 2 multiple-dose studies in healthy volunteers (lonafarnib dose of 100 mg twice daily). A typical pharmacokinetic profile is displayed in Figure 5. However, the PK in the multiple-dose studies was not assessed after the first dose. Furthermore, no pharmacokinetic parameters were determined following the maximal clinical dose of 150 mg and 175 mg after a single or twice daily repeated the dose in healthy volunteers.



F = female; LNF = lonafarnib; M = male; N = number of subjects

Figure 5. Mean Lonafarnib Concentration vs. Time (Study EIG-LNF-017, group 1) after 75 mg BID

Following a single dose of 100 mg lonafarnib (P00042), the C_{max} was 323 ng/mL (CV=55%), and the AUC_{0-t} was 2077 ng × h/mL (CV=61%). Maximal peak concentrations were observed 2 to 5 hours post-dose. Following repeated oral dosing with 100 mg twice daily (EIG-LNF-015 and EIG-LNF-017), the C_{max} was 834 to 964 ng/mL (CV=32%), and the $AUC_{0-\tau}$ was 6200 to 6940 ng × h/mL (CV=36-37%).

No absolute oral bioavailability studies have been conducted with lonafarnib. The oral bioavailability of lonafarnib appears to be relatively low as, in the mass-balance study P00260, systemic exposure of lonafarnib was only 50% of the exposure in plasma drug-derived radioactivity. Based on the high permeability characteristics of lonafarnib in humans, the absorption is most likely high, but lonafarnib is subject to extensive first-pass metabolism (substrate of CYP3A4) and potentially efflux into the intestine following absorption (substrate of P-glycoprotein).

It is recommended to administer lonafarnib with food in the HGPS and PL patient population, resulting in improved tolerability in patients with advanced tumours. Following a high-fat/high-caloric meal, the C_{max} decreased by 55% and AUC by approximately 26% relative to the fasted state. Variability in these parameters decreased following a high-fat/high-caloric meal after multiple-dose administration. Following a low fat/low caloric meal, the C_{max} decreased by 25% and AUC by approximately 22%. The t_{max} was delayed by 1 to 2 hours and between-patient variability in t_{max} increased following a high-fat/high-caloric or low fat/low caloric meal compared to fasted conditions. This is to be expected as gastric emptying under fed conditions is subject to variability between patients.

The applicant submitted a relative bioequivalence study (EIG-LNF-019) in which 75 mg lonafarnib (suspended in orange juice) and 75 mg lonafarnib (suspended in apple sauce) were compared with 75 mg lonafarnib administered as intact capsules. Administration of lonafarnib suspension in orange juice and as an intact capsule resulted in a similar concentration versus time profile. In contrast, administration of lonafarnib mixed with applesauce resulted in a higher peak exposure when compared to the intact lonafarnib capsule (1.16[1.00 to 1.35] for C_{max} and 1.15 [0.98 to 1.41] for AUC_{0-t}). The t_{max} was observed earlier for both lonafarnib in suspension with orange juice and lonafarnib mixed with applesauce. From a conservative perspective, the SmPC recommends to administer lonafarnib with orange juice instead of apple sauce only in patients that are unable to swallow the capsules. As dose

proportionality remains unclear, it is difficult to extrapolate the results obtained with the 75 mg dose to the 50 mg dose. It remains unclear whether the 50 mg formulation behaves similarly as the 75 mg formulation. The current advice relates to subjects that are unable to swallow; therefore the 50 mg could be considered more relevant for this population as these are most likely younger paediatric patients on a lower dose. At the higher dose (where more saturation in the pharmacokinetics can be expected), the influence of orange juice could be underestimated. However, as the impact of orange juice on the PK was rather mild, and the 50 mg and 75 mg are expected to be still in the relatively dose-proportional range, the clinical impact of a different exposure will probably be limited.

Distribution

The plasma protein binding of lonafarnib is high (>99%). The blood-to-plasma ratio is 0.99, indicating no accumulation of lonafarnib in red blood cells.

Lonafarnib appears to be highly distributed into tissue following a single 100 mg oral dose with an apparent volume of distribution (V_d/F) values ranging from 221 L to 279 L. However, most likely, the V_d/F is high due to extensive first-pass metabolism (low oral bioavailability).

Metabolism

Lonafarnib is extensively metabolised *in vitro* in human liver microsomes and human hepatocytes with the most common metabolic pathways including oxidation, dehydrogenation and combinations of these two processes, mainly by CYP3A4 and CYP3A5.

The metabolism profile of lonafarnib was investigated in plasma, urine and faeces. In plasma, lonafarnib was ~50% of the radioactivity, metabolites HM17 (oxidation; 15.1%) and active metabolite HM21 (dehydrogenation; 13.9%) were the major metabolites observed.

However, the plasma metabolite profile of lonafarnib was investigated using pooled samples from 6 subjects at time points 1, 4 and 8 hours. The lonafarnib t_{max} occurs around 4 h, and its elimination half-life is also 4 hours. Therefore, the identification of metabolites following a single dose at 1 to 8 hours may not be representative of the lonafarnib metabolite profile in humans. Additionally, lonafarnib is a time-dependent inhibitor of CYP3A4 and also a time-dependent CYP3A inducer and thus influences its own metabolism. Therefore, metabolite profile following a single dose may not be representative of that following multiple dosing.

There is a concern for potential late formation of metabolites as only 60% radioactivity was recovered in the mass balance study after 10 days, while elimination half-life of lonafarnib is approximately 4h, but also because signs of accumulation can be observed in non-clinical studies in monkey (i.e. presence of radioactivity after 28 days of study in lymph nodes, brown fat and eye and also presence of radioactivity in liver and intestine, the latter two presumably due to their involvement in metabolism and excretion of the remaining parent/metabolites). Also, absolute bioavailability is unknown. At this stage, the accumulation of a metabolite of lonafarnib or the parent lonafarnib cannot be excluded, besides the fact that HM21 is not the cause of this potential accumulation. Therefore, the full plasma metabolite profile of lonafarnib should be investigated. This can either be done by characterising the metabolite profile in healthy volunteers at steady state over a time frame of at least 0 to 12 hours, and preferably also after 2 weeks of wash-out (to indicate the metabolites with a long elimination half-life or slow release from tissues), or conduct a new, appropriately designed, mass balance study where recovery exceeds at least 90% of the administered dose and 80% of the radioactivity is identified as recommended by the Guideline on the investigation of drug-drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**). This new mass balance study will be submitted as a post-authorisation measure.

The Applicant characterised the pharmacokinetics of the active metabolite HM21 after multiple dosages of lonafarnib in studies EIG-LNF-015 and EIG-LNF-017. The results demonstrated that HM21 is mainly

formed by CYP3A4. The ratio between parent/metabolite is approximately 8-17% for HM21. The half-life of HM21 is approximately 7 to 12 hours. Therefore, these results did not exclude concerns around the metabolite profile of lonafarnib, but the contribution of HM21 to the overall effectivity is low.

In faeces (major elimination route), metabolite HM3 (double oxidation), HM4 (triple oxidation and dehydrogenation), HM11 (opening up of the piperidine ring with the addition of a molecule of water) and HM17 (oxidation) were present for >5% of the radioactivity, with HM3 around 10%. The absolute oral bioavailability of lonafarnib and the site of first-pass metabolism (intestine or liver) is unknown. Therefore, it is unknown if part of the observed metabolites in faeces have been absorbed, formed and eliminated or are formed directly in the intestine (wall and intestinal flora) without absorption. Information on the metabolite profile at a steady state may help to understand the observed difference in metabolite profile between plasma and faeces.

Transporters

Based on the *in vitro* data, lonafarnib is most likely a substrate of P-glycoprotein and not a substrate of BCRP, OCT1, OATP1B1 and OATP1B3.

Excretion

The major elimination route is via faeces. Non-clinical data in rats indicate that absorbed radioactivity is mainly eliminated via bile. The human elimination half-life ($t_{½}$) of lonafarnib is 3 to 4 h, and the apparent clearance (CL/F) is 50 L/h.

Dose proportionality and Time dependency

No information on the dose-proportionality in healthy subjects or the patient population was provided. Dose proportionality was assessed in paediatric patients with advanced cancer, which indicated that the pharmacokinetics of lonafarnib is most likely not dose-proportional (Figure 6). As indicated above, it is unclear whether the bioanalytical method was appropriately validated of the studies with paediatric patients with advanced cancer, and disease effects cannot be excluded; therefore, these results should be interpreted with caution.

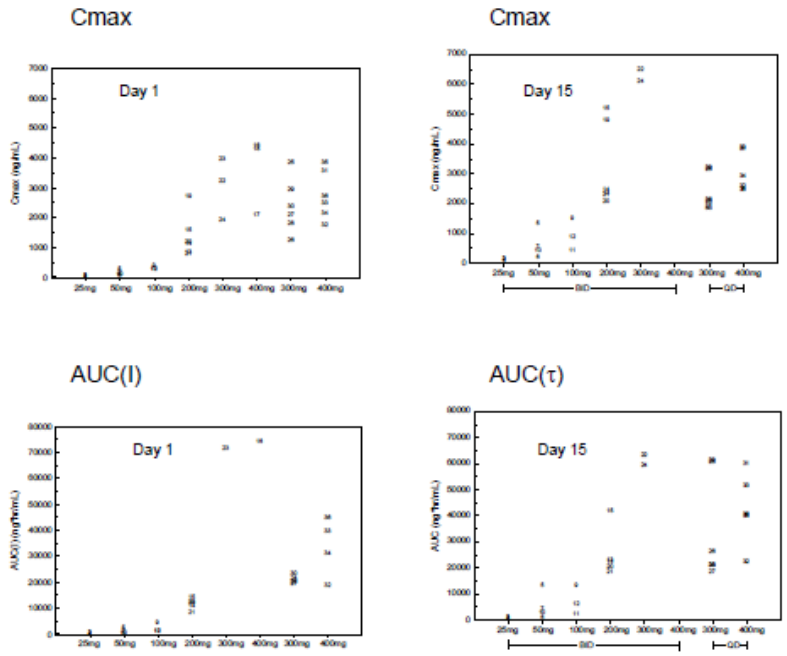


Figure 6. Individual Cmax and AUC Values of lonafarnib following once-daily oral administration on Day 1 and once- or twice-daily oral administration on Day 15 to patients with advanced cancer.

The Applicant estimates with the population pharmacokinetic model that the accumulation ratio of lonafarnib is 1.27 in healthy volunteers and HGPS and PL patients. However, based on studies conducted in patients with advanced CNS tumours without ritonavir, the accumulation ratio of lonafarnib was estimated to be 3– to 5-fold over the investigated dose range. The population pharmacokinetic model is expected to underestimate the accumulation of lonafarnib due to potentially unable to characterise 2-compartment behaviour and the fact that the auto-inhibition and other time-dependencies were not included in the structural model. It remains unclear how the pharmacokinetics of patients with advanced CNS tumours can be extrapolated to either healthy volunteers or patients with HGPS and PL, but the accumulation ratio of 3- to 5-fold is considered more reliable than the estimates of the population pharmacokinetic model.

Special populations

Patient population

The pharmacokinetics of lonafarnib in the patient population have been studied in the ProLon 1 study, in which pharmacokinetic samples were collected on at least one study visit. Samples were taken up to 8 hours after dosing. For several subjects with a t_{max} value above 4 hours, the elimination rate constant, and thus the terminal half-life, could not be reliably estimated using non-compartmental analysis. The Applicant used the data as input for a population pharmacokinetic analysis. The PK appears similar in healthy volunteers and the patients population, but the predictive performance of the model is very poor. Therefore, there is some uncertainty about whether this is actually the case. Also, several time dependencies have been identified, and the population pharmacokinetic model does not account for these time dependencies, which could be different between healthy volunteers and patients due to factors such as concomitant medication.

The Applicant derived estimates for $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ for patients included in the ProLon 1 study using the population pharmacokinetic model. The intra- and intersubject variability of $C_{max,\ ss}$ are 20.8% and 36.9%, respectively. The intra- and intersubject variability of $AUC_{0\text{-}tau,ss}$ are 21.1% and

50.8%, respectively. It should however be noted that these could be underestimated as most informative data came from healthy volunteers and the time-dependencies in the pharmacokinetics of lonafarnib were not included in the model.

Genetic polymorphisms

The effect of genetic polymorphisms of CYP3A4 (e.g. CYP3A4*22) and CYP3A5 (e.g. CYP3A5*1) on the PK of lonafarnib and HM21 have not been investigated. Genetic polymorphisms in CYP3A4 and 3A5 may lead to increased (e.g. CYP3A4*22) or decreased (or CYP3A5*1) exposure to lonafarnib which may affect the efficacy and safety. The Applicant argued that the chance of having a polymorphism in CYP3A4 or CYP3A5 in patients with PL or HGPS is low. However, the effect size of polymorphisms on CYP3A4 on the pharmacokinetics of lonafarnib is expected to be clinically relevant because an increase in plasma exposure to lonafarnib could be associated with an increased probability of developing adverse reactions (such as QTc prolongation). On the other hand, loss of efficacy can be expected with decreasing exposure. Precautionary measures for mild and moderate CYP3A4 inhibitors have been proposed by the Applicant, and the effects of polymorphisms in CYP3A4 (e.g. CYP3A4*22) are expected to result in similar increases in lonafarnib exposures as mild and moderate CYP3A4 inhibitors. SmPC section 4.4 includes a warning regarding the fact that subjects with a known dysfunctional polymorphisms in CYP3A4 should consider a dose reduction and additionally QTc monitoring at the time of initiation of treatment.

Renal impairment

Urinary excretion of the parent compound lonafarnib and also metabolites was minimal in the mass-balance study. No clinical studies were performed investigating the effect of impaired renal function on the PK of lonafarnib. However, no decreased renal function is expected in the patient population and therefore, no clinical studies are warranted investigating the effect of renal impairment on the PK of lonafarnib.

Hepatic impairment

No clinical studies were conducted investigating the effect of hepatic impairment on the PK of lonafarnib when administered as monotherapy. Considering the importance of hepatic clearance, an increase in exposure to lonafarnib is expected with a decrease in hepatic function. However, no decreased hepatic function is expected in the patient population and therefore, no clinical studies are warranted investigating the effect of hepatic impairment on the PK of lonafarnib.

Gender

Based on study P02673, healthy female subjects appear to have a slightly higher C_{max} (26%) and a higher $AUC_{0\text{-}inf}$ (44%) compared to healthy male subjects. It should be noted that these analyses were not corrected for body weight; therefore, the true effects of gender may be overestimated. In addition, no effect of gender on $AUC_{0\text{-}t}$ and C_{max} were observed in post-hoc analyses of the ProLon1 trial.

Race

The effect of race on the PK of lonafarnib has not been evaluated.

Age

The influence of age of 3 to 18 years on the PK of lonafarnib was investigated using pharmacokinetic data obtained in the ProLon1 trial. From the correlation matrices, it appears that exposure increases with age. If patients are dosed from birth on, then the ontogeny of CYP3A4, 3A5 and 3A7 may affect the PK of lonafarnib in this sub-population. However, as treatment is recommended from the age of 12 months, this is not expected to be an issue.

Elderly healthy subjects, aged >65 years, had a higher C_{max} (27%) and a higher $AUC_{0\text{-}inf}$ (59%) (study P02673). It should be noted that these analyses were not corrected for body weight; therefore, the true effects of age may be overestimated. Furthermore, the age category elderly is not considered relevant for patients with HGPS and PL.

Weight

Body weight appears to affect the exposure to lonafarnib, with higher exposure at lower body weight. The current BSA-based posology should be able to maintain approximately equivalent exposure for every patient.

Drug-drug interactions

Lonafarnib as victim

In vitro, lonafarnib is mainly metabolised by CYP3A4 and in some patients also via CYP3A5. The effect of a strong CYP3A4 inhibitor (ketoconazole; 200 mg once daily × 5 days) and strong CYP3A4 inducer (rifampin; 600 mg once daily × 7 days) on the PK of lonafarnib was investigated in clinical DDI studies. Strong inhibitors and inducers of CYP3A4 significantly affected the exposure (C_{max} and AUC) to lonafarnib (Table 6).

Table 6. Effect of other medicinal products on the PK of lonafranib

lonafarnib dose	perpetrator drug	C_{max} effect	AUC effect	study
50 mg	ketoconazole	3.7 (3.04-4.49)	5.25 (4.18-6.57)	P00393
50 mg	rifampin	0.08 (0.06-0.11)	0.019 (0.013-0.27)	EIG-LNF-007

No data is available for weak and moderate inhibitors or weak or moderate inducers.

For strong CYP3A inhibitors, the Applicant argues, based on study P00393 with a strong inhibitor (ketoconazole) administered for 5 days, that the AUC of lonafarnib was increased by 270% and 425%. However, the time-dependent inhibition and induction potential of CYP3A by lonafarnib was not considered. Based on the interaction study with midazolam, lonafarnib can be considered a strong (irreversible) inhibitor of CYP3A4. Auto-inhibition of CYP3A4 might be the reason for the unexpected 3 to 5-fold accumulation of lonafarnib at steady-state compared to single-dose exposures. Therefore, the effect of other CYP3A4 inhibitors on the exposure of lonafarnib is likely less pronounced after lonafarnib reaches a steady-state compared to the effects on a single dose (as was tested in the ketoconazole study).

The Applicant has presented no data/discussion for moderate inhibitors. A drug-drug interaction study with a clinically relevant moderate inhibitor of CYP3A4 at steady-state conditions of lonafarnib will be submitted as a post-authorisation measure. Until the study results are available, SmPC sections 4.4 and 4.5 include a warning to avoid the use of moderate-inhibitors of CYP3A4, but if avoidance is not possible, it is recommended to reduce the dose of lonafarnib by 50% and to conduct QTc monitoring.

No dose adjustments are considered necessary for weak inhibitors, but a 50% reduction (as advised for moderate inhibitors) and QTc monitoring should be recommended in case of toxicity. This was included in section 4.5 of the SmPC.

The results of study EIG-LNF-007 with the strong inducer rifampin, however, indicated that lonafarnib Cmax and AUC were decreased by 92% and 98%. Therefore, loss of efficacy can also be expected with

moderate inducers and to a lesser extent with weak inducers, although the effect might be less relevant in clinical practice as lonafarnib is also a time-dependent inducer of CYP3A. A warning as currently implemented in the SmPC is considered sufficient in this regard.

Lonafarnib may be a substrate of P-glycoprotein based on *in vitro* data. The effect of a strong P-glycoprotein inhibitor (not an inhibitor of CYP3A4) on the PK of lonafarnib was not investigated *in vivo*. A DDI study with lonafarnib and a P-gp inhibitor, which is not a CYP3A4 inhibitor, in healthy volunteers will be conducted as a post-authorisation measure.

Lonafarnib as perpetrator

Based on *in vitro* data, lonafarnib is a direct inhibitor of CYP3A4 at clinically relevant maximal intestinal and maximal systemic concentrations. In addition, lonafarnib is a time-dependent inhibitor of CYP3A4 at clinically relevant maximal intestinal and maximal systemic concentrations.

The Applicant performed clinical DDI studies to investigate the effect of lonafarnib on the PK of other drugs that are substrates of CYP3A4 (loperamide and midazolam) and CYP2C19 (omeprazole) following repeated dosing of lonafarnib (Table 7). The clinical DDI studies using repeated dosing for 5 days will show the worst-case DDI due to direct and time-dependent inhibition. Therefore, based on clinical data, lonafarnib is a clinically relevant inhibitor of CYP3A4.

Table 7. Effect of lonafarnib on the PK of other medicinal products

lonafarnib dose	victim drug	C_{max} fold increase	AUC fold increase	study
100 mg twice daily for 5 days	loperamide (CYP2C8 + 3A4)	3.1 (2.8-3.5)	4.0 (3.4-4.6)	EIG-LNF-015
100 mg twice daily for 5 days	midazolam (CYP3A4	2.8 (2.4-3.3)	7.4 (6.3-8.7)	EIG-LNF-016
100 mg twice daily for 5 days	fexofenadine (P-glycoprotein)	1.2 (0.96-1.54)	1.2 (1.1-1.5)	EIG-LNF-016
75 mg twice daily for 5 days	omeprazole (CYP2C19)	1.3 (1.0-1.6)	1.6 (1.3-1.9)	EIG-LNF-017
50 mg for 5 days	pitavastatin (OATP1B1)	1.1 (0.86-1.4)	1.1 (0.91-1.3)	EIG-LNF-009
50 mg twice daily for 5 days	rosuvsatatin (BCRP)	0.99 (0.79-1.2)	0.88 (0.75-1.0)	EIG-LNF-008

In vitro, lonafarnib is an inducer of PXR. The EC50 parameter was estimated to be 1.29 to 2.24 µM, indicating that lonafarnib could be a PXR inducer *in vivo*. The clinical implication of this finding can be evaluated using the clinical DDI study with midazolam (CYP3A4 substrate). The exposure of midazolam was increased 7-fold by lonafarnib, indicating that the net effect of lonafarnib is CYP3A4 inhibition (Table 7). However, other CYP enzymes, UGT and transporters could also be induced when PXR is induced. Interaction studies with omeprazole (CYP2C19 substrate) and fexofenadine (Pgp substrate) have been conducted (Table 7). Lonafarnib slightly increased the exposure of omeprazole, indicating

that lonafarnib is unlikely to be an inducer of CYP2C19. Also, the interaction with fexofenafine did not indicate induction of Pgp by lonafarnib. In all these interaction studies, lonafarnib was administered for 5 days, which is too short for a maximal induction effect; probably only half of the maximal induction effect is reached within this timeframe. No DDI with an oral contraceptive has been conducted and it cannot be excluded that lonafarnib can induce UGTs and hence lower exposures of oral contraceptives that UGT mainly metabolizes cannot be excluded. Considering the young age of the target population, the absence of DDI with oral contraceptives cannot be accepted. A DDI study will be conducted as a post-authorisation measure and, until the results of this study are available, the absence of such study will be acknowledged in the SmPC section 4.5, and it is recommended to use a barrier method as a method of contraception.

Based on *in vitro* data, lonafarnib is an inhibitor of P-glycoprotein, BCRP, OCT1, MATE1 and MATE2-K at clinically relevant maximal systemic concentrations. Furthermore, lonafarnib is an inhibitor of P-glycoprotein and BCRP at clinically relevant maximal intestinal concentrations. Lonafarnib may also be an inhibitor of OATP1B1 at relevant maximal portal concentrations and in some patients at relevant maximal systemic concentrations (e.g. highest C_{max} observed in patients). The Applicant performed clinical DDI studies to investigate the effect of lonafarnib on the PK of other drugs that are substrates of P-glycoprotein (fexofenadine), BCRP (rosuvastatin) and OATP1B1 (pitavastatin) following repeated dosing of lonafarnib (Table 11). Based on clinical data, lonafarnib is not a clinically relevant inhibitor of P-glycoprotein, BCRP and OATP1B1. Currently, there is no clinically sensitive substrate for OCT1, and therefore, the observed *in vitro* DDI should be included in section 4.5 of the SmPC. The Applicant has also made clear that concomitant use of metformin (a clinically relevant substrate of MATE1 and MAT2-K) in patients with HGPS and PL is very unlikely. No other clinically relevant substrates are at this moment available, but this might change in the future. Therefore, no *in vivo* DDI study is considered necessary. Based on *in vitro* data, the potential interaction for a clinically relevant interaction with MATE1 and MAT2-K is mentioned in section 4.5 of the SmPC.

The applicant evaluated the interaction potential of the active metabolite HM21. HM21 is considered an *in vitro* reversible inhibitor of CYP2C8, CYP2C19 and CYP3A4 a time-dependent inhibitor of CYP3A4. The influence of HM21 on transporters was not investigated. This interaction profile is highly similar to lonafarnib, and as HM21 is only present in plasma as 8 to 17% of the parent, the potential for clinically relevant interactions other than charactered for lonafarnib is considered to be low.

2.6.2.2. Pharmacodynamics

Mechanism of action

In normal cells, the precursor of lamin A, prelamin A, undergoes post-translational farnesylation of its C-terminal CaaX motif by farnesyltransferase. This modification localizes the prelamin A to the nuclear membrane, where zinc metalloproteinase ZPMSTE24 cleaves off 15 amino acids at the C terminus (including the new farnesyl group), leaving mature lamin A that is then incorporated into the nuclear lamina to act as a scaffold for the cell nucleus.

In HGPS, mutation of the gene encoding lamin A, LMNA, results in mutant prelamin A that cannot be processed by ZMPSTE24, resulting in the production of mutated lamin A that retains its farnesyl lipid anchor. This leads to the accumulation of a dominant negative farnesylated abnormal lamin A protein (progerin) at the nuclear membrane, significantly altering nuclear architecture and function, causing cellular damage via structural instability and functional abnormalities that lead to disease. Progerin can affect critical cellular processes, including gene transcription, DNA replication, and cell division. The most common genetic mutation of the LMNA gene found in HGPS is a de novo silent C to T substitution, typically in exon 11. PLs are caused by mutations in LMNA or mutations in proteins

affecting the post-translational pathway of LMNA, including ZMPSTE24, and can progress to clinical features that overlap with HGPS.

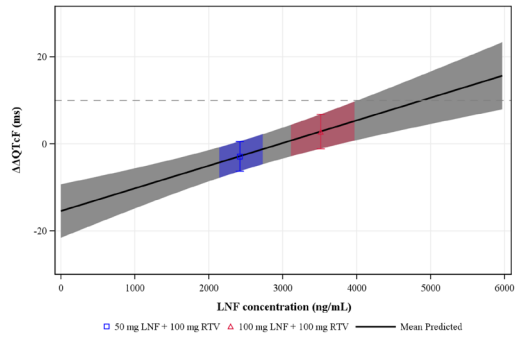
Primary Pharmacology

Lonafarnib selectively inhibits human farnesyl protein transferase (IC50=1.9 nM). Initially, no pharmacodynamic biomarkers were validated, and survival was considered the pharmacodynamic endpoint. During the procedure the Applicant submitted new data pertaining to the analyses of progerin levels in HGPS patients included in Prolon1 and prolon2 (see below). In the majority of HGPS patients, the cause of death is due to cardiovascular problems, e.g. arteriosclerosis. Notably, in the efficacy analyses, weight gain was chosen as the primary outcome and survival is not listed among secondary outcomes. In addition, cardiovascular endpoints were studied in the clinical studies. Refer to the data on clinical efficacy for details.

Secondary Pharmacology

The effect of lonafarnib in human cardiac repolarization has been investigated in EIG-LNF-010. The study was a double-blind, placebo- and moxifloxacin controlled, multiple-dose, parallel-group study with a nested crossover design for the moxifloxacin/placebo comparison, conducted in healthy volunteers.
The study demonstrates that the combination of lonafarnib and ritonavir does not prolong the Qtc interval in healthy volunteers at therapeutic doses. The effect of lonafarnib cannot be isolated from this study. However, it is unlikely that lonafarnib alone causes Qtc-prolongation >5 ms in therapeutic doses.

Figure 16: Predicted ΔΔQTcF Interval at Geometric Mean Peak Concentrations for Lonafarnib from Full Model with Interaction (Lonafarnib + RTV Analysis) (PK/QTc Populations)



LNF = lonfarnib; PK = pharmacokinetic; RTV = ritonavir
Source: EIG-LNF-010 Cardiac Safety Report Figure 14.2.3.10.1.4.1.A

Figure 7: Relationship between plasma-concentration and effect.

The Applicant has not provided an overall dose justification. No dose-escalation studies have been conducted in the target population, and no exposure-response analysis has been provided.

The starting dose of 115 mg/m^2 BID was the MTD in a population of paediatric oncology patients and applying this dose as starting dose in the HGPS, and PL population seems reasonable. Plasma concentration of lonafarnib appeared to decline with prolonged exposure which probably explains that the lonafarnib dose was increased to 150 mg/m^2 BID after 4 months in the study 07-01-007. However, it is not clear why 4 months was chosen as a cut-off for the dose-escalation.

Even though the 115 mg/m^2 -150 mg/m^2 BID dosing regimen was tolerable in the HGPS and PL population and efficient in terms of weight gain, it is not known whether a lower dose of lonafarnib

could be efficient. Additionally, the BID regimen is not adequately accounted for a T½ of about 4 hours, which could cause quite low lonafarnib Cthrough levels in a BID dosing regimen. Unfortunately, no data on Cthrough-levels or AUC to ensure efficacy in the HGPS, and PL population has been provided.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetics of lonafarnib have been investigated in healthy volunteers and patients with HGPS and PL. Several remaining DDI concerns have been resolved with the implementation of appropriate warnings in the SmPC and corresponding DDI studies will be undertaken as post-authorisation measures.

Based on the non-clinical data provided (see non-clinical section above), the pharmacological proof of concept can be considered demonstrated regarding the fact that lonafarnib inhibits farnesylation. This non-clinical observation can be translated to human *in vivo* pharmacology as under lonafarnib, the percentage of abnormal nuclei (or misshaped nuclei) in human cellular material is reduced in a dose-dependent matter.

There is no direct relation to the improvement of abnormal nuclei and pharmacodynamic/clinical endpoints such as survival or cardiovascular parameters (e.g. PWV, SBP, carotid echo density). It can be concluded that lonafarnib indeed reduces the production of progerin in cells. This adds further to the proof of concept and strongly suggests that lonafarnib blocks progerin production, which might have an impact on at least some cardiovascular parameters and potentially also on other clinical endpoints. From the non-clinical data, it can be learned that indeed in progeria mouse models under lonafarnib like molecules, cardiovascular issues are reduced, and progerin accumulation is reduced in these mouse models.

2.6.4. Conclusions on clinical pharmacology

Limited PK data has been provided for lonafarnib as monotherapy. The predictive performance of the population pharmacokinetic model is considered poor. Therefore, the model cannot be used for simulations. However, for this indication, this issue is no longer pursued. There are some concerns regarding the metabolite profile and clinical DDIs. The Applicant will conduct a new mass balance study to elucidate the metabolite profile as a post-authorisation measure. Further, a study will be conducted as a post-authorisation measure to investigate the effect of a moderate CYP3A4 inhibitor on the PK of lonafarnib. Furthermore, a DDI study with P-glycoprotein inhibitor and a DDI study with oral contraceptives will be undertaken as post-authorisation measures.

Under lonafarnib, the percentage of abnormal nuclei in human cellular material (e.g. fibroblasts) is reduced in a dose-dependent matter. Although it is considered demonstrated that under continued lonafarnib treatment, progerin levels decrease in HGPS patients, there is no direct link to clinically relevant endpoints (such as PWV, SBP and carotid echo density). Given the disease pathophysiology, there is a theoretically accepted and plausible mechanism in which progerin reduction acts on the vascular tissues inducing apoptosis and consequently inflammation and atherosclerosis. Refer to the clinical efficacy section for further details.

2.6.5. Clinical efficacy

Table 8 displays the studies that were conducted with lonafarnib in the intended patient population. Note that for the proposed indication, the studies pertaining to lonafarnib monotherapy are considered most important, e.g. study 07-01-0007 (Prolon1) and Prolon2 as part of the triple therapy study 09-06-0298.

Data on patients treated with triple therapy is considered supportive information. The pivotal clinical study submitted by the applicant is the Cohort Survival Study. Prolon1 and Prolon2 are considered supportive.

2.6.5.1. Main study(ies)

Main study

An observational cohort survival study: results from a pooled analysis of lonafarnib treatment in patients with Hutchinson Gilford progeria syndrome

General Design and Participants

This was a cohort study comparing all-cause mortality in lonafarnib monotherapy treated HGPS patients with untreated HGPS patients.

All patients (treated and untreated patients) and their associated data were identified using the Progeria Research Foundation International Registry (http://www.progeriaresearch.org/patient_registry.html), published scientific and news articles, and publicly available databases (Figure 3). Of 258 total patients in the complete natural history cohort, 211 were identified from the Progeria Research Foundation International Registry, and 47 patients' study inclusion information was derived purely from scientific publications. Minimum inclusion criteria were HGPS phenotype confirmed by clinical experts and information on living age or age of death. Additional data collected included sex, country of origin, cause of death, and genotype, when available.

The **treated** cohorts included patients from two single-arm, single-centre lonafarnib monotherapy trials, **ProLon1** (N=27) and lonafarnib monotherapy extension study (the designated **ProLon2** population; N=35).

The treated patients received oral lonafarnib (150 mg/m^2) twice daily in Prolon1 and Prolon2. Untreated patients received no clinical trial medications but may have received medication for symptomatic treatment.

Figure 3, Figure 15, Figure 16 and Figure 17 describe the selection process for the matched analyses pool, including reasons why these individuals did not participate in ProLon1 and ProLon2. It seems that patients were excluded from the Natural History Cohort due to poor health status/morbidities or incapable of visiting the clinic, precluding their participation and therefore introduces selection bias.

The earliest patient observation for both the treated cohorts and the untreated contemporaneous controls used in the survival analyses was in 1991.

Treated patients were matched with contemporaneous (birth date ≥1991) untreated patients by a random matching method using age, sex, and the continent of residency as propensity factors. Note that the patients included in the survival analysis were treated with lonafarnib in their respective studies, either Prolon1 or Prolon2.

Methods

The observational cohort survival study analysis was designed to evaluate all identified HGPS patients worldwide and compared all-cause mortality in lonafarnib monotherapy (e.g. Prolon1 and Prolon2) treated patients with HGPS with contemporaneous (birth date ≥1991) untreated patients from a natural history cohort. Thus, the cohort survival study assembled a control group external to the clinical trials.

Study Participants

Inclusion criteria

Natural History Cohort (NHC):

For inclusion in the natural history cohort, patients must have been identified from the Progeria Research Foundation (PRF) International Progeria Registry, such that they had no prior exposure to lonafarnib.

The PRF started the construction of the Natural History Cohort by harvesting data from (1) PRF's internal patient database and (2) PRF's International Registry. Sources used to identify children with HGPS for the database and registry included:

- *Case studies from W. Ted Brown, MD (Director; New York State Institute for Basic Research in Developmental Disabilities)*
- *The Sunshine Foundation, which formerly sponsored Progeria reunions annually for children with Progeria and maintained rosters and photos.*
- *Web searches of news articles and publicly available databases (e.g., Legacy.com)*
- *PubMed literature search for case report publications.*
- *A physician, family member of someone with knowledge of a child (provided parental consent was obtained) that may have HGPS might inform a PRF staffer or Dr. Leslie Gordon of a possible case of HGPS.*
- *Case studies from Dr. Leslie Gordon.*

The eligibility criteria below were used to determine patient eligibility for inclusion in the Natural History Cohort:

- *Clinical and/or genetic diagnosis of HGPS;*
- *Available data on date of birth and date of death;*
- *OR, if one of the above was missing:*
- *Age of death;*
- *OR, known vital status on January 1, 2018.*

Treated population:

For inclusion in the treated population, patients must have been enrolled in ProLon1 (Study 07-01-0007) or Monotherapy Group 2 (ProLon2 Study 09-06-0298). Both studies are described under the paragraph of supportive studies.

Exclusion criteria

Patients with non–progerin-producing laminopathies were excluded from the analyses.

Treatments

Patients in the Natural History Cohort (NHC) did not receive active treatment but may have received other medications to treat their symptoms.

Patients in the active treatment group received treatment lonafarnib monotherapy in study Prolon1 and Prolon2.

Objectives

Primary Objective

- To evaluate the association of lonafarnib monotherapy using the protein farnesyltransferase inhibitor lonafarnib with prolonging survival time in patients with HGPS in a combined analysis of the ProLon1 and ProLon2 study populations.

Secondary Objectives

• To evaluate the association of monotherapy using the protein farnesyltransferase inhibitor lonafarnib with the reduction of incidence of all-cause mortality in a combined analysis of the ProLon1 and ProLon2 study populations; and

• To evaluate the association of monotherapy using the protein farnesyltransferase inhibitor lonafarnib on the incidence rate of all-cause mortality adjusted for patient-observation time in a combined analysis of the ProLon1 and ProLon2 study populations.

Outcomes/endpoints

Principal Efficacy Variable(s)

The principal efficacy variable of this analysis was time to eligible all-cause mortality (death) before June 1, 2019.

Key Secondary Efficacy Variable(s)

The key secondary variables were:

- the incidence rate of eligible all-cause mortality before the cut-off date of June 1, 2019;
- the incidence rate of eligible all-cause mortality before the cut-off date of June 1, 2019, adjusted for patient-time.

Randomisation, blinding (masking) and Matching

Both Prolon1 and Prolon2 studies were single-arm, and therefore randomisation and blinding were not applicable.

HGPS patients from the pooled Prolon1 and Prolon2 study were randomly matched with patients from the NHC based on age, sex and continent.

Primary Matching Method (random untreated):

Unpaired treated patients were sorted by descending age at treatment initiation. For the first treated patient in this sorted list, all unpaired untreated patients of the same sex and from the same continent of residency who were alive at the age when the treated patient began lonafarnib were identified. From this group of untreated patients, one was randomly selected and used as the matched untreated patient in the analysis for this treated patient; this untreated patient was no longer available for matching with any remaining treated patient. Follow-up for both patients in the matched pair began at the age of treatment initiation for the treated patient in the matched pair.

Several other matching strategies were performed which resembles the primary matching method and all based on all untreated candidates sorted by their last known age in descending order, namely Fixed 50th Percentile, Fixed 75th Percentile, Fixed 100th Percentile, Random within Upper 50th Percentile of Untreated, and Least Favourable Match, which attempted to capture the patients with the best longevity among the untreated group.

Statistical methods

Analysis Sets

ProLon1 and ProLon2 Intention-to-Treat (ITT1_2) Analysis Population:

All patients treated with lonafarnib from ProLon1 and ProLon2 combined were included in the ITT1_2 analysis population. In addition, the 173 untreated patients in the Brown University & Progeria Research Foundation HGPS natural history pool were also included in the ITT1_2 analysis population. The ITT1_2 analysis population will be used for sensitivity analyses on ProLon1 and ProLon2 patients combined.

ProLon1 and ProLon2 Contemporaneous Intention-to-Treat (CITT1_2) Analysis Population:

All patients treated with lonafarnib from ProLon1 and ProLon2 combined were included in the CITT1_2 analysis population. From the 173 untreated patients in the Brown University & Progeria Research Foundation HGPS natural history pool, a total of 81 contemporaneous patients (born in or after 1991) who had not been included in a treatment trial were used as the CITT1_2 analysis population. The CITT1_2 analysis population was used for key analyses on ProLon1 and ProLon2 patients combined.

For the primary efficacy analysis, the CITT1_2 analysis population was used. The analysis based on the ITT1_2 population will be considered as a sensitivity analysis.

Eligible All-Cause Mortality is a subset of all deaths:

For both ProLon1 and ProLon2 patients, deaths that occurred before entering either the triple therapy or initiation of everolimus therapy (study 0000170505), including ones that had occurred after the last date of monotherapy treatment, were considered eligible.

Definition of Maximum Follow-Up Time

- For a ProLon1 and Prolon2 patient, the maximum follow-up time is defined as either the age/date at **the initiation of triple therapy or everolimus treatment**, the age/date of lost to follow-up, or the age/date of death, or June 1, 2019, whichever is earlier.
- For the untreated patients, the maximum follow-up time is either the last age/date of lost to follow-up, age/date of death, or June 1, 2019, whichever is earlier.

Censoring for Matched Data in key analyses:

For the key analysis, treated and matched untreated patients were censored at 3 years post age of treatment start.

Primary Efficacy Analysis

Kaplan-Meier survival curves, where survival is defined as not experiencing eligible all-cause mortality, for the treated and untreated matched groups through the maximum follow-up time up to 3 years post age of treatment start are presented. The 95% confidence intervals at each event time are presented.

The comparison between the treated and matched untreated group was carried out using a log-rank test stratified on sex and continent.

In addition, an unconditioned Cox proportional hazards model stratified on sex and continent was used to compare the treated and matched untreated groups.

Sensitivity Analyses

The most important sensitivity analyses are:

- The primary survival analysis performed for the ITT1_2 population. This population also includes the untreated NHC patients born before 1991.
- Primary survival analyses were performed for each individual study and for the belonging ITT and CITT populations.

Key Secondary Efficacy Analysis

- Incidence of Eligible Deaths

  A Cochran-Mantel-Haenszel test was performed to compare the treated patients with the matched untreated patients with respect to the proportion of patients with eligible death during the follow-up period up to 3 years post age of treatment start, adjusted for sex and continent (if matching by continent was feasible).

Results

Participant flow

For the participants flow refer to Figure 3.

To compare mortality rates among treated *versus* untreated patients, matching was performed whereby 62 patients from ProLon1 (n=27) plus ProLon2 (n=35) combined were randomly matched to the individuals from the pool of 81 untreated patients described above. Due to the limited number of contemporaneous patients available, the characteristics used as matching criteria were prioritized, and the most important factors in determining similarity among patients were chosen: age, sex, and the continent of residency. Matching was contemporaneous to ensure that similar medical care was available to both groups.

Baseline data

Baseline data are presented in (Table 8).

Table 8: Demographic and Baseline Characteristics of Treated and Untreated Patients in the Main Analysis Population and Random Untreated Match Population for the Survival Analysis (CITT1_2).

Characteristics	Treated (N=62)	Untreated (N=81)	Overall (N=143)	Random Untreated Match[a] (N=62)
Age at Treatment Start (years)				
Mean (SD)	7.03 (3.587)	NA	7.03 (3.587)	7.03 (3.587)
Median	6.69	NA	6.69	6.69
Min, Max	2.1, 17.5	NA	2.1, 17.5	2.1, 17.5
Age at Last Follow-up (years)				
Mean (SD)	11.70 (5.008)	10.49 (4.544)	11.02 (4.772)	10.96 (4.474)
Median	11.14	10.66	10.66	10.81
Min, Max	2.5, 21.8	2.6, 20.0	2.5, 21.8	2.9, 20.0
Sex, n (%)				
Male	33 (53.2)	42 (51.9)	75 (52.4)	33 (53.2)
Female	29 (46.8)	39 (48.1)	68 (47.6)	29 (46.8)
Born on or after 1991, n (%)				
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes	62 (100.0)	81 (100.0)	143 (100.0)	62 (100.0)
Continent, n (%)				
Africa	2 (3.2)	2 (2.5)	4 (2.8)	1 (1.6)
Asia	16 (25.8)	31 (38.3)	47 (32.9)	20 (32.3)
Australia	1 (1.6)	0 (0.0)	1 (0.7)	0 (0.0)
Europe	12 (19.4)	16 (19.8)	28 (19.6)	14 (22.6)
North America	20 (32.3)	12 (14.8)	32 (22.4)	12 (19.4)
South America	11 (17.7)	20 (24.7)	31 (21.7)	15 (24.2)
Known genotype, n (%)				
No	0 (0.0)	34 (42.0)	34 (23.8)	28 (45.2)
Yes	62 (100.0)	47 (58.0)	109 (76.2)	34 (54.8)
Mutation, n (%)				
Classic	60 (96.8)	38 (46.9)	98 (68.5)	27 (43.5)
Non-Classic	2 (3.2)	9 (11.1)	11 (7.7)	7 (11.3)
Unknown	0 (0.0)	34 (42.0)	34 (23.8)	28 (45.2)

max = maximum; min = minimum; NA = not applicable; SD = standard deviation

[a] *Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.*

Numbers analysed

Table 9: Patient Disposition Prolon1 and Prolon2.

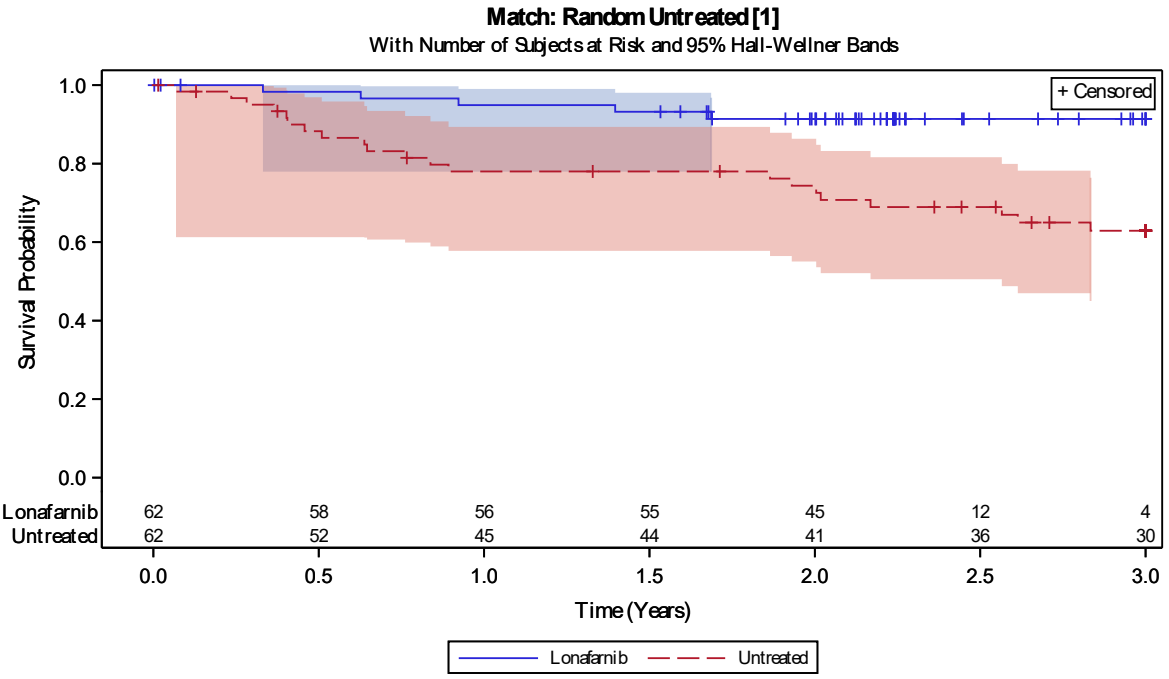
Disposition, n (%)	ProLon1 (N=27)	ProLon2 (N=35)
Completed – Continued Treatment	25 (92.6)	23 (65.7)
Completed – Did Not Continue Treatment	1 (3.7)	2 (5.7)
Death	1 (3.7)	3 (8.6)
Primary Investigator Withdrew Subject	0 (0.0)	2 (5.7)
Withdrawal by Parent/Guardian	0 (0.0)	3 (8.6)
Withdrawal by Subject	0 (0.0)	1 (2.9)
Ongoing	0 (0.0)	1 (2.9)

Outcomes and estimation

When censored at the start of another treatment or at 3 years, five of 62 patients died in the treated group, whereas 21 of 81 patients died in the untreated group.

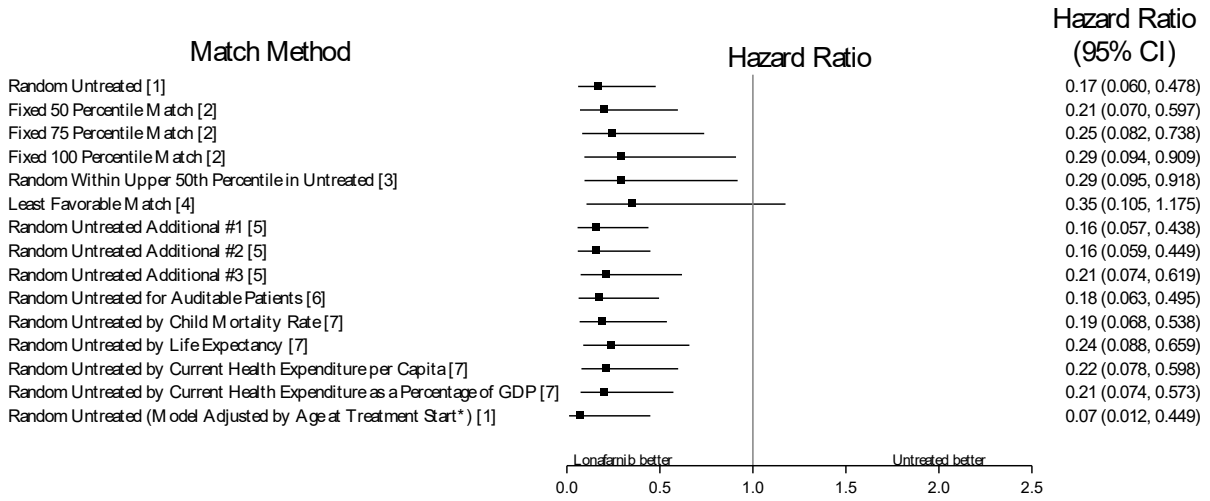
The Kaplan-Meier curves showed clear and early separation (Figure 10). A statistically significant improvement in survival time (censored at 3 years) was associated with lonafarnib treatment compared to untreated controls (mean 2.83 vs 2.34 years; p=0.0002, stratified log-rank test) and based on the CITT1_2 population.

Analysis of the survival data using the Cox proportional hazards model based on the CITT1_2 population shows an estimated HR of 0.17 (95% CI of 0.06 to 0.48). All matching methods as presented in Figure 11 showed the results for the estimated Hazard ratios (HRs).



[1] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.
Note: The remaining patients at risk for each group are listed at the bottom of the figure. The 95% Hall-Wellner confidence bands (orange and blue band in figure) can only be computed when there are a sufficient number of events.

Figure 8: Kaplan-Meier Survival Curve of Treated versus Random Untreated Match (Censored at 3 Years) – Main Analysis Population (N=143).



*CI = confidence interval; FDA = Food and Drug Administration; GDP = gross domestic product[1] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.[2] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent at the defined percentile of age (if two then the oldest is selected). Untreated patients are not assigned randomly for this match method.[3] Treated patients sorted by descending age at treatment initiation were matched to untreated patients in the upper 50th percentile of age by sex and continent.[4] Treated patients sorted by descending age at treatment initiation were first matched to untreated patients who were alive or censored and then to the untreated patients with the largest age at death.[5] Three additional independent matches were created for sensitivity analysis using the primary match method.[6] Six of the 81 untreated patients were excluded from the population prior to using the primary match method. The data for these patients is unavailable to be inspected by the FDA due to consent issues.[7] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and proxy for continent.*This Cox proportional hazards model was stratified on sex and continent/proxy; it includes treatment group as a factor, age at treatment start as a covariate, and the interaction between treatment group and age at treatment start. The hazard ratio at the average age of treatment start was summarized.*

Figure 9: Forest Plot of Hazard Ratios and 95% Confidence Intervals (Censored at 3 Years) – Main Analysis. Population (N=143).

Ancillary analyses

Sensitivity Analyses

The survival results of the sensitivity analyses show considerable variability between and within (ITT and CITT, respectively) the two individual studies (Prolon1 and Prolon2), and treatment effect estimates are typically smaller and mostly not significant, and thus not consistent with the survival results of the pooled survival analysis based on the CITT1_2 population. The survival results for the pooled studies based on the ITT1_2 population (CITT1_2 plus untreated patients born before 1991) is also inconsistent with the survival results based on the CITT1_2 population. Because the sensitivity analyses do not show consistent results, the treatment effect of the pooled primary survival analysis is uncertain. Indicating that the treatment-related survival benefit of lonafarnib monotherapy in patients with HGPS is unclear. With this censoring method (censored as start new therapy or 3 years) and this matching method (random selection of one match), the results from Prolon1 and Prolon2 are numerically comparable or better for lonafarnib at 1 and 2 years. However, censoring at adapted last-follow-up and the 'repeated random matching with replacement' is considered to mitigate possible biases due to differences in follow-up and the number of available candidates for matching.

When these analyses are performed, survival curves seem to favour the NHC patients in Prolon2 (e.g., median 7.2 in NHC vs 4.3 for lonafarnib), at least for the longer-term follow-up.

Table 10: Survival Analysis results including the sensitivity analyses: Log-Rank Test and Cox PH test on Survival Time with Sex and Continent as Stratum in Treated versus Random Untreated Match (Censored at start other treatment or 3 Years).

Study	Population		Log-Rank test				Cox PH test	
			Treated patients	Untreated patients	Difference	P-value	HR (95% CI)	P-value
Prolon1 (27 patients in each group)	CITT1	Number of Events	1	7		0.020	0.12 (0.01, 0.99)	0.049
		Probability survival after 1 years (SE)	0.963 (0.0363)	0.804 (0.0788)	0.159			
		Probability survival after 2 years (SE)	0.963 (0.0363)	0.804 (0.0788)	0.159			
	ITT1	Number of Events	1	2		0.594	0.53 (0.05, 5.81)	0.600
		Probability survival after 1 years (SE)	0.963 (0.0363)	1.00 (0.0000)	-0.037			
		Probability survival after 2 years (SE)	0.963 (0.0363)	0.926 (0.0504)	0.037			
Prolon2 (35 patients in each group)	CITT2	Number of Events	4	8		0.404	0.59 (0.17, 2.06)	0.409
		Probability survival after 1 years (SE)	0.938 (0.0428)	0.855 (0.0599)	0.083			
		Probability survival after 2 years (SE)	0.870 (0.0609)	0.855 (0.0599)	0.015			
	ITT2	Number of Events	4	9		0.221	0.48 (0.15, 1.59)	0.230
		Probability survival after 1 years (SE)	0.938 (0.0428)	0.913 (0.0482)	0.025			
		Probability survival after 2 years (SE)	0.870 (0.0609)	0.793 (0.0699)	0.077			
Prolon1 and Prolon2 pooled (62 patients	CITT1_2	Number of Events	5	21		0.0002	0.17 (0.06, 0.48)	0.0008
		Probability survival after 1 years (SE)	0.949 (0.0286)	0.780 (0.0539)	0.169			

in each group)		Probability survival after 2 years (SE)	0.914 (0.0368)	0.744 (0.0572)	0.170			
	ITT1_2	Number of Events	5	14		0.105	0.43 (0.15, 1.23)	0.115
		Probability survival after 1 years (SE)	0.949 (0.0286)	0.934 (0.0317)	0.015			
		Probability survival after 2 years (SE)	0.914 (0.0368)	0.834 (0.0480)	0.080			

Table 11: Log-Rank Test on Survival Time with Sex, and Continent as Stratum in Treated versus Repeated Random Untreated with Replacement (Censored at Adapted Last Follow-up, All Treated Deaths Considered) Population: ProLon1 Contemporaneous Intention-to-Treat Set (N=108).

Matching Method	Parameter	Statistics	Treated (n=27)	Untreated (n=81)
All Possible Matches [3]	Stratified Log-Rank Test [1]	p-value Treated versus Untreated (two-sided)	0.0060	
	Number of Patients by Censoring Status			
	Total Patients	n	27	27
	Censored	n%	12 (44.4)	5.908 (21.9)
	Not Censored (Deaths)	n%	15 (55.6)	21.092 (78.1)
	Restricted Mean Survival Time	Restricted Mean Survival Time (SE)	8.466 (0.5365)	5.841 (0.7106)
		p-value for Test of Equality	0.0027	
	Survival (Years) [2]	Mean Survival (SE)	8.642 (0.5920)	6.080 (0.8177)
		75th Percentile (95% CI)	11.0 (10.60, n/a)	9.1 (6.70, 10.22)
		50th Percentile (95% CI)	10.1 (7.15, n/a)	6.1 (3.17, 8.14)
		25th Percentile (95% CI)	6.6 (3.76, 7.71)	2.5 (0.34, 4.96)

Note: Last follow-up date for treated group is selected, including dates found in the triple therapy or monotherapy extension. The follow-up time was adapted such that in case a treated patient in a matched pair is censored, the untreated patient was censored at the same length of follow-up and only eligible deaths during the adapted follow-up time were considered.
[1] Stratified by sex and continent.
[2] Kaplan-Meier Estimates. Mean survival is the area under the survival curve from the beginning to follow-up. Standard error is calculated based on the Greenwood formula.
[3] Treated patients sorted by descending age at treatment initiation were matched to all possible untreated patients by sex and continent. Treated patients were then randomly matched to one of their possible untreated patients with replacement. This was repeated 1,000 times. The bootstrap p-value was obtained by the cumulative probability greater than the average of the 1,000 bootstrapped test statistics using a chi-square with 1 degree of freedom. All other statistics are calculated as the mean of the 1,000 replicates.

Table 12: Log-Rank Test on Survival Time with Sex, and Continent as Stratum in Treated versus Repeated Random Untreated with Replacement (Censored at Adapted Last Follow-up, All Treated Deaths Considered) Population: ProLon2 Contemporaneous Intention-to-Treat Set (N=116).

Matching Method	Parameter	Statistics	Treated (n=35)	Untreated (n=81)
All Possible Matches [3]	Stratified Log-Rank Test [1]	p-value Treated versus Untreated (two-sided)	0.5287	
	Number of Patients by Censoring Status			
	Total Patients	N	35	35
	Censored	n%	29 (82.9)	27.614 (78.9)
	Not Censored (Deaths)	n%	6 (17.1)	7.386 (21.1)
	Restricted Mean Survival Time	Restricted Mean Survival Time (SE)	3.687 (0.2597)	3.650 (0.2430)
		p-value for Test of Equality	0.5727	
	Survival (Years) [2]	Mean Survival (SE)	3.708 (0.2886)	6.423 (1.0674)
		75th Percentile (95% CI)	4.3 (n/a,,n/a)	9.2 (5.45, n/a)
		50th Percentile (95% CI)	4.3 (3.08, n/a)	7.2 (4.41, n/a)
		25th Percentile (95% CI)	3.1 (1.40, n/a)	4.9 (0.91, 7.57)

Note: Last follow-up date for treated group is selected, including dates found in the triple therapy or monotherapy extension. The follow-up time was adapted such that in case a treated patient in a matched pair is censored, the untreated patient was censored at the same length of follow-up and only eligible deaths during the adapted follow-up time were considered.
[1] Stratified by sex and continent.
[2] Kaplan-Meier Estimates. Mean survival is the area under the survival curve from the beginning to follow-up. Standard error is calculated based on the Greenwood formula.
[3] Treated patients sorted by descending age at treatment initiation were matched to all possible untreated atients by sex and continent. Treated patients were then randomly matched to one of their possible untreated patients with replacement. This was repeated 1,000 times. The bootstrap p-value was obtained by the cumulative probability greater than the average of the 1,000 bootstrapped test statistics using a chi-square with 1 degree of freedom. All other statistics are calculated as the mean of the 1,000 replicates.

Additional analyses further compared the survival result of Prolon1 with those of Prolon 2.

Additional Cox proportional hazard model and Km curves including Prolon1, 2, and naïve triple therapy patients.

The Cox proportional hazard model (Table 17) shows that age of treatment start is likely to be an independent factor in predicting the timing of patient mortality. After adjusting for this independent factor, treatment with lonafarnib was found to significantly prolong survival compared with those that were untreated.

Table 13: Cox Proportional Hazards Model on Survival Time in Treated Versus Random Untreated Stratified on Sex, Continent by Age Subgroup (N=162).

Age at Treatment	Matching Method	Parameter	Statistics	ProLon1 (n=27)	Prolon2 (n=35)	Triple Therapy (n=18)	Untreated (n=82)
All Ages	Original Random Untreated [2]	Number of Patients by Censoring Status					
		Total Patients	n	27	35	18	80
		Censored	n(%)	12 (44.4)	26 (74.3)	12 (66.7)	34 (42.5)
		Not Censored (Deaths)	n(%)	15 (55.6)	9 (25.7)	6 (33.3)	46 (57.5)
			P-value for Overall Treatment (two-sided) [1]	<.0001			
			Hazard Ratio for Treated versus Untreated (95% CI)	0.23 (0.115, 0.457)	0.35 (0,156, 0.780)	0.24 (0,084, 0.702)	
			P-value for Age (two-sided)	<.0001			
			Hazard Ratio for Age (95% CI)	1.25 (1.159, 1.345)			
≤10	Original Random Untreated [2]	Number of Patients by Censoring Status					
		Total Patients	n	23	30	15	68
		Censored	n(%)	11 (47.8)	25 (83.3)	12 (80.0)	31 (45.6)

	Not Censored (Deaths)	n(%)	12 (52.2)	5 (16.7)	3 (20.0)	37 (54.4)
		P-value for Overall Treatment (two-sided) [1]	<.0001			
		Hazard Ratio for Treated versus Untreated (95% CI)	0.19 (0.082, 0.430)	0.22 (0.072, 0.653)	0.13 (0.034, 0.489)	
		P-value for Age (two-sided)	0.0010			
		Hazard Ratio for Age (95% CI)	1.27 (1.101, 1.466)			

Note: 01AUG2021 Survival Status date is selected, and is defined as the death date or last date confirmed alive as of 01AUG2021. The follow-up time was adapted such that in case a treated patient in a matched pair is censored, the untreated patient was censored at the same length of follow-up and only eligible deaths during the adapted follow-up time were considered.
This Cox proportional hazards model was stratified on Sex and Continent; it includes study group (ProLon1, ProLon2, Triple Therapy and Untreated) as a factor and age at treatment start as a covariate. The hazard ratio of treatment was summarized.
[1] Stratified by sex and continent.
[2] Treated patients from ProLon 1, ProLon 2 and Triple Therapy were sorted by descending age at treatment initiation and matched to untreated patients by sex and continent.

Addition of 18 treatment naïve patients to Prolon 2

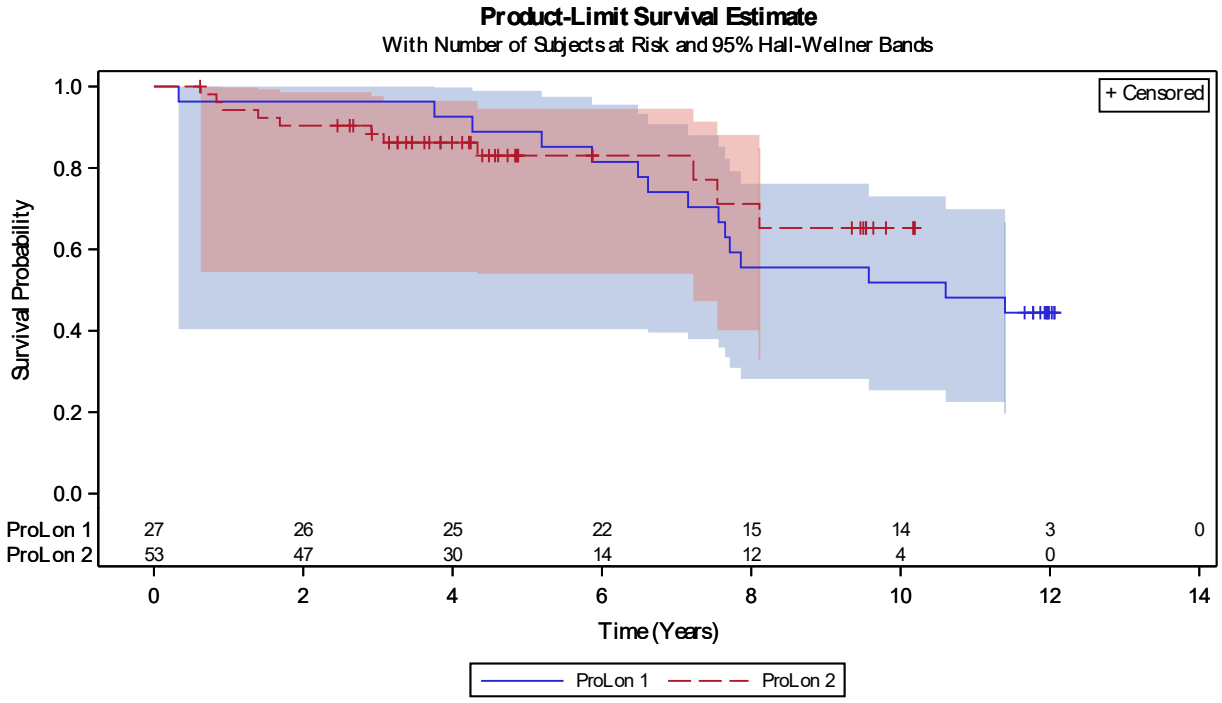
The Study 09-06-0298 Data and Safety Monitoring Board (DSMB) concluded that adding pravastatin and zoledronate to lonafarnib did not impart additional efficacy over lonafarnib alone.

To assess survival, these groups can be treated as if they were receiving lonafarnib monotherapy throughout their entire treatment.

Adding the 18 HGPS drug-naïve patients that started in the triple therapy portion of Study 09-06-0298 (Group 1) to the ProLon2 (Group 2) population eliminates the large difference in follow-up time between the two study populations and increases the ProLon2 sample size.

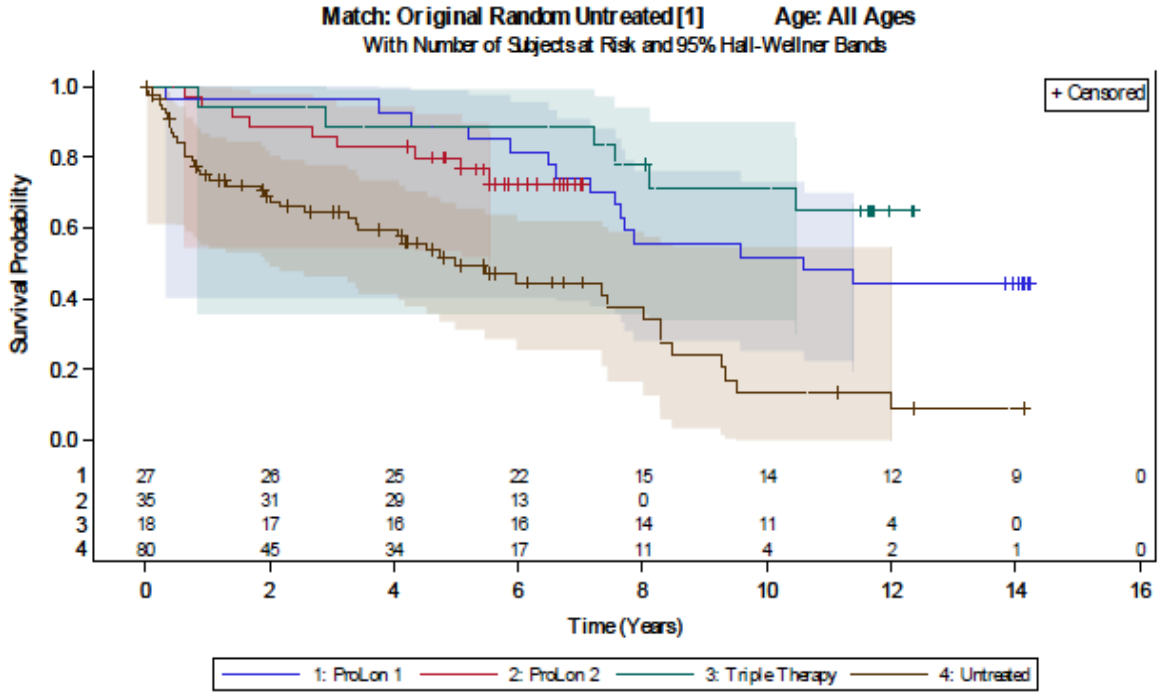
Figure 10 shows that ProLon2, when included in the drug-naïve triple therapy HGPS patients, provides the same survival benefit as ProLon1. This is especially true when early deaths are considered in ProLon2 are primarily a function of the inclusion of older patients. As previously mentioned, there were a disproportionate number of older patients in ProLon2 versus ProLon1. These patients all resided on the steeply sloped portion of the natural history KM survival curve (≥ 11 years of age), and two patients only received a few months of therapy before dying (patients 5673 and 6689).

Figure 10: Kaplan-Meier Survival Curves for ProLon1 and ProLon2 Including HGPS Drug-naïve Triple Therapy Patients (Survival Status as of June 1st, 2019).



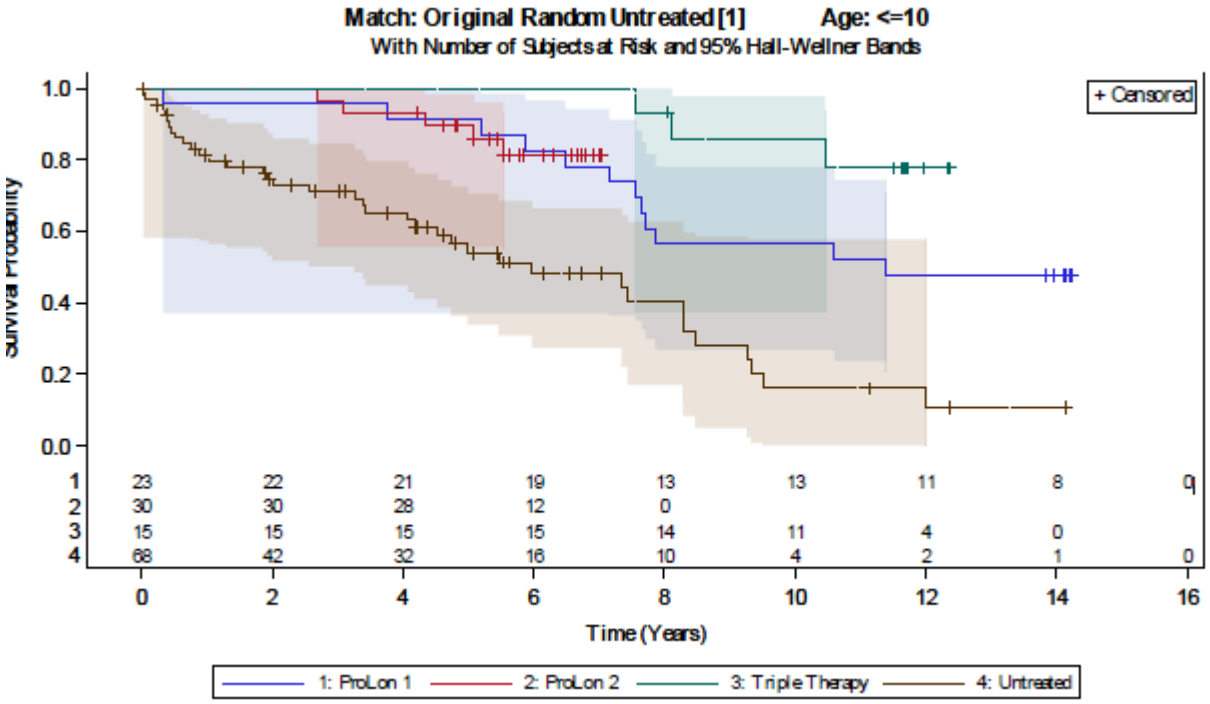
The survival curves for the individual studies were submitted (Figure 13 and Figure 14) with a cut date of 1 August 2021.

Figure 11: Kaplan-Meier Survival Curves All Ages ProLon1, ProLon2 (unrevised), Group 1 Study 09-06-0298 (Triple Therapy), and Natural History Cohorts (Survival Status as of August 1st, 2021) (N=162)



Note: The remaining patients at risk for each group are listed at the bottom of the figure. The 95% Hall-Wellner confidence bands can only be computed when there are a sufficient number of events. 01AUG2021 Survival Status date is selected, and is defined as the death date or last date confirmed alive as of 01AUG2021. The follow-up time was adapted such that in case a treated patient in a matched pair is censored, the untreated patient was censored at the same length of follow-up and only eligible deaths during the adapted follow-up time were considered.
[1] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.

Figure 12: Kaplan-Meier Survival Curves for Patients ≤10 Years of Age in ProLon1, ProLon2 (unrevised), Group 1 Study 09-06-0298 (Triple Therapy), and Natural History Cohorts (Survival Status as of August 1st, 2021) (N=162).



Note: The remaining patients at risk for each group are listed at the bottom of the figure. The 95% Hall-Wellner confidence bands can only be computed when there are a sufficient number of events. 01AUG2021 Survival Status date is selected, and is defined as the death date or last date confirmed alive as of 01AUG2021. The follow-up time was adapted such that in case a treated patient in a matched pair is censored, the untreated patient was censored at the same length of follow-up and only eligible deaths during the adapted follow-up time were considered.
[1] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.

Key secondary Analysis

Incidence of Eligible Deaths

The Cochran-Mantel-Haenszel (CMH) test was performed based on the CITT1_2 population to compare the treated and untreated groups with respect to the incidence of mortality during the follow-up period up to 3 years post age of treatment start. The estimated incidence is 8% for the treated group and 34% for the untreated group. The RR is 0.21, with a 95% CI 0.08 – 0.54 (**Table 14**).

Table 14: Cochran-Mantel-Haenszel Test on Incidence of Eligible Deaths in Treated versus Random Untreated Match Adjusted for Sex and Continent (Censored at 3 Years). Population: ProLon1 and ProLon2 Contemporaneous Intention-to-Treat Set (N=143).

Matching Method	Parameter	Statistics	Treated (n=62)	Untreated (n=81)
Random Untreated [1]	Number of Patients by Eligible Death Status			
	Total Patients	n	62	62
	Eligible Deaths	n (%)	5 (8.1)	21 (33.9)
	Not Eligible Deaths	n (%)	57 (91.9)	41 (66.1)
	Incidence	Proportion (SE)	0.0806 (0.03458)	0.3387 (0.06011)
		95% CI	(0.0129, 0.1484)	(0.2209, 0.4565)
	Cochran-Mantel-Haenszel	Relative Risks (95% CI)	0.21 (0.083, 0.542)	
		Odds Ratio (95% CI)	0.16 (0.056, 0.464)	
		p-value Treated versus Untreated	0.0002	

Note: Follow-up date for treated group is selected based on the date of initiation of triple therapy or everolimus, otherwise, last follow-up date is used. Patients are censored at 3 years if their follow-up exceeds 3 years from treatment initiation.
[1] Treated patients sorted by descending age at treatment initiation were matched to untreated patients by sex and continent. This is the primary match method.

Summary of main efficacy results

Table 15 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy and the benefit-risk assessment (see later sections).

Table 15: Summary of efficacy for the survival cohort study.

Title: An Observational Cohort Survival Study: Results from a Pooled Analysis of Lonafarnib Treatment in Patients with Hutchinson-Gilford Progeria Syndrome[1)]		
Study identifier	not applicable	
Design	Observational cohort survival study analysis was designed to evaluate all identified HGPS patients world-wide and compared all-cause mortality in lonafarnib monotherapy treated patients with HGPS with contemporaneous (birth date ≥1991) untreated patients from a natural history cohort	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Censored at 3 years not applicable not applicable
Hypothesis	Exploratory: the survival analysis was performed based on the assumption that patients treated in Prolon1 and Prolon2 showed a potential longer survival compared to untreated patients selected from the NHC.	

Treatments groups	lonafarnib monotherapy group		Lonafarnib monotherapy for 24 (Prolon1) to 36 months (Prolon2). Prolon1 n=26 classic HGPS; 1 non-classic HGPS Prolon2 n=34 classic HGPS; 1 non-classic HGPS
	Untreated NHC[2)]		Total n=81 classic HGPS = 38 non-classic HGPS = 9 mutation unknown = 35
Endpoints and definitions	Primary analysis Survival	Survival	Follow-up time for a matched pair began at the age of treatment initiation of the treated patient in the matched pair and ended at each patient's respective maximum follow-up age/date up to 3 years post age of treatment start with cut-off date of June 1 2019. Treated patients were censored at initiation of triple therapy or everolimus treatment.
	Key Secondary analysis	Cochran-Mantel_Haenszel Test stratified by sex and continent	Incidence of eligible deaths based on matched pairs
Cutoff date	1 June 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Contemporaneous Intent to treat; all HGPS patients treated with lonafarnib monotherapy in Prolon1 and Prolon2 plus contemporaneous (born after 1991) untreated NHC patients. Patients were censored at 3 years.		
Descriptive statistics and estimate variability	Treatment group	lonafarnib	Untreated group
	Number of subject	62	81
	survival time (years) (mean)	2.83	2.34
Effect estimate per comparison	Primary endpoint	Comparison groups	Treated *vs* untreated
		Difference between groups (years)	0.49
		P-value stratified log-rank test	0.0002
	1) Although the title of the study is "An Observational Cohort Survival Study", in fact it should be considered a cohort survival analysis as patients selected from Prolon1 and Prolon2 received lonafarnib treatment either in Prolo1, Prolon2, or other studies. 2) In the NHC patients could have been treated with other medication for symptomatic treatment.		
Analysis description	**Key Secondary analysis** The estimated incidence during the follow-up period up to 3 years post age of treatment start is 8% for the treated group and 34% for the untreated group. The relative risk is the RR 0.21, with a 95% CI 0.08 – 0.54.		
Analysis description	**Sensitivity analyses** Survival analyses on the individual studies Prolon1 and Prolon2 showed inconsistent results. Sensitivity analyses based on different matching strategies showed results in favour of lonafarnib monotherapy.		

Analysis performed across trials (pooled analyses and meta-analysis)

Comparison between survivors and non-survivors while on lonafarnib treatment

A comprehensive analysis of the relationship between the cardiovascular parameters and mortality for the ProLon1 and ProLon2 patients (i.e., the same population used for the survival analysis) was conducted. The mortality status of the patients in the analyses was determined as of June 1, 2019. These analyses were done for ProLon1 and ProLon2 separately and combined. There were 41 survivors and 21 non-survivors (**Table 16**).

Table 16: Demographic by End of Treatment Status (Population: All ITT patients in ProLon1 and ProLon2 (N=62)) cut off mortality status 1 June 2019)[#].

Risk Factors	Censor (N=41)	Death (N=21)	Total (N=62)
Age at Start of Treatment			
n	41	21	62
Mean (SD)	5.99 (2.893)	9.06 (3.990)	7.03 (3.587)
Median	5.62	8.95	6.69
Min, Max	2.1, 16.3	3.1, 17.5	2.1, 17.5
P value			0.0016[2]
Age at End of Treatment			
n	40	21	61
Mean (SD)	8.14 (3.030)	10.97 (3.866)	9.11 (3.576)
Median	8.01	10.97	8.77
Min, Max	2.5, 19.0	5.1, 19.2	2.5, 19.2
Age Change from Treatment Start to End			
n	40	21	61
Mean (SD)	2.20 (0.654)	1.91 (0.624)	2.10 (0.654)
Median	2.23	2.14	2.21
Min, Max	0.0, 3.1	0.3, 3.0	0.0, 3.1
P value	<.0001[1]	<.0001[1]	0.0685[2]
PWV at Baseline (m/sec)			
n	37	19	56
Mean (SD)	9.57 (3.059)	11.06 (4.181)	10.08 (3.514)
Median	8.70	9.20	8.85
Min, Max	5.1, 18.3	6.7, 18.8	5.1, 18.8
P value			0.2640[2]
PWV at End of Treatment (m/sec)			
n	33	14	47
Mean (SD)	8.11 (2.087)	9.79 (1.444)	8.61 (2.053)
Median	8.00	10.30	8.50
Min, Max	4.5, 12.6	7.1, 11.6	4.5, 12.6
P value			0.0083[2]
PWV Change from Baseline to End of Treatment (m/sec)			
n	30	13	43
Mean (SD)	-1.55 (2.061)	-2.71 (3.641)	-1.90 (2.647)
Median	-0.70	-2.10	-0.70
Min, Max	-6.6, 1.9	-8.2, 2.8	-8.2, 2.8

P value	<.0001[1]	0.0640[1]	0.5786[2]

1 Wilcoxon Signed Rank Test P-value for change from baseline value of variable.
2. Mann-Whitney U-Test P value for comparison between Censored and death group.

 # All baseline values for survivors and non-survivors are available; here, only a selection of most important for discussion are presented by the assessor.

Age at start of treatment

Patients who survived under continued lonafarnib treatment median age was 5.6 *versus* 9.0 in the non-survivor group.

Cardiovascular parameters

Pulse wave velocity

Median baseline PWV was not significantly different at 8.70 m/Sec and 9.20 m/Sec amongst survivors and non-survivors, respectively. In general, both populations of patients had statistically significant reductions from baseline to EOT. However, median EOT PWV was significantly higher at 10.30 m/Sec in the patients who died compared to 8.00 m/Sec amongst survivors (p=0.008).

Table 17: Baseline and EOT Pulse Wave Velocity.

Parameter	**Survivors**	**Deaths**
	(N=41)	**(N=21)**
Baseline	N=37	N=19
PWV ≥10 m/Sec[1]	12 (32.4%)	9 (47.4%)
PWV <10 m/Sec[1]	25 (67.6%)	10 (52.6%)
End-of-Treatment	N=33	N=14
PWV ≥10 m/Sec	7 (21.2%)	8 (57.1%)
PWV <10 m/Sec[2]	26 (78.9%)	6 (42.9%)
	N=30	N=13
BL PWV ≥10 m/Sec and EOT PWV ≥10 m/Sec[3]	5 (16.7%)	7 (53.8%)
BL PWV <10 m/Sec and EOT PWV ≤10 m/Sec	0	1 (7.7%)

1) A PWV of 10 m/Sec is used to define significant alteration in vascular function and is a risk factor for asymptomatic organ damage (Mancia et al., 2013). When EOT PWV=10 m/Sec, the probability of death = 0.4057.
2) p=0.04 Fisher's exact test two-sided p-value comparing survivors and deaths group

3) p=0.024 Fisher's exact test two-sided p-value comparing survivors and deaths group

Carotid Echodensity

The carotid artery echodensity at all sites except intima-media for both survivors and those who died was elevated at baseline compared to age- and gender-matched controls but not meaningfully different between the two groups of patients at all sites of measurement. A responder analysis for change in carotid echodensity was carried out per the protocol definition: EOT value no greater than 90% of the baseline value. There was no meaningful difference between the number or proportion of responders in each patient group (e.g. survivors vs non-survivors).

Median carotid IMT was greater at baseline amongst the patients who died 0.44 mm *versus* 0.41 mm (p=0.012) and above the limit of normal for children less than 10 years of age: CIMT is constant (0.42±0.05 mm) in healthy children younger than 10 years, regardless of sex or BMI. CIMT increases after the age of 10 years (Baroncini *et al.*, 2016). At the EOT, carotid IMT was not different between the two groups of patients (median 0.41 mm, p=0.99).

It was demonstrated that baseline PWV was correlated to baseline carotid echodensity.

Clinical data in PL patients

Of the 95 patients enrolled in all clinical studies of lonafarnib for HGPS or PL, 4 patients had PL; only one was included in Prolon1. Three of 4 patients had a processing deficient mutation that would be expected to benefit from treatment with lonafarnib. Patients 4371 (cell line 318) and 4729 (cell line 317), both have *in vitro* cell line and clinical data available for assessment. In summary, the *in vitro* cell line data support the clinical benefits experienced by both patients. As of September 2020, three of 4 PL patients enrolled in a BCH progeria study remain on lonafarnib monotherapy. All three have been taking lonafarnib alone or in combination with other study medications for at least 10 years. Limited data on the changes from baseline in PWV are available, but the data indicates an improvement in PWV under lonafarnib treatment.

For two PL patients, the effects of lonafarnib on bone structure using pQCT were available. Both patients showed improvements in measures of loadbearing capacity and bone bending strength.

Clinical studies in special populations

Not applicable. Classic Progeria is mainly a paediatric disease. Most patients will not survive beyond the second decade of life.

2.6.5.2. Supportive study(ies)

Supportive studies

Two supportive studies were performed that are considered important to the claimed indication; study **ProLon1 (or** 07-01-0007) and study **Prolon2** as part of the triple therapy study 09-06-0298. In these two studies, patients received lonafarnib monotherapy.

Study 09-06-0298 was originally designed to investigate the efficacy of triple therapy (Pravastatin + Zoledronic acid + lonafarnib), however, after an interim analysis the results were not as expected, and it was decided to switch the patients to lonafarnib monotherapy. In addition, to this group, a new treatment naïve group of HGPS patients was enrolled (Group2 or Prolon2).

As for the benefit/risk discussion the cardiovascular endpoints, especially PWV, SBP and echodensity are considered potentially supportive to survival these will be described.

Study 07-01-0007, ProLon1:

An Open Label Dose Adjusted Phase II Trial of the Oral Farnesyltransferase Inhibitor (FT) Lonafarnib (SCH66336) for Patient with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies.

Study Initiation Date: May 7, 2007

Study Completion Date: November 29, 2009

Study 09-06-0298, Triple Therapy/Monotherapy Extension/ProLon2:

An Open Label Phase II Trial of Zoledronic Acid, Pravastatin, and Lonafarnib (SCH66336) for Patients with Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies.

Study Initiation Date: March 23, 2009

Study Completion Date: Ongoing

Methods

Study Participants

Study 07-01-0007, ProLon1:

Study 07-01-0007 was a Phase 2, open-label, single-arm, dose-escalation study to evaluate the therapeutic effect of lonafarnib monotherapy in children with HGPS or PL (n=29).

All patients initiated treatment with 115 mg/m^2 lonafarnib. In the absence of significant toxicity related to drug treatment, patients continued therapy for 24 to 30 months. At the end of their 2-year assessment (which could occur from 24 to 30 months), patients were to be removed from therapy.

For inclusion into the trial, patients were required to fulfil all the following criteria:

1. Genetic Diagnosis: All patients must have had confirmatory mutational analysis showing G608G mutation in the lamin A gene.
2. Patients with progeroid laminopathies showing clinical signs of progeria but with other confirmed mutations in LMNA were eligible for therapy. This population was to be analysed separately from those with the classical mutations.
3. Patients were to have adequate organ and marrow function as defined by the following parameters:
   - Blood: absolute phagocyte count (APC) (absolute neutrophil count [ANC] + bands + monocytes = APC) > 1,000/µl, Platelets > 75,000/µl (transfusion independent); Haemoglobin >9g/dl.
   - Renal: creatinine ≤ 1.5 times normal for age or glomerular filtration rate >70 ml/min/1.73m2.
   - Hepatic: bilirubin ≤ 1.5 x upper limit of normal for age; serum glutamic-pyruvic transaminase (alanine aminotransferase) (SGPT [ALT]) < and serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) (SGOT [AST]) < 5 x normal range for age.
   - Prothrombin time (PT)/Partial thromboplastin time (PTT): PT/PTT < 120% upper limit of normal or PI approval.
4. No overt renal, hepatic, pulmonary disease or immune dysfunction.

Study 09-06-0298, Triple Therapy/Monotherapy Extension/ProLon2:

The Triple Therapy study was a Phase 2, open-label, single-arm study to evaluate the therapeutic effect of the prenylation inhibitors pravastatin and zoledronic acid in combination with lonafarnib for children with HGPS or PL for a planned duration of 24 months.

The triple therapy patient cohort (Group 1) was treated for up to 60 months with lonafarnib, pravastatin, and zoledronic acid.

Following the discontinuation of the triple therapy treatment (based on Interim Analyses 1), the study was amended (Protocol Amendment v10.0) to continue treatment of patients in Group 1 with lonafarnib alone (Group 1 Monotherapy Extension).

A second cohort of treatment naïve patients were also enrolled and treated with lonafarnib monotherapy (Group 2 or ProLon2). Prolon2 patients were to be assessed for a duration of 24 months and were offered a 12-month extension. This was to allow Prolon2 patients to be evaluated for up to a total of 36 months of therapy.

In- and exclusion criteria were similar to Study 07-01-0007.

Treatments

In all studies for treatment naïve patients, Lonafarnib was initiated at a dose of 115 mg/m^2 before increasing to 150 mg/m^2 after approximately 4 months if the therapy was tolerated. Lonafarnib was administered via capsules twice daily. For patients that could not swallow the capsules whole, the capsule contents could be dissolved in Ora Blend SF or Ora-Plus.

Patients experiencing significant drug-related Grade 3 or 4 toxicity at any time during treatment and not responding to treatment interruption or supportive care measures were to reduce their dose by one dose level in the range of 150 to 70 mg/m^2, with a possibility to increase the dose again after all of the symptoms had returned to baseline.

In the triple therapy group, pravastatin and zoledronic acid were added. Pravastatin was administered orally, once daily at 5 mg for patients weighing <10 kg or 10 mg for patients weighing >10 kg, and zoledronic acid was administered via intravenous infusion over 30 minutes (0.0125 mg/kg at baseline and 0.05 mg/kg at 6, 12, and 18 months, and study end).

Following the discontinuation of Triple Therapy treatment with pravastatin and zoledronic acid, 36 Group 1 patients were enrolled to participate in the Monotherapy Extension (18 patients who continued from ProLon1 and 18 patients who were initially drug naïve and received triple therapy). Two monotherapy extensions were implemented: an initial 24-month extension and subsequently a 12-month continuation, for a total of 36 months of monotherapy. As a result, Group 1 patients were treated with lonafarnib 150 mg/m^2 BID with the morning and evening meals for up to 96 months (up to 60 months as part of the triple therapy and 36 months as a monotherapy).

Lonafarnib monotherapy treatment was expanded to include 40 treatment-naïve patients (Prolon2). Prolon2 patients were assessed for a duration of 24 months and were offered a 12-month extension. This would allow Prolon2 patients to be evaluated for up to a total of 36 months of monotherapy. Of the 40 patients planned, 35 treatment naïve patients were enrolled and received lonafarnib 150 mg/m2 BID with the morning and evening meals.

Randomisation and blinding (masking)

Not applicable.

Objectives

Study 07-01-0007

Primary Objective

The primary objective was to evaluate the therapeutic effect of oral lonafarnib in patients with HGPS. Activity was assessed by determining the change in rate of weight gain over baseline determined pre-treatment for each patient.

Secondary Objectives

• To describe any acute and chronic toxicities associated with lonafarnib in patients with HGPS.

• To assess changes in leptin levels, glucose utilization, skeletal abnormalities consisting of bone mineral density and X-ray findings, joint contracture and function, hearing loss, dental anomalies, dermatologic changes including hair density, nutrition with calorie analysis and energy expenditure, body composition analysis by dual-energy x-ray absorptiometry (DXA) scan, and cardiovascular function.

Study 09-06-0298

Primary Objectives

The primary objective was to evaluate the therapeutic effects of lonafarnib in patients with HGPS and PL, where efficacy was to be assessed by determining the change in the rate of weight gain over baseline.

The efficacy was further to be assessed by determining the change in ultrasound measures of carotid artery adventitia compared to baseline ultrasound of the carotid artery adventitia, determined during week one of trial participation for each subject.

Secondary Objectives

• To describe any acute and chronic toxicities associated with treating patients with HGPS and PL with the combination of zoledronic acid, pravastatin and lonafarnib (Group 1 Triple Therapy).

• To describe any acute and chronic toxicities associated with treating patients with HGPS and PL with lonafarnib monotherapy (Group 1 Monotherapy Extension and Prolon2).

• To assess changes in skeletal abnormalities, including bone mineral density and X-ray findings, joint contractures and function, growth, body composition analysis by dual-energy X-ray absorptiometry (DXA) scan, and cardiovascular structure and function.

Outcomes/endpoints

Study 07-01-0007 and Study 09-06-0298

The primary efficacy endpoint for this study was the achievement of at least a 50% increase in the annual rate of weight gain.

Secondary efficacy endpoints included the following: Changes in Carotid Artery Ultrasonography, Changes in Corrected Carotid-Femoral Pulse Wave Velocity (PWVcf), Changes in DXA aBMD, Changes in pQCT parameters, Changes in Height, Changes in BMI, Changes in Body Composition by DXA Scan, Changes in ABI, and Changes in FMD.

For Study 09-06-0298 similar endpoints as for study 07-01-0007 supplemented with Changes in Echocardio data and Changes in MRI/Magnetic Resonance Angiogram (MRA) Data.

Statistical methods

The Intent-to-Treat (ITT) population is the primary efficacy analysis data set and consists of all patients who received at least one confirmed dose of lonafarnib (for both studies) and with any post-baseline efficacy information (in Study 07-01-0007 only). These requirements mean that the population selected is a modified intention to treat populations.

Primary Endpoint

The primary endpoint is the achievement of at least a 50% increase in the annual rate of weight gain over the rate documented at study entry by the study team. This will be reflected by the proportion of patients who achieved at least a 50% in the rate of annual weight gain. The Clopper-Pearson method was used to calculate the 95% CI. The proportion will be tested against 5% (Study 07-01-0007) or 4% (Study 09-06-0298) at the 0.05 significance level only for the mutation groups classical and overall, due to constraints in the sample size.

Analysis of the Secondary Efficacy Endpoints

Most secondary endpoints tested the difference between baseline and end of therapy using the Wilcoxon signed-rank test. The last post-treatment visit for the patient was considered the end of therapy visit. Neither Wilcoxon signed-rank test nor McNemar can incorporate information regarding different follow-up times. Only the endpoints considered important for the B/R discussion are presented, all other endpoints may contribute as an additional benefit for the patient.

- Changes in Carotid Artery Ultrasonography Echodensity Data:

The changes in carotid artery USG echodensity was secondary endpoint in both study 07-01-0007 and Study 09-060298. Carotid artery density was measured by ultrasound at intima-media, adventitia luminal near wall, and adventitia deep near wall.

Data was analysed at the 10th and 50th percentile. Data at these percentiles did not have white-outs and provided data points where differences can be tested for statistical significance. Actual values and fold change from baseline to end of therapy were summarized descriptively (n, mean, quartiles, standard deviation (SD), minimum and maximum) by percentile and site.

- Changes in Corrected Carotid Femoral Pulse Wave Velocity (PWVcf):

Propagation time (Δtcf) was calculated by measuring the time lag between the R-wave of the simultaneous ECG and the arrival of the arterial pulse at both the carotid (Δtc) and femoral (Δtf) arteries. The distance between the carotid and femoral arteries (lcf) was measured and recorded. PWVcf was calculated using the formula PWVcf = lcf / Δtcf.

The actual values and percent change from baseline to end of therapy were summarized descriptively (n, mean, quartiles, standard deviation (SD), minimum and maximum).

Multiplicity adjustments

No adjustments were completed with respect to multiple comparisons and multiplicity for all primary and secondary efficacy endpoints. So, adjustments for the increased risk of false-positive rate among multiple secondary endpoints was not planned.

Changes in the Planned Analyses

For Study 07-01-0007 and Study 09-06-0298, several changes had been made to the planned analyses and SAP after the data had been collected. It is not clear whether the data were accessed and partially analysed when the changes were made. It is noted that the visit windows were expanded.

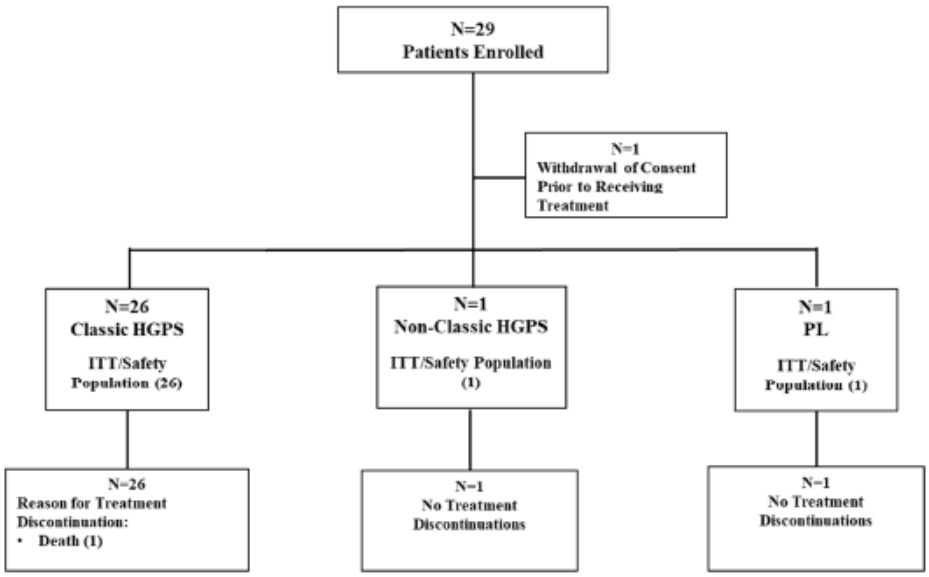
For the primary efficacy endpoint in Study 07-01-0007, the annualized change from baseline value at the end of therapy was planned in Version 2.0 but later removed.

For Study 09-06-0298, many secondary endpoints were not evaluated since no change was observed in the first interim analysis. It is concerning that secondary endpoints that did not show a treatment effect at the interim analysis were disregarded. It is noted that the ITT population was changed.

Results

Participant flow
Study 07-01-0007, ProLon1

Figure 15 depicts the disposition of patients included in Prolon1.

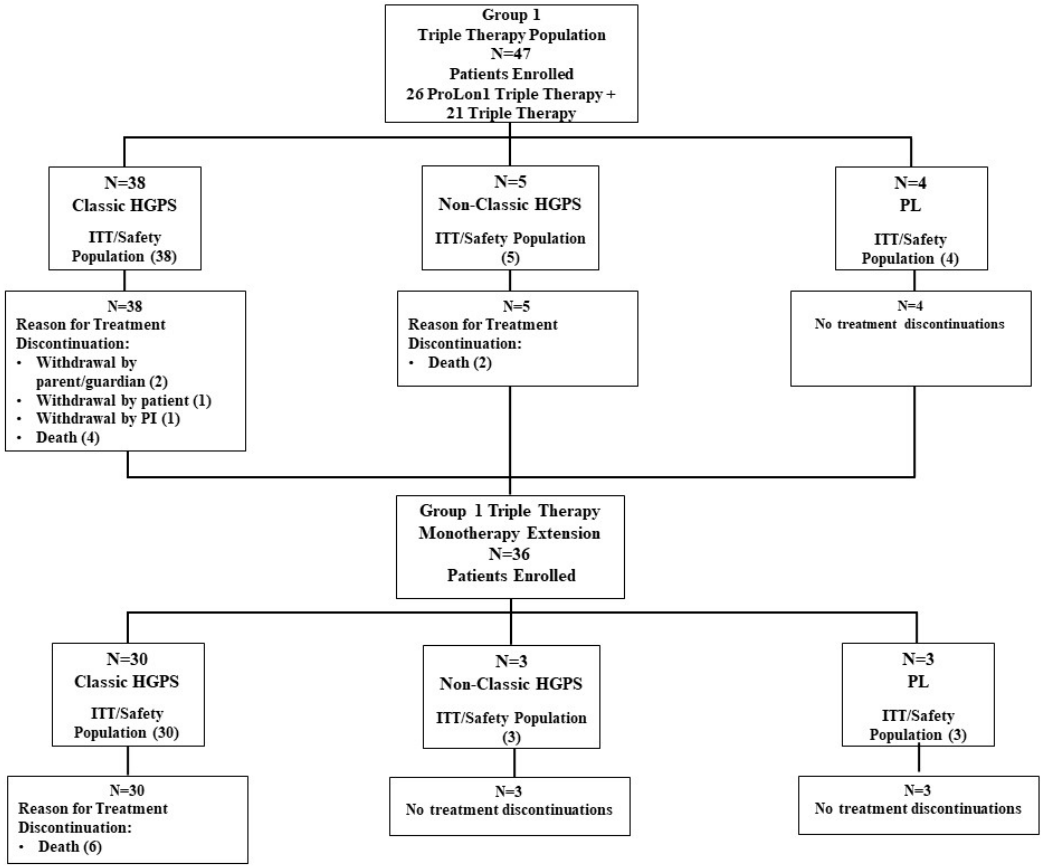


HGPS: Hutchinson-Gilford Progeria Syndrome; PL: progeroid laminopathies; ITT: intent-to-treat

Figure 13: Disposition of patients in study Prolon1.

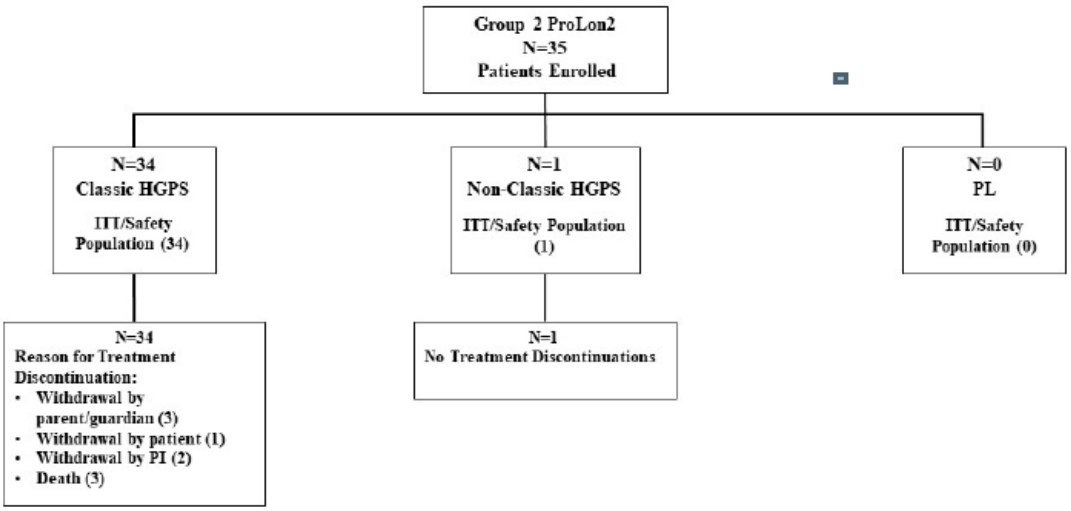
Study 09-06-0298, Triple Therapy/Monotherapy Extension/ProLon2

Figure 16 depicts the disposition of patients included in triple therapy group, and Figure 17 depicts the disposition of patients included in Prolon2.



HGPS = Hutchinson-Gilford Progeria Syndrome; ITT = Intent-to-Treat; PI = primary investigator; PL = progeroid laminopathies.

Figure 14: Disposition of patients in Triple Therapy.



HGPS = Hutchinson-Gilford Progeria Syndrome; ITT = Intent-to-Treat; PI = primary investigator; PL = progeroid laminopathies.

Figure 15: Disposition of patients in study ProLon2.

Baseline data and Numbers analysed

Study 07-01-0007, ProLon1

The ITT population included 28 patients.

In the ITT/Safety population, most patients had classic HGPS (26 [92.9%] patients), 11 (39.3%) patients were male, and 17 (60.7%) were female. Most patients were from the United States (9 [32.1%] patients). The median age was 7.5 years (range: 3 to 16 years).

Study 09-06-0298, Triple Therapy/Monotherapy Extension/ProLon2

Efficacy analyses were conducted using the ITT Population, consisting of all patients who received at least one confirmed dose of lonafarnib and provided any post-baseline efficacy information.

In the Group 1 Triple Therapy population (n=47), most patients had classic HGPS (38 [80.9%] patients), 20 (42.6%) patients were male and 27 (57.4%) were female. The median age was 6.0 years (range: 1 to 18 years). 23/47 patients included in the triple therapy group 1 were treatment naïve at baseline.

In the Group 1 Triple Therapy Monotherapy Extension population (n=36), most patients had classic HGPS (30 [83.3%] patients), 13 (36.1%) patients were male and 23 (63.9%) were female. The median age was 10.0 years (range: 2 to 19 years).

In the ProLon2 Monotherapy population (n=35), most patients had classic HGPS (34 [97.1%] patients), 22 (62.9%) patients were male and 13 (37.1%) were female. The median age was 6.0 years (range: 2 to 17 years) (**Table 18**).

Table 18: Demographic Characteristics in Study 07-01-0007 and Study 09-06-0298 (ITT/Safety Population)

Param	Stat	Study 07-01-0007				Study 09-06-0298 Group 1: Triple Therapy				Study 09-06-0298 Group 1: Triple Therapy Monotherapy Extension				Study 09-06-0298 Group 2/ProLon2: Monotherapy			
		Class. HGPS N=26	Non-Class. HGPS N=1	PL N=1	Total N=28	Class. HGPS N=38	Non-Class. HGPS N=5	PL N=4	Total N=47	Class.HGPS N=30	Non-Class. HGPS N=3	PL N=3	Total N=36	Class. HGPS N=34	Non-Class. HGPS N=1	PL N=0	Total N=35
Age at Baseline (Years)																	
	Mean (SD)	7.0 (3.16)	6.0 (N/A)	12.0 (N/A)	7.1 (3.19)	7.4 (4.19)	6.0 (3.67)	5.5 (5.80)	7.1 (4.23)	11.3 (3.64)	6.7 (4.51)	11.3 (6.81)	10.9 (4.06)	6.1 (3.92)	7.0 (N/A)		6.1 (3.86)
	Med.	7.5	6.0	12.0	7.5	6.5	6.0	3.5	6.0	10.5	7.0	9.0	10.0	5.5	7.0		6.0
	Min, Max	3, 16	6, 6	12, 12	3, 16	2, 18	2, 11	1, 14	1, 18	4, 18	2, 11	6, 19	2, 19	2, 17	7, 7		2, 17
Age Group at Baseline																	
2-11 Years	n (%)	25 (96.2)	1 (100)	0	26 (92.9)	33 (86.8)	5 (100)	3 (75.0)	41 (87.2)	16 (53.3)	3(100)	2 (66.7)	21 (58.3)	30 (88.2)	1(100)	0	31 (88.6)
12-<18 Years	n (%)	1 (3.8)	0	1 (100)	2 (7.1)	4 (10.5)	0	1 (25.0)	5 (10.6)	13 (43.3)	0	0	13 (36.1)	4 (11.8)	0	0	4 (11.4)
Gender																	
Male	n (%)	11 (42.3)	0	0	11 (39.3)	16 (42.1)	1 (20.0)	3 (75.0)	20 (42.6)	10 (33.3)	1 (33.3)	2 (66.7)	13 (36.1)	21 (61.8)	1 (100)	0	22 (62.9)
Female	n (%)	15 (57.7)	1 (100)	1 (100)	17 (60.7)	22 (57.9)	4 (80.0)	1 (25.0)	27 (57.4)	20 (66.7)	2 (66.7)	1 (33.3)	23 (63.9)	13 (38.2)	0	0	13 (37.1)
Region																	
Europe	n (%)	8 (30.8)	0	0	8 (28.6)	10 (26.3)	1 (20.0)	0	11 (23.4)	9 (30.0)	1 (33.3)	0	10 (27.8)	4 (11.8)	0	0	4 (11.4)
North America	n (%)	11 (42.3)	0	0	11 (39.3)	12 (31.6)	2 (40.0)	3 (75.0)	17 (36.2)	7 (23.3)	2 (66.7)	2 (66.7)	11 (30.6)	5 (14.7)	1 (100)	0	6 (17.1)
ROW	n (%)	7 (26.9)	1 (100)	1 (100)	9 (32.1)	16 (42.1)	2 (40.0)	1 (25.0)	19 (40.4)	14 (46.7)	0	1 (33.3)	15 (41.7)	25 (73.5)	0	0	25 (71.4)

Class. = classic; HGPS = Hutchinson-Gilford Progeria Syndrome; Max = maximum; Med = median; Min = minimum; N/A = Not applicable; Param. = Parameter; PL = progeroid laminopathy; ROW = rest of the world; SD = standard deviation; Stat = statistic
Note: Percentages are based on the total number of patients in each mutation group

Concomitant medication

In the ProLon1 and ProLon2 combined group, there were 47 (74.6%) patients with at least one concomitant medication. The most commonly reported (used by ≥ 20% of patients) concomitant medication were analgesics (30 [47.6%] patients), vitamins (28 [44.4%] patients), mineral supplements (23 [36.5%] patients), and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (13 [20.6%] patients). Nine of 63 patients (14.3%) used a lipid-modifying agent (e.g. pravastatin, atorvastatin).

There was a greater proportion of patients in ProLon1 that reported the use of at least one concomitant medication compared to ProLon2 (26 [92.9%] patients and 21 [60.0%] patients, respectively).

Outcomes and estimation

Study 07-01-0007, ProLon1

Primary Efficacy Analysis – Annual Rate of Weight Gain

The baseline mean (SD) weight gain rate was 0.4011 (0.44011) kg/year, and at the end of treatment, this was 0.4032 (0.41607) kg/year. This is not considered a relevant change. The primary endpoint was not met.

Secondary Efficacy Analyses - Carotid Artery Ultrasonography

- For the adventitia luminal near wall, the median decrease from baseline in echodensity was -17.00 (range: -142.0, 70.0), p=0.0367 for the 50th percentile. (not significant for 10th percentile)
- For the adventitia deep near wall, the median decrease from baseline in echodensity was -29.00 (range: -173.0, 85.0) for the 10th percentile, p=0.0271. For the 50th percentile, the median decrease from baseline in echodensity was -42.50 (range: -180.0, 108.0), p=0.0271.
- For the intima media, the median decrease from baseline in echodensity was -15.25 (range: -109.0, 34.0) for the 10th percentile, p=0.0070. For the 50th percentile, the median decrease from baseline in echodensity was -23.50 (range: -98.0, 38.0), p=0.0018.

For the single PL patient, echodensity of the carotid artery intima media and adventitia deep near wall decreased from baseline to end of therapy at both 10th and 50th percentiles.

Secondary Efficacy Analyses - Corrected Carotid-Femoral Pulse Wave Velocity

At the end of treatment, PWVcf decreased from a median 12.85 m/sec (range: 7.2, 18.8) at baseline to 10.50 m/sec (range: 7.6, 12.6) at the end of therapy (normal range 4.8 to 6.6 m/sec for ages 7 years and above) (median decrease from baseline of 15.30% [range: -43.6%, 34.1%], p=0.0028, Wilcoxon signed-rank test).

Secondary Efficacy Analyses – Other

The other clinical endpoints measured, e.g. areal bone mineral density (aBMD), change in height, body mass Index (BMI) showed a significant statistically change from baseline.

Changes in Peripheral Quantitative Computed Tomography, Ankle-Brachial Index, Endothelium-Dependent Flow-Mediated Vasodilation, were not significantly in favour of the treatment.

During the scientific advice procedure, insight on the quality of life (QoL) for which the Physical and Occupational Therapy (COPM) was deemed potentially suitable was requested. Unfortunately, the patients did not experience much improvement – except for tolerating heat – on the several items measured.

Study 09-06-0298, Triple Therapy/Monotherapy Extension/ProLon2

Primary Efficacy Analysis - Annual Rate of Weight Gain

In general, the annual rate of weight gain did not increase in patients from baseline to end of study in any of the groups (Triple Therapy/Monotherapy Extension/ProLon2) within study 09-06-0298. The primary endpoint was thus not met.

Secondary Efficacy Analysis - Carotid Artery Ultrasonography

Group 1 Triple Therapy

For the adventitia luminal near wall, the median increase from baseline in echodensity was 46.25 (range -77.0, 151.5) pixels for the 50th percentile, p<0.0001.

For the adventitia deep near wall, the median increase from baseline in echodensity was 79.50 (range -101.0, 216.0) pixels for the 50th percentile, p<0.0001.

For the intima media, the median increase from baseline in echodensity was 21.00 (range -74.0, 197.0) pixels for the 50th percentile, p=0.0004.

Group 1 Triple Therapy Monotherapy Extension

For the adventitia luminal near wall, the median decrease from baseline in echodensity was -20.50 (range -218.0, 50.5) pixels for the 10th percentile, p=0.0003. For the 50th percentile the median decrease from baseline in echodensity was -11.00 (range -193.0, 16.0), p<0.0001.

For the adventitia deep near wall, the median decrease from baseline in echodensity was -44.00 (range -170.0, 82.0) for the 10th percentile, p=0.0003. For the 50th percentile the median decrease from baseline in echodensity was -33.00 (range -167.0, 68.0) pixels, p=0.0002.

For the intima media, the median decrease from baseline in echodensity was -16.50 (range -94.0, 52.5) for the 10th percentile, p=0.0167. For the 50th percentile the median decrease from baseline in echodensity was -20.00 (range -99.0, 60.0) pixels, p=0.0057.

For the three PL patients, there was a similar decrease as observed in the HGPS patients from baseline to end of therapy for all sites and percentiles, with the exception that no decrease was observed for the adventitia luminal near wall 10th percentile.

Group 2/ProLon2 Monotherapy

For the adventitia luminal near wall, the median decrease from baseline in echodensity was -48.50 (range -111.5, 27.2) pixels for the 10th percentile, p<0.0001. For the 50th percentile the median decrease from baseline in echodensity was -31.50 (range -101.0, 57.0) pixels, p=0.0013.

For the adventitia deep near wall, the median decrease from baseline in echodensity was -53.50 (range -156.5, 8.0) pixels for the 10th percentile, p<0.0001. For the 50th percentile the median decrease from baseline in echodensity was -59.50 (range -181.0, -7.5) pixels, p<0.0001.

For the intima media, the median decrease from baseline in echodensity was -11.75 (range -98.0, 56.0) pixels for the 10th percentile, p=0.0350. For the 50th percentile the median decrease from baseline in echodensity was -22.00 (range -107.0, 42.0) pixels, p=0.0016.

Secondary Efficacy Analysis - Corrected Carotid-Femoral Pulse Wave Velocity

Group 1 Triple Therapy

The median PWVcf was 8.60 m/sec (range 5.6, 11.7) at baseline and was 8.64 m/sec (range 5.4, 16.4), P=0.978).

Group 1 Triple Therapy Monotherapy Extension

The median PWVcf was 8.24 m/sec (range 5.4, 16.4) at baseline (conclusion of Triple Therapy/initiation of monotherapy) and 7.67 m/sec (range 5.3, 11.4) at the EOT (p=0.2679).

Group 2/ProLon2 Monotherapy

In Prolon2 23 out of 35 patients had baseline and end of therapy evaluations. At the EOT, PWVcf improved with lonafarnib treatment and decreased from a median 7.68 m/sec (range 5.1, 11.5) at baseline to 7.32 m/sec (range 4.5, 10.7) at the end of therapy (normal range 4.8 to 6.6 m/s), representing a median decrease from baseline of 5.60% (range: -57.7%, 24.7%) (p=0.0171). Normal range data are only available for children 7 years of age and older.

Secondary Efficacy Analyses – Other

For all groups, e.g. group1 triple therapy, Group 1 Triple Therapy Monotherapy Extension and Group2/Prolon2 the following general observations were made.

- For height, a statistically significant median increase from baseline to end of therapy was observed.
- Changes in Ankle-Brachial Index, Endothelium-Dependent Flow-Mediated Vasodilation, and Echocardio data did not reveal any significant findings.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant submitted a survival cohort analysis for substantiation, which is considered the pivotal study for the benefit/risk discussion. In addition, two supportive datasets for non-OS outcomes were provided by the Applicant; Study 07-01-0007 (ProLon1) and study 09-06-0298.

Survival study

In the primary survival analysis, 62 patients treated with lonafarnib from the pooled Prolon1 and Prolon2 study were matched to patients using randomly selecting (1:1) a match from candidate HGPS patients in the natural cohort (NHC) with the sex and continent. Within each matched pair, the value of the "age at start of treatment" for the untreated patient was taken the same as that for the lonafarnib treated patient. Only patients born in 1991 or after were included in the survival analysis, which was justified and agreed with.

Study 07-01-0007 (ProLon1) and study 09-06-0298

Prolon1 (Study 07-01-0007) was an open-label, single-arm trial that evaluated the efficacy and safety of lonafarnib monotherapy in children (n=29) with HGPS or PL over a minimum period of two years (24-30 months, between 2007-2009). In study 07-01-0007 the primary objective focused on annual weight changes.

Following the completion of Prolon1, patients were eligible to enrol in "Study 09-06-0298, Group 1 Triple Therapy", the second Phase 2, open-label, single-arm study to evaluate the therapeutic effect of the prenylation inhibitors pravastatin and zoledronic acid in combination with lonafarnib for children with HGPS or PL (n=47) for a planned duration of 24 months (24-60 months, between 2009-2013). The Triple Therapy group consisted of 26 patients from ProLon1 and 21 treatment-naïve patients.

Consequently, the study design for study 09-06-0298 was amended, pravastatin and zoledronic acid were discontinued, but 36 patients continued treatment with lonafarnib monotherapy in "Study 09-06-0298, Group 1 Monotherapy Extension" (between 2014-2018). Eighteen of these patients were originating from Prolon1.

In parallel, in 2014, a monotherapy group was set up with a cohort of 35 treatment naïve patients named "Study 09-06-0298, Group 2 Monotherapy/**ProLon2**". These patients were also enrolled into the monotherapy extension of Study 09-06-0298, and 1 patient was still ongoing at the time of the

preparation of data for submission. In study 09-06-0298, the change in ultrasound measures of carotid artery adventitia was added to the primary objective of annual weight changes.

During the conduct of the studies, it was observed that treatment seemed to extend the survival of these HGPS patients. Subsequently, the survival analysis was conducted.

The inclusion and exclusion criteria are considered relevant and will select the intended population to be treated in clinical practice. They were similar between the studies.

Prolon1 patients started on lonafarnib monotherapy 115 mg/m^2. After 4 months, the dose is escalated to 150 mg/m^2. When drug-related Grade 3 or 4 toxicity is reported, treatment is interrupted, or supportive care measures are taken. This is in line with the proposed posology in the SmPC and agreed with. In study Prolon2 patients started lonafarnib monotherapy 150 mg/m^2; in line with Prolon1, doses could be decreased based on toxicity. The dose rationale is weak, but the proposed maintenance dose of 150 mg/m^2 twice daily is the only dose that has been studied and is the dose for which B/R is assessed.

Weight is not considered to contribute to the survival of the patients as HGPS patients mainly succumb due to cardiovascular failure; this endpoint is to be considered irrelevant for the B/R discussion. At best, it contributes to the overall benefit of lonafarnib treatment.

From the secondary endpoints, PWV and carotid echodensity are considered of limited relevance. Aforementioned parameters are indicators for cardiovascular problems and maybe predictors of cardiovascular failure.

High PWV is a hallmark of arteriosclerosis. It has been recognized that aortic pulse wave velocity (PWV) is a marker of arterial stiffness and, consequently, of cardiovascular outcome (Reusz *et al.*, 2010).

Unfortunately, the Applicant did not request CHMP scientific advices in the early stages of clinical development, which is a missed opportunity, although the reasons for developing a treatment for Progeria are fully understood. In retrospect, a study design in which data was prospectively collected and patients were matched, for instance, 1:1, to demonstrate the effect of lonafarnib on cardiovascular parameters (e.g. death, myocardial infarction, cerebral infarction, etc.) might have been advised. Nevertheless, as HGPS, non-classic HGPS and PL are ultra-rare diseases, no additional clinical data is to be expected in the short term. For this reason, an application for a marketing authorisation under Exceptional Circumstances was accepted by CHMP.

Efficacy data and additional analyses

Survival

The median age of death for untreated HGPS is 14.5 years of age and range from 1.5 to 27.5 years.

The Applicant has presented numerous analyses applying different methods. The different analyses show different effects sizes and inferential statistics. The analyses provided by the Applicant were, among others, hampered by the post-hoc character, the lack of sufficient patients and follow-up, the intercurrent add-on treatments, and the use of historical controls (with only limited information available). Matching should preferably have been performed on important prognostic factors. As no prognostic factors (except age at the start of treatment and mutation) have been collected for the NHC, matching on age and mutation status is considered the best possible.

Due to the multitude of analyses undertaken and the unclarity of which analysis would be methodologically the most appropriate, CHMP asked BSWP for an independent opinion. This opinion

was based on information on the study groups, the NHC, and methodological aspects of all performed analyses, but without providing results of the analyses.

The main aspects of the BSWP response are the following:

The OS results are exploratory (lack of pre-specification and no type I error control). The choice of the NHC is not problematic (as it is the only source of external controls), but this does not mean that this control group per se closely resembles the study groups (there may be subtle selection mechanisms not directly captured by in/exclusion criteria). Immortal time bias is not a problem as the disease starts already at birth. Because it is a strong prognostic factor, "credible and clinically meaningful results may only be obtained when the age of starting treatment with lonafarnib is included in the statistical model". Given the potential for bias and confounding, estimated effects should be sufficiently large despite potential bias. Sensitivity analyses are therefore important. This relates to:

- The different study groups should have similar effects or the reasons for difference should be understood.
- Both HR and RMST as complementary effect measures should show consistently a positive effect.
- As the monotherapy period in Prolon 1 and 2 could be shorter than 3 year; also time windows for the RMST of 1 and 2 years are of relevance. As an upper-bound for the lonafarnib effect, also the time window until 'last follow-up' is important.
- As no relevant data beyond age (at start), sex, and region are available, BSWP does not see possibilities to improve matching algorithms and "..., choosing the control group by 1:1 matching and defining time 0 for controls as age of starting treatment for the matching partner as done by the applicant appears reasonable".
- Matching or adjusting are both based on the assumption that no unmeasured confounders would typically lead to similar estimates "if the matching methods do not substantially reduce the original dataset". Therefore, "Large discrepancies between results obtained via matching versus an adjusted analysis would generally raise concerns about the robustness of the results. It should also be noted that both approaches are often mixed". Thus, consistency across these different approaches is considered important.
- Tipping points analyses using different methods how to choose the matching in the same sex & continent stratum (random choice, 50th percentile, least favourite, etc) should show consistently positive effects.

The initial survival analyses presented by the Applicant showed an estimated additional survival of 0.49 years after 3 years of lonafarnib monotherapy treatment on Prolon 1 and 2 pooled.

However, based on the most plausible analysis (including those requested by the BSWP) the mean RMST after 3 years of treatment increased from 0.44 to 0.47 years (without and with adjustment for age at start treatment, respectively). Given the limited information in the datasets, the estimated monotherapy effect over 3 years can be down to 0.2 given the 95%-CI.

Most relevant analysis:

The BSWP was in favour of a tipping point analysis censored at 3 years. The mean RMST difference for treated versus untreated patients using the tipping point analyses was somewhere in the range between 0.2 and 0.5 years, all favouring the lonafarnib treated patients.

An analysis censored at 3 years, fixed 50th percentile matching by mutation status, gender, and continent showed a statistically significant difference in restricted mean survival of 0.24 years when censored at 3 years.

The analysis showed a statistically significant difference in restricted mean survival 2.5 years at the last follow-up (2019 data cut-off).

A Cox proportional hazards analysis, matched on sex, continent and age at start of lonafarnib treatment was conducted on the last follow-up at 1 August 2021, with survival time and start age as covariates and study (Prolon 1, Prolon 2, Triple therapy) as a factor. This analysis showed for Prolon1 a HR (95% CI) of 0.23 (0.115, 0.457), for Prolon2: 0.35 (0,156, 0.780), and the 18 naïve patients on triple therapy (TT): 0.24 (0,084, 0.702).

As the BSWP expressed uncertainty of using 3-year window for RMST analysis, 1-year and 2-year RMST analyses on the Prolon1 and Prolon2 pooled dataset as suggested by BSWP were conducted. The survival benefit for 1-year and 2-year follow up are 0.1 (95% CI: 0.03, 0.15; p=0.002) and 0.2 (95% CI: 0.07, 0.40; p=0.004), respectively.

The numerous additional analyses confirmed the improvement in survival of lonafarnib treated patients compared to untreated controls during the 3 years monotherapy phase.

The BSWP favoured using the survival results at last follow-up to have an upper bound of the effects of lonafarnib on the survival of the patients. RMST in treated versus random untreated (censored at 1 August 2021, ProLon1 and ProLon2 Contemporaneous Intention-to-Treat Set [N=144], adjusting for age at start treatment along with the original matching methodology) was 4.3 years with a 95%-CI from 2.6 to 6.1. Given the limited information in the datasets, the upper bound of the long term effect of lonafarnib can be down to 2.6 years in view of the 95%-CI.

Although the improvement of the mean RMST at last follow up was considered important (by the BSWP), the results should be interpreted with some caution as patients underwent additional (potentially beneficial) treatments. Based on the most favourable analyses, the mean RMST at last to follow-up ranged from 4.3 to 5.2 years. When in the Cox proportional hazards analysis, only patients were included with an age ≤10 years at start of treatment HRs (95% CI) were 0.19 (0.082, 0.430), 0.22 (0.072, 0.653), 0.13 (0.034, 0.489), for Prolon1, Prolon2 and triple therapy, respectively with all results statistically significant.

Pooling

Initially, no cause for the seemingly different survival results could be found it was questioned if the populations from ProLon1 and ProLon2 could be pooled. No confounder could be identified after a detailed assessment of available literature. Therefore from a clinical perspective, there is no reason not to pool ProLon1 and ProLon2. To further analyse the observed difference in survival between ProLon1 and ProLon2, separate survival data for the Prolon1 and Prolon2 studies were requested, including using the 'censoring at adapted follow-up' and repeated random matching with replacement. This was to mitigate possible biases due to the differences in follow-up and the number of available candidates for matching. Using these analyses, no statistically significant differences in survival in Prolon1 and Prolon2 were observed. Another observation is the much shorter follow-up in Prolon 2 than in Prolon 1, blocking a comparison of long-term survival, but not short-term survival. Therefore, there is no reason not to pool the Prolon1 and Prolon2 data from a clinical and methodology perspective.

Further analysis identified age at start of treatment as a possible confounder and effect modifier. The first is obvious as a patient started later will have a shorter survival from that point, given the limited life span of the patients.

A difference in age profile at the start of treatment might contribute to the differences between ProLon1 and ProLon2 as observed in the Kaplan Meijer curve, for two reasons. First, more patients with a starting age >10 years were included in Prolon 2, that died much earlier. Second, the remaining

patients in Prolon 2 were comparatively younger at the start of treatment than in Prolon 1. Combined with the shorter follow-up in Prolon 2, the Prolon 2 patients' ages at follow-up are mostly not yet in the range where the largest contrast with NHC is expected. Therefore, the differences in age distribution might serve as a reasonable explanation for the observed differences. The Applicant was previously requested to submit an analysis of patients starting before the age of 10 for ProLon1 and ProLon2 (unrevised) separate and combined contrasted against NHC; these analyses indeed confirmed better survival result when considering the younger patients and more similar curves (both early separation).

Additional data in the NHC

There is no additional data on cardiovascular or other parameters available for the patients in the NHC. Therefore, this cannot be used for matching, which is unfortunate. When considering age at treatment initiation and mutation status as important for matching (besides sex and region) in a heterogenous Progeria population, Prolon1 and Prolon2 patients are separately be compared to NHC.

The reason why treated patients did not continue the treatment or were withdrawn by investigator/parent/patient could be related to the treatment. In this case, censoring of the discontinuations cannot be regarded as non-informative. The Applicant elaborated on the reasons for discontinuation. Six patients discontinued the study due to other reasons than death (e.g. TEAEs n=3; withdrawn by a caregiver, n=1; lost to follow-up, n=2), and these occurred only in Prolon 2. Lost-to-follow-up could be non-informative; TEAEs need not indicate that the patient is dying soon (but is a kind of treatment failure), so could be considered non-informative; withdrawal would be considered informative, and the impact of one possible death may not be negligible against six recorded deaths in Prolon 2. However, the Applicant explained that all these patients are still alive, hence this issue is now solved.

- ***Study 07-01-0007 (ProLon1) and study 09-06-0298***

In Prolon1 and Prolon2 patients with classic HGPS (n=60), non-classic HGPS (n=2) and progeroid laminopathy (PL) (n=1) were included. Given the ultra-rare nature and the infaust disease progression of classical HGPS, the number of included patients suffering from classic HGPS is considered acceptable. The Applicant informed that there are 9 HGPS patients and 1 non-classic patient ≤3 years of age that started lonafarnib and completed the clinical program. Five patients 3 years of age were included in the safety and survival analyses. Vital status for all but 1 of the 10 patients starting lonafarnib at ≤3 years of age was known through June 1, 2019. All 9 were known to be alive. Patient 6378 was lost to follow-up. Seven of the 10 remained on study.

To demonstrate the importance of lonafarnib treatment on cardiovascular endpoints (change from baseline to EOT), additional analyses were conducted in those patients that survived under continued lonafarnib treatment and those that were non-survivors despite lonafarnib treatment (see below).

- **Rate of Weight gain**

The mean annual rate of weight gain did not increase from baseline to end of the study in any of the studies. The primary endpoint for both Prolon1 and study 09-06-0298 were not met.

- **Corrected Carotid-Femoral Pulse Wave Velocity**

High PWV is a hallmark of arteriosclerosis. Redheuil *et al.* (2010) found that PWVcf increased from 6.2 ± 0.7 m/s at ages 20–29 years, to values comparable to the HGPS population at ages 60–69 (12.8 ±

3.9) and over 70 (13.8 ± 5.3 m/s), and exhibited a highly significant relationship with ageing. The normal range for PWV in healthy controls is 4.8 to 6.6 m/s.

In both study cohorts (Prolon1 and Prolon2), the change from baseline to EOT in PWV was statistically significant. At baseline the PWV in the ProLon2 group was lower than in ProLon1, median 7.68 m/sec (range 5.1, 11.5) and median 12.85 m/sec (range: 7.2, 18.8) respectively. This is due to the younger age of the ProLon2 participants creating a difference in disease burden, and thus less improvement is to be expected.

- **Carotid Artery Ultrasonography**

The results for carotid artery ultrasonography echodensity measured at the adventitia luminal near wall, adventitia deep near wall and intima-media showed improvement when compared with baseline in study Prolon1 and prolon2. The improvement (change from baseline to end of treatment) was statistically significant within the group.

The relevance of the carotid artery ultrasonography echodensity in this respect remains unknown, though it is to be noted that improvements in echodensity are observed for some patients individually. However, PWV and carotid artery echodensity are not standards-of-care and are not validated for Progeria patients or the paediatric population. The analysis was performed to better understand the impact of cardiovascular parameters to survival. As the data is based on data in treated patients only, no firm conclusions can be drawn.

- **Indication**

The indication proposed for ZOKINVY is:

ZOKINVY is indicated for the treatment:

- of patients 12 months of age and older above with a genetically confirmed diagnosis of Hutchinson-Gilford Progeria Syndrome;
- or a processing-deficient Progeroid Laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.

ZOKINVY is not expected to be effective for the treatment of progeroid syndromes caused by mutations in genes other than *LMNA* or *ZMPSTE24* and laminopathies not associated with the accumulation of progerin-like proteins. ZOKINVY is not expected to be effective in the treatment of the following progeroid syndromes: Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum, trichothiodystrophy and ataxia-telangiectasia.

The indication is based on the survival analysis of the main study including 60 classic HPGS patients and 2 non-classic HGPS patients who received lonafarnib monotherapy in study Prolon1 or Prolon2. The submitted pivotal analysis indicated an improvement in survival, and additional analyses showed improvement of PWV and SBP under lonafarnib treatment which is sufficient as a justification of the indication.

In the complete clinical program, only 4 PL patients were included, with only one patient with PL included in Prolon1. PL is even rarer than classic HGPS. Based on extrapolation of *in vitro* data, lonafarnib has a similar effect on misshapen nuclei in human fibroblasts of HGPS and PL patients. In addition, limited clinical efficacy data showed that PL patients also had beneficial effects on PWV and bone-related parameters. The presence of a farnesylated prelamin A in PLs tends to yield a phenotype

that affects the bones more than the cardiovascular system. Therefore, PL patients can be added to the indication. The indication is restricted to those PL patients that are either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.

ZOKINVY is available for patients with a BSA of >0.30 m^2.

- **Registry**

The applicant proposes to conduct a *Prospective Observational Study of Patients with Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathy.* The proposed study will evaluate the safety and effectiveness of lonafarnib treatment and quality of life (QoL) among patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathy (PL) within a real-world setting. In general, the observational study is welcomed, given that there is no long term follow-up data in HGPS patients, and this should provide more insight into the survival under continued lonafarnib treatment. In addition, as in the current application very limited data on non-classic HGPS and PL patients were submitted, the proposed study will enable collecting additional data in these patients (Specific Obligation).

Additional expert consultation

CHMP Request to BSWP – February 2022:

This CHMP request concerns a marketing authorisation application following article 8(3) via the centralised procedure for the product lonafarnib. The Applicant claims that lonafarnib (as monotherapy) reduces mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome (HGPS) or Progeroid Laminopathies (PL) with a processing-deficient mutation in LMNA or ZMPSTE24. The evidence provided in this application is based on data from two monotherapy cohorts originating from two single-arm, single-center, pivotal studies that did not meet their predefined primary endpoint (weight change) and an observational natural history cohort (NHC) population as an indirect comparison. The treated cohorts switched to other cohorts of studies with additional treatments on top of lonafarnib after the monotherapy period or 3 years. Age is a known prognostic factor for this population. The average lifespan is 14.5 years, and the effect of treatment possibly depends on the age at the start of treatment. The Applicant conducted numerous analyses resulting in different effect estimates. Consequently, an unambiguous statement about the effect of lonafarnib treatment and the magnitude thereof (expressed in terms of prolonged survival) in patients suffering from HGPS or PL on survival can currently not be made.

The following additional background information on the lonafarnib MAA was shared with BSWP:

- 0. overall introduction to the attachments
- 1. Methods_attachment_APPLICANT_analyses
- 1. Methods_attachment_SAP_APPLICANT_analyses_at_submission
- 2. Programming_attachment_INHOUSE_analyses
- 2. Programming_attachment_variables
- 3. Data_attachment _lonafarnibstudiesinfo

The CHMP asks the Biostatistics Working Party for input on the following questions

1) ***General questions on statistical conduct***

a. What is the view of the BSWP on the impact of the switch to the survival endpoint (EP) in the context of the initial endpoint weight change?

The switch to the survival EP happened post-hoc after demonstrating a statistically significant but clinically unconvincing effect on the initial primary EP of weight change (which may have been considered as a surrogate EP by the sponsor). From a statistical point of view, all analyses for the survival EP must be considered **exploratory** due to the **lack of pre-specification and T1E control**. An additional concern is that the survival EP was added completely post-hoc, i.e. was not a secondary or exploratory EP in the initial protocol. Usually, post-hoc introduction of an EP raises concerns on potentially worse data quality; however, it is expected that the date of death was obtained irrespectively of survival not being a formal EP of the study.

The switch of the primary EP happened when all unblinded results were available and would need to be considered data-driven if triggered by the applicant. However, survival as an EP undisputably has the potential of being indicative of a **major clinical benefit**. A mitigating aspect is also that regulatory authorities have triggered the change in EP and that the hypothesized surrogate EP of weight change was not a complete failure (in the sense that it was statistically significant albeit not considered of clinical relevance). Nevertheless, even if triggered by third parties, results may still depend on the choice of analysis methods such that the **post-hoc specification of methods** is of concern. Therefore, a demonstration that conclusions do not critically depend on the choice of methods is a crucial requirement. Further, replication of findings across the two studies may provide reassurance that the observation reflects a true effect, rather than a chance finding.

Taking into account these arguments as well as considerations about feasibility of performing additional studies on lonafarnib in the target population, BSWP considers that the switch of EP may **exceptionally be acceptable** in this setting. However, it is considered that the analysis of the survival EP would have to provide very **compelling and robust results** (which include sufficient understanding about prognostic or predictive factors, the biological plausibility of the beneficial effect of lonafarnib on survival supported by results of relevant endpoints, as well as potential differences between the trials and sensitivity analyses; see also other responses).

b. What is the BSWP view on the validity in assessing a treatment benefit in a time-to-event endpoint by comparing the survival data for treated single-arm cohorts with the survival data of an external Natural History Cohort (NHC)?

It is generally not possible to conclude on a treatment benefit for a time-to-event EP such as overall survival based on the **stand-alone results** from single-arm trials (SATs). While life expectancy in progeria patients is low, BSWP considers that the disease course is **not highly predictable,** which renders the stand-alone interpretation of data on time to death impossible.

When comparing results from a SAT versus an external comparator, there are general concerns concerning **bias** and **confounding** since patients in clinical trials usually differ regarding their demographic and disease characteristics and background care compared to those treated in practice. Age at death can be considered an **objective outcome** that should be recorded with sufficient adequacy both in the trials as well as in the NHC (i.e. no bias introduced due to differences in ascertaining the outcome). However, the lack of a very good understanding about the impact of baseline and treatment variables on survival makes a comparison very challenging. Furthermore, comparison against the NHC will unlikely overcome deficits of the SAT results not being able to determine whether a factor is prognostic or predictive of outcome.

Exceptionally, for the lonafarnib dossier, the **post-hoc choice of the source for external controls** does not raise any strong additional concern since it is the only available source in this disease setting. However, this **does not ensure that the control group closely resembles the study groups**. In general, the more restrictive the in-/exclusion criteria for the trials, the greater the concerns about comparability to the control group from the NHC, particularly when in-/exclusion criteria are based on information that is not available for the NHC. In addition, there may be subtle selection mechanisms not being directly captured by in-/exclusion criteria that are associated with prognosis.

When comparing data from a SAT to external controls regarding a time-to-event EP, defining **'time 0',** i.e. the start of follow-up, is a particular challenge that has a direct impact on the results. Care must be taken to define time 0 such that there is no **immortal time bias** favouring the experimental treatment arm. While the start of treatment is the natural choice for patients from the SATs, the choice for control patients is less obvious. The choice should be made to achieve 'exchangeability' of treated patients and controls, i.e. the expected outcome of the study would be the same for the counterfactual scenario in which treated patients and controls were exchanged at time 0. This is closely related to the usually unknown '**history at risk'**, i.e. the time since the start of being diseased, which is highly prognostic of the disease outcomes. Exceptionally, the history at risk is well characterized in this setting where patients are born with the disease. Therefore, choosing the control group by 1:1 matching and defining time 0 for controls as age of starting treatment for the matching partner as done by the applicant appears reasonable. However, exchangeability is given only if all prognostic factors are known and considered for matching, which is a strong assumption that cannot be verified.

In conclusion, survival is one of many EPs that does generally not allow to draw conclusions about efficacy based on the stand-alone results from SATs. Given the challenges of assessing the dossier, **comparison against the NHC may exceptionally support the demonstration of efficacy**; however, this is associated with many uncertainties (which are not necessarily time-to-event EP specific). Statistical comparisons may likely not overcome bias introduced due to external comparison; hence estimated effects should be considered sufficiently large and robust so that there is **confidence about a clinically relevant effect despite potential bias** (see also the response to Question 2 b. ii). Sensitivity analyses are a minimum requirement to examine the robustness of the results. In addition, the plausibility of the assumption of no unmeasured confounding needs to be assessed.

2) ***Specific questions related to data and their analysis***

a. What is the view of BSWP on whether the two treated cohorts should be pooled or assessed individually, also regarding observed differences in age and length of follow-up?

In general, BSWP considers that pooling of the data from ProLon1 and ProLon2 might – under certain circumstances – be acceptable in the context of this very rare disease due to the **overall similarities** of the study populations and study designs as well as the expected **increase in precision** of effect estimates.

However, it is of high importance that **results are also presented by trial** and **be interpretable** as such. The results from the separate trials are expected to be consistent and show positive trends. In particular, the reasons for any differences between the trials, including the **size of effect as well as shape of the survival curves**, need to be well understood while acknowledging uncertainties due to the limited size of the studies. As stated in the Points to consider on appliations with 1. Meta-Analyses; 2. One pivotal study '*In particular, a meta-analysis cannot be used to reconcile the conflicting results of one positive and one inconclusive study*'.

Differences in calendar time of performing the trials, age of trial participants and length of follow-up between the trials may not per se prevent the pooling of the data, but their impact on survival needs

to be well-enough understood. Accordingly, the impact of these factors should be taken into consideration for the **choice of statistical analysis method**.

BSWP does not consider it plausible that the external control (NHC) should be more similar to any of the ProLon1 or ProLon2 populations than ProLon1 to ProLon2. Consequently, if there are major concerns about pooling the data due to **unexplained differences between the trials**, BSWP considers that the data cannot be meaningfully compared against an external control because in that case, the external control would consequently be uncomparable to at least one of the studies.

b. Given the data available, can the BSWP recommend a preferred statistical methodology for estimating a treatment effect of lonafarnib that is credible, clinically interpretable, and robust? In addition, a clear description of the level of uncertainty therein is welcomed. Finally, what are the assumptions and arguments to advise this method, particularly in view of other methods? In their response, CHMP will welcome considerations on, including, but not necessarily restricted to:

i. What is the view of BSWP on the restricted mean survival time (RMST) method and its estimation? Is the definition of a time window (tau) of 3 years versus observed survival time methodologically convincing, also considering the (remaining) life expectancy of this pediatric population, but also the data dependent time-point of this definition, and including considerations on robustness? Often Propensity-score based approach advisable Inverse Probability of Treatment Weighting.

Generally, for time-to-event endpoints, describing the treatment effect by **different effect measures** is meaningful to provide a comprehensive summary.

Based on the background information about the disease, BSWP considers that **credible and clinically interpretable results** may only be obtained when the age of starting treatment with lonafarnib is included in the statistical model. Particularly, effect measures on the absolute scale such as the (difference in) RMST may strongly depend on the age of starting treatment simply because remaining life expectancy changes with increasing age, i.e. independently from being treated, the life expectancy for the next 3 years differs between a 5-year old patient and a 10-year old patient. Sensitivity analyses should also be presented to model an interaction term of treatment with age of starting treatment with lonafarnib. This is to account for the possibility that **age of starting treatment with lonafarnib may not only be prognostic but also predictive** for the outcome.

Looking at the **model assumptions** underlying the Cox proportional-hazards model and the adjusted regression-based RMST, BSWP cannot identify concrete concerns about model assumptions that will likely be violated and which would hence particularly question the **robustness of the results** of either model. The particular strength of RMST of not requiring the proportional hazards assumption plays an important role only if there are strong deviations from the proportional hazards assumption, for which there is no a-priori belief for lonafarnib. On the other hand, BSWP considers that the interpretation of the difference in RMST as gain/loss of life expectancy may generally be easier to grasp for clinicians and patients than a hazard ratio (HR).

There is usually some degree of arbitrariness when defining a **time window for the RMST**. In this case, the 3-year window was chosen because it was the maximum length of follow-up in the SATs. However, as most patients in the lonafarnib group were treated shorter than 3 years (approx. 2 years for ProLon1 and 1-3 years for ProLon2), it is unclear whether a robust estimation of the RMST for the 3-year time window is possible. Therefore, BSWP recommends looking not only at one fixed time window but rather results after **1, 2 and 3 years** (see also response to Question 2) b. iii).

Overall, BSWP considers that the RMST (or the difference thereof) and the estimated HR can be seen as **complementary measures** and lack of a convincing estimate for either of those should overall raise concerns about the robustness of the results.

ii. Can BSWP comment on matching to the external cohort versus adjusting in the analysis. If matching is desired, can a preferred matching algorithm be advised?

Before considering matching methods, it is important to understand **the comparability of the trial populations and the NHC**. In particular, it needs to be critically examined what might be potential reasons for one patient of the same age being included in the study but not the other (e.g. calendar shift, different geographical location, only specific centers recruiting patients, other in-/exclusion criteria) as these could lead to a **selection bias and confounding** when comparing the cohorts.

The **pool of potential controls from the NHC should usually be restricted** to patients that would have been eligible to participate also in ProLon1 and ProLon2 based on the in-/exclusion criteria. This will likely not be feasible in the comparison for lonafarnib due to the **small comparator pool** and that **not all data may be available in the NHC**. Consequently, it needs to be considered whether there are any in-/exclusion criteria that are known or suspected to be so strongly prognostic of the outcome and where this would warrant at least a partial restriction of eligible control patients. In that context, restriction to **contemporaneous controls** is important, however, additional restrictions may be warranted based on clinical judgement of potential confounders. A descriptive comparison of the demographics and disease characteristics in the SATs and the (matched) NHC including information about missing data are a minimum requirement.

Regarding the preference of matching to the external cohort or adjusting in the analysis, no definite recommendation for either method is made by BSWP as both are based on similar assumptions and usually lead to similar conclusions if the matching method does not substantially reduce the original dataset. Large discrepancies between the results obtained via matching versus an adjusted analysis would generally raise concerns about the robustness of the results. It should also be noted that both approaches are often mixed, i.e. patients are matched but analysis is still adjusted. Importantly, both matching and adjusting the analysis rely on the **assumption of no unmeasured confounding**. This assumption can generally not be verified, however, knowledge and availability of data on important prognostic factors is a key issue for assessing the plausibility of the assumption.

The matching algorithms used by the applicant only match patients by age, sex and geographic region; however, there will be other (known) confounders. Consequently, matching or adjusting only for these confounders will have limited value in terms of addressing potential bias in the comparison against the NHC. Possibilities for improvements with regard to matching algorithms, e.g. via **propensity-score based methods**, depend on knowledge and availability of data on potential confounders at the time of starting treatment with lonafarnib (or similarly, the defined time 0 in controls). If no relevant data beyond age, sex and the geographic region were available in the NHC, either because they are not measured at all or because these are covariates that change over time and are insufficiently captured in the NHC, BSWP would not see possibilities to improve the matching algorithms beyond what was already provided.

Analyses should be adjusted for the age of starting lonafarnib, including sensitivity analyses with a treatment by age of starting treatment interaction term (see the response to Question 2 b. i.). Overall, **sensitivity analyses** such as the tipping point analysis provided by the applicant with **different matching algorithms** (some of them designed to bias the comparison in favour of the control) are considered important in order to understand the impact of assumptions on the robustness of the results. Of note, although such sensitivity analyses will provide reassurance on the size of the estimate, they cannot clarify whether the analysis provides an estimate for the effect of treatment or for differences in prognosis between the populations. The assumption of no unmeasured confounding is key to this issue.

iii. What is the BSWP view on the impact of censoring survival times when patients switch to treatment combinations from monotherapy?

Based on the background information provided, it can be assumed that **censoring at the end of ProLon1 or ProLon2 is non-informative** since the trials ended with patients being given a choice to become part of a follow-up trial (Triple Therapy or Lonafarnib + Everolimus). Accordingly, almost all patients switched after the end of ProLon1 or ProLon2 and consequently, this does not directly raise concerns over censoring survival times after switch to Triple Therapy or Lonafarnib + Everolimus.

However, it must be noted that the **follow-up times differed** between the two trials with patients in ProLon1 being censored after approximately 2 years, whereas the censoring for ProLon2 patients happened in a range of 1 to 3 years. The applicant has chosen to censor survival times after 3 years for external controls. How the set of patients at risk of death changes over time may introduce a bias in favour of the treatment group. Consequently, BSWP recommends requesting performing **sensitivity analyses where survival times in the control arm are censored already after 1 or 2 years**.

In addition, the **analysis irrespectively of censoring at the switch to treatment combinations** is also considered of relevance. It is acknowledged that this analysis may not isolate the effect of lonafarnib as it cannot be excluded that the additional therapies have an influence on survival. However, the analysis may still provide relevant supportive data, particularly additional information on long-term effects and the upper bound of the effect.

2.6.7. Conclusions on the clinical efficacy

There is currently no cure or approved treatment for HGPS or PL, and the median survival for patients is 14.5 years.

The difficulties in studying a new therapy in an ultra-rare condition are acknowledged, and the unmet medical need is understood.

The strategy of the Applicant to demonstrate efficacy during the assessment phase is a concern. The presented non-clinical package supported by published data is considered sufficient as non-clinical support for the pharmacological rationale.

The initially proposed primary endpoint - *annualised rate of weight change* – although statistically significant showed no clinically meaningful differences. Given the lack of clinically relevant results, it is understandable that the Applicant looked into the collected data to see whether there are additional valuable clinical outcomes that can be used in the case of lonafarnib. It was observed that patients treated with lonafarnib had a better survival than the survival mentioned in the literature. Therefore, the CHMP agreed that the survival analyses are to be the basis for the B/R assessment. Thus, the benefit is expected to be based on survival outcomes compared to a natural, historic cohort with all the well-known associated caveats and biases (e.g. in general only basic demographics were collected for the NHC (age of diagnosis, birth date, date of death, gender, geographical region and mutation status if known). According to the ICH-E10 guideline, a natural cohort might be acceptable. As only one (1) register, including all known patients with HGPS*,* is available, this registry was chosen as comparator.

The initial survival analyses showed that patients who received lonafarnib monotherapy in Prolon1 (P1) and in group 2 study 09-06-0298 (P2) and matched to untreated contemporaneous patients (birth date ≥1991) that there is a beneficial effect of lonafarnib treatment based on the pooled data of P1 + P2 (data cut-off 1 June 2019). Based on the most plausible analysis (including those requested by the BSWP (see above)) the mean RMST after 3 years of treatment increased from 0.44 to 0.47 years. Given the limited information in the datasets, the estimated monotherapy effect over 3 years can be down to 0.2 in view of the 95%-CI.

Although the improvement of the mean RMST at last follow-up was considered important (by the BSWP), the results should be interpreted with some caution as patients underwent additional

(potentially beneficial) treatments. Based on the analysis with the original random matching methodology with adjusting for age at start, the mean RMST at last to follow-up is 4.3 with a 95%-CI from 2.6 to 6.1.

Additional support for the clinical effect of lonafarnib are the observed reductions of progerin in patients, and the improvements of PWV and echodensity. These add to the totality of clinical evidence in favour of lonafarnib.

2.6.8. Clinical safety

The lonafarnib for Progeria clinical development program includes two clinical studies that provide data for the evaluation of the safety of lonafarnib monotherapy in patients with HGPS and PL; Study 07-01-0007 and Study 09-06-0298. The results of a third ongoing clinical study, Study 0000170505, are not included in this submission. The main focus will be on the naïve patients treated with lonafarnib monotherapy (ProLon1 and 2). The overall population (including the patients in the triple therapy group (group 1)) will be discussed when relevant and available.

In the ProLon1 and ProLon2 Combined Safety Population 60 classic HGPS patients (95.2%), 2 patients with non-classic HGPS (3.2%) and 1 one patient with PL (1.6%) were presented. The median age of patients at baseline was 6.0 years (range: 2, 17 years), with the majority of patients (57 [90.5%] patients) 1 to 11 years of age. There was a similar proportion of males (33 [52.4%] patients) and females (30 [47.6%] patients).

2.6.8.1. Patient exposure

Sixty-three drug naïve patients were enrolled and received at least one confirmed dose of lonafarnib (28 patients in Study 07-01-0007 (ProLon1) and 35 patients as part of ProLon2 in Study 09-06-0298). These 63 patients are included in the ProLon1 and ProLon2 Combined Safety Population. Of these patients, 52 (81.3%) completed the study, and 11 (17.2%) discontinued treatment. Generally, patient disposition was similar between ProLon1 and ProLon2; however, the majority of patients who discontinued the study were in ProLon2 (9 [25.7%] patients) compared to ProLon1 (2 [6.9%] patients).

The Triple Therapy study (Study 09-06-0298, Group 1) evaluated the therapeutic effect of pravastatin and zoledronic acid in combination with lonafarnib for children with HGPS or PL. Forty-seven patients (≥1 year of age) were enrolled in Group 1, 38 with classic HGPS, five with non-classic mutations, and four with PL. Twenty-six participants had previously received at least 2 years of continuous lonafarnib monotherapy in Study 07-01-0007, and 21 were treatment-naïve. The lonafarnib dose was 150 mg/m^2 BID administered orally.

In the ProLon1 and ProLon2 combined group, the median duration of exposure (total days drug taken) was 809 days (range: 8, 1148 days). The mean daily dose was 154.67 mg (standard deviation [SD]: 32.37), and the median daily dose was 149.08 mg (range: 94.55, 239.28 mg). The mean and median dosing varied around 150 mg daily. Given a body surface area varying between 0.37 m^2 and 0.95 m^2, the daily dose expressed per surface area is within the expected and advised dosing regimen (the goal for treatment was 150 mg/m^2). In the ProLon1 and ProLon2 combined group, no patient reached the proposed SmPC's capped dose of 300 mg/350 mg daily for patients with HGPS/PL, respectively (daily dose range was 94.55, 239.28 mg).

Overall, of the 84 patients who received lonafarnib treatment, 90.5% were treated for at least one year and approximately 50% were treated ≥5 years. To date, 8 (9.5%) patients have been treated for ≥10 years.

The most frequent reasons for treatment discontinuation were withdrawal by parent/guardian or death (4 (36.4%) patients each). Reason for parental withdrawal were intercurrent adverse events (vomiting, pneumonia and a combination of elevated ALT and AST, hyperglycaemia, and hypertriglyceridemia).

The remaining discontinuations were withdrawal of informed consent by a patient and withdrawal by the primary investigator with no reason for withdrawal mentioned.

2.6.8.2. Adverse events

The most commonly reported TEAEs were vomiting (88.9%), nausea (46.0%), diarrhoea (81.0%), fatigue (50.8%), upper respiratory tract infection (46%), decreased appetite (47.6%) and headache (52.4%). The reported TEAEs were similar between ProLon1 and ProLon2.

In the ProLon1 and ProLon2 combined group, nausea and vomiting were frequently reported TEAEs in patients receiving lonafarnib. All cases of treatment-related vomiting and nausea were considered mild to moderate. During the first four months of treatment in ProLon1, 19 (67.9%) patients had treatment-related vomiting, and 10 (35.7%) patients had treatment-related nausea. By the end of therapy, no patients had treatment-related nausea or vomiting. However, a few patients (4 (14.3%) patient) required antiemetics or anti-nauseants after those 4 months.

The majority of the patients in ProLon1 and 2 (about 93%) experienced mild or moderate diarrhoea (Grade 1 or 2), requiring no change in the dose of lonafarnib. The diarrhoea appears to be time-dependent as during the first 4 months, 46 patients (73%) reported diarrhoea. From 4 months on the frequency of diarrhoea reported was between 5 and 11.5%. In the ProLon1 group of patients 12 (42.9%) patients were treated with loperamide. In the ProLon2 group no patients required antidiarrheals such as loperamide.

Treatment-Related Adverse Events

In the ProLon1 and ProLon2 combined group, there were a total of 519 treatment-related TEAEs (TRAEs) in 61 (96.8%) patients. The most commonly reported TRAEs are presented in table 19.

Table 19: Treatment-Related Treatment-Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term and Time Period (ProLon1 and Group 2/ProLon2: Monotherapy - Safety Population).

		Time Period Specified (Months on Treatment)						
Preferred Term	**Statistics**	**0 - < 4 Months (N=28)[a]** (N=35)[b]	**4 - < 8 Months (N=27)[a]** (N=35)[b]	**8 - < 12 Months (N=27)[a]** (N=34)[b]	**12 - < 16 Months (N=27)[a]** (N=33)[b]	**16 - < 20 Months (N=27)[a]** (N=33)[b]	**20 - End Months (N=27)[a]** (N=32)[b]	**0 - End Months (N=28)Error! Reference source not found.[a]** (N=35)[b]
Diarrhoea (total)	n (%)	46 (73.0)	6 (9.7)	7 (11.5)	3 (5.0)	5 (8.3)	4 (6.8)	49 (77.8)
Vomiting (total)	n (%)	49 (77.8)	16 (25.8)	6 (9.8%)	6 (10.0)	6 (10.0)	3 (5.0)	54 (85.7)
Nausea (Total)	n (%)	18 (28.6)	5 (8.1)	0 (0.0%)	1 (1.7)	3 (5.0)	1 (1.6)	24 (38.1)

[a] Indicates the number of patients alive within the time period ProLon1
[b] Indicates the number of patients alive within the time period ProLon2
MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
Notes: TEAEs were coded using MedDRA Version 22.0.

Adverse Events of Special Interest

Dehydration

In the ProLon1 and ProLon2 combined group, although infrequent, treatment-related dehydration was reported in 3 (4.8%) patients. One patient experienced Grade 1 dehydration while the others reported Grade 2 dehydration (one patient reported dehydration that was an SAE).

Eye Disorders

Preclinical electroretinography findings suggest the potential for impairment of night vision. There was 1 (2.9%) patient who reported Grade 4 iritis that was considered an SAE; however, it was considered not related to the study drug. The patient had a head injury and concussion and subsequently developed traumatic iritis with mild optic disc oedema. Overall, there were no patients who experienced TRAEs associated with visual disturbances or acuity.

Haematological Events

Anaemia, thrombocytopenia, leukopenia, and neutropenia are expected events based on findings in preclinical studies and have been reported in clinical studies in cancer patients. However, no patients experienced TRAEs suggestive of myelosuppression.

Adverse Events in Other Patient Populations

Oncology Program

Over 1,500 oncology patients were treated with lonafarnib prior to the termination of development for oncology due to a lack of clear clinical activity. In oncology patients, lonafarnib administered at doses above 200 mg BID was associated with dose-limiting gastrointestinal toxicities, including nausea, vomiting, diarrhoea, anorexia, and myelosuppression. In combination with chemotherapy, myelosuppression (thrombocytopenia, neutropenia) was observed at dose levels above 100 to 150 mg BID in previously treated solid tumour patients. In most patients, diarrhoea related to lonafarnib was effectively managed with over-the-counter anti-diarrheal agents (e.g., loperamide). In the oncology studies of lonafarnib, the most frequently observed AEs in all patients who received lonafarnib monotherapy (N=374) were gastrointestinal and were mainly mild to moderate in severity. The most frequently reported treatment-related AEs included diarrhoea, nausea, vomiting, fatigue, and decreased appetite. Similarly, the most frequently reported Grade 4 treatment-related AEs in monotherapy studies included diarrhoea, fatigue, decreased appetite, nausea, and vomiting.

Hepatitis D Program

Lonafarnib is being developed to treat HDV infection in patients co-infected with hepatitis B virus (HBV).

Lonafarnib has been administered as monotherapy and in combination with RTV in a number of Phase 1 studies. In addition, lonafarnib + RTV was administered with and without peginterferon alfa-2a (PEG IFN-alfa-2a) in a Phase 3 study and with peginterferon lambda-1a (lambda) in a Phase 2 study. Lonafarnib was also administered with other therapies in drug-drug-interaction studies. Studies evaluating single doses used lonafarnib 50 mg + RTV 100 mg and lonafarnib 75 mg. In multiple-dose Phase 1 studies, lonafarnib was administered BID for up to 10 days at doses of 50 mg or 100 mg with RTV 100 mg and lonafarnib monotherapy 75 mg and 100 mg. In later phase studies, lonafarnib 50 mg and RTV 100 mg BID were administered with and without 180 µg PEG IFN-alfa-2a once weekly (for up to 48 weeks), and 180 µg lambda (for up to 24 weeks).

To date, 281 healthy adult subjects, including 16 otherwise healthy subjects with hepatic impairment, and 4 otherwise healthy subjects with renal impairment, and >110 adult patients with HDV have been

administered lonafarnib for up to 48 weeks. In patients with HDV, dose-limiting toxicities include diarrhoea, nausea, dyspepsia, vomiting, anorexia, abdominal pain/abdominal pain upper, decreased weight/weight loss, decreased appetite, asthenia, fatigue, epigastric pain, and inguinal pain.

The most common treatment-related side-effects in HDV-infected patients receiving lonafarnib with or without RTV were diarrhoea, nausea, fatigue, decreased appetite, vomiting, abdominal pain/abdominal pain upper, and weight decreased.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In ProLon1 and ProLon2, 34 SAEs were reported in 24 (38.1%) patients. The most frequently reported SAEs were cerebral ischaemia (6 (9.5%) patients), haematoma (4 (6.3%) patients), myocardial infarction (3 (4.8%) patients), and pneumonia, upper respiratory tract infection, (2 (3.2%) patients, each). There was a greater proportion of patients who reported at least one SAE in ProLon1 (12 (42.9%) patients) relative to ProLon2 (12 (34.3%)). There was 1 (1.6%) patient who reported an SAE of iritis.

There were 6 SAEs that were considered to be treatment-related reported by 5 (7.9%) patients, all in the ProLon1 group. Treatment-related SAEs included cerebral ischaemia (2 [3.2%] patients) and pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, and dehydration (1 [1.6%] patients, each).

Among Group 1 Triple Therapy patients enrolled following ProLon1, there were 4 (15.4%) patients who reported at least one SAE (myocardial infarction (n=2), haematoma (n=1) and death (n=1)). Among Group 1 Triple Therapy treatment naïve patients, 2 (9.5%) patients reported at least one SAE (pneumonia and death, both n=1). None of the SAEs was considered treatment-related by the Investigator.

Deaths

In the ProLon1 and ProLon2 combined group, of the 63 patients treated, 5 (7.9%) patients died while on study or within 30 days of concluding treatment. There were two deaths due to myocardial infarction, one due to a severe stroke leading to death, and one death due to heart failure. In addition, there was one death that was associated with disease progression.

Of the 84 patients who received lonafarnib treatment in the total lonafarnib for progeria safety population, a total of 17 (20.2%) patients died while receiving lonafarnib, irrespective of the treatment regimen; 14 (16.7%) classic HGPS patients and 3 (3.57%) non-classic HGPS patients. There were no deaths in PL patients. The primary causes of death across studies included myocardial infarction (7 (8.33%) patients), deaths without an associated CTCAE term (not otherwise specified (NOS)) (4 (4.76%) patients), disease progression (2 (2.38%) patients), heart failure, severe stroke, epidural haematoma, and pneumonia (1 (1.19%) patient, each). None of the deaths was considered by the investigator to be treatment-related.

2.6.8.4. Laboratory findings

Overall, there was no clear or consistent pattern of changes in haematology, clinical chemistry or urinalysis from baseline to the end of therapy suggestive of an adverse drug effect.

In the ProLon1 and ProLon2 combined population, a substantial proportion of haemoglobin, neutrophil and lymphocyte counts were elevated at baseline (28.6%, 68.3% and 12.7%, respectively). Four (4)

cases of haematoma were graded as ≥ Grade 3 AE were reported by different patients. No clear signs of myelosuppression were reported.

The only consistent pattern seen was an increase in ALT and AST levels throughout the study. The majority of the increases were mild. Of the 14 (22.2%) patients who reported increased ALT, 11 (17.5%) patients reported Grade 1 increases, and 2 (3.2%) patients reported Grade 3 increases. Similarly, of the 18 (28.6%) patients who reported increased AST, 17 (27.0%) patients reported Grade 1 increases and 1 (1.6%) patient-reported a Grade 3 increase. The Grade 3 increases of ALT and AST were also considered SAEs.

The majority of the treatment-related increases in ALT and AST occurred during the first 8 months of treatment, and the frequency of these events decreased as time progressed.

2.6.8.5. Vital signs

Blood pressure

The overall systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were generally age-appropriate throughout the lonafarnib treatment period. Occasional changes from baseline for SBP of ≥20 mmHg were seen in 20 (31.7%) patients, and changes from baseline for DBP of ≥15 mmHg were seen in 26 (41.3%) patients. However, these were generally isolated occurrences. Six of these patients were taking antihypertensive or vasodilator agents.

ECG

For ProLon1 patients, ECG measures were to be taken pre-therapy, during week 16, 32, 52, 68, 84, and 116, as well as at the end of therapy for all patients, while for ProLon2 patients, ECG measures were to be taken pre-therapy and at end of therapy (week 52-156) only if signs or symptoms of cardiac disease were present.

Overall, in the ProLon1 and ProLon2 combined group, there was no meaningful difference between the QTcB and QTcF data with the exception of the number of patients with QTc values ≥0.450 sec in males or ≥0.460 sec in females. Seven males had on-treatment QTcB ≥0.450 sec and two females had on-treatment QTcB ≥0.460 sec compared to no patients using Fridericia's correction. No patients had QTc values ≥0.500 sec.

In ProLon1, three patients had decreases in the QTc interval, whereas 23 patients had ≥0.010-sec increases from baseline for QTcB or QTcF. In ProLon2, 8 patients had decreases in either QTcB or QTcF interval when compared to baseline. Another 40 patients had ≥0.010-sec increases for QTcB or QTcF.

Six patients in ProLon1, also reported TEAEs of hypokalaemia. One of the patients in ProLon 2 with an increase in QTc interval had an AE of hyperkalaemia. None of the patients reporting hypokalaemia had evidence of cardiac rhythm disturbance.

2.6.8.6. Safety in special populations

Age and Gender

There is a relationship between lonafarnib exposure and age and gender. In a study of healthy adults, an analysis of PK parameter values for lonafarnib stratified by the covariates of age (young vs elderly) and sex (males vs females) demonstrated that, in general, maximal peak concentrations were observed earlier for the young and male subjects relative to elderly and females (Study P02673).

A meta-analysis was performed in order to understand how patients' demographics affect lonafarnib exposure (07-01-0007). The analysis identified a statistically significant association between exposure and height and age for the 150 mg/m^2 capsule group. Height and age had an approximate doubling of lonafarnib exposures. However, since height increases with age, these are most likely confounding covariates. No covariate tested (weight, height, BMI, age) was highly correlated and statistically significant across all dose and preparation groups (i.e., capsule and suspension).

Hepatic Impairment

Study EIG-LNF-003, a Phase 1, open-label, parallel-group study assessed the effects of mild and moderate hepatic impairment on the single-dose PK of lonafarnib 50 mg + ritonavir 100 mg compared to healthy matched control subjects with normal hepatic function. Of the 27 subjects, 9 had a mild hepatic impairment, 7 had a moderate hepatic impairment, and 11 had no hepatic impairment (i.e., matched controls). There were no clinically meaningful changes in mean lonafarnib C_{max} and AUC(s) for either of the hepatically impaired groups relative to the healthy matched controls.

Overall, the administration of lonafarnib was generally well-tolerated in both healthy subjects and those subjects with mild or moderate hepatic impairment. No clinically relevant differences between treatment groups were noted, and no new clinically significant safety signals were observed (EIG-LNF-003).

Renal Impairment

PK data indicate the severe renally impaired subjects have clinically meaningful increases for both lonafarnib and RTV.

The incidence of AEs was higher in subjects with severe renal impairment than in their matched control group (75.0% vs 0.0%), but it could not be ruled out that these AEs were partly due to the poorer health status of the subjects with severe renal impairment. An SAE of chronic obstructive pulmonary disease was reported for 1 patient with severe renal impairment. The outcome was reported as recovered/resolved. Overall, the incidence of AEs after treatment with a single dose of lonafarnib + RTV was low in this study, and AEs occurred without a specific pattern. No safety concerns were observed during the current study (EIG-LNF-006).

Pregnancy and lactation

Lonafarnib has not been administered to pregnant or lactating women.

Overdose

There have been no reports of an overdose in clinical studies of HGPS and PL patients. A small number of oncology patients received an overdose of lonafarnib as a single agent or in combination therapy, with the highest reported dosage of 800 mg/day. The resulting AEs (anorexia, fatigue, diarrhoea, vomiting, dehydration, and AST and ALT elevation) were expected and known to be associated with lonafarnib when administered at the recommended dose.

2.6.8.7. Immunological events

No analysis of immunological events was submitted.

2.6.8.8. Safety related to drug-drug interactions and other interactions

In vitro and *in vivo* studies have demonstrated that lonafarnib is a potent CYP3A time-dependent and mechanism-based inhibitor and moderate CYP2C19 inhibitor. Concomitant administration of lonafarnib with sensitive CYP3A or CYP2C19 substrates, including herbal supplements, can increase exposure of

the co-administered medicinal product (i.e., sensitive substrate). Lonafarnib administration with strong or moderate CYP3A4 inhibitors inducers, including herbal supplements can increase exposures of the lonafarnib resulting in risk of clinically significant adverse events or decrease exposure of lonafarnib, which may impact efficacy.

2.6.8.9. Discontinuation due to adverse events

Three ProLon2 patients (4.8%) patients had TEAEs that led to the discontinuation of the study drug. The first patient had pneumonia (that was also reported as an SAE), and the second patient had treatment-related vomiting (Grade 2). The third patient had elevated ALT and AST (both Grade 1) that were considered treatment related and hyperglycaemia (Grade 3) and hypertriglyceridaemia (Grade 4) that were considered not treatment related; as these TEAEs were reported on the last study visit, this patient was considered to have completed Study 09-06-0298; however, conservatively, these were also considered as TEAEs that led to drug discontinuation.

The most frequent reason for treatment discontinuation was the withdrawal by parent or guardian or death (4 [36.4%] patients each). Of the patients whose parent/guardian withdrew the informed consent one did before starting lonafarnib. Of the remaining withdrawals, 3 withdrew the informed consent due to adverse events. An additional one withdrew the informed consent him/herself, and two patients were withdrawn by the treating physician. No reason for withdrawal was provided for the last 3 patients.

2.6.8.10. Post marketing experience

No post marketing experience is available for this medicinal product.

2.6.9. Discussion on clinical safety

Safety population

The safety analysis includes all patients from ProLon1 in study 07-01-0007 (first part of ProLon1) and all patients from ProLon2 enrolled in study 09-06-0298 (first part of ProLon2). This analysis is provided in the ProLon1 and ProLon2 Combined Safety Population. The full safety profile for all patients in Group 1 Triple Therapy and Group 1 Monotherapy Extension treatment groups, as well as data from those in Study 09-02-074 (triple therapy pilot study) and pravastatin in children with HGPS and the ongoing lonafarnib + everolimus study (Study 0000170505), are only included in this assessment when relevant.

Safety data from PL and non-classic HGPS patients in the ProLon1 and ProLon2 combined group was limited to n=1 subject and n=2 subjects, respectively. The safety profile in these patients cannot be based on these 3 subjects and might be extrapolated from that observed for HGPS.

The analysis of the ProLon1 & 2 safety population provides the best impression of the safety profile possible. Due to the very limited number of patients included in the ProLon1 and ProLon2 Combined Safety Population, an analysis including all patients treated with lonafarnib, was presented. The emerging safety profile is comparable with that reported for the combined ProLon 1 and 2 analysis. One of the issues hampering the assessment of the overall group, including patients treated with everolimus, is that both medicinal products exhibit nausea, vomiting, and diarrhoea as adverse events. The minor differences that can be observed should, therefore, be attributed to the differences in the regimen.

While the Applicant's position regarding the ethical feasibility of exposing HGPS patients to a non-active control is acknowledged, the lack of comparative safety data limits the interpretation of the AE analyses. As the efficacy is limited in alleviating the signs and symptoms of the underlying condition, a thorough discussion comparing the safety data from Study 07-01-0007 and Study 09-06-0298 (group 2, ProLon2) with a historical (matched) cohort would be helpful. However, it is not possible to compare lonafarnib safety data with untreated HGPS patients, as the information relating to the Natural History Cohort used for matching was essentially limited to basic demographic characteristics

Based on the demographic data from the ProLon1 and ProLon2 Combined Safety Population, the patients represent the general classic HGPS population currently known. Only two patients with non-classic HGPS were included, and 1 patient was suffering from PL. It is assumed that the 3 patients suffering from non-classic HGPS and PL do not bias the safety profile observed in the ProLon 1 and 2 studies.

The claimed indication covers children from 12 months on. It is understood that farnesylation is an important step in the processing of a range of cellular proteins. Clinical studies have not uncovered findings indicating lonafarnib interferes with the development of human organs; however, renal and retinal toxicities and impaired fertility may be potential concerns based on animal studies, and these concerns are addressed in the SmPC.

For the ProLon1 and ProLon2 combined group, the majority of patients (57/63 (90.5%)) were in the age group 1 to 11 years as specified in the original submission (which did not include any 1-year-olds). As requested, an analysis of AE data for the ProLon1 and ProLon2 study populations split around the median age (i.e. age group <7 years vs age group ≥7 years) was submitted. Based on the data and clinical narratives provided together with the summary of TEAEs by median age group, no apparent trend was seen indicating a difference between age groups split by median age in the frequency or severity of TEAEs in the ProLon1 or ProLon2 safety populations.

Exposure

Sixty-three (63) drug naïve patients who were enrolled and received at least one confirmed dose of lonafarnib (28 patients in Study 07-01-0007 (ProLon1) and 35 patients as part of ProLon2 in Study 09-06-0298) were included in the ProLon1 and ProLon2 Combined Safety Population. Of these patients, 52 (81.3%) completed the study, and 11 (17.2%) discontinued treatment.
Overall, 84 patients received lonafarnib treatment, 90.5% were treated for at least one year, and approximately 50% were treated for at least three years and ≥5 years. To date, 8 (9.5%) patients have been treated for ≥10 years. As this considers an ultra-rare disease, the number of patients should be considered the best possible. However, due to the limited number of patients, the conclusion cannot be considered robust.

The mean and median dosing varied around 150 mg daily. Given a body surface area varying between 0.37m^2 and 0.95 m^2, the daily dose expressed per surface area is within the expected and advised dosing regimen (the goal for treatment was 150mg/m^2). The SmPC provides a table in section 4.2 with the recommended dose per BSA.

The median follow-up was 809 days (range: 8, 1148 days). Taken into consideration that 4 patients died 40, 220, 294 and 368 days after the start of the treatment, and 6 withdrew consent after 53, 58, 150, 667, 670, and 975 days of treatment (the 1 patient who withdrew the consent before any treatment started was not included) the follow-up is considered sufficient.

Discontinuation

The most frequent reason for treatment discontinuation was the withdrawal by a parent or guardian or death (4 (36.4%) patients each).

The most commonly reported (used by ≥20% of patients) concomitant medication were analgesics (30 (47.6%) patients), vitamins (28 (44.4%) patients), mineral supplements (23 (36.5%) patients), and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (13 (20.6%) patients).

Some minor differences between ProLon1 and 2 were observed. Most striking is the low use of antidiarrheals and/or antiemetics in the ProLon2 population. This was based on the experiences in Prolon1 and the triple therapy study; antidiarrheals and/or antiemetics were only prescribed if indicated by the physician.

Adverse events

The majority (98%) of patients experienced AEs, and the mean number of AEs was 31 and 14 AEs per patient in Study ProLon1 and ProLon2, respectively. In ProLon1, a substantial number of study subjects (12 patients (42.9%)) were treated with loperamide or anti-emetics. However, GI symptoms often improved despite continued therapy, and their incidence declined after dose escalation at Month 4. Furthermore, only 4 patients discontinued study participation following GI events, and >20 patients in the MAP have been treated with lonafarnib for a decade or longer, lending support to long-term tolerability. Based on the summary of TEAEs by SOC and PT by Action Taken for the safety population *within the initial 4 months of treatment*, 15/63 (22%) patients required some form of dosing adjustment and only 1/63 (2%) patients discontinued treatment. The remaining 14 patients were able to complete the study. For 10 patients (10/63, 16%), the action taken was associated with gastrointestinal (GI) disturbance, a known and common side-effect of lonafarnib: 1 discontinuation, 3 dose reductions and 6 dose interruptions. These results are mentioned in the SmPC section 5.1.

The most commonly reported TEAEs were vomiting (56 (88.9%) patients; grade 1 or 2), diarrhoea (51 (81.0%) patients, grade 1 or 2), and fatigue (32 (50.8%) patients).

The majority of the patients reporting diarrhoea (about 93%) experienced mild or moderate diarrhoea (Grade 1 or 2), requiring no change in the dose of lonafarnib; however, 12 (42.9%) patients were treated with loperamide. The diarrhoea appears to be time-dependent as, during the first 4 months, 46 patients (73%) reported diarrhoea. From 4 months on, the frequency of diarrhoea reported was between 5% and 11.5%. In the ProLon1 group of patients, 12 (42.9%) patients were treated with loperamide. In the ProLon2 group, no patients required antidiarrheals.

During the first four months of treatment in ProLon1, 19 (67.9%) patients had treatment-related vomiting and 10 (35.7%) patients reported treatment-related nausea; all AE were mild to moderate. After 4 months of treatment, no patients reported treatment-related nausea or vomiting. In proLon1, all patients started with antiemetics or anti-nauseants at baseline; after 4 month only a few patients (4 (14.3%) patients) required antiemetics or anti-nauseants. In ProLon2 (use of antiemetics or anti-nauseants was not mandatory at start of treatment), no patients required antiemetics or anti-nauseates.

Nausea and vomiting are important identified risks of lonafarnib that were not associated with high rates of serious complications and mainly occurred during the first few months of treatment. Careful management of nausea, vomiting and diarrhoea is important to counteract the development of volume depletion. This is included as a warning, and additional dosing advice on how to treat these signs and symptoms is provided in the SmPC.

In both the ProLon1 and ProLon2 studies, the total number of TEAEs and the proportion of patients with TEAEs declined continuously during the first eight weeks of treatment.

The Applicant informs that 4 cases of haematoma were graded as ≥ Grade 3 AE; none were associated with thrombocytopenia. In the ProLon1 and ProLon2 combined population, a substantial proportion of haemoglobin, neutrophil and lymphocyte counts were elevated at baseline (28.6%, 68.3% and 12.7%,

respectively). Inspection of the data reveals that the majority of instances were either marginal increases (e.g., haemoglobin 138 g/L (ULN 134 g/L)), or <2x ULN (Listing 1.244.4.1). Given the magnitude of the increase, the baseline abnormalities can be considered to be representative of physiologic fluctuation and of no clinical significance.

Serious adverse events

In ProLon1 & 2 safety population, 34 SAEs were reported in 24 (38.1%) patients. The most frequently reported SAEs were cerebral ischaemia (6 (9.5%) patients), haematoma (4 (6.3%)) patients), myocardial infarction (3 (4.8%)) patients), and pneumonia, upper respiratory tract infection, (2 (3.2%) patients, each). There was a greater proportion of patients who reported at least one SAE in ProLon1 (12 (42.9%) patients) relative to ProLon2 (12 (34.3%)). Six (6) SAEs were considered related to lonafarnib. These SAEs included cerebral ischemia (2 (3.2%) patients) and pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, and dehydration (1 (1.6%) patients, each).

In the ProLon1 and ProLon2 combined group, of the 63 patients treated, 5 (7.9%) patients died. All of the patients died due to a cardiovascular or cerebrovascular event. None of the deaths was considered by the Investigator to be treatment-related.

Other safety issues

In the ProLon1 and ProLon2 combined group, most of the measured laboratory parameters shifted. There was no clear or consistent pattern of changes in laboratory parameters. The most relevant changes observed were related to liver function. No cases of Hy's law were reported in any of the studies of lonafarnib. Further, elevations >3xULN were reported in 3 patients in ProLon1 and 6 patients in ProLon2 and were only reported for ALT. Only 1 patient in ProLon2 had an ALT excursion >5x ULN; the ALT for this patient was 6.1x ULN. No patients in the ProLon1 or ProLon2 populations had increases in bilirubin. In general, the larger increases, above 3x ULN, tended to occur within the first 4 months following initiation of treatment.

In the ProLon1 and ProLon2 combined group, creatinine clearance was within the normal values for age and sex, indicating that most patients had a normal renal function.

Special patient groups

The overall analysis of the available safety data indicates a relation between dose, gender, weight and age (with age and weight considered confounders).

According to the Applicant's PopPK analysis, in patients with HGPS, females had an 18.6% reduction in clearance of lonafarnib compared to males of the same size. It is accepted that a difference of such magnitude does not in itself support a gender-based dosing recommendation.

The frequency of adverse events reported in the group of patients with mild to moderate hepatic impairment was higher. The more frequently reported adverse events are diarrhoea, nausea, abdominal pain, abdominal faeces, oesophageal varices and vomiting. However, the differences between treatment groups were not considered clinically relevant.

The incidence of AEs was higher in subjects with severe renal impairment than in their matched control group (75.0% vs 0.0%). Most adverse events reported were vomiting and nausea, an increase in liver function parameters and infections. As only the minority of lonafarnib is renally cleared (< 1%), the observed imbalance is considered a chance finding.

SmPC

One patient discontinued the study after 38 days of treatment due to study related vomiting. As vomiting is treatment-related and because this adverse event is most severe in the first phase of the treatment, this is included as a warning in the SmPC.

Lonafarnib is a potent CYP3A4 mechanism-based inhibitor. As lipid modifying agents are commonly used by HGPS and lonafarnib is expected to increase plasma concentrations of statins, concomitant use of lonafarnib with lovastatin, simvastatin, and atorvastatin is contraindicated due to an increased risk of myopathy, including rhabdomyolysis. Further, concomitant use of lonafarnib with orally administered midazolam is also contraindicated. This is reflected in the SmPC and agreed.

Lonafarnib administration with strong or moderate CYP3A4 inhibitors or inducers, including herbal supplements, can increase exposures of the lonafarnib resulting in a risk of clinically significant adverse events or decrease exposure of lonafarnib, which may impact efficacy, respectively. Concomitant use of strong or moderate CYP3A4 inhibitors or strong CYP3A4 inducers are contraindicated in the SmPC.

Additional safety data needed in the context of a MA under exceptional circumstances

See discussion on efficacy above for details on the additional data required.

2.6.10. Conclusions on the clinical safety

As HGPS concerns an ultra-rare disease, the number of patients (N=63) should be considered the best possible. However, due to the limited number of patients, the conclusions on safety cannot be considered robust.

The safety of lonafarnib was mainly investigated in patients included in Study 07-01-0007 (ProLon1) and Study 09-06-0298, ProLon2. Only 63 patients were enrolled and treated in these non-controlled studies. Thus, both the study design and the few patients included in the trials limits firm conclusions; however, this may be accepted due to the rarity of the disease.

Most (98.4%) of the patients experienced AEs while treated with lonafarnib, and the majority of these patients experienced multiple AEs. The majority of the AEs were reported within the initial 4 months of the treatment, and the most commonly reported adverse events comprise gastrointestinal AEs, including nausea, vomiting and diarrhoea (all grade 1 or 2). Of the patients reporting diarrhoea 12 (42.9%) were treated with loperamide. Of the patients reporting nausea/vomiting 4 patients were treated with anti-nausea or anti-emetic treatment. The majority of the patients experienced one or more moderate/severe AE(s). In the SmPC it is stated that prevention or treatment of vomiting and/or diarrhoea with an anti-emetic and/or anti-diarrhoeal medicinal product can be considered, which is considered sufficient.

Serious AEs were reported in 24 (38.1%) patients, including 6 (9.5%) patients with cerebral ischaemia and 3 (4.8%) patients with AMI; these SAEs could be related to disease (progression). The SAEs related to hepatic function (increased alanine aminotransferase and aspartate aminotransferase) were considered related to lonafarnib.

Five (5) patients died during the period under observation. All of the patients died due to a cardiovascular or cerebrovascular event. None of the deaths was considered to be treatment-related by the Investigator.

In the ProLon1 and ProLon2 combined group, most of the measured laboratory parameters shifted. There was no clear or consistent pattern of changes in laboratory parameters.

Concomitant administration of lonafarnib with sensitive CYP3A or CYP2C19 substrates, including herbal supplements, can increase the exposure of the co-administered medicinal product (i.e., sensitive substrate). In addition, Lonafarnib administration with strong CYP3A4 inhibitors, including herbal supplements, can increase the exposure of lonafarnib, resulting in a risk of clinically significant adverse events or decreased exposure of lonafarnib, which may impact efficacy, respectively. These are contraindicated in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 20: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Diarrhoea, nausea, vomiting • Drug interaction with loperamide • Increased AST/ALT
Important potential risks	• Drug interaction with midazolam (including parentally administered midazolam) and other sensitive CYP3A or CYP2C19 substrates • Drug interaction with weak CYP3A inhibitors • Drug interaction with P-gp substrates • Drug interaction with select* HMG CoA reductase inhibitors
Missing information	• None

* Only lovastatin, simvastatin, and atorvastatin are contraindicated due to CYP3A metabolism.

2.7.2. Pharmacovigilance plan

Table 21: Additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Prospective Observational Study of Patients with Hutchinson-Gilford Progeria (HGPS) and Progeroid Laminopathy (PDPL)	The overall objective of this study is to evaluate the long-term safety and effectiveness of lonafarnib treatment among patients with HGPS or a PDPL in real-world clinical care settings and assess important identified and potential risks, and missing information listed in the	• diarrhoea, nausea, and vomiting • drug interaction with loperamide • increased AST/ALT • drug interaction with parenterally	Protocol submission Registration in the EU PAS Register: Prior to start of data collection	September 2022 Prior to start of data collection

Planned	lonafarnib RMP. The primary objective: Among patients with HGPS or a PDPL managed in a real-world setting: • Characterise safety events during treatment with lonafarnib including AEs, SAEs, and AESIs including vomiting, diarrhoea, nausea, abdominal pain, constipation, fatigue, upper respiratory tract infection, decreased weight, decreased appetite, and dehydration. The secondary objective: • Describe the overall survival • Evaluate the incidence of MACEs • Assess HRQoL • Describe concomitant use of medications that may interact with lonafarnib (loperamide, parenterally administered midazolam and other sensitive cytochrome P450, family 3, subfamily A (CYP3A) or cytochrome P450 2C19 (CYP2C19) substrates, weak cytochrome P450 3A4 (CYP3A4) inhibitors, Pglycoprotein (P-gp) substrates, and select 3- hydroxy-3-methylglutaryl coenzyme A (HMG	administered midazolam and other sensitive CYP3A or CYP2C19 substrates • drug interaction with weak CYP3A4 inhibitors • drug interaction with P-gp substrates • drug interaction with HMG CoA reductase inhibitors	Start of data collection/first patient in (FPI): Final protocol + 1 year Last patient in (LPI): FPI + 5 years End of data collection / last patient out (LPO): LPI + 5 years Date(s) of study progress reports: Every year during patient enrolment Interim report(s) of study results: Every year after FPI Final report of study results: LPO + 1 year	Final Protocol + 1 year FPI + 5 years LPI + 5 years Every year during patient enrolment Every year after FPI LPO + 1 year

	CoA) reductase inhibitors) and occurrence of safety events • Describe occurrence of increased aspartate transaminase (AST)/alanine aminotransferase (ALT) • Describe use of lonafarnib among patients with severe hepatic impairment			

2.7.3. Risk minimisation measures

Table 22: Summary table of risk minimisation activities by safety concern proposed in the RMP version 0.6.

Safety concern	Risk minimisation measures
Diarrhoea, nausea, and vomiting	Routine risk minimisation measures: Sections 4.4 (Special Warnings and Precautions for Use) , 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) and 4.8 (Undesirable Effects) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures
Increased AST/ALT	Routine risk minimisation measures: Sections 4.4 (Special Warnings and Precautions for Use) and 4.8 (Undesirable Effects) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures
Drug interaction with loperamide	Routine risk minimisation measures: Sections 4.4 (Special Warnings and Precautions for Use) and 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures

Drug interaction with parentally administered midazolam and other sensitive CYP3A or CYP2C19 substrates	Routine risk minimisation measures: Sections 4.3 (Contraindications) 4.4 (Special Warnings and Precautions for Use) and 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures
Drug interaction with weak CYP3A inhibitors	Routine risk minimisation measures: Sections 4.2 (Posology and method of administration) and 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures
Drug interaction with P-gp substrates	Routine risk minimisation measures: Section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) Additional risk minimisation measures: No additional risk minimisation measures
Drug interaction with select* HMG CoA reductase inhibitors	Routine risk minimisation measures: Sections 4.3 (Contraindications) and 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction) of the lonafarnib SmPC Additional risk minimisation measures: No additional risk minimisation measures

* only lovastatin, simvastatin and atorvastatin are contraindidated due to CYP3A metabolism

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.6 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.11.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the Package Leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lonafarnib EigerBio Europe Limited (lonafarnib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU, and as the marketing authorisation is approved under exceptional circumstances.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.9.3. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:
- the Group accepted the request due to the ultra-rarity of the diseases and the extremely low number of patients.

The Applicant committed to providing a printed Package Leaflet in each patient's native language with all orders, and will ensure that all HCPs are provided with all native language SmPCs in printed format upon request.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lonafarnib is a specific inhibitor of farnesyltransferase (FTI). The proposed indication for lonafarnib monotherapy is the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford Progeria Syndrome or a processing-deficient Progeroid Laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare multi-systemic "premature ageing" disease in which children mostly die of severe atherosclerosis and accompanied cardiovascular complications at an average age of 14.5 years. A mean survival of classic HGPS of 12.4 (range: 1.5–27) years was

found in the literature. The incidence of HGPS is approximately 1 in 4 million births with a prevalence of 1 in 20 million living individuals. Progeroid laminopathies, rarer than HGPS, are genetically related to HGPS and have clinical features that overlap with HGPS, including severe cardiovascular disease. As of October 2021, 133 children with the classic HPGS phenotype and 63 patients with progeroid laminopathies (who have a mutation in the lamin pathway but do not produce progerin) are known to be alive[3].

HGPS is characterized by an increase in arteriosclerosis and vascular wall fibrosis due to the presence of progerin. Further, HGPS is characterized by severe failure to thrive, characteristic faces (receding mandible, narrow nasal bridge and pointed nasal tip), total alopecia, global lipodystrophy, joint contractures, skeletal dysplasia, sclerodermatous skin, dental abnormalities, and low-frequency conductive hearing loss.

3.1.2. Available therapies and unmet medical need

There are no medicinal products approved for the treatment of children with HGPS or PL. Patients are given the best standard of care to treat the signs and symptoms. Medications used to treat HGPS include low-dose aspirin, statins, antihypertensives, anticoagulants, and various other medications.

3.1.3. Main clinical studies

To demonstrate the clinical efficacy of lonafarnib monotherapy 150 mg/m2 capsules twice daily p.o. in patients with Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies, a survival cohort study was conducted. This survival analysis included 60 classic HGPS patients and 2 non-classic HGPS who received lonafarnib monotherapy in studies Prolon1 (n=27) and Prolon2 (n=35). For the primary survival analysis, HGPS patients were compared to untreated controls retrieved from a retrospective natural history cohort (n=81), matched in pairs (based on sex and continent when possible; the value for 'age at start treatment' for the untreated patient in a pair was set to the corresponding value of the lonafarnib treated patient). During the procedure, numerous additional analyses were submitted.

Supportive data from two open-label, single-arm, single-site Phase II studies of different design and subgroups (Study 07-01-0007/Prolon1 and Study 09-06-0298 group2/Prolon2) were submitted. The studies enrolled a global study population of 84 distinct patients from 34 countries across five continents. There was no age limitation for enrolment. Among others, changes in Corrected Carotid Femoral Pulse Wave Velocity (PWVcf) and Carotid artery ultrasonography echodensity were measured as explorative endpoints. In the NHC no data on cardiovascular parameters were collected.

3.2. Favourable effects

In animal studies and *in vitro* using human fibroblasts, it was demonstrated that lonafarnib blocks the farnesylation of progerin, leading to the formation of more normal nuclei. Furthermore, the reduction of abnormal nuclei under lonafarnib was dose-dependent. The improvement of the nuclei morphology was also observed in fibroblasts obtained from patients with non-classic HGPS or PL.

It was demonstrated that progerin levels for the HGPS patients included in studies Prolon1 and Prolon2 decreased under continued lonafarnib treatment. Progerin levels remained at a low level during continued lonafarnib treatment.

[3] https://www.progeriaresearch.org/meet-the-kids/

The generalizability of the data is high because the study populations in the clinical studies include most patients identified with HGPS worldwide as young as 12 months of age. In addition, few patients were prematurely discontinued (3 patients) or underwent dose reductions (4 patients) in the combined group of lonafarnib treated patients.

Pooling of Prolon 1 and Prolon 2 is considered sufficiently justified. There were no clinical reasons for why Prolon 1 and Prolon 2 would be different in terms of inclusion, and the apparent differences in survival results reported for ProLon1 and 2 are likely the result of a different age profile with ProLon2 including older patients, which affect survival outcome as age at the start is currently identified as a prognostic factor for the treatment result.

Survival

Analysis submitted by the Applicant of **the pooled data of Prolon1 and Prolon2** showed some improvement in mean survival time (censored at 3 years) in patients with lonafarnib monotherapy as compared to untreated controls (estimated mean 2.83 vs 2.34 years; p=0.0002, stratified log-rank test; primary analysis as per SAP: censored at 3 years, a randomly selected match without replacement). There is no indication that the original matching (Original Random Untreated) with adjustment for age at start of treatment is the most optimistic implementation of the random matching procedure due to chance, given the 21 implementations of random matching that the Applicant has shown. It yields a mean survival benefit of 0.47 years (95% CI: 0.2, 0.7; p-value=0.0005).

Additional, requested survival analyses censored at 3 years (i.e. the maximum duration of the initial monotherapy phase of the studies) were performed using various censoring and matching methods. The estimates for RMST vary between 0.44 and 0.47 years (without and with regression adjustment for age at start, respectively). Given the limited information in the datasets, the estimated monotherapy effect over 3 years can be down to 0.2 in view of the 95%-CI.

The BSWP was in favour of a tipping point analysis censored at 3 years. The mean RMST difference for treated versus untreated patients using the tipping point analyses was somewhere in the range between 0.2 and 0.5 years, all favouring the lonafarnib treated patients.

As the BSWP expressed uncertainty of using 3-year window for RMST analysis, a 1-year and 2-year RMST analysis on the Prolon1 and Prolon2 pooled dataset as suggested by BSWP was conducted. The survival benefit for 1-year and 2-year follow up are 0.1 (95% CI: 0.03, 0.15; p=0.002) and 0.2 (95% CI: 0.07, 0.40; p=0.004), respectively.

An analysis censored at 3 years, fixed 50th percentile matching by mutation status, gender, and continent showed a statistically significant difference in restricted mean survival of 0.24 years when censored at 3 years.

The analysis showed a statistically significant difference in restricted mean survival 2.5 years at the last follow-up.

A Cox proportional hazards analysis, matched on sex, continent and age at the start of lonafarnib treatment, was conducted on the last follow-up at 1 August 2021, with survival time and start age as covariates and study (Prolon 1, Prolon 2, Triple therapy) as a factor. This analysis showed for Prolon1 a HR (95% CI) of 0.23 (0.115, 0.457), for Prolon2: 0.35 (0.156, 0.780), and the 18 naïve patients on triple therapy (TT): 0.24 (0,084, 0.702).

The numerous additional analyses confirmed the improvement in survival of lonafarnib treated patients compared to untreated controls during the 3 years monotherapy phase of the analysis.

The BSWP favoured using the survival results at the last follow-up to obtain an upper bound of the longer-term effects of lonafarnib on the survival of the patients. RMST in treated versus random untreated (censored on 1 August 2021, ProLon1 and ProLon2 Contemporaneous Intention-to-Treat Set

[N=144]) was 4.3 years with a 95%-CI from 2.6 to 6.1. Given the limited information in the datasets, the upper bound of the long-term effect of lonafarnib can be down to 2.6 years in view of the 95%-CI.

Using age at the start of treatment as a continuous covariate and the original matching methodology, the mean survival benefit was 4.7 years.

When in the Cox proportional hazards analysis only patients were included with an age ≤10 years at the start of treatment, HRs (95% CI) were 0.19 (0.082, 0.430), 0.22 (0.072, 0.653), 0.13 (0.034, 0.489), for Prolon1, Prolon2 and triple therapy, respectively with all results statistically significant.

PWVcf and carotid artery ultrasonography

Improvements (change from baseline to end of treatment) for both PWVcf and carotid artery ultrasonography (echodensity) – both exploratory endpoints - were statistically significant within the group compared to baseline.

Other clinical endpoints such as weight gain, height gain, and SBP showed marginal improvements.

3.3. Uncertainties and limitations about favourable effects

It is not clear if the potency of lonafarnib is comparable in human and non-clinical species. However, proof of concept has been established *in vitro*.

The primary studies for ProLon1 and ProLon2 cohorts are two open-label, single-arm, single-site Phase II studies of different designs and subgroups (Study 07-01-0007/Prolon1 and Study 09-06-0298 group2/Prolon2) that did meet their predefined primary endpoint (weight increase). This increase in body weight, however, was considered (by the Applicant) clinically irrelevant.

Sample size

The sample size is very limited and hampers the interpretation of the results reported. However, given the ultra-rare nature of Progeria, the number of 60 classic HGPS patients, 2 non-classic HGPS and 4 PL patients included in the clinical studies should be considered the best possible.

After careful consideration, it is concluded that ProLon1 and ProLon2 can be pooled, although the overall effect is mainly driven by the results obtained in ProLon1.

The exploratory cardiovascular outcomes like PWV and hypotension are well-known indicators for cardiovascular complications later in life. In patients suffering from HGPS these could be prognostic. For the NHC, this kind of data is not available and cannot be used for matching.

As no other parameters besides age, gender, region, mutation status (or the lack thereof), date of birth/death were collected in the NHC, there are limited possibilities to match patients.

Survival analysis

Selection bias cannot be excluded as an external control was used as a comparator, and no randomisation could be applied to balance known and unknown confounding factors.

The initially proposed primary endpoint was discarded during the assessment process.

The post-hoc strategy of the Applicant to demonstrate survival benefits is a concern. The benefit of the treatment is based on survival outcomes of two cohorts from different studies and compared to a natural, historical cohort from a third source with all the well-known associated caveats and biases. The lack of predefined analysis to support the application jeopardizes the ability to draw robust conclusions based on the existing data.

The appreciation of the results is further complicated by the many different analyses and methods submitted by the Applicant, and as a result the BSWP was asked for independent advice on which is/are the most adequate analyses. All analyses show different effects sizes. Based on the preferred analyses (including those of the BSWP) for the 3-years follow-up (i.e. lonafarnib monotherapy) the mean RMST benefit ranges from 0.44 to 0.47 years, and while considering the last FU the survival ranges from 2.0 (1.989) tot 5.0 (4.964) years. However, the last FU analyses are further hampered by the start and stop of additional treatments that may affect the effect estimates (e.g., pravastatin + zoledronic acid and/or everolimus).

Pooling ProLon1 and 2 and triple therapy

When monotherapy data (i.e., up to the first three years of follow-up) from existing ProLon 1 and 2 cohorts is evaluated separately, the survival found in the ProLon1 cohort and retrospective natural history cohort could not confirm the analyses of the ProLon 2 cohort vs NHC when including all NHC patients. The age distribution might partly explain that 3 out of 5 of the older patients in Prolon2 died during the follow-up period, while none of the patients died in Prolon1.

After an unplanned interim efficacy analysis, the Applicant initially excluded the patients treated in the triple therapy part of study 09-06-0298. As a result, the remaining patients in study 09-06-0298 (to become ProLon2) received monotherapy again.

The planning and handling of the interim analysis of study 09-06-0298 and the missing data points for cardiovascular data resulted in GCP-related concerns. Therefore, the interpretation of the explorative cardiovascular endpoints should be made with utmost caution.

Notwithstanding these concerns, an initial request for a GCP inspection was lifted as the survival analyses were considered the main source of evidence.

Cardiovascular parameters

There is no external control, as in the NHC no cardiovascular data were collected.

PWV data analysed did not include patients undergoing triple therapy.

No meaningful differences in carotid echodensity at EOT was observed in the additional responder analyses conducted between survivors and non-survivors.

Carotid echodensity data analysed did not include patients undergoing triple therapy.

The observed changes in PWV and Carotid echodensity cannot be benchmarked against an untreated group of progeria patients.

Lower age limit

Study 09-06-0298 (Group 1/Triple therapy and Group 2/ProLon2) included 10 patients ≤3 years of age. Of these children, 5 ProLon2 patients were included in the survival and safety analyses. Nine out of the 10 patients starting lonafarnib at ≤3 years of age were known to be alive through 1 June 2019. One patient was lost to follow-up. Seven of the 10 patients remained on study. The Applicant provided an update for the patients with a cut-off date of 1 August 2021.

3.4. Unfavourable effects

Sixty-three (63) drug-naïve patients were included in the ProLon1 and ProLon2 Combined Safety Population. Of these patients, 52 (81.3%) completed the study, and 11 (17.2%) discontinued treatment. The median follow-up was 809 days (range: 8, 1148 days).

The mean and median dosing varied around 150 mg daily. Given a body surface area varying between 0.37 m^2 and 0.95 m^2, the daily dose expressed per surface area is within the expected and advised dosing regimen (the goal for treatment was 150 mg/m^2).

Most (98.4%) of the patients experienced AEs while treated with lonafarnib, and the majority of these patients experienced multiple AEs. Most patients (96.8%) experienced TRAEs. The majority of the patients (79%) experienced one or more moderate/severe AE(s). The most commonly reported TEAEs were vomiting (88.9%, grade 1 or 2), nausea (46.0%, grade 1 or 2), diarrhoea (81.0%, grade 1 or 2), fatigue (50.8%), upper respiratory tract infection (46%), decreased appetite (47.6%) and headache (52.4%). Diarrhoea, nausea, and vomiting are reported to be drug-related. "Weight decreased" was noted for 17 (27.0%) patients, and transaminase elevations were commonly observed (>50% of patients in ProLon1).

In the ProLon1 group, 12 (42.9%) patients were treated with loperamide or anti-emetics, whereas in the ProLon2 group, no patients required antidiarrheals or anti-emetics/antinauseants. Further, the frequency of nausea and vomiting decreased over time, with only a few patients reporting treatment-related nausea or vomiting at the end of the study.

In ProLon1 & 2 safety population, 34 SAEs were reported in 24 (38.1%) patients. The most frequently reported SAEs were cerebral ischaemia (6 (9.5%) patients), haematoma (4 (6.3%)) patients), myocardial infarction (3 (4.8%)) patients), pneumonia, and upper respiratory tract infection, (2 (3.2%) patients, each), which all could be considered disease-related as the investigators reported that these were not drug-related. Six (6) SAEs (cerebral ischaemia (2 (3.2%) patients) and pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, and dehydration (1 (1.6%) patients, each) were considered related to lonafarnib.

There was a greater proportion of patients who reported at least one SAE in ProLon1 (12 (42.9%) patients) relative to ProLon2 (12 (34.3%)).

Five (5) patients died during the period under observation. All of the patients died due to a cardiovascular or cerebrovascular event. None of the deaths was considered by the Investigator to be treatment-related.

Most of the measured laboratory parameters shifted in the ProLon1 and ProLon2 combined group. There was no clear or consistent pattern of changes in laboratory parameters. Elevations >3xULN were reported in 3 patients in ProLon1 and 6 patients in ProLon2 and were only reported for ALT. Only 1 patient in ProLon2 had an ALT excursion >5x ULN; the ALT for this patient was 6.1x ULN. No patients in the ProLon1 or ProLon2 populations had increases in bilirubin. In general, the larger increases, above 3x ULN, tended to occur within the first 4 months following initiation of treatment. There were no patients with a Hy law case.

Lonafarnib is a substrate of CYP3A4, a strong CYP3A4 inhibitor and affects various metabolic enzymes and transporters. There is a significant risk of DDIs with lonafarnib, both as victim drug and perpetrator.

3.5. Uncertainties and limitations about unfavourable effects

Dealing with an ultra-rare disease, the number of patients (N=63) is limited but should be considered the best possible. However, due to the limited number of patients, the conclusions on safety cannot be considered being robust. No clear or unexpected adverse events were reported in this additional analysis. Further, the lack of comparative data and the general high frequency and seriousness of morbidity associated with the disease hamper interpretation of the safety findings.

The most frequent reason for treatment discontinuation was the withdrawal by parent or guardian or death (4 (36.4%) patients each). The remaining patients withdrew due to GI-related adverse events. Except for the low use of antidiarrheals and/or antiemetics in the ProLon2 population, only minor differences in comedication between ProLon1 and 2 were observed. The difference in the use of antidiarrheals and/or antiemetics between both studies can be explained by the fact that in ProLon2, these medications were not provided as standard co-medication but only prescribed on medical indication.

The incidence of AEs was higher in subjects with severe renal impairment than in their matched control group (75.0% vs 0.0%). The most frequent adverse events reported were vomiting and nausea, an increase in liver function parameters and infections. As only the minority of lonafarnib is renally cleared (<1%), this observation is considered a change finding.

There is a discrepancy between the high number of moderate and severe AEs and the low number of patients with either dose-reduction or withdrawal from the study due to AEs. This is considered due to the temporality of the adverse events; after about 4 months, the most important adverse events (vomiting, nausea, diarrhoea and elevated liver function tests) decrease in frequency or are not reported at all.

3.6. Effects Table

Table 23: Effects Table for Zokinvy (data cut-off: 1 August 2022, OS follow-up during monotherapy only, so censored at 3 years).

Effect	Short Description	Unit	Treatment	Control group	Uncertainties/ Strength of evidence	References
Survival	Overall survival	Survival probability at 3yr (standard error)	P1 0.957 (0.0425) P2 0.870 (0.0609)	P1 0.723 (0.0891) P2 0.766 (0.0726)	**SoE:** The estimates for RMST benefit for the combined population (P1 and P2) vary between 0.44 and 0.47 years (without and with regression adjustment for age at start, respectively). Given the limited information in the datasets, the estimated monotherapy effect over 3 years can be down to 0.2 in view of the 95%-CI **Unc**: differences in the estimates hamper B/R assessment.	Prolon1 CITT1 population Prolon 2 CITT2 population and Combined P1 and P2
		Survival probability at 3 year (standard error)	0.914 (0.0368)	0.681 (0.0627)	**SoE:** p=0.0014 log-rank test, p=0.0008 Cox PH test , censored at 3 years Survival Probability treated vs matched NHC: 1-y: 0.95 (0.029); 0.85 , 3-y: 0.91 (0.037); 0.63 (0.63) Difference in restricted mean survival over 3 years of follow-up (standard error): 2.829 (0.0755) vs 2.450 (0.1298), p=0.0117). **Unc:** RMST in treated versus random untreated (censored on 1st August 2021, ProLon1 and ProLon2 Contemporaneous Intention-to-Treat Set [N=144]) was 4.3 years with a 95%-CI from 2.6 to 6.1. Given the limited information in the datasets, the upper bound of the long term effect of lonafarnib can be down to 2.6 years in view of the 95%-CI.	Pooled analyses CITT1_2 population
Vomiting (grade 1 or 2)		%	88.9		**SoE:** for the vomiting/nausea only 4 patients were treated after 4 months of treatment with anti-emetics, after 4 months of treatment vomiting/nausea were not reported. **Unc:** uncontrolled, Prolon1 24-30 months; Prolon2 24 -36 months, AE's occurred mainly in the first 4 months of treatment, low number of patients no information on anti-emetics during the first 4 months.	Combined Safety Population
Nausea (grade 1 or 2)			46.0			
Diarrhoea (grade 1 or 2)			81.0			

Abbreviations: NHC: natural cohort patients; BL: baseline; CI: confidence interval; ET: end of treatment in either Prolon1 or Pronlon2; MCID: minimal clinical important difference; AE: adverse event SoE: strength of evidence; Unc: uncertainties

Notes :

1) *A PWV of 10 m/sec is used to define significant alteration in vascular function and is a risk factor for asymptomatic organ damage (Mancia et al., 2013; ESC/ESH guidelines).*

The survivor/non-survivor is based on post-hoc analysis amongst the 62 patients treated in Prolon1 and Prolon2 (also used in the survival analysis).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In vitro studies confirmed the proof of concept of lonafarnib and showed that lonafarnib dose-dependently prevents nuclear blebbing in dermal fibroblasts from HGPS patients.

Currently, it is poorly understood how progerin accumulation results in HGPS typical cardiovascular (CV) complications.

Non-clinical information demonstrates a linkage between farnesyl transferase inhibition and reduction of CV disease in progeria. This conclusion is mainly based on the changes in cardiovascular disease seen in transgenic G608G LMNA mice. In these mice the loss of vascular smooth muscle cells (one of the CV features seen in progeria) can be prevented by treatment with the farnesyl transferase inhibitor (FTI) tripifarnib (Capel *et al.,* 2008). It is also suggested that endoplasmic reticulum stress and unfolded protein due to progerin accumulation can lead to loss of vascular smooth muscle cells and, consequently, atherosclerosis (Hamzcyk *et al.,* 2019). This mechanism of endoplasmic reticulum stress has also been shown to be present in HGPS patient-derived cells.

The analyses provided by the Applicant were, among others, hampered by the post-hoc character, the lack of sufficient patients and follow-up, the intercurrent treatments, and the use of historical controls (with only limited information available). Therefore, matching should preferably have been performed on important prognostic factors. As no prognostic factors (except age at the start of treatment and mutation) have been collected for the NHC, matching on age and mutation status is considered the best possible.

The initial survival analyses showed a beneficial effect of lonafarnib treatment. The estimated additional survival is 0.49 years after 3 years of lonafarnib monotherapy treatment. Based on the most plausible analysis (including those requested by the BSWP), the mean RMST after 3 years of treatment increased from 0.44 to 0.47 years (without and with adjustment for age at start, respectively). Given the limited information in the datasets, the estimated monotherapy effect over 3 years can be down to 0.2 in view of the 95% CI. In other words, 2.4 months of enhanced survival is the most conservative estimate consistent with the data according to these new analyses. Although the improvement of the mean RMST at the last follow up was considered important (by the BSWP), the results should be interpreted with some caution as patients underwent additional (potentially beneficial) treatments. Based on the most preferred analysis, the mean RMST at the last follow-up is 4.3 years with a 95% CI from 2.6 to 6.1. Given the limited information in the datasets, the upper bound of the long-term effect of lonafarnib can be down to 2.6 years in view of the 95% CI.

The lack of cardiovascular parameters in the NHC and the absence of standardisation in measurements prevent comparisons, and limits the added value and potential associations or explanations of observed treatment effects on PWV and carotid echodensity.

Improvements from baseline to EOT in PWV and echodensity as observed in the Prolon1 and Prolon2 patients suggest some decrease in the risk of cardiovascular complications.

Diarrhoea, nausea, and vomiting occurred mainly in the first 4 months of treatment but were manageable with or without medicinal treatment. The GI adverse events during the first 4 months of treatment seem not to be expressed in a decreased quality of life. The use of antidiarrheals or anti-emetics/antinauseants, and potential measures are sufficiently addressed in the SmPC.

3.7.2. Balance of benefits and risks

The mean improvement of the mean RMST after 3 years of treatment ranges from 0.44 to 0.47 years. At the last follow-up, the improvement in mean RMST was 4.3 with a 95%-CI from 2.6 to 6.1. During the first 4 months, most patients reported vomiting, nausea and diarrhoea. These adverse events could be managed with or without medication for most patients.

Given the modest and not exactly defined improvement of survival after mono-therapy (i.e. at 3 years), the further improved survival benefit at last follow-up and the manageable vomiting, nausea and diarrhoea, it is considered that the treatment should not be withheld from the patients accepting the side effects, dominating during the first 4 months of treatment, taking in consideration that the size of treatment effect (although positive) is not well-defined.

3.7.3. Additional considerations on the benefit-risk balance

There is currently no cure or approved treatment for HGPS or PL. The median life span for HGPS is about 14.5 years. It is acknowledged that the development of lonafarnib in this rare-occurring condition with a high unmet medical need, claiming exceptional circumstances marketing authorization, has not been a strict pre-defined development process.

The proof of concept that lonafarnib inhibits progerin production is demonstrated using animal data and *in vitro* data from human-derived fibroblast cell lines obtained from HGPS patients. In transgenic C608G LMNA mice, FTI treatment showed significant improvements in both the ascending and descending aorta regarding the increased abundance of vascular smooth muscle cells. The observed reduction in cardiovascular disease progression affected all vessels, including the descending aorta, ascending aorta, carotid artery, and abdominal aorta. In contrast, there are no indications of improving the vascular system or increased survival in the long-term rat or monkey studies.

Initial postulated research objectives and outcome measures have been adopted based on an iterative process of continuously gathering clinical evidence about the medicine's benefits and risks from an environment of use and setting.

It is not likely that the Applicant will be able to collect and provide prospective additional data on the efficacy and safety of lonafarnib under normal conditions of use, considering the indication's rarity and the proportion of Progeria patients included in a research environment and already treated with the product. Therefore, the possibility to conduct additional large co-operative multicentre studies with a scientifically sound research design is practically not possible.

The Applicant used an NHC as a comparator; this is in line with the ICH-E10 guideline (choice of a control group in clinical trials), and the data used for matching can be traced back into the patient’s dossiers. The NHC is compiled of chart review data of known HGPS patients. In general, it should be mentioned that for orphan medicinal products - which were approved in the past - for the natural history cohort, limited data was available in most cases. Therefore, the availability of birth date, date of death, gender and region may be the best that could have been collected in the case of Progeria. Importantly, all patients treated in the clinical program (e.g. Prolon1, Prolon2, triple therapy) and those NHC patients matched in the survival analyses (all patients born in or after 1991) are all derived from one registry. It is reassuring that the HGPS patients used for matching received similar best standard of care; this was confirmed by analysing the survival data of treated and untreated HGPS patients born ≥1991 (contemporaneous NHC patients) and those who were alive in 2007.

As with other orphan diseases it is universally accepted by the scientific community that treatment as early as feasible in life may lead to a better perspective for the patient. This also seems to apply to the treatment of Progeria. Therefore, to better appreciate the effect on survival for patients with a starting

age <10 years, the Applicant was requested to submit an analysis of patients for ProLon1 and Prolon2 (unrevised) separate and combined to investigate the influence of age when starting lonafarnib. In this analysis, the influence of starting age was assessed not only as a prognostic factor but also as an effect modifier; do patients starting at a younger age demonstrate a stronger effect (in terms of hazard ratio or difference in restricted mean survival) than patients starting at an older age. The analyses suggest that age at start presents as an important prognostic factor but not as an effect modifier because the effect of lonafarnib and age on survival follows the proportional hazards assumption.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, the Applicant requested a marketing authorisation under exceptional circumstances in the initial submission.

It is considered that the Applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication applied for is encountered so rarely that the Applicant cannot reasonably be expected to provide comprehensive evidence. The prevalence of HGPS is 1 in 20 million living individuals, with only about 132 HGPS patients and 64 patients with progeroid laminopathies (who have a mutation in the Lamin pathway but do not produce progerin) alive as of January 2022. Therefore, the requirements for accepting a MA under exceptional circumstances are fulfilled and in view of the positive benefit risk balance, the recommendation of a marketing authorisation under exceptional circumstances is considered appropriate.

It is considered important to note that the data suggest that lonafarnib treatment should be initiated as soon as a diagnosis is made. Both age at initiation and PWV are contributing factors to survival, in which age and BL PWV seem to have a plausible relationship.

Patients with progeroid laminopathies and non-classic HGPS

In the clinical program (Prolon1 and Prolon2) 60 classic HGPS patients were included. However, only 2 patients with non-classic HGPS and four patients with PL were included in the clinical program. Based on limited (pre)clinical data, the results may be extrapolated with some reservation. However, as this application is submitted under exceptional circumstances, no additional data in non-classic and PL patients is to be collected in the short term, and these patients are in need for treatment; therefore, the proposed indication for non-classic and PL patents can be accepted.

Registry

The Applicant proposes to conduct a *Prospective Observational Study of Patients with Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathy.* The study will evaluate the safety and effectiveness of lonafarnib treatment and quality of life (QoL) among patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathy (PL) in a real-world setting. The proposal is welcomed given that there is no long-term follow-up data in the HGPS patients, and this may hopefully provide more insight into the survival under continued lonafarnib treatment. In addition, as in the current application very limited data on non-classic HGPS and PL patients were submitted, the proposed study will enable the collection of additional data in these patients.

3.8. Conclusions

The overall benefit/risk balance of Zokinvy is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zokinvy is favourable in the following indication(s):

> Zokinvy is indicated for the treatment of patients 12 months of age and older with a genetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome or a processing-deficient progeroid laminopathy associated with either a heterozygous *LMNA* mutation with progerin-like protein accumulation or a homozygous or compound heterozygous *ZMPSTE24* mutation.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional Post authorisation safety study (PASS): in order to further characterise the safety, effectiveness and health-related quality of life of Zokinvy in patients with	Annual study reports will be submitted with the annual re-assessment

Hutchinson-Gilford Progeria Syndrome and Processing Deficient Progeroid Laminopathies, the MAH shall submit the results of a prospective observational cohort study based on a registry.	

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lonafarnib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0258/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.