

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213969Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213969
PDUFA Goal Date	November 20, 2020
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Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Laura Zendel, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	November 17, 2020
Subject	Evaluation of Need for a REMS
Established Name	Lonafarnib
Trade Name	Zokinvy
Name of Applicant	Eiger Biopharmaceuticals, Inc.
Formulation	50 mg and 75 mg oral capsules
Dosing Regimen	Starting dose: 115 mg/m ² orally twice daily; if well tolerated after 4 months, may increase to 150 mg/m ² orally twice daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity lonafarnib is necessary to ensure the benefits outweigh its risks. Eiger Biopharmaceuticals, Inc. submitted a New Drug Application (NDA) 213969 for lonafarnib with the proposed indication in patients 12 months of age or older with a body surface area of 0.39 m² and above to reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome and the treatment of processing deficient Progeroid Laminopathies in patients with a heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. The most common adverse events associated with lonafarnib include vomiting, diarrhea, nausea, and weight loss. Most serious adverse events and deaths in the trials were attributed to disease progression. Other risks associated with lonafarnib include hypertension, the potential for QTc prolongation, and reproductive toxicity and embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Rare Diseases and Medical Genetics have determined that a REMS is not needed to ensure the benefits of lonafarnib outweigh its risks in this small patient population with a current life expectancy of 14.5 years as the demonstrated safety profile of lonafarnib at the indicated doses was acceptable. The risks will be communicated in labeling using warnings and precautions that include embryo-fetal toxicity and reproductive toxicity, renal and retinal toxicities, and drug interactions that may reduce lonafarnib's efficacy. A Medication Guide will also be included in lonafarnib labeling to communicate the risks to patients.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) lonafarnib is necessary to ensure the benefits outweigh its risks. Eiger Biopharmaceuticals, Inc. (Eiger) submitted a New Drug Application (NDA) 213969 for lonafarnib with the proposed indication in patients 12 months of age or older with a body surface area of 0.39 m² and above to reduce the risk of mortality in patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and the treatment of processing deficient Progeroid Laminopathies (PL) in patients with a heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. This application is under review in the Division of Rare Diseases and Medical Genetics (DRDMG). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Lonafarnib, a new molecular entity, is a specific inhibitor of farnesyltransferase proposed for use in patients 12 months of age or older with a body surface area of 0.39 m² and above to reduce the risk of mortality of patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and the treatment of Progeroid Laminopathies (PL) processing deficient Progeroid Laminopathies (PL) in patients with a heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous

ZMPSTE24 mutations . Lonafarnib will be the first-in-class-approved drug for farnesyltransferase inhibitors. Lonafarnib is proposed as an oral capsule taken as 115mg/m² twice daily as a starting dose, and if well tolerated after 4 months, can be increased to 150 mg/m² twice daily. Lonafarnib inhibits farnesylation of progerin protein, preventing the building and accumulation of progerin the defective progerin-like proteins. It is metabolized hepatically and excreted in feces. Lonafarnib is extensively metabolized by CYP3A and CYP2D6, and coadministration with strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers is proposed to be contraindicated due to pharmacokinetic changes of lonafarnib seen in nonclinical studies. It is proposed to be available as 50 mg and 75 mg oral capsules that may be opened and suspended in orange juice or applesauce. Lonafarnib is not currently approved in any jurisdiction, but Eiger submitted a Marketing Authorisation Application (MAA) for the same indication to the European Union in March 2020.¹

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 213969 relevant to this review:

- 08/22/2018: Eiger took over lonafarnib development program from Progeria Research Foundation and help first pre-IND meeting with the Agency
- 10/17/2018: Agency granted IND 139923 and granted Rare Pediatric Disease Designation for HGPS and PL (RPD-2018-189)
- 11/02/2018: Eiger submitted IND 139923 with breakthrough designation request
- 12/12/2018: The Agency granted Breakthrough Therapy Designation for lonafarnib for the treatment of HGPS and PL
- 07/03/2019: Agency granted Orphan Designation for lonafarnib for the treatment of HGPS and PL
- 11/15/2019: FDA granted rolling review
- 12/12/2019: NDA 213969 nonclinical pharmacology and toxicology submission received
- 01/31/2020: NDA 213969 chemistry, manufacturing, and controls and quality overall summary received
- 03/20/2020: NDA 213969 clinical submission received

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL) are ultra-rare, progressive, fatal autosomal dominant genetic disorders. The estimated worldwide incidence of HGPS is 1 in 4,000,000 live births. HGPS is caused by a mutation in the LMNA gene, leading to an accumulation of abnormal farnesylated lamin A protein (progerin). Progerin implants as a scaffold protein in the inner nuclear membranes of cells, causing structural instability. Processing deficient progeroid laminopathies

result from defects in protein processing downstream from where progerin is processed. This similarly results in a buildup progerin-like protein. The clinical manifestations and disease course of PL are similar to HGPS due to the similar mechanism of progerin-like protein accumulations in cell membranes caused by mutations in either the lamin A or ZMPSTE24 genes.^{2,3}

Patients with HGPS have a normal appearance at birth, but by 9 to 12 months of age, they begin to exhibit the hallmark features of HGPS. These include: failure to thrive, alopecia, prominent forehead, scalp veins, and eyes, a beak-like nose, small jaw, global lipodystrophy, limited joint mobility, thin, tight skin, skeletal dysplasia, and short stature of 3 to 3 and ½ feet. Children who have HGPS have normal intellectual development but can experience cognitive difficulties from strokes and cerebrovascular complications. Accelerated cardiovascular disease is fatal to HGPS patients, with a mean life expectancy of 14.5 years. Half of HGPS patients will have a stroke by age 8, with 80% of fatalities due to complications of accelerated atherosclerosis, and 20% of fatalities due to heart attacks and strokes.⁴

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no currently approved therapies for either HGPS or PL. Current supportive therapies may include treatment of secondary cardiovascular outcomes, including antiplatelet agents, statins, and antihypertensives. Growth hormones may be used for patients with failure to thrive.

4 Benefit Assessment

Due to the rarity of HGPS and PL, two single-arm studies evaluated lonafarnib treatment in patients with HGPS versus an external comparator group comprised of 81 matched, untreated patients born after 1991 that were a part of a natural history study maintained by the Progeria Research Foundation. Patients were matched by age, sex, and continent of residence.

Study 07-01-0007 (ProLon1, NCT 00425607), enrolled 28 pediatric subjects (26 subjects with classic HGPS, 1 with nonclassic HGPS, and 1 with PL) treated with lonafarnib monotherapy. Subjects started on lonafarnib 115 mg/m² twice daily and could increase the dose to 150 mg/m² after 4 months. Subjects were seen for follow-up every 4 months for 2 years. Study 09-06-0298 (NCT 00916747), is a currently ongoing trial including 2 groups of patients. Group 1 consists of 47 subjects at least 1 year old with classic HGPS, PL, and nonclassic HGPS. Twenty-six of these patients had been enrolled in ProLon1, and 21 were treatment naïve. Subjects in Group 1 were treated with a triple therapy regimen including lonafarnib, pravastatin, and zoledronic acid. Group 2, which became pivotal study ProLon2, consists of 35 previously untreated pediatric patients with HGPS with an LMNA or ZMPSTE mutation and clinical signs of progeria treated with lonafarnib monotherapy. All subjects were started on 150 mg/m² and allowed to decrease the dose to 115, 90, or 80 mg/m² if drug toxicity was observed. This dosing regimen was based on phase 1 and phase 2 findings from earlier clinical trials testing lonafarnib efficacy in adult and pediatric patients with certain cancers.¹ Group 2 subjects were seen for follow-up at 6, 12, and 18 months, between 28-38 months, 48 months, and 60 months.⁵

The primary efficacy endpoint for both trials was at least a 50% increase in the annual rate of weight gain over the rate documented at study entry. Secondary efficacy endpoints included changes in carotid

artery ultrasonography, corrected carotid-femoral pulse wave velocity (PWVcf), height, weight, body mass index (BMI). While not originally an endpoint in these trials, survival outcome was assessed retrospectively to evaluate the efficacy of lonafarnib monotherapy on mortality rate reduction. The primary efficacy outcome of this retrospective analysis was the time to all-cause mortality by the cut-off date of June 1, 2019.

The efficacy population consisted of 62 subjects with HGPS on lonafarnib monotherapy in ProLon1 or ProLon2. A single subject with PL was not included due to not having an untreated, matched comparator.

The table and Kaplan-Meier curves below demonstrate that for follow-up time censored at 3 years, the survival probability estimates were 91% (95%CI: 84% to 99%) for lonafarnib treated subjects and 80% (95% CI: 70% to 91%) for patients in the untreated matched group. Since both groups had a >50% survival probability estimate, the median survival times weren't estimable. For follow-up times censored at last follow-up, the survival probability estimates at 5 and 10 years of follow up were 79% (95% CI: 66% to 93%) and 44% (95% CI: 29% to 67%) in the lonafarnib treated group. The survival probability estimates at 5 and 10 years of follow up were 57% (95% CI: 42% to 77%) and 17% (95% CI: 6% to 46%) in the matched untreated group. The median survival times (time point at which survival probability estimate drops below 50%) were approximately 7.8 years in the lonafarnib treated subjects and 5.3 years in the untreated matched group. At both censoring times, the restricted mean survival time (area under the survival curves at any given time period) were higher in lonafarnib treated subjects than the untreated matched group. The restricted mean survival time (RMST) at 3, 5, and 10 years were 0.26 years, 0.57 years, and 2.21 years longer for lonafarnib treated subjects than their untreated matched counterparts. The hazard ratio (risk of death) for follow-up censored at 3 years was 0.30 (95% CI: 0.10 to 0.89) and for follow-up censored at last follow-up was 0.40 (95% CI 0.21 to 0.77).

The Kaplan-Meier curves demonstrate that at both censoring times of 3 years and time of last follow-up, subjects treated with lonafarnib treated group had improved survival compared to those in the untreated matched group ($p = 0.02$ for censoring at 3 years, and $p = 0.005$ for censoring at last follow-up).

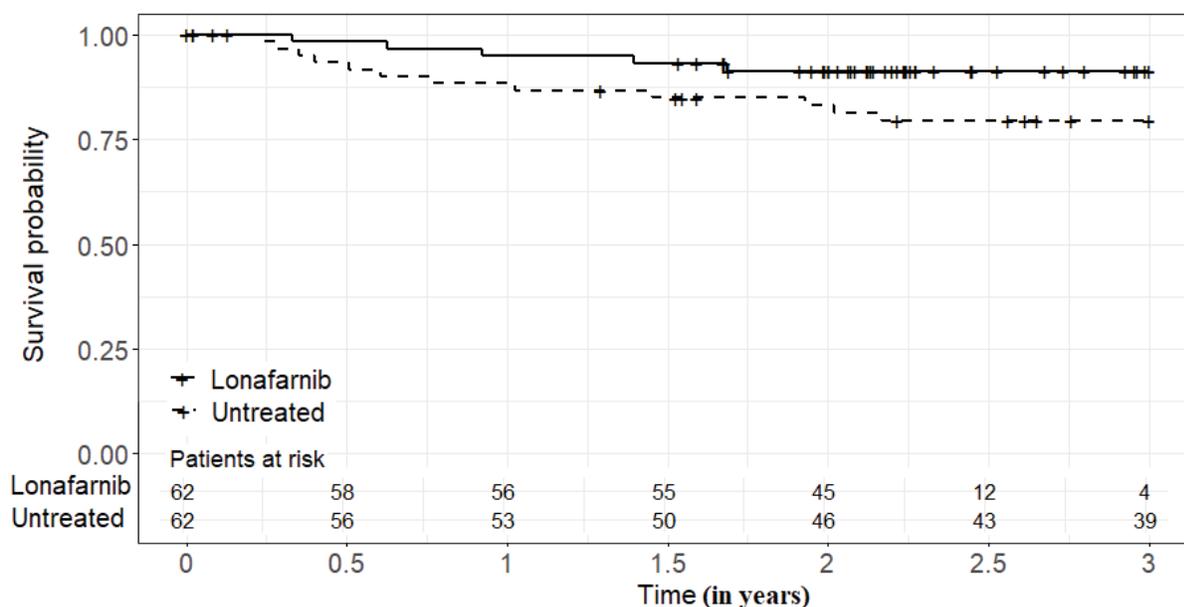
Table 1. Efficacy Results of Survival Time (Fixed 50th Percentile Matching Algorithm)

Summary	Censored at 3 Years		Censored at Last Follow-Up	
	Untreated (N=62)	Treated (N=62)	Untreated (N=62)	Treated (N=62)
Number of deaths (%)	12 (19.4)	5 (8.1)	25 (40.3)	21 (33.9)
RMST	2.59	2.83	5.54	8.01
(95% CI)	(2.37, 2.81)	(2.68, 2.98)	(4.32, 6.75)	(6.91, 9.10)
(95% CI)	(2.36, 2.79)	(2.68, 2.95)	(4.29, 6.78)	(6.32, 9.05)
Difference in RMST		0.24		2.47
(95% CI)	--	(-0.03, 0.50)	--	(0.84, 4.11)
(95% CI)		(-0.03, 0.50)		(0.74, 3.87)
Hazard ratio		0.30		0.40
(95% CI)	--	(0.10, 0.89)	--	(0.21, 0.77)
P-value (HR)		0.0304		0.0064
P-value (log-rank test)		0.0235		0.0053

Source: FDA Review Team Analysis in ongoing Lonafarnib Unireview (Accessed on 11/13/2020)

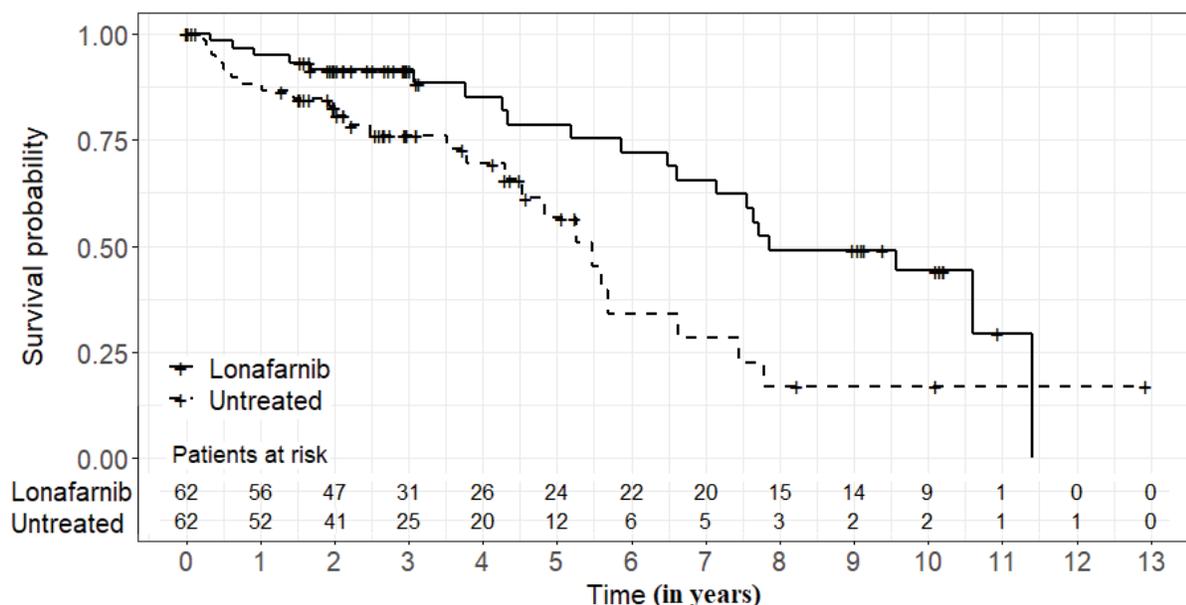
Abbreviations: CI, confidence interval; HR, hazard ratio; RMST, restricted mean survival time

Figure 1. Kaplan-Meier Survival Curve of Treated vs. Untreated Groups Censored at 3 Years



Source: FDA Review Team Analysis in ongoing Lonafarnib Unireview (Accessed on 11/13/2020)

Figure 2 Time to All-Cause Mortality Censored at Last Follow Up



Source: FDA Review Team Analysis in ongoing Lonafarnib Unireview (Accessed on 11/13/2020)

In the ongoing clinical review of lonafarnib, the clinical reviewer determined that lonafarnib has a survival benefit for patients with HGPS, and extends that benefit to processing deficient PL based on 3 patients with PL who had been taking lonafarnib for over 10 years, case reports of symptom similarities to HGPS, a nonclinical study of the use of lonafarnib in PL, and in vitro studies of similarities in disease progression and response to lonafarnib.

5 Risk Assessment & Safe-Use Conditions

The safety population consisted of 63 subjects with HGPS or PL on lonafarnib monotherapy in studies ProLon1 and ProLon2. Sixty-two subjects had HGPS, and 1 subject had PL.

The most common adverse events (incidence $\geq 10\%$) included vomiting, diarrhea, nausea, abdominal pain, constipation, fatigue, upper respiratory tract infection, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased weight, decreased appetite, and musculoskeletal pain.

Gastrointestinal adverse events (vomiting, diarrhea, nausea) were reported in approximately 80% of study subjects. All cases of vomiting and nausea were determined to be mild or moderate, and only 4.8% of subjects experienced severe diarrhea. Fourteen percent of patients were treated with an antiemetic/anti-nauseant, and 42.9% treated diarrhea with loperamide. These adverse events may lead to intravascular volume depletion, in turn causing a rise in serum creatinine. Transient electrolyte abnormalities have been noted in the pivotal studies, with many of these events tied to vomiting and diarrhea or concurrent infections.

Many subjects had liver enzyme elevations at baseline, and several developed further elevations. There were no cases of Hy's Law. Seventeen (27%) patients experienced an AE of increased ALT, and twenty-two (35%) had an AE of increased AST. Two patients had a severe (greater than 5.0 to 20.0 times ULN if baseline was normal or abnormal) ALT elevation, and 1 patient had a severe increase in AST. Most ALT and AST elevations occurred within the first 8 months of treatment. No trend in the degree of elevation of ALT or AST was seen by the clinical review team, except for one patient who had an ALT greater than 3 times the ULN at the end of the study.

Animal studies of lonafarnib point to potential visual acuity or night vision loss. Animal studies also have shown the potential for nephrotoxicity with urinalysis and chemistry changes at equivalent human plasma exposures.

Serious Adverse Events (SAEs)

The clinical reviewer considered 5 treatment emergent adverse events (TEAEs) in ProLon1 to be serious. Two SAEs of cerebral ischemia occurred, including 1 fatal episode. One case of elevated ALT and AST occurred while the subject had a viral illness, with a mild initial rise at Day 28, and peak to ALT 202 U/L and AST 324 U/L on Day 56. By Day 85, the ALT remained mildly elevated, and AST had normalized. The patient completed ProLon1, continued to triple therapy, and lived another 6.5 years. One subject had severe dehydration and hypokalemia potentially from gastrointestinal intolerance to lonafarnib. The fifth TEAE was a hospitalization for a viral infection with fever, vomiting, and diarrhea, which was not likely related to lonafarnib.

The clinical review team evaluated TEAEs categorized as grade 3 severity and higher and found 24 TEAEs in 12 patients in ProLon2. Four patients had fatal cardiovascular events, as described in Section 5.1 below, 4 events of stroke were observed, and 4 reports of heart attacks. A report of valve disorder and 1 report of heart failure were related to these cardiovascular SAEs. Other SAEs classified as TEAEs included 2 reports each of diarrhea, hypertriglyceridemia, abdominal pain, and pneumonia and 1 report each of hyperglycemia, hematoma, seizure, and gastrointestinal hemorrhage. Serious adverse events deemed not treatment-related included grade 4 iritis, stomatitis after infection, and 1 case of prolonged bleeding time.

Cerebral ischemia events were reported as adverse events by the Applicant, but as they are part of the disease course of HGPS and the studies having no placebo comparator, causality was difficult to discern.

In the ongoing clinical review, the clinical reviewer determined that the demonstrated safety profile of lonafarnib at the indicated doses was acceptable.

5.1 DEATHS

In ProLon1, a nine-year old patient had a fatal stroke on study day 121. Her past medical history included transient ischemic strokes, stroke, and ongoing chest pain prior to receiving lonafarnib. Concomitant medications included clopidogrel, propranolol, nitroglycerin, isosorbide mononitrate, and pravastatin. Fourteen days into lonafarnib treatment, she experienced right-sided tingling, initially thought to be seizures. She was later diagnosed with a grade 3 (severe) stroke with left-sided cerebral ischemia. The patient continued lonafarnib after recovery but continued to have sequelae. She

experienced a second stroke on study day 121 that required emergency surgery and later a third stroke that led to her passing. Due to her history of strokes, death was not attributed to lonafarnib.

In ProLon2, 4 patients died, all from cardiovascular related causes. A 14-year-old female with classic HGPS, died due to a myocardial infarction on study day 229. She had evidence of structural heart disease, mild left ventricular hypertrophy, mild diastolic left ventricular dysfunction, mild mitral valve and tricuspid regurgitation. She experienced fatigue on study days 173-180 and was diagnosed with exertion cardiac pericarditis. The cause of death was communicated to the investigators by the patient's mother. An 11-year-old male passed away from myocardial infarction on study day 347. The patient had a prior history of significant valve disease, nonobstructive asymmetric septal hypertrophy, hypertrophic cardiomyopathy, mitral and aortic stenosis, diastolic left ventricular dysfunction, and patent foramen ovale, and the patient had evidence of prior cerebral ischemia. The patient presented at the hospital on day 332 and was diagnosed with non-ST segment elevation myocardial infarction (also reported as SAE). He presented again with a non-ST segment elevation myocardial infarction and gastritis 9 days later. The patient passed away the following day. A 15-year-old male with classic HGPS passed away from heart failure on study day 511. He had no prior cardiac history and presented to the hospital on day 510 with vomiting, dehydration, and difficulty breathing. He was diagnosed with sepsis and metabolic acidosis of pH 7.12, and hyponatremia (serum sodium 121 mEq/L). The patient then passed away. A nine-year-old male with non-classic HGPS was away 22 days after completion of ProLon2. His medical history contained severe cardiovascular and valvular heart disease and asthma. One study day 1,102, the patient was admitted to the hospital with chest pain and in severe respiratory distress. ECG showed complete AV block, found to be hypoxic, and treated for pneumonia. He passed away 2 days after admission, with cause of death presumed to be cerebral ischemia due to severe cardiovascular disease.

In the ongoing clinical review, the clinical reviewer states that as no past studies suggest cardiac or cerebrovascular toxicity with lonafarnib and given the HGPS natural history course where patients are expected to have strokes by age 8 and death from myocardial infarction or heart failure by 14, the stroke and cardiovascular events resulting in death are likely progression of underlying disease. When considering the poor health of the patients based on accelerated cardiovascular events and lack of a control arm, lonafarnib's effect on cardiovascular factors is difficult to discern.

5.2 HYPERTENSION

At baseline, 24.2% (15/62) subjects had systolic blood pressure above the 95th percentile for their height and gender, and 27.4% (17/62) had diastolic blood pressure above the 95th percentile. As cardiovascular disease is a natural part of HGPS progression, this was not unexpected. However, during the pivotal studies, 8.1% (5/62) of subjects developed hypertension, while 29% (18/62) had hypertension (based on systolic and diastolic blood pressure readings above the 95th percentile) based on readings from 3 separate occasions.

Upon analysis, a correlation between sustained hypertension and/or increase in systolic blood pressure and likelihood of death was noted. While survival status comparisons found no difference in baseline blood pressure, the survivors had a mean blood pressure decrease of 5.5 mmHg. An end of trial

comparison of surviving versus deceased subjects found a 10 mmHg difference in blood pressure. Arterial pressure was also lower in survivors by a mean of 4.6 mmHg.

As hypertension is also associated with disease progression of HGPS and PL, it is uncertain exactly how much of a role lonafarnib plays in exacerbating this condition. The information seen from ProLon1 and ProLon2 will be described in Section 6 of labeling so prescribers will be aware this was an adverse effect seen in the pivotal trials.

5.3 QT PROLONGATION

No thorough QT prolongation study using lonafarnib monotherapy was performed. The Applicant submitted double-blind, randomized, placebo-and active-controlled, parallel-group, nested crossover TQT study of lonafarnib 50 mg twice daily with ritonavir 100 mg twice daily, and lonafarnib 100 mg twice daily with ritonavir 100 mg twice daily. Ritonavir, being a strong CYP3A4 inhibitor, increases the exposure of lonafarnib. The Applicant then predicted the QT effect of lonafarnib monotherapy based on the exposure-response analysis. The analysis suggested a QT-shortening effect by ritonavir, which is contrary to prior experience with ritonavir, and when ritonavir concentration was not included in the QTc analysis, modeling then suggested a biologically implausible conclusion for lonafarnib. A second limitation of the study was inadequate exposure to major metabolites HM17 and HM21.

ProLon1 and ProLon2 analyzed QTc prolongation ≥ 0.010 from baseline and added to those subjects whose statistics were analyzed by Bazett's formula to account for pediatric subject's faster heart rate, found 41 patients experienced QTc prolongation.

The Applicant agreed to conduct a study as a Postmarketing Requirement (PMR) to evaluate the effect of lonafarnib on the QT interval prolongation according to the International Council for Harmonisation (ICH) guideline.

5.4 EMBRYO-FETAL TOXICITY AND REPRODUCTIVE TOXICITY

While no human data is currently available, data from monkeys showed toxicity in male reproductive tract at plasma drug exposures lower than the human dose in HGPS. Studies in rats demonstrated severe male fertility impairment at 3 times the human dose, and impairment of female fertility at plasma exposures equivalent to human doses.

Human data is also not available for embryo-fetal toxicities, but in studies of rats and rabbits post-implantation loss was noted at human equivalent doses and skeletal malformations were seen at plasma exposures lower than the human dose.

Due to the nature of the disease and median survival age of 14.5 years, the review team determined that impaired fertility, impact on pubertal development, and embryo-fetal toxicity will be communicated in labeling as individual warnings and precautions as the primary way to mitigate these risks.

6 Expected Postmarket Use

Lonafarnib is likely to be prescribed by genetic specialists familiar with HGPS and PL and used by patients on an outpatient basis. These prescribers are expected to monitor these patients' vital signs

such as blood pressure and chemistry, and treat adverse events such as hypertension, QTc prolongation, and organ toxicity accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lonafarnib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Lonafarnib demonstrated a survival benefit in patients with HGPS that can be extrapolated to patients with PL caused by a processing-deficient mutation in LMNA or ZMPSTE24. The clinical reviewer recommends approval based on this survival benefit in a rare, lethal disease that has no currently approved treatments.

DRM and DRDMG considered the benefit of lonafarnib treatment with the risks including hypertension, QTc prolongation, and fertility impairment and embryo-fetal toxicity, as well the potential for drug-drug interactions due to being metabolized by CYP3A4. The review team discussed how best to mitigate these risks and if a REMS was necessary. Lonafarnib is the first in class therapy and the only therapy for HGPS and processing-deficient PL. Even though lonafarnib will be first in class, many other products are metabolized by CYP3A4 and have drug-drug interactions and use contraindications and warnings and precautions to convey this risk to prescribers. Lonafarnib will also use warnings and precautions and a table of clinically significant drug interactions in Section 7.1 of labeling to inform prescribers of how best to manage this risk. The risk of hypertension in lonafarnib-treated HGPS patients will be outlined in Section 6.1 of labeling as clinical trial experience demonstrated this risk, however it is unclear how much disease progression is a contributing factor. It is expected those who prescribe lonafarnib will be closely monitoring their patients' cardiac status, and blood pressure would be taken at each visit and treated accordingly. The risks of nephrotoxicity and retinal toxicity seen in animal studies will be labeled as warnings and precautions, with instructions to perform ophthalmological evaluations regularly. Patients with HGPS are closely followed by their healthcare providers, so monitoring visual disturbances and urine chemistries are not unusual. Due to lonafarnib being used to treat rare diseases that are fatal by the teenage years, both fertility impairment and embryo-fetal toxicities will be conveyed as warnings and precautions. Safety messages will also be conveyed to patients in a Medication Guide. We expect these patients are seen on a regular basis by prescribers who are familiar with the health risks of HGPS and processing-deficient PL. Therefore, risk mitigation measures beyond labeling, such as a REMS, are not needed for lonafarnib.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of lonafarnib outweigh the risks that include hypertension, the potential for QTc prolongation, and fertility impairment and embryo-fetal toxicity. The risks will be communicated in labeling using warnings and precautions that

include embryo-fetal toxicity and impaired fertility, renal and retinal toxicities, and drug interactions that may reduce lonafarnib's efficacy. A Medication Guide for patients is also included in lonafarnib labeling.

At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DRDMG have any concerns or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 REFERENCES

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4. National Library of Medicine MedlinePlus Hutchinson-Gilford progeria syndrome. <https://medlineplus.gov/genetics/condition/hutchinson-gilford-progeria-syndrome/>. Updated August 18, 2020. Accessed 9/25/2020, 2020.
5. Eiger Biopharmaceuticals, Inc. Summary of Clinical Safety for Lonafarnib.

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/s/

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