CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213969Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 19, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 213969
Product Name and Strength:	Zokinvy (lonafarnib) capsules, 50 mg and 75 mg
Applicant/Sponsor Name:	Eiger BioPharmaceuticals, Inc. (Eiger)
OSE RCM #:	2020-558-2
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on November 19, 2020 for Zokinvy. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels for Zokinvy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels are acceptable from a medication error perspective and we have no further comments.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 19, 2020

[a]Abraham A. Label and Labeling Review for Zokinvy (NDA 213969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 10. RCM No.: 2020-558-1

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
11/23/2020 11:44:59 AM

IDALIA E RYCHLIK
11/23/2020 11:57:59 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 10, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 213969
Product Name and Strength:	Zokinvy (lonafarnib) capsules, 50 mg and 75 mg
Applicant/Sponsor Name:	Eiger BioPharmaceuticals, Inc. (Eiger)
OSE RCM #:	2020-558-1
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), Instructions for Use (IFU), container labels and carton labeling received on November 4, 2020 for Zokinvy. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for Zokinvy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised PI, IFU, and carton labeling are acceptable from a medication error perspective. However, we note, that the container labels are unacceptable from a medication error perspective and provide additional recommendations to Eiger in Table 1 below.

3 RECOMMENDATIONS FOR EIGER BIOPHARMACEUTICALS, INC. (EIGER)

We recommend the following be implemented prior to approval of this NDA:

[a]Abraham A. Label and Labeling Review for Zokinvy (NDA 213969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 20. RCM No.: 2020-558

Table 1. Identified Issues and Recommendations for Eiger Biopharmaceuticals, inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Labels			
1.	As currently displayed, the net quantity statement competes with strength statement for prominence.	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is prominent.	Decrease the prominence of net quantity statement similar to the presentation on the carton labeling.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 4, 2020

Prescribing Information received on November 4, 2020

\\CDSESUB1\evsprod\nda213969\0026\m1\us\114-label\1141-draft-label\proposed-patient-info.docx

Instructions for Use (IFU) received on November 4, 2020

\\CDSESUB1\evsprod\nda213969\0026\m1\us\114-label\1141-draft-label\ifu.docx

Container labels

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
11/10/2020 12:25:12 PM

IDALIA E RYCHLIK
11/10/2020 07:16:47 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 29, 2020

To: Mari Suzuki, M.D.
Division of Rare Diseases and Medical Genetics (DRDMG)

Jenny Doan, BSN, MSN, PMP, Regulatory Health Project Manager, (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for ZOKINVY (lonafarnib)

NDA: 213969

In response to DRDMG consult request dated March 24, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for ZOKINVY (lonafarnib) capsules, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG (Jenny Doan) on October 16, 2020, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on October 28, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 14, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADEWALE A ADELEYE
10/29/2020 12:10:27 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 28, 2020
To:	Jenny Doan, BSN, MSN, PMP Regulatory Health Project Manager Division of Rare Diseases and Medical Genetics (DRDMG)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ZOKINVY (lonafarnib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 213969
Applicant:	Eiger BioPharmaceuticals Inc.

1 INTRODUCTION

On March 20, 2020, Eiger Biopharmaceuticals Inc., submitted for the Agency's review an original New Drug Application (NDA) 213969 for ZOKINVY (lonafarnib) capsules. The Applicant proposes ZOKINVY (lonafarnib) capsules for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL). The Agency granted Breakthrough Designation for lorafarnib for the treatment of HGPS and PL on December 12, 2018.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rare Diseases and Medical Genetics (DRDMG) on June 27, 2020, and March 24, 2020, respectively for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU), for ZOKINVY (lonafarnib) capsules, for oral use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft ZOKINVY (lonafarnib) capsules PPI and IFU received on March 20, 2020, and received by DMPP and OPDP on October 16, 2020.
- Draft ZOKINVY (lonafarnib) capsules Prescribing Information (PI) received on March 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 16, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN W REDWOOD
10/28/2020 09:58:56 AM

ADEWALE A ADELEYE
10/28/2020 11:00:40 AM

SHARON R MILLS
10/28/2020 11:19:23 AM

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 20, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 213969
Product Name and Strength:	Zokinvy (lonafarnib) capsules, 50 mg and 75 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eiger BioPharmaceuticals, Inc. (Eiger)
FDA Received Date:	March 20, 2020 (Carton Labeling, Container Labels, and Prescribing Information) September 25, 2020 (Instructions for Use)
OSE RCM #:	2020-558
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

Eiger BioPharmaceuticals, Inc. submitted NDA 213969 Zokinvy (lonafarnib) capsules, on March 20, 2020 as part 3 of 3 of a rolling submission. Zokinvy (lonafarnib) was granted Breakthrough Therapy status for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL). The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Zokinvy prescribing information (PI), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Information Requests	C
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

On March 20, 2020, Eiger submitted their final proposed clinical sections and draft labels and labeling as part 3 of 3 of the rolling submission for NDA 213969. Zokinvy (lonafarnib), a farnesyltransferase inhibitor is indicated as follows:

• 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).

On July 23,2020, August 17, 2020, September 2, 2020, September 8, 2020, and September 18, 2020, we issued information requests (IRs) to Eiger regarding medication error safety concerns regarding the Sponsor's proposed patient population and how inclusion of this patient population aligned with the dosage strengths and dosage forms proposed. (b) (4)

(b) (4)

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), instructions for use (IFU), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	As currently displayed, the place holder, "Tradename" is used instead of the conditionally approved name, "Zokinvy" throughout the prescribing information (PI).	Proposed proprietary name, Zokinvy, found conditionally acceptable by DMEPA on April 20, 2020 under IND 139923.	Replace the "Tradename" with approved name, "Zokinvy" throughout the PI.
2.	Use of confusing symbols or abbreviation(e.g.,"±", "<", "≥ ","≤", "AM", "PM", "BSA" etc).	The usage of symbols and abbreviations can cause misinterpretation and confusion.[a]	Replace the symbols and abbreviations with their intended meaning.
Highlights of Prescribing Information			
1.	Dosage and Administration (D&A) section of the highlights is text heavy and burdensome to read.	Decreased readability and prominence of complex dosing and administration information may lead to medication error.	To enhance accessibility of the D&A information, consider using a table format for D&A information in the Highlights of the Prescribing Information. (Guidance: Implementing the PLR Content and Format Requirements, February 2013) Additionally, consider deleting the first bullet point as it does

[a]ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

			not speak to product dosing and administration directions.
2.	The bulleted administration information: *Take twice daily, whole, with water and food, approximately 12 hours apart*, lacks clarity.	The bulleted statement is an incomplete sentence. The subject of the sentence, the prescribed dose in capsule(s), is missing which may lead to confusion.	Revise the sentence to read, "Take the prescribed dose twice daily, approximately 12 hours apart, with food. Swallow whole.". Additionally, consider adding a statement under Dosage and Administration heading in Highlights of the PI to alert the healthcare provider that additional important administration information is in the FPI. (e.g., See Full Prescribing Information for instructions on dosing, preparation and administration).
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Dosage and Administration (D&A) section in Section 2.1 is text heavy and burdensome to read.	Decreased readability and prominence of dosing and administration information may lead to medication error.	To enhance accessibility of the D&A information, consider using a bullet format for D&A information in Section 2.1. For example, <u>Patients with Hutchinson-Gilford Progeria Syndrome:</u> • The recommended starting dosage regimen in patients 12 months of age and older is 115 mg/m2 twice daily (See Table 1). After 4 months of treatment, the dose may be increased to 150 mg/m2 twice daily (see Table 2) (b) (4) [redacted] Total daily dosages

			should be rounded to the nearest 25 mg increment. Patients with a Processing-deficient Progeroid Laminopathy: • The recommended starting dosage is 115 mg/m2 twice daily with morning and evening meals (see Table 1). After 4 months of treatment, the dose should be increased to 150 mg/m2 twice daily (see Table 2); (b) (4) [redacted] • Total daily dosages should be rounded to nearest 25 mg increment. If a dose is missed, take the dose as soon as possible, up to 8 hours prior to the next scheduled dose (within 8 to 16 hours), with food. If less than 8 hours remains before the next scheduled dose, skip the missed dose, and resume taking ZOKINVY at the next scheduled dose.
2.	Tables 1 and 2 display Body Surface Area (BSA) with a defined number instead of a BSA range.	The BSA range is recommended to provide clear dosing parameters.	Revise the BSA (m2) column to include a range rather than a defined number. For example, 0.39 to 0.48
3.	Administration Instructions found in Section 2.3 are text heavy and burdensome to read.	Decreased readability and prominence of dosing and administration information may lead to medication error.	To enhance accessibility of important preparation information, consider using a subsection format for in Section 2.3.

			For example, 2.3 Administration Instructions <u>Patients Able to Swallow Capsules</u> • Administer ZOKINVY capsules (b) (4) whole with a sufficient amount of water. Do not chew the capsules. <u>Patients Unable to Swallow Capsules</u> • The entire contents of ZOKINVY capsules can be mixed with Ora Blend SF® or Ora-Plus® or, for patients unable to access or tolerate Ora Blend SF or Ora-Plus, the contents of ZOKINVY capsules can be mixed with orange juice or applesauce (see preparation instructions below). Do not mix with any juice containing grapefruit or Seville oranges. • The mixture must be prepared fresh for each dose and be taken within approximately 10 minutes of mixing. *Preparation of Dose in Ora Blend SF, Ora-Plus, or Orange Juice*

			1. For each capsule, empty contents of the capsule into a container containing 5 mL or 10 mL of the liquid. 2. Mix thoroughly with a spoon. 3. Consume entire serving. *Preparation of Dose in Applesauce* 1. For each capsule, empty contents of the capsule into a container containing 1 teaspoonful or 2 teaspoonfuls of applesauce. 2. Mix thoroughly with a spoon. Consume entire serving.
4.	The title and content of Table 1 and Table 2 located in Section 2.1 lack clarity.	Presenting important dosage and administration information in a text heavy format decreases readability and prominence of key information. This may lead to misinterpretation and confusion and result in medication preparation and administration errors. Furthermore, the title of Table 2 suggests that the 150 mg/m2 dosing may be used as a starting dose; this contradicts dosing information provided	Revise the titles of Tables 1 and 2 in Section 2.1 to accurately reflect the intended meaning of the tables. For example: • Table 1: Recommended dosage and administration for 115 mg/m2 body surface area-based dosing. • Table 2: Recommended dosage and administration for 150 mg/m2 body surface

		throughout the rest of the PI.	area-based dosing. Consider, deleting columns from the tables that distract the reader from the identified dose and administration information. (i.e. delete the columns titled: Dose (mg), Total Daily Dose (mg), ~mg per Administration) . Additionally, revise the column titled *Daily Dose Rounded to the Nearest 25 mg* to read Total Daily Dose Rounded to the Nearest 25 mg.
5.	As currently presented, the preparation directions for patients unable to swallow a capsule do not specify the recommended volume of vehicle (Ora Blend SF®, Ora-Plus®, orange juice, and apple sauce) to use for mixing. Furthermore, the inclusion of a final concentration range (b) (4) is confusing.	Lack of clarity in preparation instruction.	For patients who are not able to swallow the capsule(s) whole, clarify preparation instruction by defining the volume of vehicle needed for preparation. Delete the final concentration statement.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statement "Do not store above 25°C (77°F)" lacks clarity.	As currently stated, the drug product can be stored at any temperature below 25°C (77°F) which implies acceptable storage in the refrigerator or freezer. Lack of clear and accurate storage information may result in improper handling of drug and adulterated	Revise the storage statement to include a specified temperature range.

		product.	
Instructions for Use (IFU):			
1.	The schematic images and description of Zokinvy 50 mg capsule and 75 capsule are displayed in the beginning of the IFU.	The schematic images and description of the capsules are not typically presented in the beginning of the IFU. Additionally, they are not beneficial in the preparation or administration of the product.	Remove the schematic images and description of Zokinvy 50 mg/75 mg capsule displayed in the beginning of the IFU.
2.	Repetitive statements are found throughout the "How to Use Zokinvy" section. For example, " (b) (4)	Patient or caregiver may skim over the repetitive content and inadvertently miss important preparation information	Delete the repetitive text and relocate other information to either " (b) (4) " section.
3.	A 20 mL oral dosing syringe is pictured to measure 5 mL or 10 mL of Ora Blend SF®, Ora-Plus or orange juice.	Using a 10 mL oral dosing syringe is more accurate to measure 5 mL or 10 mL of liquid rather than 20 mL one. Additionally, 10 mL oral dosing syringes are more commonly available than 20 mL oral dosing syringes.	We recommend depicting a 10 mL oral dosing syringe rather than 20 mL oral dosing syringe to measure 5 mL or 10 mL volume of Ora Blend SF®, Ora-Plus, or orange juice.
4.	Preparation instructions for prescribed doses that require more than once capsule lack prominence.	Totally vehicle volume for preparing multi-capsule dependent dosing is different than what is required for single capsule preparation. A lack of prominence of this information may lead to preparation errors.	In Step 4, we recommend bolding the sentence, *If only one capsule is to be taken by the patient, skip to Step 6. If two capsules are to be taken by the patient proceed to Step 5.* Additionally, to enhance the use of bolding as a mechanism for prominence and remove reference bolding throughout the IFU (i.e. **See Figure X** and **Step** X- located within the text

			of each step).
5.	The figures F and G are not depicting any valuable information.	The figures F and G are distracting the reader without any valuable information. The reader may overlook important information with unnecessary additional images.	We recommend deleting figures F and G.
6.	In step 6, the expiration time (10 minutes) of admixture of Zokinvy capsule and Ora Blend SF®, Ora-Plus, orange juice, or apple sauce lacks prominence.	To minimize the risk of administering expired products.	Bold the expiration statements as below: "Consume the entire serving of the ZOKINVY mixture with food **within 10 minutes of preparing**." We recommend adding a picture of a clock to show 10 minutes expiration time.

Table 3. Identified Issues and Recommendations for Eiger BioPharmaceuticals, Inc. (Eiger) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently displayed, the place holder, "Tradename" is used instead of the conditionally approved name, "Zokinvy".	Proposed proprietary name, Zokinvy, found conditionally acceptable by DMEPA on April 20, 2020 under IND 139923.	Replace the "Tradename" with conditionally approved name, "Zokinvy" on all container labels and carton labeling.
2.	As currently displayed, the strength statement lacks prominence.	21 CFR 201.15(a)(6)	Increase the prominence of the strength statement and relocate it to the line directly below the established name.
3.	The net quantity statement is overly prominent and takes the reader's attention away	Post-marketing experience shows that the risk of numerical confusion between the strength and	Decrease the prominence of net quantity statement.

Table 3. Identified Issues and Recommendations for Eiger BioPharmaceuticals, Inc. (Eiger) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	from more important product information, such as the proprietary name, established name, and product strength.	net quantity increases when the net quantity statement is more prominent.	
4.	The statement (b) (4) [redacted]" is inconsistent with prescribing information (PI).	21 CFR 201.55. The container labels and carton labeling should be consistent with prescribing information (PI) on the wording of dosage information presentation.	Revise the statement, (b) (4) [redacted]" to read "Recommended Dosage: See prescribing information."
5.	The format for expiration date is undefined.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	**Submit expiration date in the format that is stated below.** FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in **YYYY-MM-DD format** if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to

Table 3. Identified Issues and Recommendations for Eiger BioPharmaceuticals, Inc. (Eiger) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			separate the portions of the expiration date.
6.	The storage information includes the use of error prone symbols, such as "-".	Lack of clarity. Misinterpretation and confusion over symbols may lead to prescribing or administration errors.[a]	Revise the sentence to read "Store between 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F)".
Container Label(s)			
1.	The "Rx only statement" is overtly prominent.	The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP such as established name, dosage form, and strength statement.	Decrease the prominence of the "Rx only statement" by decreasing the font size and utilizing black font..
2.	It is unclear what the intended meaning of the undefined cod (b) (4) which is located immediately below the net quantity statement and the Rx only statement.	PDP is reserved for the most important information such as the proprietary and established names, dosage form, and strength.	Define the meaning of the undefined codes (b) (4) which is located immediately below the net quantity statement and the Rx only statement. If it is an internal code, relocate to the side panel and decrease the prominence.
3.	As currently presented, the linear barcode is missing on the container labels.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	We request you add the product's linear barcode to each individual container as required per 21CFR 201.25(c)(2). Please note, the barcode should be surrounded by sufficient white space to allow scanners to correctly read the

Table 3. Identified Issues and Recommendations for Eiger BioPharmaceuticals, Inc. (Eiger) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			barcode in accordance with 21 CFR 201.25(c)(i). Additionally, in accordance with 21 CFR 201.25(c)(ii), the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
Carton Labeling			
1.	As currently presented, the linear barcode is on the inner flap of the carton labeling and won't be readily visible when the carton is closed.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature.	Relocate the linear barcode to a more visible location on the carton labeling.
2.	As currently displayed, the manufacturer name("Eiger") is more prominent in size than the most important information (i.e., proprietary and established names, strength, and dosage form).	The primary display panel (PDP) should be reserved for important product information. Duplicative manufacturer information located on the PDP takes readers' attention away from more important information such as proprietary and established names, strength, and dosage form.	Remove the manufacturer name ("Eiger") from the PDP as it is already present on the back panel.
3.	The statements, "Each capsule contains XX mg of lonafarnib" and "Keep out of sight and reach of children" are identified on the PDP.	PDP is reserved for the most important information such as the proprietary and established names, dosage form, and strength. Sentences with less significant information should be on the side panel.	Relocate the statements, "Each capsule contains XX mg of lonafarnib" and "Keep out of sight and reach of children" to the side panel.

4 CONCLUSION

Our evaluation of the proposed Zokinvy prescribing information (PI), instructions for use (IFU), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Eiger BioPharmaceuticals, Inc. (Eiger) so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zokinvy that Eiger BioPharmaceuticals, Inc. (Eiger) submitted on March 20, 2020.

Table 4. Relevant Product Information for Zokinvy

Initial Approval Date	N/A
Active Ingredient	lonafarnib
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).
Route of Administration	oral
Dosage Form	capsules
Strength	50 mg and 75mg
Dose and Frequency	Hutchinson-Gilford Progeria Syndrome patients: should initiate treatment at 115 mg/m^2 twice daily, (b) (4) increase to 150 mg/m^2 twice daily (b) (4) ll doses should be rounded to nearest 25 mg increment. Processing Deficient Progeroid Laminopathies patients: should initiate treatment at 115 mg/m2 twice daily, (b) (4)
How Supplied	30-count bottles of 50 mg or 75 mg oral capsules
Storage	Do not store above 25°C (77°F)

APPENDIX C. INFORMATION REQUEST:

Information requests and responses from Eiger Biopharmaceuticals, Inc. received on July 23, 2020 and July 31, 2020:

FDA Additional Labeling Comments Received on 23 July 2020:

We acknowledge your proposal for lonafarnib (NDA 213969) capsules to be indicated for use for patients 12 months of age and older. As currently outlined in the proposed product labeling patient daily dosing is rounded to the nearest 25 mg and initiated at 115 mg/m2 twice daily, then increased to 150 mg/m2 twice daily after 4 months of use. We note the proposed dosage form and strengths are 50 mg and 75 mg capsules for oral use; for patients unable to swallow capsules whole, the intent is for patients to mix the contents of lonafarnib capsule(s) with Ora Blend SF®, Ora-Plus®, orange juice, or applesauce.

We recommend that drug products maintain consistency between the recommended dosing regimens, available strengths, and packaging. As explained in FDA's guidance on safety considerations for product design to minimize medication errors,[1] a product strength that is incongruent with the dosage and administration of the product complicates the calculation, preparation, and administration of a dose and has led to medication dosing errors. Your proposed dosing tables located in subsection 2.1 of the Prescribing Information initiates dosing at a body surface area (BSA) of (b) (4). The proposed dosing does not take into account the possibility of a patient who is 12 months of age or older with a BSA below (b) (4). For example, the initial prescribed dose following the recommended dosage of 115 mg/m² twice daily for a pediatric patient with a BSA of (b) (4) (b) (4) Please explain your proposal to achieve doses for patients 12 months of age and older with a BSA below (b) (4) and include detailed preparation and administration instructions for these patients.

Additionally, the proposed preparation instructions for capsule dissolution is based on a final product concentrations range between (b) (4) mg/mL; placing the onus of calculating the final dose concentration on the patient or caregiver may lead to medication preparation errors. Please provide a definitive volume, expressed in a readily accessible unit of measure (m L(s) and teaspoon(s)), per capsule necessary for preparation. For example, 1 teaspoon (5 mLs) of Ora Blend SF®, Ora-Plus®, orange juice or applesauce per X capsule(s).

Eiger's responses:

The initial draft of the dosing regimen Eiger submitted was based on the dosing regimen used in Progeria clinical trials (i.e., dosage based on body surface area). However, because the Agency recently requested us to conduct population pharmacokinetics (popPK) analysis and further evaluate

dosing regimen, based on the popPK results (submitted to NDA 213,969, SN0013 on 17 July 2020), Eiger now considers it is more appropriate for the body weight based dosing.

In FDA's comments to the labeling received on 20 May 2020, the Agency indicated that "*Initial edits are included in subsection 2.1; however, dosage recommendations under subsection 2.1 are still under review.*" Eiger subsequently checked with the Agency whether we should directly include revisions of dosing regimen based on popPK results in the revised labeling. Per the Agency's agreement (email received on 24 July 2020), Eiger updated Section 2 Dosage and Administration in the labeling based on body weight dosing regimen. Therefore, the comments related to body surface area (BSA) dosing regimen are no longer applicable.

The proposed preparation instructions for capsule dissolution is also updated. A definitive volume, expressed in a readily accessible unit of measure (mL) is provided. Please note that the final concentration statements remain. Per Monica Kleinman, MD, the Principal Investigator for the ProLon1 and ProLon2 studies, the most used mixing concentrations are 25 mg/mL and 5 mg/mL. The lower volume could help avoid nausea and vomiting, and the higher volume could help the taste. Eiger believes that using these two concentrations is easily understood by caregivers and best suits the Progeria patient population.

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Late-cycle Meeting Background Package dated September 14, 2020

Section 2 (Dosage and Administration):

We reviewed your response, received on September 8, 2020, in regards to the Agency's concern for the risk of medication errors in the preparation and administration of dosing for pediatric patients with a BSA below (b) (4). In order to address this risk, we note that you propose (b) (4)

(b) (4)

We appreciate your proposals for risk mitigation strategies; however, your current proposals are not considered sufficient. We would like to discuss potential options to address the risk of over-dosage in low BSA patients during the late cycle meeting and look forward to your response. At this point, we are willing to consider either of the following options:

1. Limiting the indication to patients 12 months-of-age and older with a BSA of ≥0.39 m^2 (b) (4)

   (b) (4)

2. (b) (4)

Late-cycle meeting minutes dated September 25, 2020:

***Discussion:* Agreement was reached on the following for the labeling:**

- ***Section 2 (Dosage and Administration): Eiger elected to limit the indication to patients 12 months-of-age and older with a BSA of ≥0.39 m^2*** (b) (4)

  (b) (4)

(b) (4)

- *Section 6 (Adverse Reactions): Addition of hypertension and opthalmic adverse events to the label.*

- *Instruction for Use (IFU): Eiger is creating an IFU detailing the preparation and administration process of lonafarnib. The FDA recommended Eiger consider human-factors studies in the IFU development process. The FDA offered to provide guidances on Human Factors Studies after the meeting (see Section 3.0 Post-Meeting Comments).*

3.0 POST-MEETING COMMENTS

The FDA sent additional comments on the PI to Eiger on September 18, 2020. Eiger is to submit an updated PI on September 25, 2020.

In addition, further guidance on the IFU is provided as follows:

After further review of the proposed PI, we find that a proactive risk assessment is not necessary to develop your IFU. We recommend that you leverage information from similar, currently available, marketed products to help guide the development of your instructions for use.

Currently, the PI states, "For each capsule, empty contents of the capsule into a container containing 5 mL to 10 mL of the liquid/1 teaspoonful to 2 teaspoonfuls of applesauce." However, dependent on the patient's BSA, certain proposed dosing regimens may require more than one capsule per dose. In these instances, provide clarity on the following:

1. *Is total volume of applesauce or liquid compounded based on the number of capsules per dose?*

2. *What are the risks associated with compounding the prescribed dose in an inaccurate vehicle volume?*

Eiger's response dated September 25, 2020, regarding our post meeting minute notes:

Currently, the PI states, "For each capsule, empty contents of the capsule into a container containing 5 mL to 10 mL of the liquid/1 teaspoonful to 2 teaspoonfuls of applesauce", however, dependent on the patient's BSA, certain proposed dosing regimens may require more than one capsule per dose. In these instances, provide clarity on the following:

1. **Is total volume of applesauce or liquid compounded based on the number of capsules per dose?**

Eiger's responses:

For each capsule, it is based upon the patient's personal preference to use 5 mL or 10 mL of liquid or one or two teaspoons of applesauce. If it is required to take two capsules for any given dose, the patient is instructed to repeat the preparation step for the second capsule (i.e., each capsule is mixed independently). Please refer to proposed Instruction for Use (submitted in Module 1.14.1.3) for detailed instruction.

2. **What are the risks associated with compounding the prescribed dose in an inaccurate vehicle volume?**

Eiger's responses:

The patient is instructed to consume the entire serving of the ZOKINVY mixture. Therefore, there should not be any risk because the patient must take the full amount regardless of the vehicle volume used. The total dose taken is not affected even with an inaccurate vehicle volume.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Zokinvy labels and labeling submitted by Eiger BioPharmaceuticals, Inc. (Eiger)

- Container label(s) received on March 20, 2020
- Carton labeling received on March 20, 2020
- Instructions for Use received on September 25, 2020
  \\CDSESUB1\evsprod\nda213969\0023\m1\us\114-label\1141-draft-label\ifu.docx
- Prescribing Information (Image not shown) received on March 20, 2020
  \\cdsesub1\evsprod\nda213969\0003\m1\us\114-label\1141-draft-label\annotated.pdf

F.2 Label and Labeling Images

Container label(s)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
10/20/2020 03:56:22 PM

IDALIA E RYCHLIK
10/21/2020 11:27:14 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Memorandum

Date:	October 15, 2020
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Associate Director:	Wei Hua, PhD MS MHS Division of Epidemiology I
Drug Name:	lonafarnib (Zokinvy®)
Subject:	Audit of Survival Data for Untreated Patients With Hutchinson-Gilford Progeria Syndrome
Application Type/Number:	NDA 213969
Applicant/sponsor:	Eiger Biopharmaceuticals
OSE RCM #:	2020-551

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Responding to a request from the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) audited survival data submitted to lonafarnib NDA 213969 for untreated patients with Hutchinson-Gilford Progeria Syndrome (HGPS).

The DRDMG request concerned lonafarnib, a farnesyltransferase inhibitor presented in NDA 213969 as a treatment for HGPS (an extremely rare autosomal dominant genetic disorder). DRDMG asked DEPI to cross-check survival data for natural history patients in NDA 213969 against patient narratives submitted by a research foundation to Drug Master File (DMF) (b) (4)

DEPI used a manual method to find high concordance between NDA 213969 and DMF (b) (4) with respect to vital status and age at last contact or death for 62 untreated (natural history) patients with HGPS.

DEPI recommended that DRDMG assess (with assistance from the Division of Biometrics IV) the analytic importance (if any) of possible deviations in the censoring ages for four patients.

1 INTRODUCTION

Responding to a request from the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) audited survival data submitted to lonafarnib NDA 213969 for untreated patients with Hutchinson-Gilford Progeria Syndrome (HGPS).

The DRDMG request concerns lonafarnib, a farnesyltransferase inhibitor presented in NDA 213969 as a treatment for HGPS (an extremely rare autosomal dominant genetic disorder of premature aging due to mutant lamin A) [1]. To demonstrate treatment efficacy, NDA 213969 presents survival outcomes from two clinical studies of lonafarnib.[a] For comparison, NDA 213969 includes data from untreated (natural history) patients enrolled to an international registry managed by the Progeria Research Foundation (PRF).[b] To assess data quality, DRDMG asked DEPI to cross-check survival data for natural history patients in NDA 213969 against patient narratives submitted separately by PRF.

---

[a] Study 07-01-007 (ProlLon1; ClinicalTrials.gov Identifier: NCT00425607) – An Open Label Dose Adjusted Phase II Trial of the Oral Farnesyltransferase Inhibitor (FTI) Lonafarnib (Sch66336) for Patients With Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies; Study 09-06-0298 (ProLon2; ClinicalTrials.gov Identifier: NCT00879034) – An Open Label Phase II Trial of Zoledronic Acid, Pravastatin, and Lonafarnib (Sch66336) for Patients With Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies

[b] Progeria Research Foundation, International Registry, accessed at https://www.progeriaresearch.org/international-registry-2/ on August 27, 2020.

2 REVIEW METHODS AND MATERIALS

DRDMG provided DEPI with the subject identification numbers for 62 natural history patients used in efficacy analysis (**APPENDIX 1**). [c] For each patient, DEPI manually cross-checked data values shown in tabulation datasets for NDA 213969 (eCTD 0003, Date March 20, 2020) against narratives submitted by PRF to Drug Master File (DMF) (b) (4) on March 17, 2020.

3 REVIEW RESULTS

The 62 untreated patients used for efficacy analysis covered three distinct subgroups, (1) N=7 patients known to PRF as case reports published in medical literature [2-8], (2) N=40 patients known to PRF through non-literature sources as deceased, and (3) N=15 patients known to PRF through non-literature sources as not deceased.

3.1 Patients known to PRF as case reports

Table 1 summarizes data extracted by DEPI from either DMF (b) (4) or published cases reports for seven untreated (natural history) patients known to PRF as case reports. DEPI used results shown in Table 1 to check data in the DD and SUPPDM tabulation datasets for country, sex, vital status, and age at death or last contact. This check identified one exception. The published case report for SUBJID (b) (6) might fix the age at last contact alive at ≈9 years, rather than 6 years (as recorded in DMSUPP).

Table 1: Data extracted by DEPI from primary sources for patients known from case reports.

SUBJID	YEAR PUB	DMF REF	C'TRY	SEX	VS	AGE	VS SOURCE
(b) (6)	2002 [2]	(b) (4)	BRA	F	D	13.5	email from author to Progeria Research Foundation
	2007 [3]		RWA	F	A	12	Il s'agit d'une patiente, âgée de 12 ans, née en 1994
	2011 [4]		IND	F	A	12	a 12-year-old girl
	2012 [5]		EGY	M	A	10	a 10-year-old Egyptian boy
	2015 [8]		CHN	M	A	6	a 6-year-old boy / at follow-up 3 years later
	2014 [7]		CHN	M	A	5.8	email from author to Progeria Research Foundation
	2013 [6]		JPN	M	D	10	he died suddenly at age 10 years

LEGEND:

[c] Listing of subject identification numbers provided as an attachment to an email received by J. Weissfeld (DEPI) from M. Suzuki (DRDMG) on August 24, 2020.

SUBJID	Subject Identification Number
YEAR PUB	Year of report with reference to publication
DMF REF	Page reference to Drug Master File (DMF) (b) (4)
C'TRY	Patient country of residence: BRA – Brazil, CHN – China, EGY – Egypt, IND – India, JPN – Japan, RWA – Rwanda
SEX	F – female, M – male
VS	Vital status, A – alive, D – dead
AGE	Age (years) at death or last contact
VS SOURCE	Text extracted by DEPI from DMF or case report to validate vital status and age

3.2 Deceased patients known to PRF from non-literature sources

Table 2 summarizes data extracted by DEPI from DMF (b) (4) for 40 untreated (natural history) patients known to PRF as deceased. DEPI used results shown in Table 2 to check data in the DD tabulation dataset for country, sex, vital status, date of birth, and date of death. This check identified two exceptions. NDA 213969 imputed a missing day of death for SUBJID (b) (6). DMF (b) (4) presented inconsistent information regarding sex for SUBJID (b) (6). (DEPI used patient first name to resolve sex as male for SUBJID (b) (6).)

Table 2: Data extracted by DEPI from DMF 034712 for patients known to PRF as deceased.

SUBJID	DMF REF	C'TRY	SEX	DATE OF BIRTH	DATE OF DEATH	AGE	VS SOURCE
(b) (6)	(b) (4)	IDN	F		(b) (6)	11.35	contact with physician
		TUR	M			11.50	email from physician colleague
		USA	M			10.66	telephone contact with mother
		COL	M			11.76	Sunshine Foundation
		CAN	M			18.61	email from mother who sent a link to his obituary
		PRI	F			13.48	information provided by family
		GBR	M			8.25	Sunshine Foundation
		USA	M			8.58	emergency department report
		BRA	M			9.15	email from family friend
		BRA	F			7.21	Facebook posting by father
		BRA	M			11.57	email from aunt
		COL	F			9.97	email from mother

SUBJID	DMF REF	C'TRY	SEX	DATE OF BIRTH	DATE OF DEATH	AGE	VS SOURCE
(b) (6)	(b) (4)	FRA	F		(b) (6)	15.69	Sunshine Foundation and internet posting
		POL	M			8.63	Sunshine Foundation
		FRA	M			9.70	email from mother
		DEU	M			13.80	email from family friend
		CAN	F			17.91	telephone contact with mother
		USA	M			18.28	internet obituary
		GBR	F			14.45	internet posting
		NLD	M			10.13	communication received during Sunshine Foundation reunion
		DEU	F			14.02	parent of another child with progeria
		AUT	F			14.73	Sunshine Foundation
		IND	M			15.33	email from physician
		CHL	F			13.73	Sunshine Foundation
		BRA	M			16.98	email from family friend
		COL	M			10.44	telephone contact with mother
		BRA	F			12.38	email from family friend
		ESP	F			16.27	telephone contact with mother
		PER	F			14.72	Facebook
		GTM	F			13.89	YouTube video
		IND	F			7.67	telephone contact with father
		KOR	M			14.52	telephone contact with father

SUBJID	DMF REF	C'TRY	SEX	DATE OF BIRTH	DATE OF DEATH	AGE	VS SOURCE
(b) (6	(b) (4)	COL	F		(b) (6)	12.82	Facebook and on-line news report
		PER	F			15.06	Facebook
		RUS	M			7.81	email from mother
		VNM	M			10.53	email from director of a non-provide organization
		CHL	M			11.13	Facebook
		COL	F			16.79	Facebook and online-news report
		GTM	M			10.95	telephone contact with mother
		PHL	F			8.49	notification by director of a collaborating organization

LEGEND:

SUBJID	Subject Identification Number
DMF REF	Page reference to Drug Master File (DMF) (b) (4)
C'TRY	Patient country of residence: AUT – Austria, BRA – Brazil, CAN – Canada, CHL – Chile, COL – Columbia, DEU – Germany, ESP – Spain, FRA – France, GBR – Great Britain, GTM – Guatemala, IDN – Indonesia, IND – India, KOR – South Korea, NLD –Netherlands, PER – Peru, PHL – Philippines, POL – Poland, PRI – Puerto Rico, RUS – Russia, TUR – Turkey, USA – United States of America, VNM – Viet Nam
SEX	F – female, M – male
AGE	Age (years) at death (calculated by DEPI)
VS SOURCE	Text summarized by DEPI from DMF to indicate reporting source for date of death

3.3 Non-deceased patients known to PRF from non-literature sources

Table 3 summarizes data extracted by DEPI from DMF (b) (4) for 15 untreated (natural history) patients known to PRF as not deceased. DEPI used results shown in Table 3 to check data in the DD and SUPPDM datasets for country, sex, vital status, date of birth, and age on a censoring date. This check identified several exceptions. For these 15 patients, SUPPDM presented age as of December 31, 2017, whereas DEPI calculated age on a censoring date defined as the earliest of (1) date patient last known to PRF as alive, (2) date before patent started lonafarnib, and (3) June 1, 2019 (defined by PRF as the "data inclusion end date for FDA submission"). DEPI identified three patients (SUBJIDs (b) (6)) with a censoring date earlier than December 31, 2017 (date used to calculate age for SUPPDM).

Table 3: Data extracted by DEPI from DMF (b) (4) for patients known to PRF as not deceased.

SUBJID (b) (6)	DMF REF (b) (4)	C'TRY	SEX	DATE OF BIRTH	CENSOR DATE (b) (6)	AGE	VS SOUR,CE
		IND	M			8.78	telephone contact with father
		USA	M			14.95	email from parents
		IDN	F			10.16	telephone contact with father
		CHN	M			7.63	email contact with physician
		SAU	M			2.61	telephone contact with father
		IND	M			13.83	telephone contact with pediatrician who "believed the child was still living"
		PHL	F			7.00	lonafarnib started on next day (Protocol 00017505)
		USA	F			4.87	telephone contact with mother
		LKA	M			12.13	lonafarnib started on next day (Protocol 00017505)
		PAK	F			10.14	telephone contact with father
		RUS	M			4.95	telephone contact with mother
		IND	M			11.85	lonafarnib started on next day (everolimus trial)
		BRA	F			4.50	contact with physician
		NPL	F			14.30	telephone contact with father
		IND	F			7.79	lonafarnib started on next day (Protocol 00017505)

LEGEND:

SUBJID	Subject Identification Number
DMF REF	Page reference to Drug Master File (DMF) (b) (4)
C'TRY	Patient country of residence: BRA– Brazil, CHN– China, IDN – Indonesia, IND – India, LKA – Sri Lanka, NPL – Nepal, PAK– Pakistan, PHL – Philippines, RUS – Russia, SAU – Saudi Arabia, USA – United States of America
SEX	F – female, M – male
AGE	Age (years) at last contact (calculated by DEPI)
VS SOURCE	Text summarized by DEPI from DMF to indicate reporting source for vital status as alive

4 DISCUSSION

DEPI used a manual method to find high concordance between NDA 213969 and DMF (b) (4) with respect to vital status and age at last contact or death for 62 untreated (natural history) patients with HGPS. DEPI identified four exceptions of possible interest to data analysis. Information in a published case report might extend age at last contact for one patient from 6 to 9 years (SUBJID (b) (6)) [8]. NDA 213969 might have inappropriately extended age at last contact for three patients with a censoring date (according to PRF) earlier than December 31, 2017 (SUBJIDs (b) (4), (b) (6)). These deviations might impact analyses in NDA 213969 that compare lonafarnib-treated and matched untreated (natural history) patients for time to death.

With one possible exception, narratives in DMF (b) (4) referenced reporting sources (*e.g.*, email or telephone contacts with family members) that expressed confidence in the vital status and dates of death or last contact for the 55 living or dead patients known to PRF from sources other than literature (Table 2 and Table 3). A physician reporter expressed uncertainty regarding the vital status for SUBJID (b) (6) (Table 3).

Additionally, the PRF narratives for five deceased patients (SUBJIDs (b) (6) ; Table 2) referenced the Sunshine Foundation as possibly the only source of information for date of death. DRDMG might not regard the Sunshine Foundation as a reliable data source.[d]

Of note, Dr. Leslie G. Gordon signed the patient narratives submitted by PRF to DMF (b) (4) The PRF website identifies Dr. Gordon as the Medical Director for PRF and the co-chair for Progeria clinical drug trials at Boston Children's Hospital.[e] Dr. Gordon authored the JAMA article that reported possible mortality benefit from lonafarnib treatment for HGPS [1]. Eiger Biopharmaceuticals listed Dr. Gordon as a clinical investigator for NDA 213969.[f]

5 CONCLUSIONS

DEPI finds high concordance between NDA 213969 and DMF (b) (4) with respect to vital status and age at last contact or death for 62 untreated (natural history) patients with HGPS.

---

[d] The Sunshine Foundation answers "the dreams of chronically ill, seriously ill, physically challenged and abused children ages three to eighteen, whose families cannot fulfill their requests due to financial strain that the child's illness may cause." See, Sunshine Foundation, About Us, accessed at https://www.sunshinefoundation.org/about-sunshine-foundation/# on August 28, 2020.

[e] Progeria Research Foundation, Officers and Staff, accessed at https://www.progeriaresearch.org/officers-and-staff/ on August 28, 2020.

[f] Certification: Financial Interests and Arrangements of Clinical Investigators (FORM 3454), submitted to NDA 213969 (eCTD 0003) on March 20, 2020.

6 RECOMMENDATIONS FOR DRDMG

DEPI recommends that DRDMG assess (with assistance from the Division of Biometrics IV) the analytic importance (if any) of possible deviations in NDA datasets with respect to the censoring ages for patients identified as SUBJID (b) (6)

7 REFERENCES

1. Gordon LB, Shappell H, Massaro J, et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford progeria syndrome. JAMA. 2018 Apr 24;319(16):1687-95.

2. de Paula Rodrigues GH, das Eiras Tamega I, Duque G, Spinola Dias Neto V. Severe bone changes in a case of Hutchinson-Gilford syndrome. Ann Genet. 2002 Jul-Sep;45(3):151-5.

3. Mutesa L, Pierquin G, Cwiny-Ay N, Buzizi P, Bours V. Hutchinson-Gilford progeria syndrome: clinical and molecular analysis in an African patient. Rev Med Liege. 2007 Mar;62(3):155-8.

4. Hanumanthappa NB, Madhusudan G, Mahimarangaiah J, Manjunath CN. Hutchinson-Gilford progeria syndrome with severe calcific aortic valve stenosis. Ann Pediatr Cardiol. 2011 Jul;4(2):204-6.

5. Kalil KA, Fargalley HS. Hypoparathyroidism in an Egyptian child with Hutchinson-Gilford progeria syndrome: a case report. J Med Case Rep. 2012 Jan 17;6:17.

6. Narazaki R, Makimura M, Sanefuji M, et al. Bilateral stenosis of carotid siphon in Hutchinson-Gilford progeria syndrome. Brain Dev. 2013 Aug;35(7):690-3.

7. Huang S, Liang Y, Wu W, Fu X, Liao L, Luo X. Analysis of a case with typical Hutchinson-Gilford progeria syndrome with scleroderma-like skin changes and review of literature. Zhonghua Er Ke Za Zhi. 2014 Feb;52(2):112-6.

8. Chu Y, Xu ZG, Xu Z, Ma L. Hutchinson-Gilford progeria syndrome caused by an LMNA mutation: a case report. Pediatr Dermatol. 2015 Mar-Apr;32(2):271-5.

CC: Pinheiro S / Sandhu S / Hua W / Callahan C / Lerro C / Booth B / Dunson A / Sun S / Calloway P (OSE)

Jeng L / Suzuki M / Doan J (DRDMG)

APPENDIX 1: SUBJID Listing for Untreated Patients

MATCHID	SUBJID Untreated
1	(b) (6)
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	

MATCHID	SUBJID Untreated
32	(b) (6)
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
61	
62	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
10/15/2020 02:23:08 PM

CATHERINE L CALLAHAN
10/15/2020 02:24:47 PM

WEI HUA
10/15/2020 02:46:26 PM

Clinical Inspection Summary

Date	10/6/2020
From	Zana H Marks, MD, MPH Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Linda Jeng, MD Mari Suzuki, MD Division of Rare Diseases and Medical Genetics (DRDMG) Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM)
NDA #	213969
Applicant	Eiger BioPharmaceuticals, Inc.
Drug	Lonafarnib
NME (Yes/No)	Yes
Therapeutic Classification	Farnesyltransferase Inhibitor
Proposed Indication	Treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL)
Consultation Request Date	April 2, 2020
Summary Goal Date	October 6, 2020
Action Goal Date	November 20, 2020
PDUFA Date	November 20, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant submitted clinical data from two single-center clinical trials (Study 07-01-0007 and Study 09-06-0298) in support of a new drug application (NDA 213969) for lonafarnib for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL). The clinical investigator currently maintaining the study materials for both studies, Dr. Monica E. Kleinman, was inspected in support of this application. Study 07-01-0007 was initiated and conducted by Dr. Mark Kieran from 2007-2009; the study documents were subsequently transferred to Dr. Kleinman in 2018. Study 09-06-0298 was initiated by Dr. Mark Kieran in 2009 and was subsequently transferred to Dr. Kleinman in 2018. The inspection included the investigator Dr. Leslie Gordon to verify survival data collected and maintained by Dr. Gordon for the population of subjects initially enrolled in Studies 07-01-0007 and 09-06-0298.

Based on the results of the inspection, Study 07-01-0007 and Study 09-06-0298 appear to have been conducted adequately. The data submitted by the Applicant for Study 07-01-0007, Study

09-06-0298, and the follow-up data collected by Dr. Gordon appear reliable in support of the proposed indication, with the addition of the previously unreported death of Subject (b) (6), and the few additional data discrepancies detailed in Tables 1 and 2 of Section III.

II. BACKGROUND

Eiger BioPharmaceuticals, Inc. seeks approval of lonafarnib for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL). In support of the NDA, the Applicant submitted clinical data from Study 07-01-0007 and Study 09-06-0298, as well as follow-up survival data for the enrolled study subjects which was collected separately from the original treatment studies. Studies 07-01-0007 (initiated in 2007) and 09-06-0298 (initiated in 2009) began as investigator-initiated single-center studies conducted at Boston Children's Hospital. As of 2018, Eiger assumed sponsor responsibilities for both studies.

Study 07-01-0007, entitled: "An Open Label Adjusted Phase II Trial of the Oral Farnesyltransferase Inhibitor (FT) Lonafarnib for Patients with Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies" was a single-arm, single-center trial conducted from 2007-2009 that evaluated the efficacy of lonafarnib in 28 subjects with HGPS or PL. Subjects were to receive lonafarnib over 24-30 months, followed by a 30-day follow-up period.

Study 09-06-0298, entitled: "An Open label Phase II Trial of Zoledronic Acid, Pravastatin, and Lonafarnib for Patients with Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies" is an ongoing single-center trial that began in 2009. The study population of interest for the NDA submission is the 35 treatment naïve subjects with HGPS enrolled into a monotherapy phase of the study, and the 3 subjects with PL enrolled in a monotherapy extension cohort. Subjects were to receive lonafarnib for up to 3 years, followed by a 30-day follow-up period.

The original objective of both Study 07-01-0007 and Study 09-06-0298 was to evaluate the therapeutic effect of lonafarnib by determining the change in the rate of weight gain over baseline. For the purposes of the NDA review, the primary efficacy assessment is a survival analysis of subjects enrolled in both trials, including follow-up of some of the subjects that occurred after they were no longer enrolled in the trials. Follow-up survival data regarding the subjects initially enrolled in Studies 07-01-0007 and 09-06-0298 was submitted in the NDA under a meta-analysis conducted by Eiger entitled: "An Observational Cohort Survival Study: Results from a Pooled Analysis of Lonafarnib Treatment in Patients with Hutchinson-Gilford Progeria Syndrome."

The goal of the inspection was to evaluate the conduct of Studies 07-01-0007 and 09-06-0298 and to verify the submitted data critical to the application review (including the genetic mutation status, the date of birth, dates of study drug treatment, and date of death or last known follow-up) for the 28 subjects originally enrolled in Study 07-01-0007 and 38 of the subjects of interest originally enrolled in Study 09-06-0298. During the inspection, it was determined that in order to verify the survival data that was collected after subjects were no longer enrolled in Studies 07-

01-0007 or 09-06-0298, the scope of the inspection needed to be expanded to allow for access to follow-up data collected by Dr. Leslie Gordon at Brown University.

III. RESULTS

1. **Dr. Monica E. Kleinman**
   Boston Children's Hospital
   300 Longwood Ave Bader 634
   Boston, MA 02115-5724

This clinical investigator was inspected on August 4; 6-7; 10-14; 17-20, 2020. This was the first FDA inspection for this investigator.

Study documents for Study 07-01-0007 and Study 09-06-0298 were maintained by Dr. Kleinman at the site. Documents reviewed for the evaluation of conduct of both studies included Form FDA 1572s, screening and enrollment logs, IRB approvals and communications, communications regarding adverse event reporting to the Data Safety Monitoring Board (DSMB), and monitoring plan and monitoring report (available for Study 07-01-0007 only).

Source records reviewed for both studies included subject diaries, informed consent documents, and provider notes. Source records additionally included subject records contained in Powerchart, Boston Children's Hospital electronic health medical records (EHR) system; subject data from the EHR was made available for source data verification during the inspection.

Study 07-01-0007 was conducted from 2007-2009 under Clinical Investigator Mark Kieran. The study files were later transferred to Dr. Kleinman (after completion of the study). For Study 07-01-0007, a total of 29 subjects were screened, 28 were enrolled, and 27 subjects completed the study. One subject died during the study (Subject (b) (6)).

Study 09-06-0298 was initiated by Clinical Investigator Dr. Kieran beginning in 2009, was subsequently transferred to Dr. Kleinman, and is currently on-going. For Study 09-06-0298, 37 subjects were screened and 35 were enrolled in the treatment-naïve monotherapy cohort. The disposition of the 35 enrolled subjects is as follows:

- Three subjects died during the treatment portion of the study (Subjects (b) (6))
- One subject died after the treatment portion of the study, during the 30-day follow-up period, while also enrolled in Study 17505 (Subject (b) (6))
- Four subjects withdrew consent during treatment due to side effects (Subjects (b) (6))
- Two subjects were lost to follow-up (Subjects (b) (6))
- 25 subjects completed the study (this includes Subject (b) (6) who completed the study treatment and subsequently died during the 30-day follow-up period)

[1] Subject (b) (6) is the same patient as Subject (b) (6). The patient had failed screening as Subject (b) (6) and was later rescreened and enrolled as Subject (b) (6)

- One subject is currently in the study on treatment (Subject (b) (6))

Additionally, 3 subjects with PL were enrolled in the monotherapy extension of Study 09-06-0298; all completed the study (Subjects (b) (6)).

No monitoring documentation was available for Study 09-06-0298 apart from the safety monitoring by the DSMB. Dr. Kleinman reported during the inspection that source data verification and study procedures were reviewed during internal reviews by study staff. After study sponsorship was transferred to Eiger, audits were initiated to include trial conduct, informed consent, adverse event reporting, data collection, and source data verification (including retrospective source data verification).

Reviewer comment: Formal monitoring was limited until Eiger took over study sponsorship. This is not uncommon for investigator-initiated studies conducted at a single-center, in which the investigator provides informal oversight including staff training, study conduct assessment, and source data verification internally as was the case here. The inspection demonstrated no evidence of inadequate oversight of the studies in terms of study conduct or source data verification. Specifically, all consent documents were adequate, and there were no protocol deviations or significant adverse events that were unreported to the IRB or the Agency.

The subject study data for both studies were entered and maintained as electronic spreadsheet files (using Microsoft Excel) during and after the conduct of the studies. Study staff entered data from source records and periodically reviewed the data for missing or suspect data points. Inadequate controls were in place to ensure the integrity of the study data maintained within the electronic spreadsheets. Although there were no adequate controls in place to ensure the integrity of data that were maintained within electronic spreadsheets, the inspection found that all source records (including study-specific records regarding study assessments, as well as the hospital's EHR data) were appropriately maintained and available for review during the inspection.

Reviewer comment: Despite the lack of audit trails for the study data entered and maintained in electronic spreadsheets as case report forms, all source study data were maintained and available for review at the site.

There were no study conduct concerns regarding informed consent, IRB involvement, or financial disclosures. There was no under-reporting of adverse events or protocol deviations noted during this inspection.

Source data verification (SDV) was performed for all 28 subjects enrolled and treated initially under Study 07-01-0007 and for 38 subjects enrolled and initially treated in Study 09-06-0298.

The date of birth and the genetic mutation for all subjects was verified using documentation of laboratory test results available in the EHR. The date of death for the five subjects who had died while on Study 07-01-0007 or Study 09-06-0298 was verified with source documentation. The last follow-up age of the one subject who remains enrolled in Study 0298 (Subject (b) (6)) was verified using the date of first exposure to lonafarnib under Study 09-06-0298 and the subject

date of birth.

Discrepancies were identified for the last date of lonafarnib administration between source data (subject diaries and provider notes) and data submitted to the agency for three subjects in Study 07-01-0007 (Subject #s (b) (6)) as detailed in Table 1.

Table 1: Discrepant Last Lonafarnib Treatment Date for Subjects in Study 07-01-0007

Subject	Data submitted to Agency	Source Records*	Discrepancy
(b) (6)	7/28/2009	7/29/2009	+1 day
	11/7/2009	11/6/2009	-1 day
	10/5/2009	11/4/2009	+30 days

**Dates from subject diaries and provider notes reviewed during inspection*

Except for the data discrepancies in Table 1, the data relevant to the survival analysis obtained during the conduct of Studies 07-01-0007 and 09-06-0298 was verified with source documentation.

Reviewer comment: The data discrepancies in Table 1 are of limited significance. For Subjects (b) (6), the discrepant dates are one day apart. For Subject (b) (6), while the error affects an analysis of the treatment period, it does not affect the survival data because the last lonafarnib treatment date is not the last follow-up date for this subject (the last follow-up date for this subject is the date of death, (b) (6)).

2. **Dr. Leslie Gordon**
   Brown University
   121 South Main Street, Suite 617
   Providence, RI 02912

This clinical investigator records were reviewed on August 4; 6-7; 10-14; 17-20, 2020.

In order to verify the dates of death and dates of last known survival that occurred outside of the conduct of Studies 07-01-0007 and 09-06-0298, the investigation included a review of source documentation provided by Dr. Gordon for Study 17505 and for a survival analysis study.

Dr. Gordon's source records are maintained at Brown University and were made available for inspection electronically during the inspection of Dr. Monica Kleinman at Boston Children's Hospital.

The dates of death for the 14 subjects who died after having previously been enrolled in Study 07-01-0007 (Subjects (b) (6)) and for the 1 subject who died after having previously been enrolled in Study 09-06-0298 (Subjects (b) (6)) were confirmed using source documents including emails from local physicians/family, memos regarding phone calls with local physicians/family, and printouts of information available online (obituaries, new articles).

The dates of last known follow-up were confirmed according to the description of the last known follow-up as submitted in the Observational Cohort Survival Study meta-analysis. This included the everolimus start date for 33 subjects, the end of Study 09-06-0298 for 7 subjects, and the last follow-up age for one subject (verified previously for Study 09-06-0298). Verification of the everolimus start dates was done using source documents from Study 17505 including signed consent forms and nursing notes. Fourteen of the subjects had a discrepancy between the submitted everolimus start date and the source documents, as detailed in Table 2. Only three of the discrepancies consisted of a difference of more than 1 week (indicated by light-shaded rows in Table 2).

For the 7 subjects for whom the end of Study 09-06-0298 was the last known follow-up date, there was one discrepancy consisting of an unreported death. Specifically, source documents demonstrated that Subject (b) (6) died on (b) (6) (indicated by dark-shaded row in Table 2). The last follow-up description for Subject (b) (6) should have been the known date of death (b) (6), rather than the Study 09-06-0298 end date (8/13/2016).

Reviewer comment: The unreported death of Subject (b) (6) would not affect the survival analysis given that this subject had withdrawn from Study 09-06-0298 on 8/13/2016 and would have been censored at that time. The review division will need to determine the potential impact, if any, of discrepant dates on survival analysis in the case of Subjects (b) (6).

Table 2: Survival Data (Post Studies 07-01-0007 and 09-06-0298) Discrepancies

Subject ID	LASTDESC*	LASTDESC date	Last follow-up type by source documents	Last follow-up date by source documents	Discrepancy Duration
Subjects initially enrolled in Study 07-01-0007					
(b) (6)	Everolimus Start Date	9/5/2017	Everolimus first dose	6/6/2018	+274 days
	Everolimus Start Date	9/11/2017	Study 17505 ICF date	9/12/2017	+1 day
Subjects initially enrolled in Study 09-06-0298					
(b) (6)	Everolimus Start Date	12/14/2017	Everolimus first dose	12/11/2017	-3 days
	ProLon 2 End Date	8/13/2016	Date of death	(b) (6)	+970 days
	Everolimus Start Date	12/21/2017	Everolimus first dose	12/19/2017	-2 days
	Everolimus Start Date	9/26/2017	Everolimus first dose	9/25/2017	-1 day
	Everolimus Start Date	7/2/2018	Everolimus first dose	6/13/2018	-19 days
	Everolimus Start Date	5/17/2018	Everolimus first dose	5/14/2018	-3 days
	Everolimus Start Date	2/2/2018	Everolimus first dose	1/30/2018	-3 days
	Everolimus Start Date	1/8/2018	Study 17505 ICF date	1/11/2018	+3 days

(b) (6)					
	Everolimus Start Date	3/8/2018	Everolimus first dose	3/5/2018	-3 days
	Everolimus Start Date	3/8/2018	Study 17505 ICF date	3/5/2018	-3 days
	Everolimus Start Date	7/1/2018	Study 17505 ICF date	6/11/2018	-20 days
	Everolimus Start Date	6/8/2018	Study 17505 ICF date	6/4/2018	-4 days
	Everolimus Start Date	6/28/2018	Everolimus first dose	6/25/2018	-3 days

**From Observational Cohort Survival Study submission, ADSL, "LASTDESC" (description of last follow-up)*
ICF=informed consent form

The inspections of Drs. Kleinman and Gordon verified the data critical to the application, including data obtained during the conduct of Studies 07-01-0007 and Study 09-06-0298, and the survival data collected after subjects had completed the treatment trials. Data discrepancies were few and are delineated in Tables 1 and 2 above. There were no significant study conduct issues identified for Study 07-01-0007 or for Study 09-06-0298.

{See appended electronic signature page}

Zana H. Marks, M.D. , M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

NDA 213696
Review Division /Division Director/Kathleen Donohue
Review Division /Project Manager/ Jenny Doan
Review Division/Cross Discipline Team Lead/Linda Jeng
Review Division/Clinical Reviewer/Mari Suzuki
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khan
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Karen Bleich
OSI/DCCE/GCP Reviewer/Zana Marks
OSI/ GCP Program Analysts/ Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZANA H MARKS
10/06/2020 04:53:49 PM

KAREN B BLEICH
10/06/2020 04:55:45 PM

KASSA AYALEW
10/06/2020 05:05:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 9/11/20 **Date consulted:** 3/24/20

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Rare Diseases and Medical Genetics (DRDMG)

Drug: Zokinvy (Lonafarnib)

NDA: 213969

Applicant: Eiger Biopharmaceuticals, Inc. (Eiger)

Subject: Pregnancy and Lactation Labeling

Indications: To reduce the risk of mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome (HGPS)
For the treatment of progeroid laminopathies (PL) with a processing-deficient mutation in LMNA or ZMPSTE24

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 213969
- Applicant's response to FDA's Information Request for NDA 213969
- DPMH consult request dated 3/24/20, DARRTS Reference ID 4580359

Consult Question: To request assistance with the labeling review.

INTRODUCTION AND BACKGROUND

On March 20, 2020, Eiger submitted a New Drug Application (NDA) for ZOKINVY for initial FDA approval. On March 24, 2020, DRDMG consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History[1]

- October 17, 2018: Lonafarnib granted Rare Pediatric Disease Designation
- November 2, 2018: Eiger filed IND 139, 923 and expanded access program (EAP) protocol
- December 12, 2018: Lonafarnib was granted Breakthrough Therapy Designation
- July 3, 2019: Lonafarnib granted Orphan Drug Designation (ODD)
- November 15, 2019: Eiger submitted NDA 213, 969 under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and FDA granted rolling submission and Priority Review
- July 29, 2020: Information request (IR) sent regarding pregnancy information studied in patients for other indications. The IR was received from the applicant on August 10, 2020.

Lonafarnib Drug Characteristics[2]

- The recommended starting dosage regimen for patients with HGPS is 115 mg/m^2 twice daily ([redacted (b) (4)]. After 4 months of treatment, the patient's dose should be increased to 150 mg/m^2 twice daily. The recommended starting dosage regimen in patients with a confirmed processing deficient Progeroid Laminopathy is 115 mg/m^2 twice daily [redacted (b) (4)]. After 4 months of treatment, the patient's dose should be increased to 150 mg/m^2 twice daily.
- Lonafarnib is a farnesyltransferase inhibitor which inhibits the farnesylation of progerin, the abnormal protein in HGPS.
- Mean terminal half-life: 4.22 hours.
- Molecular mass: 638.8 g/mol
- Plasma protein binding: ≥ 99%

REVIEW

PREGNANCY

Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL) and Pregnancy

HGPS is a rare, fatal multi-systemic disease of premature aging caused by mutations of the gene LMNA of lamin A, a protein involved in maintaining the structure and integrity of cell nuclei. In HGPS, there is accumulation of an abnormal farneslyated lamin A protein (progerin) that leads to cellular damage and the process of premature aging. It is estimated that the incidence of HGPS is one in four to eight million newborns worldwide and that there are between 200 to 250 children living with progeria.[3] Progeria patients typically die from heart disease or severe atherosclerosis at 13 to14 years with a range of about eight to 21 years.[4]

[1] Applicant's submission, clinical reviewer guide, page 4
[2] Refer to proposed labeling, 3/20/20
[3] https://rarediseases.info.nih.gov/diseases/7467/hutchinson-gilford-progeria-syndrome
[4] https://rarediseases.org/rare-diseases/hutchinson-gilford-progeria/

HGPS patients appear normal at birth but develop severe growth failure, characteristic facies (e.g., receding mandible, narrow nasal bridge), alopecia, loss of subcutaneous fat, and abnormal skin, dentition and musculature. Cognitive development is normal. Sexual maturation is typically delayed.[5] One study evaluating pubertal development of females with HGPS (n=15) found that more than half of females (60%) experienced menarche, even in the setting of little to no signs of pubertal development. The article states there are no published cases of pregnancy for anyone with HGPS.[6]

There is one published case report of pregnancy in a woman with non-classical progeria.[7] A 23-year-old woman with "mild" HGPS became pregnant and delivered a healthy baby via caesarean section which was performed for fetopelvic disproportion. The pregnancy was uneventful except for third trimester hypertension. She lived until 32 years.

Reviewer comment: This case report was published in 1989 and describes a patient with "mild" HGPS based on clinical features. It is not clear if this patient would meet current HGPS diagnostic criteria (i.e., confirmatory genetic testing), particularly given the difference in her clinical course and prolonged life relative to other patients diagnosed with HGPS.

Progeroid laminopathies (PL) are rarer than HGPS. PLs that are processing-deficient are caused by the mutations in the ZMPSTE24 and LMNA gene that lead to permanently farnesylated prelamin A which have clinical features that overlap with HGPS.

There is currently no cure or approved treatment for HGPS and PL.

Nonclinical Experience

In an embryo-fetal development study in rats, oral administration of lonafarnib during organogenesis produced an increase in post-implantation loss (resorptions) and decreases in fetal body weight and number of live fetuses at 30 mg/kg/day (1.1 times the AUC [area under the plasma concentration-time curve] in humans at the recommended dose of 150 mg/m^2 BID). No effects on embryo-fetal development in rats were observed at systemic exposures lower than the human AUC at 150 mg/m^2 BID.

In rabbits, oral administration of lonafarnib during organogenesis resulted in skeletal malformations and variations at systemic exposures lower than the human AUC at the recommended dose of 150 mg/m^2 BID, and maternal toxicity (body weight loss and abortion) at 120 mg/kg/day (25 times the human AUC at 150 mg/m^2 BID).

[5] Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. 2003 Dec 12 [Updated 2019 Jan 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www ncbi.nlm.nih.gov/books/NBK1121/

[6] Greer MM, Kleinman ME, Gordon LB, Massaro J, D'Agostino RB Sr, Baltrusaitis K, Kieran MW, Gordon CM. Gordon pubertal progression in adolescent females with progeria. J Pediatr Adolesc Gynecol. 2018;31:238–41.

[7] Corcoy, R., Aris, A., & De Leiva, A. (1989). Case Report: Fertility in a Case of Progeria. *The American Journal of the Medical Sciences.*, *297*(6), 383–384.

No effects in offspring were observed in a pre-/postnatal development study in rats with maternal administration of up to 20 mg/kg/day orally (AUC lower than the human AUC at 150 mg/m^2 BID) during organogenesis through lactation.

Reviewer comment: The Pharmacology/Toxicology review is pending at the time of this review.

Clinical Experience
Lonafarnib has been used in clinical trials and is not currently approved in any country.

Lonafarnib was originally investigated as a potential oncology product (b) (4) in Phase 1, Phase 2, and Phase 3 studies in patients with solid tumors and hematologic malignancies. More than 1,500 oncology patients were treated prior to termination of development for oncology due to lack of clear clinical activity[8] and there were no reported pregnancies in these studies.[9]

Eiger is currently evaluating lonafarnib, in combination with ritonavir, as a potential treatment for chronic hepatitis delta (HDV infection) in patients who are co-infected with hepatitis B virus (b) (4) [11]

For HGPS and PL patients, lonafarnib has been administered to 84 patients and there have not been any reported pregnancies.

There are no published reports with the use of lonafarnib in pregnant women in either PubMed, Embase, Micromedex,[12] Reprotox,[13] or TERIS.[14]

LACTATION
Nonclinical Experience
Studies in lactating rats have shown that lonafarnib is excreted into milk.

Clinical Experience:
Lonafarnib is not currently approved as a drug product in any country. There is no clinical information about the use of lonafarnib during lactation in the following databases or published literature; PubMed, Embase, ReproTox, TERIS, LactMed, or *Medications and Mothers' Milk.*[15]

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Reproductive toxicity has been evaluated in fertility studies in rats, embryo-fetal development studies in rats and rabbits, and a peri- and post-natal development study in rats. In both rat and rabbit reproductive toxicity studies, lonafarnib, especially at higher doses, resulted in changes in

[8] Applicants clinical summary, page 82
[9] Applicant's clinical information amendment, page 1
[10] Applicant's summary of clinical safety, page 9
[11] Applicant's clinical information amendment, page 1
[12] https://www.micromedexsolutions.com, accessed 6/9/20.
[13] Truven Health Analytics information. Reprotox, accessed 6/9/20.
[14] Truven Health Analytics information. Teris, accessed 6/9/20.
[15] Hale TW. Hale's medications and mother's milk. 2019. Springer Publishing Co. NY, New York.

the male and female reproductive tracts and increased fetal abortions and resorptions. In rabbits, a test article-related increased incidence of fetal skeletal malformations and variations were seen at the lowest evaluated dose of 10 mg/kg. In a peri- and postnatal development study in rats, no test-article related effects were observed up to the highest dose of 20 mg/kg.

In nonclinical studies of up to 6 months in rats and one year in monkeys, higher doses of lonafarnib resulted in testicular toxicity.

Reviewer comment: DPMH reached out to Pharmacology/toxicology regarding testicular toxicity findings and the potential risk of permanent infertility as a consideration for labeling in 8.3. The final Pharmacology/toxicology review is pending.

Clinical Experience
Lonafarnib is not currently approved as a drug product in any country. There was no information on fertility effects with the use of lonafarnib in pregnant women in either PubMed, Embase, Reprotox, or TERIS.

DISCUSSION AND CONCLUSIONS
Pregnancy
There are no available data on lonafarnib use in pregnant women. In pregnant rats, oral lonafarnib led to embryo-fetal toxicity at exposures that were 1.1 times the human exposure at recommended doses. In pregnant rabbits, oral administration of lonafarnib during embryogenesis produced skeletal malformations and variations at exposures lower than the human exposure. Given that pregnancy is plausible, and animal data are of concern, DPMH recommends adding language in 5, 8.1, and 17 to indicate that lonafarnib may cause fetal harm and is not recommended during pregnancy.

Due to the disease rarity, delayed sexual maturation, and early death of HGPS and PL patients, pregnancy in this population would be highly unlikely. There is only one published report detailing a normal pregnancy outcome in a woman with a mild form of HGPS who has not taking Lonafarnib. Given that pregnancy is highly unlikely in this rare disease population, postmarketing pregnancy safety studies would not be feasible.

Lactation
There are no data on the presence of lonafarnib in the milk of humans. Animal data in rats indicate that lonafarnib is excreted into milk. Given that lactation would be highly unlikely in this rare disease population with early death, a lactation study would not be feasible.

Females and Males of Reproductive Potential
There are no human fertility data with lonafarnib use in females and males of reproductive potential. Animal data in rats suggests lonafarnib may reduce fertility in males and females of reproductive potential.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on September 15,

2020. The final Pharmacology/Toxicology Review is pending and DPMH defers to Pharmacology/Toxicology on the final review and input for relevant PLLR language. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------- WARNINGS AND PRECAUTIONS----------
•Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.x, 8.1, 8.3)

FULL PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS
5.X Embryo-fetal toxicity
Based on findings from animal reproduction studies, ZOKINVY can cause embryofetal harm when administered to a pregnant patient. Advise females of reproductive potential of the risk to a fetus and to use an effective method of contraception [(*see Use in Specific Populations (8.1, 8.3)]*

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on findings from animal studies, ZOKINVY can cause embryofetal harm when administered to a pregnant woman. There are no human data on ZOKINVY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of lonafarnib in pregnant rats during organogenesis produced embryo-fetal toxicity at exposures that were (b) (4)-times the human exposure at the recommended dose of 150 mg/m^2 BID. In pregnant rabbits, oral administration of lonafarnib during organogenesis produced skeletal malformations and variations at exposures lower than the human exposure at 150 mg/m^2 BID, and maternal toxicity at (b) (4) times the human exposure at 150 mg/m^2 BID *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to20%, respectively.

Data
Animal Data
In an embryo-fetal development study in rats, oral administration of lonafarnib during organogenesis produced an increase in post-implantation loss (resorptions) and decreases in fetal body weight and number of live fetuses at 30 mg/kg/day (1.1 times the AUC [area under the plasma concentration-time curve] in humans at the recommended dose of 150 mg/m^2 BID). No

effects on embryo-fetal development in rats were observed at systemic exposures lower than the human AUC at 150 mg/m^2 BID.

In rabbits, oral administration of lonafarnib during organogenesis resulted in skeletal malformations and variations at systemic exposures lower than the human AUC at the recommended dose of 150 mg/m^2 BID, and maternal toxicity (body weight loss and abortion) at 120 mg/kg/day ((b) (4) times the human AUC at 150 mg/m^2 BID).

No effects in offspring were observed in a pre-/postnatal development study in rats with maternal administration of up to 20 mg/kg/day orally (AUC lower than the human AUC at 150 mg/m^2 BID) during organogenesis through lactation.

Reviewer comment: The final Pharmacology/Toxicology labeling edits are pending.

8.2 Lactation

Risk Summary

There are no data on the presence of lonafarnib in human milk, the effects on the breastfed infant, or the effects on milk production. Lonafarnib is excreted in rat milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOKINVY and any potential adverse effects of the breastfed infant from ZOKINVY or from the underlying maternal condition.

Data

Lonafarnib is excreted in milk following oral administration in lactating rats, with a mean milk to plasma concentration ratio of 1.5 at 12 hours.

8.3 Females and Males of Reproductive Potential

Contraception

ZOKINVY may cause embryo-fetal harm when administered to pregnant patients *[see Use in Specific Populations (8.1)].* Advise females of reproductive potential to use effective contraception during treatment with ZOKINVY.

Infertility

Based on findings in rats, ZOKINVY may reduce fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

Reviewer comment: The final Pharmacology/Toxicology labeling edits are pending.

17 PATIENT COUNSELING INFORMATION

Embryo-fetal toxicity *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.1, 8.3)*

Advise pregnant women and female patients of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZOKINVY.

Infertility

Advise females and males of reproductive potential that ZOKINVY may impair fertility *[see Use in Specific Populations (8.3)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEAN L LIMPERT
09/29/2020 12:02:41 PM

MIRIAM C DINATALE
09/29/2020 12:06:33 PM

LYNNE P YAO
10/05/2020 04:42:07 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 8th, 2020

To: Kathleen Donohue, M.D., Director (Acting)
Division of Rare Diseases and Medical Genetics

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: Lonafarnib, NDA 213969
Zokinvy: 50 and 75 mg capsules for oral administration
Indication(s): to reduce the risk of mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome and 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)
Sponsor: Eiger Pharmaceuticals
PDUFA Goal Date: November 20, 2020

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA 213969

Table of Contents

I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Rare Diseases and Medical Genetics to evaluate the abuse potential of lonafarnib (trade name: Zokinvy) submitted by Eiger pharmaceuticals in NDA 213969. Lonafarnib is indicated to reduce the risk of mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome and 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). Lonafarnib is available in 25 and 75 mg capsules for oral administration.

Lonafarnib is a new molecular entity and according to the Sponsor, is a farnesyltransferase inhibitor (FTI). Farnesyltransferase is an enzyme that posttranslationally-modifies proteins include the Ras protein, which is involved in cell cycle progression.

2. Conclusions

- Based on the receptor binding profile, preclinical assessment of CNS activity, and adverse event profile in clinical trials, lonafarnib does not appear to present a potential for abuse and should not be scheduled under the Controlled Substances Act.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

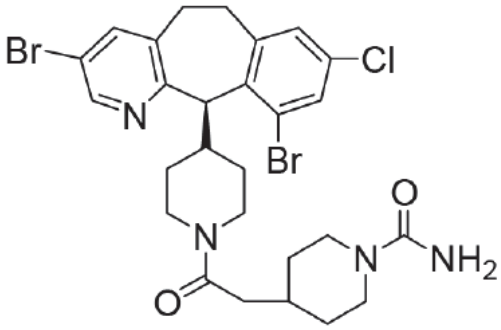
1. CSS does not recommend scheduling of lonafarnib under the Controlled Substances Act (CSA)
2. No section 9.0 (Drug Abuse and Dependence) is necessary in the drug label

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Lonafarnib is described by the Sponsor as a white to off-white powder and the IUPAC name of lonafarnib is:
4-[2-[4-[(11*R*)-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. The molecular formula is $C_{27}H_{31}Br_2ClN_4O_2$ and the chemical structure of lonafarnib appears below:



2. Nonclinical Pharmacology

Lonafarnib is a farnesyl protein transferase inhibitor (FTI). According to the Sponsor, the IC_{50} value is 1.9 nm. The primary pharmacodynamic studies were based on the published literature.

2.1 Receptor Binding and Functional Assays

The Sponsor evaluated the secondary pharmacology of lonafarnib and its primary metabolite, HM21 in receptor binding studies (studies US073-0012557, TW04-0007251, 100053293, and 100053670). To produce receptor binding curves, lonafarnib was tested at a concentration of 10 µM. Based on the results of initial testing, 10-fold dilutions were examined thereafter if relevant binding was observed. A total of 51 molecular targets were examined and the functional activity of lonafarnib was assessed. According to the Sponsor, lonafarnib and HM21 had relevant activity (defined as activity at a concentration 10 µM or lower) at seven receptor subtypes. Lonafarnib showed antagonist activity with an IC_{50} < 10 µM at four molecular targets: B1 adrenoceptors (ADRB1) (IC_{50} = 2.1 µM), cannabinoid-1 (CNR1) (IC_{50} = 1.2 µM), cannabinoid 2 (CNR2) (IC_{50} = 2.0 µM), and orexin 1 (OX1) (IC_{50} = 7.1 µM). The HM21 metabolite showed antagonist activity with an IC_{50} < 10 µM at three molecular targets, including ADRB1 (IC_{50} = 3.5 µM), CNR2 (IC_{50} = 4.4 µM), and mu-1 opioid receptor (OPRM1) (IC_{50} = 3.6 µM). HM21 showed agonist activity was observed at a single receptor subtype, the 5-HT1B receptor (EC_{50} = 2.2 µM).

The Sponsor also estimated the likelihood of clinically relevant activity at the seven receptors with EC/IC_{50} values less than 10 µM, using peak plasma concentration (Cmax) values obtained from clinical studies. After accounting for the high degree of plasma protein binding (~99%), estimated free drug (i.e., unbound drug) concentrations were calculated. Based on these estimations, the Sponsor asserts that in vivo concentrations of lonafarnib would be at least 30-fold lower than the EC/IC_{50} values determined from the binding studies.

Taken together, the receptor binding data suggest that lonafarnib does not have functional activity at receptors associated with abuse and would not be present at high enough concentrations to produce activity at abuse-related receptors in vivo.

2.3 Findings from Safety Pharmacology and Toxicology Studies

As part of the safety pharmacology assessment of lonafarnib, the Sponsor performed an assessment of CNS activation in rodents (Study p-6339) using a modified Irwin method. Groups of six rats (n =6 each group) were administered oral doses of 10, 30, and 100 mg/kg lonafarnib. Evaluations of behaviors using a scale ranging from -3 (decreased relative to baseline) to +3 (increased relative to baseline) were performed 1, 2, 4, and 6 hours after dosing. According to the Sponsor, no lethalities occurred and no changes in behavioral, neurological, or autonomic function were observed. The Sponsor concluded that lonafarnib does not produce meaningful CNS-related effects.

Single dose toxicity studies examined single doses of lonafarnib of 0, 300, 1000, and 2000 mg/kg p.o. in juvenile (i.e., 6 week old) male and female rats (study 96025). Observations occurred immediately after dosing, 0.25, 0.5, 1, 3, and 5 hours after dosing and then daily thereafter for 14 days. Stool abnormalities and decreased weight were noted at the highest dose (2000 mg/kg) along with a death in one of the female rats. According to the Sponsor, no CNS-related signs were observed.

Similar outcomes were observed across several other toxicity studies (Studies 96026, 96027, 97266, 96028, and 97267) utilizing similar dosing regimens and routes of administration (either p.o., or i.p. doses of lonafarnib from 0-2000 mg/kg). In these studies, some CNS-related observations were present (e.g., hypoactivity, tremor, ataxia and convulsions) but only at doses resulting in mortality. Similarly, in the multiple dose studies where animals were administered daily doses of 0-180 mg/kg for three (study 96030) or six months (study 96034) the Sponsor did not observe any CNS-related signs at any of the doses tested. Three month and one year toxicology studies in cynomolgus monkeys using p.o. doses of 0-60 mg/kg/day produced similar results (e.g., no CNS-related effects). The Sponsor claims that the monky studies achieved AUC values that were at least 4 times higher than those observed in progeria patients at clinically efficacious doses.

2.5 Tolerance and Physical Dependence Studies in Animals

Dedicated physical dependence and withdrawal studies were not performed, however, several of the animal toxicology/safety studies included recovery period observations where animals were assessed after drug cessation. According to the Sponsor, after a 3 month toxicology study in rats (study 96030) examining lonafarnib doses of 0, 30, 90, and 180 mg/kg, animals at the highest dose had decreased body weights. However, bodyweights returned to normal levels after drug cessation, accompanied by increased food consumption. Similar results (i.e., decreased food consumption relative to control levels during acute dosing followed by a brief, transient increase after drug cessation) were observed across several studies examining lonafarnib doses up to 60 mg/kg/day including a 6 month study in rodents (study 96034), a 3 month toxicology study in monkeys (study 96612), and a 1 year (52 week) study in monkeys (study 96036). According to the Sponsor, overall, no signs of dependence and withdrawal observed. No clinical studies of withdrawal or dependence were performed.

3. Clinical Pharmacology

According to the Sponsor, after oral administration the Tmax of lonafarnib is 2-4 hours. The average half life (T½) of lonafarnib is 3-4 hours after single dose administrations and increases to 4-5 hours after multiple dose administration. Exposure (i.e., AUC) is dose-proporational between 25 – 200 mg. Lonafarnib produces two metabolites: HM17 and HM21. The Sponsor states that HM21 is similar to the parent drug and HM17 is unstable, less than 10% opf the parent drug, and cannot be synthesized.

4. Clinical Studies

The proposed indication for lonafarnib includes Hutchinson-Gilford Progeria Syndrome (HGPS) and Progeroid Laminopathies (PL). These are exceptionally rare conditions with HGPS occurring in approximately 1 in 4 million live births and a prevalence of 1 in 20 million living persons. There are fewer than 40 patients with PL worldwide. A total of 21 clinical studies were peformed. However, eight of the studies (P00042, P00260, P02673, P00393, P00394, I97-211, C97-258, and C97-262) were conducted approximately 20 years ago by a different Sponsor and for a different indication.

The studies included efficacy, bioavailability, drug-drug interaction (DDI), and/or PK and tolerability studies. The majority of studies did not utilize a placebo control or other comparator. Moreover, the severe phenotype observed in the proposed indications (e.g., an average life expectancy of ~14 years old) precludes meaningful analysis of efficacy studies utilizing lonafarnib. Nonetheless, all clinical studies were reviewed for abuse-related, treatment emergent adverse events (AEs).

Across the 21 clinical studies, the majority (19 of 21) had less than one abuse-related adverse event. The two studies with >1 abuse-related AE included studies EIG-LNF-009 and 07-01-0007. Study EIG-LNF-009 had one report of somnolence and one report of euphoric mood. However, EIG LNF-009 was a DDI and the reports of somnolence and euphoric mood occurred in a subject administered a combination of lonafarnib, midazolam, and ritonavir (an antiretroviral drug indicated for the treatment of HIV/AIDS) which complicates assessing causality and the role of lonafarnib in producing the AEs. In addition there was no placebo control to use as a comparator. Study 07-01-0007 (ProLon1) produced 4 reports of mood altered, 3 reports of depressed mood, and 2 reports of dizziness. However, this study also lacked a placebo control comparator arm and was an open-label study. In addition, study 07-01-0007 (ProLon1) was an efficacy study performed in subjects with a severely debilitating phenotype (i.e., patients with HPS and PL) with a median age of 7.5 years. The validity of abuse-related AE analyses in this unique patient population is completely unknown. Overall, there was a paucity of abuse-related AEs observed across the lonafarnib development program, and no signs of abuse potential.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHAD REISSIG
09/28/2020 11:31:27 AM

DOMINIC CHIAPPERINO
09/28/2020 12:20:18 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 213969
Submission Number	003
Submission Date	3/20/2020
Date Consult Received	4/1/2020
Drug Name	Lonafarnib
Indication	Treatment of Hutchinson-Gilford Progeria Syndrome and Progeroid Laminopathies
Therapeutic dose	Up to 150 mg/m^2 BID, no more than 350 mg daily
Clinical Division	DRDMG

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 4/1/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND (b) (4) dated 05/29/2018, 08/03/2018, and 10/29/2018 in DARRTS;
- Previous IRT review under NDA 21906 dated 05/09/2008 in DARRTS;
- EIG-LNF-010 clinical study report and cardiac safety report (Submission 0003);
- Proposed label (Submission 0003); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0003).

1 SUMMARY

No significant QTc prolongation effect of lonafarnib (LNF) and ritonavir (RTV) combination was detected in this QT assessment. The data were not adequate to assess the effect of lonafarnib monotherapy on the QTc interval because the study did not include a lonafarnib alone arm, the exposure-response analysis results were not interpretable, and due to differences in the metabolic profile, it's not known whether there was adequate exposure to the major metabolites (HM17 and HM21).

The effect of LNF and RTV combination was evaluated in EIG-LNF-010, a double-blind, randomized, placebo- and active-control, parallel-group study with nested crossover design in healthy volunteers. The highest dose evaluated was LNF 100 mg and RTV 100 mg BID x 5 days, which covers approximately 1.4-fold the therapeutic exposure of LNF, but the exposure margin for the major metabolites are not known. The data were analyzed using by-time analysis as the primary analysis, which did not suggest that the combination is associated with significant QTc prolonging effect (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis were supported by categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Treatment	Study Day	Time (hour)	ΔΔQTcF (msec)	90% CI (msec)
LNF 50 mg + RTV 100 mg BID	5	24.0	-4.0	(-12.3 to 4.3)
LNF 100 mg + RTV 100 mg BID	10	12.0	2.6	(-5.3 to 10.6)
Moxifloxacin 400 mg*	1	4.0	11.8	(7.0 to 16.7)

** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints was 5.1 msec. For further details on the FDA analysis please see section 4.*

Cmax is reported to be around 2500 ng/mL at 150 mg/m^2 BID dose in the target patient population. The highest exposure scenario for LNF is with concomitant use of a strong CYP3A inhibitor (3.7-fold increase with ketoconazole), and this increase in LNF exposure is not covered by the highest tested dose in this TQT study. The effect of severe hepatic impairment on LNF exposure is also not known. Metabolite exposure following daily administration of LNF may not be covered in this TQT study due to the differences in the metabolic profile with concomitant use of RTV (strong CYP 3A inhibitor).

The pre-specified primary analysis was exposure-response analysis. The analysis suggested a QT shortening effect by RTV (negative slope), which could not be explained by our prior knowledge of RTV. Therefore, we do not agree with predicting the QTc effect of LNF monotherapy based on exposure-response analysis results from combination treatments.

In nonclinical evaluation, the ratio between hERG IC50 and the mean LNF free $C_{max,ss}$ (~25 ng/mL assuming fu=1%) is 33-fold. The sponsor has not provided data regarding the effect of major metabolites (HM17 and HM21) in the hERG assay.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Ritonavir prolongs the PR interval — ritonavir 400 mg BID increased the PR interval by a mean of 22 msec. In this study, there was a modest PR prolongation with a mean of 5 to 7 msec on days 5 and 10. Although RTV concentrations were similar on days 5 and 10, there was the large variability associated with the PR interval data. It's likely that the observed PR prolongation was caused by RTV, but we cannot rule out some contribution by LNF and RTV combination.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

If the Division considers it necessary to know whether lonafarnib prolongs the QTc by ≥10 msec as per ICH E14 guideline, we recommend that a thorough QT study is conducted to get a better estimate of the QTc prolongation effect of the monotherapy. We defer the timing of this study to the Division.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0003 from the IRT. Our changes are highlighted (addition, ~~deletion~~) for suggestions only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

(b) (4)

[redacted]

We propose not to report QT findings from this TQT study for the proposed indication, because the TQT study is not adequate to assess the QT effect by LNF monotherapy. However, if the Division decides to report QT findings from this TQT study, we propose to describe the study treatments and state the limitation of TQT study design for this proposed indication.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The IRT reviewed the QT study protocol previously under IND (b) (4) (dated 05/29/2018, 08/03/2018, and 10/29/2018 in DARRTS). (b) (4)

[redacted]

In the current NDA submission, the sponsor is developing LNF capsule as a monotherapy for to reduce the risk of mortality in patients 12 months of age or older with Hutchinson-Gilford Progeria Syndrome and 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). The proposed indication is an ultra-rare premature aging disease in pediatric patients. The maximum recommended therapeutic dose is 150 mg/m^2 BID, (b) (4), with the morning and evening meal. All doses should be rounded to nearest 25 mg increment. Cmax is reported to be around 2500 ng/mL after multiple doses of the capsule or suspension formulations at 150 mg/m^2 BID dose in patients with HGPS.

LNF is primarily eliminated by hepatic metabolism (mostly by CYP3A), and it is also an inhibitor of CYP3A (strong inhibition) and CYP2C19. For LNF monotherapy, the mean terminal elimination half-life is 3-4 hour after single dose (75 mg) and 4.2-5.6 hours after multiple doses (75 or 100 mg BID). Ketoconazole increases LNF Cmax to 3.7-fold and food decreases LNF exposure (~50% reduction in Cmax in the presence of high-fat/high-calorie meal; ~20% reduction with low-fat/low-calorie meal). The sponsor reported 25-30% higher Cmax in elderly subjects (>65 y.o. vs. 18-45 y.o.) and in females vs. in males. The effect of severe hepatic impairment on LNF exposure and the effect of age and sex in pediatric patients were not known. LNF has two significant metabolites, HM17 and HM21 that accounted for 15% and 14% of total plasma radioactivity (LNF: 50-57%). The sponsor has not provided PK properties of these metabolites. Systemic exposure of the metabolites could be different with or without RTV.

RTV is an HIV protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. In vitro studies suggested that CYP3A is the major isoform involved in ritonavir metabolism, and CYP2D6 also contributes to the metabolism. RTV is an inhibitor of CYP3A (strong inhibition) and CYP2D6, and it appears to be an inducer of other hepatic enzymes. No significant effect on the QTc interval was observed with RTV 400 mg BID x 2.5 days (IRT review under NDA 21906 dated 05/09/2008 in DARRTS). A positive exposure-response relationship was observed for RTV (slope = 0.255 ms per ug/mL, p-value = 0.0256; the estimated intercept was not statistically significant), but the upper bound of 90% CI for the predicted ΔΔQTcF at geometric mean Cmax (19.9 ug/mL) was lower than 10 msec. The same treatment prolonged the PR interval by a mean of 22 msec after adjusting for baseline and placebo. Literature data suggested an hERG IC50 value of 8.2 uM[1] and a plasma protein binding of 1-2%[2].

In the submitted QT study, a total of 65 subjects were randomized with 32 subjects to Group 1, 16 subjects to Group 2A and 17 subjects to Group 2B. 27 subjects in Group 1, 15 subjects in Group 2A, and 17 subjects in Group 2B completed the study treatment, and completed PK sampling. 31 subjects in Group 1, 15 subjects in Group 2B, and 17

---

[1] Anson BD, Weaver JG, Ackerman MJ, et al. Blockade of HERG channels by HIV protease inhibitors. Lancet. 2005;365(9460):682-686. doi:10.1016/S0140-6736(05)17950-1

[2] NORVIR (ritonavir) product label

subjects in Group 2B completed the safety assessments through Day 24. The following data were excluded from the sponsor's analysis:

- Subject (b) (6) in Group 2B had a moxifloxacin dose on Day 1 but did not have any observed concentrations for moxifloxacin. This subject was removed from the assay sensitivity analysis and the by-time point and categorical analysis for moxifloxacin.
- ECGs were extracted at 5 hours post-dose on Days −1, 1, and 11 only, but not on Days 5 and 10. Change-from-baseline values for active drug and corresponding placebo at this time point on Days 5 and 10 and change-from-baseline values for placebo in Groups 2A and 2B at this time point were not available. This time point was therefore removed from all analyses for both active drug and moxifloxacin.
- ECGs were extracted at 7, 9, and 10 hours post-dose on Days −1, 5, and 10, but not on Days 1 and 11. Change-from-baseline values for moxifloxacin at these time points were not available. These time points were removed from all analyses for moxifloxacin.

3.1.2 Nonclinical Safety Pharmacology Assessments

Lonafarnib inhibited the hERG potassium channel current in mouse L-929 cells (IC50=1.3 μM).

Lonafarnib had no effects on QT or QTc interval in vivo in anaesthetized guinea pigs exposed to total plasma levels of up to 30 μM (at a dose of 50 mg/kg). Lonafarnib produced modest and isolated effects on the QT interval of ECG in rats (≥30 mg/kg). In repeated-dose toxicity studies, there were no ECG changes observed in monkeys following repeat dosing of lonafarnib for up to 1 year.

Reviewer's comment: *The sponsor reported protein binding >99%. Assuming a Cmax of 2500 ng/mL, fu=1%, and MW of 638.8 g/mol, the ratio between hERG IC50 and free $C_{max,ss}$ is 33-fold.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for lonafarnib and ritonavir was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Sponsor has provided by-time analysis results for all intervals.

Reviewer's comment: *FDA reviewer used different linear mixed effect model for by-time analysis. FDA reviewer also adjusted for baseline values as a fixed effect covariate. Time trend is similar with consistent differences. FDA reviewer's analysis shows PR prolongation at both dose levels. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

By-time analysis for assay sensitivity shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis also shows that assay sensitivity was established by moxifloxacin arm. Please see 4.3 for additional details.*

The prespecified assay sensitivity analysis (concentration-QTc analysis) failed to demonstrate assay sensitivity as the lower bound of the 2-sided 90% CI of the predicted effect on ΔΔQTcF was less than 5 ms at the geometric mean peak of moxifloxacin concentrations. In the additional assay sensitivity analysis, the random slope was removed and the lower bound of the 90% CI of the predicted effect on ΔΔQTcF exceeded 5 msec. The population slope estimation and the predicted ΔΔQTcF were similar; the SE of the predicted ΔΔQTcF from the prespecified assay sensitivity was larger.

Reviewer's comment: *The reviewer's analyses results are similar to the sponsor's results. Because assay sensitivity could be established with the by-timepoint analysis and there was no negative bias in the QT measurement, the reviewers agree that assay sensitivity is established in this study.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

Sponsor used QTc population for categorical analysis. There were no significant outliers per the sponsor's analysis for QTcF (i.e., > 500 msec), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline). But there was one subject who experienced ΔQTcF > 60 msec. Two subjects experienced HR >100 beats/min with 25% increase from baseline HR.

Reviewer's comment: *FDA reviewer's analysis used safety population for categorical analysis and ΔQTcF was calculated subtracting overall mean (across all time points) instead of time-matched mean, which shows that none of the subjects experienced* ΔQTcF *> 60 msec. 3 subjects experienced HR greater than 100 beats/min in lonafarnib 50 mg + ritonavir 100 mg BID group and among them two subjects HR was greater than 25% increase from baseline HR, which is similar to the sponsor's results.*

3.2.3 Exposure-Response Analysis

The relationship between plasma concentrations of LNF and RTV and ΔQTcF was quantified using linear mixed-effects modeling with a full model approach. The full model had ΔQTcF as the dependent variable, time-matched concentrations of LNF and RTV and their interaction as fixed effects, treatment and time as categorical factors, and random intercept and slopes per subject. The model selection procedure was conducted by using AIC and the t-value for the treatment effect-specific intercept estimator. AIC and slope estimates for different models were shown below.

Table 14.2.2.9.A AIC values for all models from concentration-QTc analysis (LNF + RVT analysis) (PK/QTc populations)

				Estimated Slope (*P* value)		
Model	Terms Used in Model	AIC Value	Treatment Effect Estimate (*t*-value)	LNF	RTV	LNF × RTV
1	LNF + RTV + LNF×RTV	9919.9	-4.99 (-1.41)	0.0018 (0.1752)	-0.0071 (0.0046)	0.00000231 (0.0012)
2	LNF + RTV	9914.8	-11.18 (-3.55)	0.0039 (0.0024)	0.00028 (0.8092)	
3	LNF	9923.0	-10.98 (-3.35)	0.0037 (0.0011)		
4	RTV	10022.9	-1.17 (-0.53)		0.0015 (0.1981)	

Models 2 and 3 above were not selected due to significant treatment effect. Model 4 was not selected due to high AIC value. The sponsor's final model included both LNF and RTV concentrations and their interaction term as fixed effect. The upper bounds of the predicted ΔΔQTcF at the geometric mean peak LNF and RTV concentrations at the two studied dose levels were both below 10 msec. The sponsor concluded that an effect on ΔΔQTcF exceeding 10 ms can be excluded up to LNF plasma concentration of 4240 ng/mL.

Reviewer's comment: *Because the study did not include RTV or LNF alone treatment arm and the RTV exposure are similar the two study treatments, it is not possible to assess the effect of the individual components on the QTc interval. The sponsor's final model suggested a negative slope for RTV concentration, which is contradictory to our prior experience with ritonavir. While the sponsor's model reasonably described the observed data in this TQT study, the reviewer does not agree with the sponsor's proposal to use the model for predicting LNF effect in the monotherapy setting.*

3.2.4 Safety Analysis

No SAEs or deaths occurred. In LFN+RTV group, 4 (12.5%) subjects experienced AEs that led to study discontinuation. The non-serious AEs were vomiting, dehydration and nausea.

Subject (b) (6) experienced Grade 2 syncope on Day 10 after treatment with moxifloxacin on Day 1 that was considered by the investigator as probably treatment.

There was 1 reading of ventricular tachycardia. There were no episodes of ventricular or atrial fibrillation. There was 1 reading of atrial fibrillation that was assessed by the PI to be sinus rhythm/sinus tachycardia.

- The ECG reading of 1 of the 3 Day 5, predose ECGs for Subject (b) (6) (Group 2B: placebo/moxifloxacin) was "supraventricular tachycardia premature ventricular complexes or aberrantly conducted complexes no interpretation due to signal problem." After reviewing the ECG, the PI reported artifact and movement, and determined the ECG to be NCS.
- The ECG reading of 1 of the 3 Day 10, predose ECGs for Subject (b) (6) (Group 1: LNF +RTV) was "atrial fibrillation with normal mean ventricular response right axis deviation slight high-lateral repolarization disturbance, consider ischemia, LV overload or aspecific change negative." The PI who reviewed the ECG assessed it as sinus rhythm/sinus tachycardia (data on file) and determined the ECG to be NCS.

Arial fibrillation was not observed at the other 2 predose ECGs, nor was the event reported as an AE.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF for LNF/RTV (Table 2) and moxifloxacin (Table 3). This analysis does not suggest the presence of significant negative treatment bias.

Table 2: Lonafarnib QTcF bias assessment by treatment

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	20884	-0.27 (10.22)	3.03 [2.46 to 3.6]
LNF + RTV	8636	-1.23 (11.25)	4.22 [3.38 to 5.06]
Placebo	12248	0.41 (9.36)	1.24 [0.47 to 2.02]

Table 3: Moxifloxacin QTcF bias assessment by treatment

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	15344	0.34 (9.41)	0.75 [0.08 to 1.43]
Moxifloxacin	3096	0.07 (9.57)	-0.64 [-2.09 to 0.82]
Placebo	12248	0.41 (9.36)	1.24 [0.47 to 2.02]

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. FDA reviewer used Day 5 and Day 10 data for by-time analysis.

The statistical reviewer used linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes a compound

symmetry (cs) covariance matrix to explain the associated between repeated measures (time within subject * treatment).

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 4.

Figure 1: Mean and 90% CI of ΔΔQTcF Time Course (unadjusted CIs).

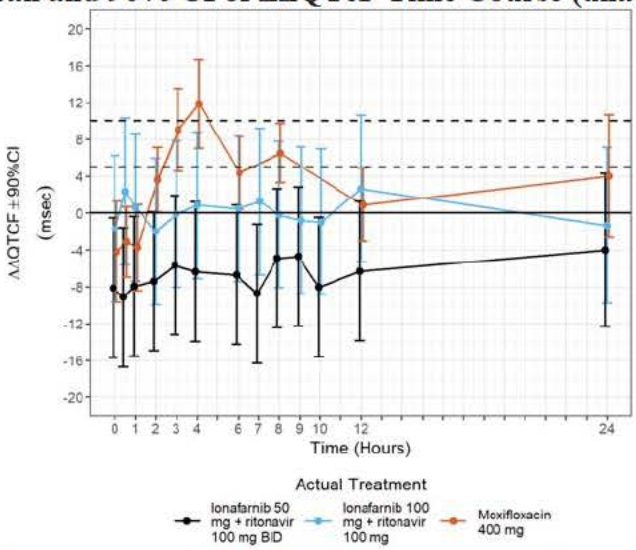


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
LNF 50 mg + RTV 100 mg BID	24.0	-4.0	(-12.3 to 4.3)
LNF 100 mg + RTV 100 mg BID	12.0	2.6	(-5.3 to 10.6)

Reviewer's comment: *Hour 24 had only 9 subjects in lonafarnib low dose arm and 11 subjects in lonafarnib high dose arm. There were 23 subjects in hour 12 in lonafarnib high dose arm.*

4.3.1.1 Assay sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure response analysis - see section 4.5.1.1 for details.

Statistical reviewer also performed by-time analysis for moxifloxacin arm using linear mixed model. One subject (USUBJID: (b) (6)) was excluded from the assay sensitivity analysis due to missing concentration data. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period. The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 5).

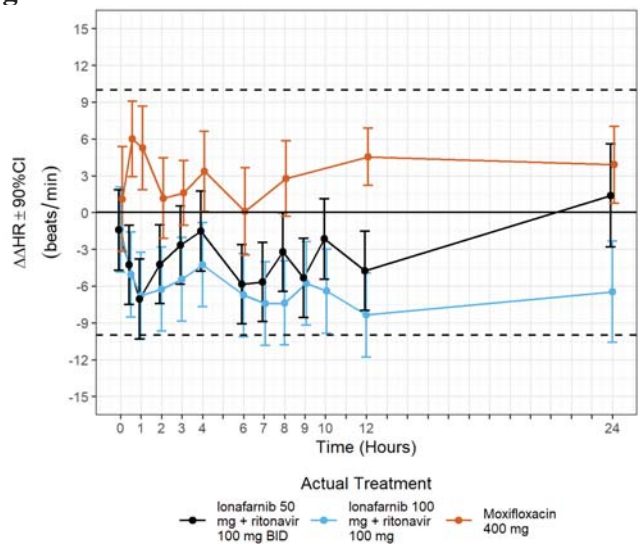
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTc

Actual Treatment	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400mg	4.0	11.8	(7.0 to 16.7)	(5.1 to 18.6)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

Figure 2: Mean and 90% CI of ΔΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups. The maximum ΔΔPR values by treatment are shown in Table 6.

Figure 3: Mean and 90% CI of ΔΔPR Time Course

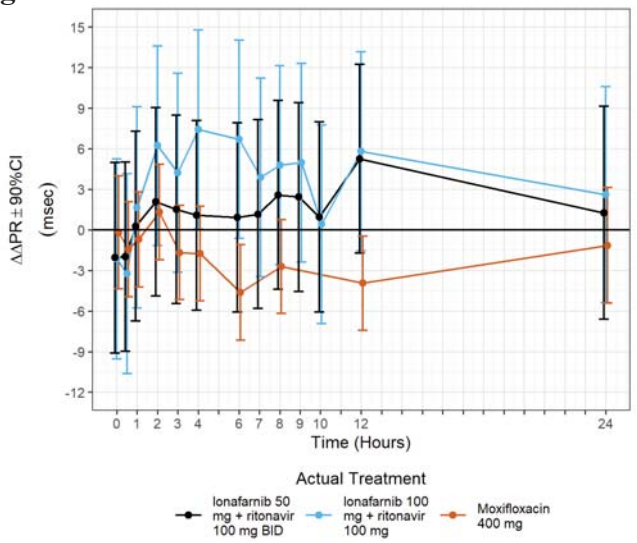


Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔPR

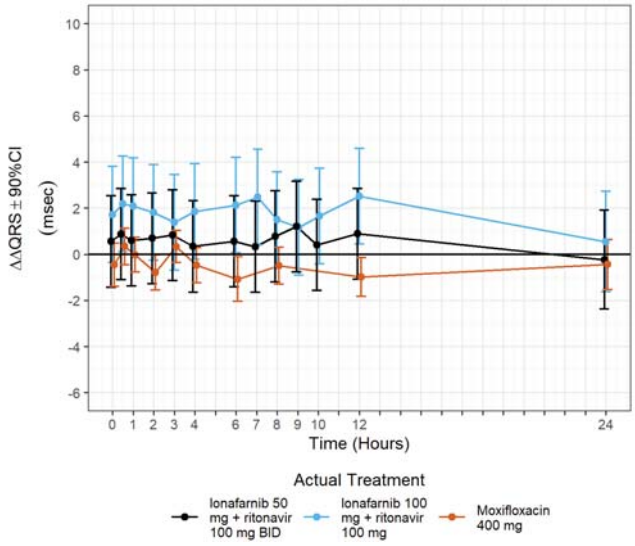
Actual Treatment	Time (Hours)	ΔΔPR (msec)	90.0% CI (msec)
LNF 50 mg + RTV 100 mg BID	12.0	5.3	(-1.7 to 12.2)
LNF 100 mg + RTV 100 mg BID	4.0	7.4	(0.1 to 14.8)

Reviewer's comment: *By-time analysis shows PR prolongation in both dose levels of lonafarnib combined with ritonavir.*

4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. Categorical analysis included data from Day 1, Day 5 and Day 10.

4.4.1 QTc

None of the subjects experienced QTcF greater than 500 msec or ΔQTcF, change from baseline, greater than 60 msec in two different combinations of lonafarnib and ritonavir.

4.4.2 HR

Three subjects experienced HR greater than 100 beats/min in lonafarnib 50 mg + ritonavir 100 mg BID group.

Table 7: Categorical Analysis for HR (maximum)

	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
Actual Treatment	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
LNF 50 mg + RTV 100 mg BID	32	627	29 (90.6%)	624 (99.5%)	3 (9.4%)	3 (0.5%)

	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
Actual Treatment	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
LNF 100 mg + RTV 100 mg BID	27	281	27 (100.0%)	281 (100.0%)	0 (0%)	0 (0%)
Placebo	32	895	29 (90.6%)	892 (99.7%)	3 (9.4%)	3 (0.3%)

4.4.3 PR

None of the subjects experienced PR greater than 220 msec with 25% increase from baseline in two different combinations of lonafarnib and ritonavir.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec with 25% increase from baseline in two different combinations of lonafarnib and ritonavir.

4.5 Exposure-Response Analysis

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK. Because ritonavir concentration in this study (Cmax <2 ug/mL) is substantially lower than that was observed in the previous IRT review (Cmax: 19.9 ug/mL), the reviewer did not expect QT prolonging effect by RTV and default to the analysis of LNF only.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔΔQTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of ΔΔHR and suggested an absence of significant ΔΔHR changes.

Figure 5 evaluates the time-course of drug-concentration and ΔΔQTc. RTV PK profiles were overlapping on both days. Based on prior experience with RTV, the effect of RTV on QTc interval is expected to be minimal at the studied dose level. Therefore, the reviewer's analysis will focus on LNF. There was dose-dependent increase in LNF exposure and the PK profiles show low fluctuation on both days. Similar to LNF PK profiles, there were clear separation in ΔΔQTc time profiles on the two study days. As ΔΔQTc time profiles were fairly flat on both days, there does not appear to be signs for significant hysteresis.

Figure 6 shows the relationship between drug concentration and ΔQTc and generally supports the use of a linear model despite of deviation from linearity at the very high concentration range (<3%).

Figure 5: Time course of drug concentration (top) and QTc (bottom)

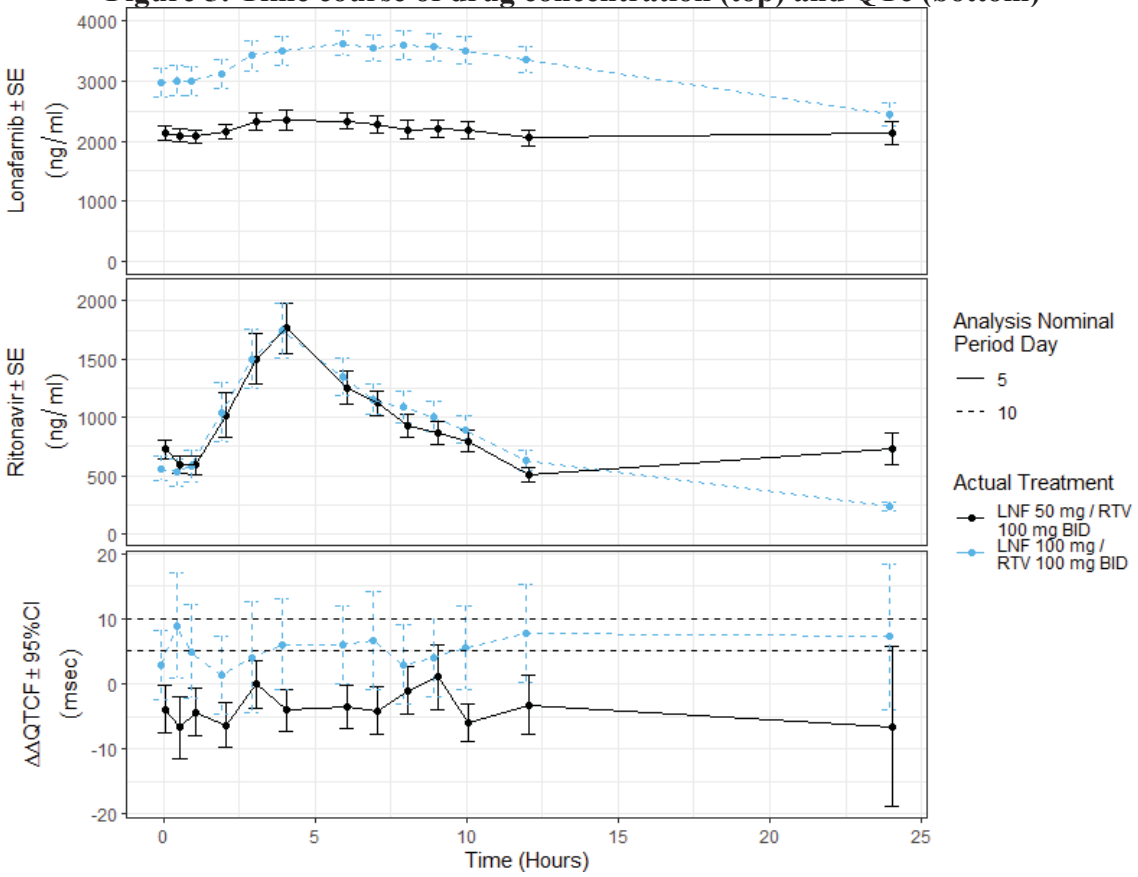
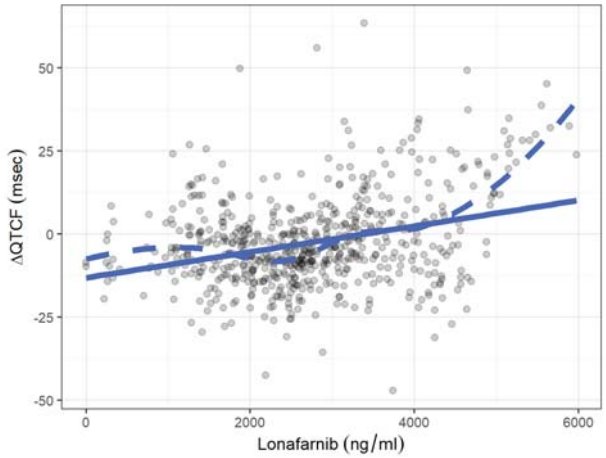


Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model recommended in the scientific white paper was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 8. Note that the model suggested a statistically significant intercept which is not biologically plausible and it not consistent with the primary model assumption (i.e. no effect from RTV). The model cannot be used to predict the effect of LNF on the QTc interval in the monotherapy setting.

Figure 7: Goodness-of-fit plot for QTc

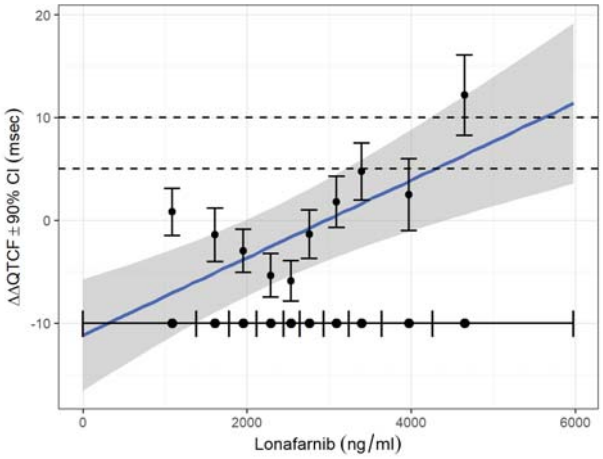


Table 8: Predictions from concentration-QTc model

Actual Treatment	Lonafarnib (ng/ml)	ΔΔQTCF (msec)	90.0% CI (msec)
LNF 50 mg + RTV 100 mg BID	2,427.1	-2.0	(-5.8 to 1.7)
LNF 50 mg + RTV 100 mg BID	3,513.4	2.1	(-2.3 to 6.5)

4.5.1.1 Assay sensitivity

The time-course of moxifloxacin-concentration and ΔΔQTc is shown in Figure 8. The goodness-of-fit plot using the prespecified model in the scientific white paper is shown in Figure 8 and the predicted QTc at the geometric mean Cmax is listed in Table 9. The estimated slope (3.42 msec per ug/mL) is not statistically significant at p=0.05 level. After removing the random effect on slope, the estimated slope became the only significant fixed effect in the model (3.1 msec per ug/mL, p=0.009). The predicted ΔΔQTCF is 7.5 msec (90% CI: 5.3-9.7 msec).

Figure 8. Time course of moxifloxacin concentration (top) and QTc (bottom)

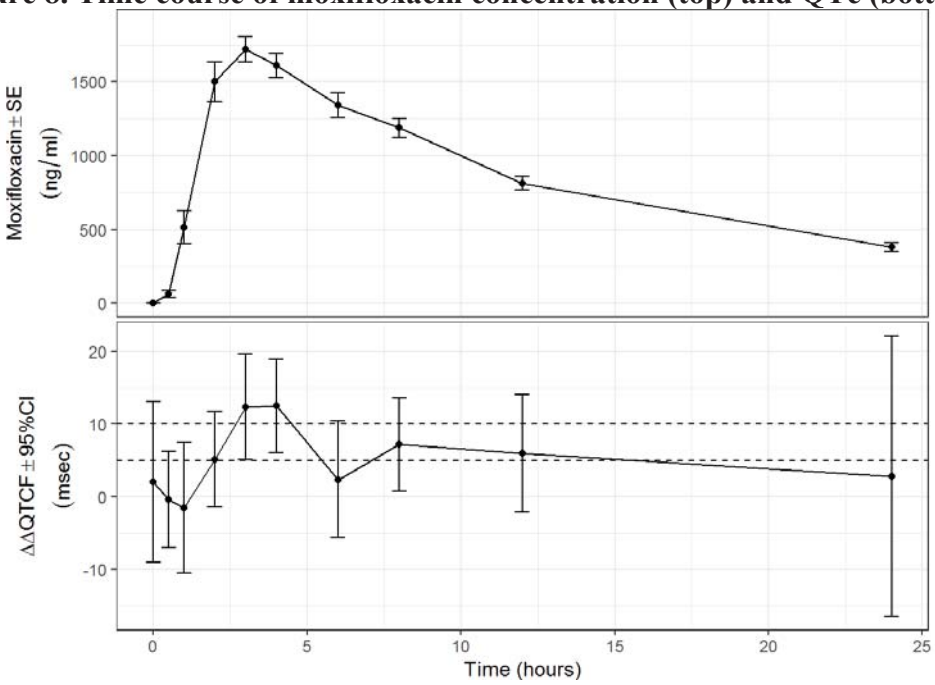


Figure 9: Goodness-of-fit plot for ΔΔQTc for moxifloxacin

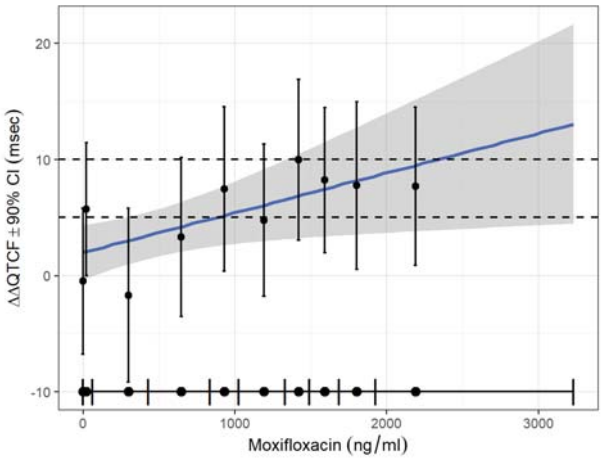


Table 9: Predictions from concentration-QTc model for moxifloxacin

Actual Treatment	Moxifloxacin (ng/ml)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1,697.3	7.8	(3.5 to 12.1)

In additional analyses when data from 5-, 7-, 9-, 10-hour was added back, the results are similar. The prespecified model prediction was associated with larger variability in prediction and failed to establish assay sensitivity, while the model without random effect on the slope met the criteria of assay sensitivity.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAN ZHENG
06/19/2020 11:34:33 AM

FERDOUSE BEGUM
06/19/2020 11:47:38 AM

DALONG HUANG
06/19/2020 11:56:33 AM

JOSE VICENTE RUIZ
06/19/2020 12:00:56 PM

MICHAEL Y LI
06/19/2020 01:13:22 PM

CHRISTINE E GARNETT
06/19/2020 02:08:51 PM