CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214094Orig1s000

OTHER REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 3, 2020

TO: Assessment #1 of NDA 214094 Quality Assessment - Labeling

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II
Lawrence Perez, Ph.D.
Chemistry Reviewer, OPQ/ONDP/DNDAPI

THROUGH Wendy Wilson, Ph.D.
Division Director (Acting Chief, Branch 4), OPQ/ONDP/DNDP II

SUBJECT: **Final Recommendation on Labeling/Labels and (b) (4) Assessment**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 22-May-2020, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see N214094 Labeling R01, Section 3.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0033, eCTD-0037, eCTD-0038, and eCTD-0040. In addition, (b) (4) risk assessment submitted in eCTD-0035 was evaluated and concluded to be low risk of contamination.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC labeling/label perspective.

Assessment Notes

Labeling deficiencies from Quality Assessment were identified in Assessment Cycle #1 dated 22-May-2020 (see N214094 Labeling R01, Section 3.0). Subsequently, labeling amendments were submitted. In addition, (b) (4) risk assessment was submitted in eCTD-0035. These amendments, as listed below, are the subject of this addendum. This addendum was written by Jane Chang, except for Section 3.1 (b) (4) Assessment for Drug Substance (page 20), which was written by Drug Substance Assessor, Lawrence Perez.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Assessors
eCTD-0033 (SDN-34)	08/26/2020	Jane Chang
eCTD-0035 (SDN-36)	09/10/2020	Lawrence Perez, Jane Chang
eCTD-0037 (SDN-38)	09/24/2020	Jane Chang
eCTD-0038 (SDN-39)	10/09/2020	Jane Chang
eCTD-0040 (SDN-41)	10/30/2020	Jane Chang

1.0 PRESCRIBING INFORMATION

The information provided in eCTD-0040 dated 10/30/2020 is summarized below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1) TITLE

ORLADEYO™ (berotralstat) capsules, for oral use
Initial U.S. Approval: 20YY

2) DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg, 110 mg

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	ORLADEYO™ (berotralstat) capsules	**Acceptable**
Dosage form, route of administration	capsules, oral	**Acceptable**
Initial U.S. Approval	20YY	**Acceptable** The drug substance is an NME. The year this drug is approved will be listed.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Capsules: 150 mg, 110 mg	**Acceptable**

Conclusion: Satisfactory

Information in HIGHLIGHTS section meets the regulatory requirements.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 3: DOSAGE FORMS AND STRENGTHS

Capsules:

- 150 mg: a white opaque body with a black imprint "150" and a light blue opaque cap with a black imprint "BCX".
- 110 mg: light blue opaque capsules with a white imprint "110" on body and a white imprint "BCX" on cap.

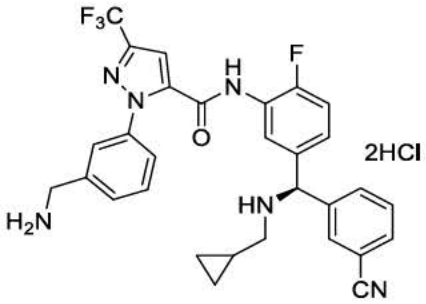
Item	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	capsules	**Acceptable**
Strengths: in metric system	150 mg, 110 mg	**Acceptable**
Active moiety expression of strength	Strength is based on free base content (150 mg and 110 mg).	**Acceptable**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	150 mg: a white opaque body with a black imprint "150" and a light blue opaque cap with a black imprint "BCX" 110 mg: light blue opaque capsules with a white imprint "110" on body and a white imprint "BCX" on cap	**Acceptable**

Conclusion: **Satisfactory**

Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.2 Section 11: DESCRIPTION

ORLADEYO (berotralstat) capsules is a plasma kallikrein inhibitor. Berotralstat is presented as the dihydrochloride salt with the chemical name 1-[3-(aminomethyl)phenyl]-*N*-(5-{(*R*)-(3-cyanophenyl)[(cyclopropylmethyl)amino]methyl}-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride. The chemical structure is:



Berotralstat dihydrochloride is a white to off-white powder that is soluble in water at pH ≤ 4. The molecular formula is $C_{30}H_{26}F_4N_6O \cdot 2HCl$ and the molecular weight is 635.49 (dihydrochloride).

ORLADEYO is supplied as 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride) and 110 mg (equivalent to 124.2 mg berotralstat dihydrochloride) hard gelatin capsules for oral administration. Each capsule contains the active ingredient berotralstat dihydrochloride and the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and pregelatinized starch.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	ORLADEYO (berotralstat) capsules	**Acceptable**
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Capsules, oral	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	150 mg: equivalent to 169.4 mg berotralstat dihydrochloride 110 mg: equivalent to 124.2 mg berotralstat dihydrochloride	**Acceptable**
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	colloidal silicon dioxide, crospovidone, and magnesium stearate, and pregelatinized starch	**Acceptable**
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	a plasma kallikrein inhibitor	**Acceptable** Per Established Pharmacologic Class (EPC) terms in eLIST, there is no established pharmacological/ therapeutic

		class for berotralstat. This is likely due to the NME status of berotralstat.
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	1-[3-(aminomethyl)phenyl]-*N*-(5-{(*R*)-(3-cyanophenyl)[(cyclopropylmethyl)amino]methyl}-2-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide dihydrochloride	**Acceptable**
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	Berotralstat dihydrochloride is soluble in water at pH ≤ 4.	**Acceptable**
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

Conclusion: **Satisfactory**

The issue regarding the dosage form "capsules" in the proprietary and established names, which was deleted in eCTD-0038, i.e., ORLADEYO (berotralstat), has been corrected in eCTD-0040. Information in DESCRIPTION submitted in eCTD-0040 as shown above meets the regulatory requirements.

1.2.3 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

ORLADEYO capsules:

- 150 mg: a white opaque body with a black imprint "150" and a light blue opaque cap with a black imprint "BCX". NDC 72769-101-01.
- 110 mg: light blue opaque capsules with a white imprint "110" on body and a white imprint "BCX" on cap. NDC 72769-102-01.
- A 28-day supply of ORLADEYO is provided in a carton containing four child-resistant shellpaks, each containing a 7-capsule blister card.
- Each carton contains a tamper evident seal.
- Do not use if tamper evident seal is broken or missing.

Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59ºF to 86ºF) [*see USP Controlled Room Temperature*].

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	capsules	**Acceptable**
Strength of dosage form in metric system	150 mg, 110 mg	**Acceptable**
Available units (e.g., bottles of 100 tablets)	a carton containing four shellpaks, each containing a 7-capsule blister card	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	150 mg: a white opaque body with a black imprint "150" and a light blue opaque cap with a black imprint "BCX" 110 mg: light blue opaque capsules with a white imprint "110" on body and a white imprint "BCX" on cap	**Acceptable**
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*	**Acceptable**
Include information about child-resistant packaging (if manufacturer choose to include)	child-resistant shellpaks	**Acceptable** In 3.2.P.7, the applicant states that the shellpak meets the Consumer Product Safety Commission's (CPSC) standards under 16 CFR 1700.

Conclusion: Satisfactory

Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.4 Section 17: PATIENT COUNSELING INFORMATION

Manufactured for:
BioCryst Pharmaceuticals, Inc.
Durham, NC 27703

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Manufactured for: BioCryst Pharmaceuticals, Inc. Durham, NC 27703	**Acceptable**

Conclusion: Satisfactory

The information in Section 17 meets the regulatory expectation.

2.0 CARTON AND CONTAINER LABELS

The following issues were identified in Assessment Cycle #1 dated 22-May-2020.

1. Revise the proprietary name, established name, and strength as below for the blister card, shellpack, and carton labels.

   Orladeyo
   (berotralstat) capsules 150 mg

   Please note strength should not be in the middle of the proprietary name and established name. Capsules (i.e., the plural form) should be used. Proprietary name should be capitalized.

   Revise the proprietary name, established name, and strength for the 110 mg capsules accordingly for the blister card, shellpack, and carton labels.

2. Add the name of the manufacturer, packer, or distributor to the blister card label.
3. Revise the salt equivalence statement from "equivalent to (b) (4) mg Berotralstat dihydrochloride" to "equivalent to 169.4 mg Berotralstat dihydrochloride" for the shellpack and carton labels.
4. Revise the statement from "(b) (4)" to "Recommended Dosage: See Prescribing Information" for the shellpack and carton labels.

After completion of Labeling Assessment Cycle #1, OND recommended adding the 110 mg strength for marketing. Therefore, the following comments were conveyed to the applicant on 08/11/2020:

1. Revise the proprietary name, established name, and strength for the 150 mg capsules as below for the blister card, shellpack, and carton labels.

   Orladeyo
   (berotralstat) capsules 150 mg

   Please note strength should not be in the middle of the proprietary name and established name. Capsules (i.e., the plural form) should be used. Proprietary name should be capitalized.

   Revise the proprietary name, established name, and strength for the 110 mg capsules accordingly for the blister card, shellpack, and carton labels.

2. Add the name of the manufacturer, packer, or distributor to the blister card label for both strengths.

3. For the 150 mg capsules, revise the salt equivalence statement from "equivalent to (b) (4) mg berotralstat dihydrochloride" to "equivalent to 169.4 mg berotralstat dihydrochloride" for the shellpack and carton labels.

   For the 110 mg capsules, revise the salt equivalence statement from "equivalent to (b) (4) mg berotralstat dihydrochloride" to "equivalent to 124.3 mg berotralstat dihydrochloride" for the shellpack and carton labels.

4. Revise the statement from "(b) (4)" to "Recommended Dosage: See Prescribing Information" for the shellpack and carton labels for both strengths.

2.1 CONTAINER LABEL

The blister card labels provided in eCTD-0033 dated 08/26/2020 are shown below.

The name of the manufacturer, distributor, or packager was not to the blister card labels. The applicant reasoned that the blister is part of an integrated shellpack design. Therefore, a limited set of identifying information was proposed for the blister card labels. Furthermore, the space above the capsules is very limited.

The applicant stated that they have produced approximately (b) (4) blisters (equivalent to ~ (b) (4) patient years of dosing) with the labeling previously submitted. They will make the requested changes in Request 1 above at the next printing. However, they request the Agency's agreement to use the already produced blisters for initial commercialization of the product. The shellpack to

be used for initial commercialization of the product will have all of the requested product information.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) capsules 150 mg orladeyo (berotralstat) capsules 110 mg	**Acceptable**
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Not provided	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Names of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Bar code [21CFR 201.25(c)(2)]	Not provided	**Acceptable**

		Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Not provided	**Acceptable** Not required per 21 CFR 201.10(i)(1) for small drug container labels.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Not provided	**Unacceptable**

Conclusion: **Unsatisfactory**

The issue regarding the established name identified in Assessment Cycle #1 dated 22-May-2020 has been addressed. The applicant stated that they preferred to keep the stylized "o" in the proprietary name at the same size as the rest of the name. Several recently approved drugs are with the proprietary name comprised of letters of the same size (see 1.14.1.5, page 3). Based on these precedents, it is acceptable that the proprietary name uses the same size letters.

The applicant's response for not including the manufacturer, distributor, or packager on the blister card labels is not acceptable. This information is required for container label per 21 CFR 201.10(i)(1).

From CMC perspective, it is acceptable to use the previous blister card label that have already been produced for the initial commercialization since the desired labeling information will be provided on the shellpack and carton labels. The final decision on the acceptability for the use of the previous blister card label is deferred to DMEPA and OND.

The following issue should be conveyed to the applicant:

1. Your proposal for not including the name of the manufacturer, packer, or distributor to the blister card labels is not acceptable. Per 21 CFR 201.10(i)(1), the name of the manufacturer, packer, or distributor should be included in the container label that is too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1) (A)(ii) and (B) of the act. Please include the manufacturer, packer, or distributor information to the blister card labels for both strengths.

In eCTD-0037, updated blister card labels, as shown below, were provided.

Conclusion: Satisfactory

The applicant has included the name of the distributor to the blister card labels. The strength is included in each blister per DMEPA's recommendation. All other required information, i.e., proprietary name, established name, strength, lot number, and expiration date, is included.

2.2 SHELLPACK LABEL

The information provided in eCTD-0033 dated 08/26/2020 is shown below.

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Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) capsules 150 mg orladeyo (berotralstat) capsules 110 mg	**Acceptable**
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For ORAL USE ONLY	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each capsule contains: berotralstat 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride). Each capsule contains: berotralstat 110 mg (equivalent to 124.3 mg berotralstat dihydrochloride).	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]&	Seven (7) 150 mg capsules Seven (7) 110 mg capsules	**Acceptable**
Names of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	150 mg: NDC (b) (4) 110 mg: NDC	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	Store capsules at room temperature, 20°C to 25°C (68°F to 77°F)	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended dosage: One capsule once per day. See Prescribing Information.	**Acceptable**

Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured For: BioCryst Pharmaceuticals, Inc. Durham, NC 27703 Phone: 1-833-633-2279 www.orladeyo.com	**Acceptable**
And others, if space is available	To Open: Step 1: Press and hold button gently Step 2: Pull out medication card	**Acceptable**

Conclusion: Satisfactory

Information on the shellpack labels meet the regulatory requirements.

In eCTD-0037, updated shellpack labels, as shown below, were provided.

(b) (4)

Conclusion: Satisfactory

Changes to the updated shellpack labels include larger and bold font for the middle three-digit NDC number (101 and 102) as well as "Recommended Dosage: See prescribing information". The updated shellpack labels remain adequate.

2.3 CARTON LABEL

The information provided in eCTD-0033 dated 08/26/2020 is shown below.

(b) (4)

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	orladeyo (berotralstat) capsules 150 mg orladeyo (berotralstat) capsules 110 mg	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For ORAL USE ONLY	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each capsule contains: berotralstat 150 mg (equivalent to 169.4 m mg berotralstat dihydrochloride). Each capsule contains: berotralstat 110 mg equivalent to 124.3 mg berotralstat dihydrochloride).	**Unacceptable** Replace "169.4 m mg" with "169.4 mg" for the 150 mg strength label. Add "(" in front of "equivalent to 124.3 mg berotralstat dihydrochloride)" for the 110 mg strength label.

Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Carton contains 4 shellpacks of 7 capsules each (28 day supply)	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Acceptable** Names of inactive ingredients is not required for oral drugs.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided on the main panel, upper right corner	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Provided on the main panel, upper left corner. 150 mg: NDC (b) (4) 110 mg: NDC	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided on the side panel	**Acceptable**
Storage conditions	Store capsules at room temperature, 20°C to 25°C (68°F to 77°F)	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]****	Space allocated on the side panel	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: One capsule once per day. See Prescribing Information.	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Manufactured For: BioCryst Pharmaceuticals, Inc. Durham, NC 27703 Phone: 1-833-633-2279 www.orladeyo.com	**Acceptable**

Conclusion: Unsatisfactory

The following issue should be conveyed to the applicant:

1. Please address the following issues regarding the salt equivalence statements for carton labels:
   a Replace "169.4 m mg" with "169.4 mg" for the 150 mg strength label.
   b Left parenthesis is missing for the 110 mg strength label. Add "(" in front of "equivalent to 124.3 mg berotralstat dihydrochloride)" for the 110 mg strength label.

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(b) (4)

Conclusion: Satisfactory

The revisions are summarized below.

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Active moiety expression of strength with equivalence statement (if applicable)	Each capsule contains: berotralstat 150 mg (equivalent to 169.4 mg berotralstat dihydrochloride). Each capsule contains: berotralstat 110 mg (equivalent to 124.3 mg berotralstat dihydrochloride).	**Acceptable**
NDC number	Provided on the main panel, upper left corner. 150 mg: NDC (b) (4) 110 mg: NDC	**Acceptable**
Net content	28 capsules Contains a 28-dau supply 4 shellpacks each containing a 7-capsule blister card	**Acceptable**

Adequate directions for use or "Recommended Dosage: See Prescribing Information"	Recommended Dosage: See prescribing information.	**Acceptable**

The issues identified previously have been addressed adequately.

3.0 (b) (4) ASSESSMENT

In eCTD-0035, the applicant provided (b) (4) assessment for berotralstat, which covered drug substance starting materials and manufacturing process, drug product manufacturing process (including excipients) and packaging.

3.1 DRUG SUBSTANCE

This section was written by the Drug Substance Assessor, Lawrence Perez.

The NDA applicant BioCryst Pharmaceuticals, Inc. has conducted a risk assessment for the potential presence of (b) (4) impurities in the drug substance berotralstat dihydrochloride in accordance with the published guidance (b) (4) The risk assessment for the drug substance includes the following: (i) starting material, (ii) manufacturing process for the drug substance, and (iii) possible contamination at the drug substance manufacturer(s).

For the starting materials (b) (4), no risk of formation of (b) (4) was identified because (b) (4) . For the starting material (b) (4) , a possible risk for (b) (4) formation. After examination of the (b) (4), the likelihood for the formation of a (b) (4) impurity is low, and thus the risk for (b) (4) formation in the manufacturing of the proposed registered starting material.

A risk assessment was conducted by the drug substance manufacturers (b) (4) for possible (b) (4) contamination and the results have identified no risk in the manufacturing process, (b) (4)), and in the drug substance storage, packaging and stability.

Assessment: Satisfactory

No risk of contamination with (b) (4) was identified for the drug substance berotralstat dihydrochloride and additional testing is not needed at this time.

3.2 DRUG PRODUCT

This section was written by the Drug product Assessor, Jane Chang. The risk assessment pertaining to drug product is summarized below.

- Excipients: Sources of [redacted] were evaluated and no risk was identified. Potential low levels of [redacted] may be present in [redacted] confirmed that no [redacted] was detected in representative lots.
- Manufacturing process (including equipment, packaging materials): No risk identified. No [redacted] are used in the process. Bulk packaging consists of [redacted] The manufacturers of the blister packaging materials confirm there is no addition of [redacted] in the manufacturing process of the materials, and no risk of cross-contamination with any [redacted]

The applicant concluded that no risk of contamination with [redacted] was identified for berotralstat, therefore confirmatory testing is not required.

Assessment: Satisfactory

The applicant's risk assessment on the drug product covers the area recommended in the FDA guidance entitled [redacted] (file:///C:/Users/CHANGJa/Desktop/Current/Review%20Tool/FDA%20Guidance/[redacted] es%20Sep%202020.pdf), including the risk of [redacted] impurities that may arise from the drug product.

Regarding the drug product, the drug substance contains [redacted]. The applicant performed risk assessment on individual excipient, e.g., whether a [redacted] is present. [redacted] Testing of representative lots of [redacted] confirmed that none of [redacted] impurities was detected. The drug product manufacturing process does not use any [redacted]. The drug product packaging materials do not involve [redacted] in the manufacturing process. The applicant's risk assessment indicates low risk of contamination with [redacted] Therefore, it is acceptable that no confirmatory testing is proposed for drug product.

Jane Chang

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Date: 11/04/2020 01:42:48PM
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Lawrence Perez

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Date: 11/04/2020 02:18:02PM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 11/04/2020 04:38:43PM
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Comments: Concurrence on behalf of DS and DP disciplines

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/s/

CRAIG M BERTHA
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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:	September 29, 2020
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214094
Product Name and Strength:	Orladeyo (berotralstat) Capsules, 110 mcg and 150 mg
Applicant/Sponsor Name:	Biocryst Pharmaceuticals Inc.
OSE RCM #:	2019-2512-1
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 24, 2020 for Orladeyo. Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Orladeyo (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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Owens, L. Label and Labeling Review for Orladeyo (NDA 214094). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 04. RCM No.: 2019-2512.

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/s/

LISSA C OWENS
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IDALIA E RYCHLIK
09/29/2020 10:57:15 AM

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:	September 24, 2020
To:	Phuong Nina Ton, PharmD Senior Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ORLADEYO (berotralstat)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 214094
Applicant:	BioCryst Pharmaceuticals

1 INTRODUCTION

On December 3, 2019, BioCryst Pharmaceuticals submitted for the Agency's review an original New Drug Application (NDA) 214094 for ORLADEYO (berotralstat) capsules, for oral use. This NDA is proposing an indication for prophylaxis treatment to prevent attacks of hereditary angioedema in patients 12 years of age and older.

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 Pulmonology, Allergy, and Critical Care (DPACC) on January 2, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ORLADEYO (berotralstat) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ORLADEYO (berotralstat) PPI received on December 3, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 2, 2020.
- Draft ORLADEYO (berotralstat) Prescribing Information (PI) received on December 3, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 2, 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 document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is 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 is 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.

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SHARON W WILLIAMS
09/24/2020 09:49:45 AM

LASHAWN M GRIFFITHS
09/24/2020 10:33:09 AM

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

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

Memorandum

Date: September 14, 2020

To: Shaz Siddiqi, Clinical Reviewer
Division of Pulmonary, Allergy, and Critical Care (DPACC)

Nina Ton, Regulatory Project Manager, (DPACC)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for ORLADEYO™ (berotralstat) capsules, for oral use

NDA: 214094

In response to DPACC's consult request dated January 2, 2020, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for ORLADEYO™ (berotralstat) capsules, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DPACC (Nina Ton) on September 2, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

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 26, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
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Clinical Inspection Summary

Date	September 14, 2020
From	Tina Chang, M.D., Reviewer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shaz Siddiqi, M.D., Medical Officer Stacy Chin, M.D., Clinical Team Leader Nina Phuong Ton, PharmD, Regulatory Project Manager Division of Pulmonology, Allergy, and Critical Care Products (DPACC)
NDA/BLA #	214094
Applicant	BioCryst Pharmaceuticals, Inc.
Drug	Orladeyo (berotralstat)
NME (Yes/No)	Yes
Therapeutic Classification	small-molecule inhibitor of human plasma kallikrein
Proposed Indication(s)	Prophylaxis to prevent attacks of hereditary angioedema in patients 12 years and older
Consultation Request Date	January 9, 2020
Summary Goal Date	July 3, 2020 (original); November 3, 2020 (extension)
Action Goal Date	December 3, 2020
PDUFA Date	December 3, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators, Dr. Douglas Johnston (Site# 033) and Dr. William Lumry (Site# 035), were inspected for one Phase 3 study BCX7353-302 (Part 1).

The study conduct and data derived from these two clinical investigator sites, based on the results of the inspections, are considered acceptable in support of this application.

II. BACKGROUND

Orladeyo (berotralstat) is a small-molecule inhibitor of human plasma kallikrein administered as an oral capsule for the prevention of attacks in hereditary angioedema (HAE) in adolescent and adult patients.

The sponsor conducted one Phase 3 study (BCX7353-302), to evaluate the efficacy of berotralstat for prophylaxis treatment to prevent attacks of hereditary angioedema (HAE) in subjects 12 years of age and older. Hereditary angioedema is characterized by clinical recurrent episodes of angioedema of the skin, pharynx, larynx, gastrointestinal tract, genitals, and extremities. Study BCX7353-302 is a two-part study. Part 1 was the placebo-controlled portion of the study that encompassed the primary analysis for efficacy, and Part 2 was an open uncontrolled portion designed to evaluate safety and tolerability. Parts 1 and 2 were conducted in sequence with Part 2 conducted as a continuous roll-over from Part 1.

Study BCX7353-302, Part 1

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Two Dose Levels of BCX7353 as an Oral Treatment for the Prevention of Attacks in Subjects with Hereditary Angioedema

This was a Phase 3 multi-center, randomized, double-blinded placebo-controlled study of subjects 12 years of age and older with hereditary angioedema (HAE) to determine the efficacy of prophylactic berotralstat 110 and 150 mg administered orally and daily for 24 weeks. Subjects were randomized in a 1:1:1 ratio into 1 of 3 treatment groups:

- Group 1: Berotralstat 110 mg, n=41
- Group 2: Berotralstat 150 mg, n=40
- Group 3: Placebo, n=40

The primary objective of the study was to determine the efficacy of prophylactic berotralstat 110 mg and 150 mg administered once daily for 24 weeks compared to placebo with hereditary andgioedema.

The primary efficacy endpoint of the study was the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period.

The study enrolled 121 subjects from 40 sites in 11 countries. The first subject was enrolled on 14 March 2018 and the last patient completed Part 1 of the study on 10 April 2019.

Rationale for Site Selection

Dr. Douglas Johnston (Site# 033) and Dr. William Lumry (Site# 035) were selected for routine clinical site inspections. Both sites were chosen for having a large enrollment and higher response rates on the primary efficacy endpoint compared to other sites in the United States. Dr. William Lumry also had a history of a complaint in November 2002 resulting in a For Cause inspection which was conducted on 8/5-8/7/2003. A form FDA 483 was issued for failure to adhere to protocol. Dr. Lumry was last inspected from 5/31/2016 to 6/9/2016 and classified as VAI. Dr. Lumry was cited for the following deficiencies: 1) An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan, 2) Failure to prepare or maintain accurate case histories with observation and data

pertinent to the investigation.

III. RESULTS:

1. **Dr. Douglas Johnston, Site# 033 (8045 Providence Rd, Ste 300, Charlotte, NC 28277; Inspection dates: July 28 – 30, 2020.)**

   For study BCX7353-302, this site screened 10 subjects and enrolled 9 subjects. Among the 9 enrolled subjects, 6 subjects completed Part 1 of the study. Records for 9 enrolled subjects were reviewed during the inspection. Consent documents were reviewed for all 10 consented subjects.

   The inspection evaluated the following: regulatory records, training, investigational product (IP) accountability, informed consent, review of subject records including inclusion/exclusion criteria, adherence to protocol, adverse event reporting, exposure to IP, comparison of source records to data listings and verification of primary and secondary endpoints.

   The primary efficacy endpoint was verifiable. There was one unreported adverse event which was a common cold for Subject (b) (6). Otherwise, there was no under-reporting of adverse events.

   At the conclusion of the inspection, the following items were discussed with the clinical investigator:

   - Subject (b) (6), who was assigned to placebo group, experienced a common cold of moderate severity from (b) (6) and this adverse event was not recorded in the eCRF. Subject (b) (6)'s common cold was treated with acetaminophen, dextromethorphan HBr and Phenylephrine HCI, and these concomitant medications were not recorded in the eCRF.

     Reviewer's comment: This was an isolated incident and not reported as a protocol deviation in the study. Subject (b) (6) was assigned to the placebo group and unlikely to change the overall safety profile of the product.

   - Four subjects (Subjects (b) (6)) were presented with informed consent documents dated (b) (6) and/or assent documents dated (b) (6) instead of the updated versions of the IRB approved documents dated (b) (6) Five subjects (Subjects (b) (6)) were not presented with the updated IRB approved informed consent or assent versions at the earliest visit.

     Reviewer's comment: These events were not reported as protocol deviations. Although Subjects (b) (6) did not sign the

most updated version of the informed consent and/or assent forms, the only difference between the two versions was the addition of a statement regarding reimbursement for travel expenses. These deviations appear unlikely to have impact on the safety or efficacy data of the study.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

2. William Lumry, Site# 035 (10100 N Central Expy, Suite 125, Dallas, TX 75231; Inspection dates: August 3 - 5, 2020.)

The inspection evaluated the following documents: informed consent forms, monitoring logs, delegation logs, enrollment logs, Institutional Review Board correspondence and approvals, sponsor correspondence, adverse events, serious adverse events, case report forms, electronic case report forms, investigational drug accountability records, and source documentation.

For study BCX7353-302, this site screened 9 subjects and enrolled 7 subjects. Among the 7 subjects enrolled in the study, 4 subjects completed the study. All 9 subjects that were screened in the study were reviewed.

The primary efficacy endpoint was verifiable. There was no under-reporting of adverse events noted.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
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:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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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:	September 4, 2020
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214094
Product Name and Strength:	Orladeyo (berotralstat) Capsules, 110 mcg and 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biocryst Pharmaceuticals Inc.
FDA Received Date:	December 3, 2019 and August 26, 2020
OSE RCM #:	2019-2512
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Orladeyo (berotralstat) Capsules, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Orladeyo prescribing information (PI), 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
ISMP Newsletters	C-N/A
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

Table 2 below include the identified medication error issues with the submitted 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 Biocryst Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The strength is presented throughout as 'xx' mg vs 'xx' mg per capsule.	May cause confusion as to how much product is contained in a single unit compared to the total content of the entire blister.	Revise the strength presentation to 110 mg per capsule or 150 mg per capsule.

Table 2. Identified Issues and Recommendations for Biocryst Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Draft Guidance: Container and Carton, April 2013 (lines 586-591) ISMP: Guessing not appropriate Institute for Safe Medication Practices. Guessing not appropriate. ISMP Med Saf Alert Acute Care. 2006;11(9):1-4.	
2.	The strength is not prominent.	May cause product selection errors. Draft Guidance Container and Carton, April 2013 (lines 374-375)	Revise the font color of the proprietary name or revise the color scheme of the strength, so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the same color font for the proprietary name and the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.
Container Label(s)			
1.	The individual blister cells do not contain the strength.	May cause confusion as to how much product is contained in a single unit as compared to the total content of the entire blister card. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformatio	Include the strength on each individual blister cell.

Table 2. Identified Issues and Recommendations for Biocryst Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		n/Guidances/UCM349009.pdf	
2.	The manufacturer, packer, or distributor is not listed.	The manufacturer, packer, or distributor should be present on small labels per 21 CFR 201.10(i) Draft Guidance: Container and Carton, April 2013 (lines 753-757)	Add the manufacturer, packer, or distributor information to the blister label.
Carton Labeling			
1.	The strengths are not clearly differentiated.	Lack of adequate differentiation may contribute to selection errors.	Consider the use of different colors; (b) (4), to provide adequate differentiation between the two different strength carton labels.
2.	The usual dose statement on the carton is currently presented as: "Recommended dosage: (b) (4) See Prescribing Information."	The usual dosage statement should meet 21 CFR 201.55 and maintain consistency with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement, "Recommended dosage: (b) (4) See Prescribing Information" to read "Recommended Dosage: See prescribing information."
3.	The first letter 'o' in the name orladeyo is presented in a different color from the remaining letters of the name.	Depending on the color of the letter, this may cause confusion as the letter may be overlooked if the letter is in a lighter hue than the rest of the name. If presented in a darker hue than the rest of the name, those letters may be overlooked and cause confusion.	Revise the first letter 'o' of the proprietary name to align with the color of the remaining letters of the name.

Table 2. Identified Issues and Recommendations for Biocryst Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The net quantity is not listed on the principal display panel (PDP).	The carton should contain the net quantity of the contents per 21 CFR 201.51	Add the net quantity to the PDP under 'For oral use only' and away from the strength to minimize confusion. See #5 below regarding the format.
5.	The quantity statement does not specify the total number of capsules.	May cause confusion of the total quantity.	Revise the statement (b) (4) to read" 28 tablets Contains a 28-day supply 4 shellpacks each containing a 7-capsule blister card
6.	The middle digits of the NDC numbers are in sequential order.	Assigning sequential numbers for the middle digits is not an effective differentiating feature (i.e. (b) (4) and may lead to selection errors. Draft Guidance: Container and Carton, April 2013 (lines 524-528)	Revise the middle digits of one of the strengths. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: xxxx-XXXX-xx

4 CONCLUSION

Our evaluation of the proposed Orladeyo 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 Applicant. We ask that the Division convey Table 2 in its entirety to Biocryst Pharmaceuticals Inc. 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 3 presents relevant product information for Orladeyo from the SCPI that DPACC submitted on September 2, 2020.

Table 3. Relevant Product Information for Orladeyo	
Initial Approval Date	N/A
Active Ingredient	berotralstat
Indication	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older
Route of Administration	Oral
Dosage Form	Capsules
Strength	110 mg and 150 mg
Dose and Frequency	1 capsule once daily
How Supplied	A 28-day supply of ORLADEYO is provided in a carton containing four child-resistant shellpaks, each containing a 7-capsule blister card
Storage	Store at 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature].

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,[a] along with postmarket medication error data, we reviewed the following Orladeyo labels and labeling submitted by Biocryst Pharmaceuticals Inc.

- Container label(s) received on August 26, 2020
- Carton labeling received on August 26, 2020
- Blistercards received on August 26, 2020
- Prescribing Information (Image not shown) received on September 2, 2020 (SCPI provided by DPACC)

F.2 Label and Labeling Images

Container label(s)

Blister:

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

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214094
Submission Number	001
Submission Date	1/3/2020
Date Consult Received	1/7/2020
Drug Name	Berotralstat
Indication	Prevent attacks of hereditary angioedema in patients 12 years and older
Therapeutic dose	150 mg once daily
Clinical Division	DPARP

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 1/7/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 10/24/2017 under IND-135058 in DARRTS (link);
- Previous IRT review dated 11/08/2018 under IND-135058 in DARRTS (link);
- Previous IRT review dated 06/17/2019 under IND-142879 in DARRTS (link);
- Previous IRT review dated 09/18/2019 under IND-142879 in DARRTS (link);
- Sponsor's clinical study report # BCX7353-101 (SN0000 / SDN001; link);
- Sponsor's clinical study report # BCX7353-106 (SN0000 / SDN001; link);
- Sponsor's QT analysis report # BCX7353-101 (SN0000 / SDN001; link);
- Sponsor's QT analysis report # BCX7353-106 (SN0000 / SDN001; link); and
- Sponsor's proposed product label (SN0000 / SDN001; link).

1 SUMMARY

Berotralstat caused a dose and concentration-dependent increase in the QT interval over the range of doses evaluated in this QT assessment. Berotralstat did not prolong the QT interval to any clinically relevant extent at the peak concentrations with the recommended dose of 150 mg once daily (Day 14). At a dose of 450 mg once daily (Day 14), exposures were ~3-fold higher than achieved at the recommended dose and the mean QTc increased by 16.5 msec (90% upper CI bound of 28.8 msec).

The effect of berotralstat was evaluated in QT study (Study # BCX7353-106) which was a phase-1, randomized, double-blind, placebo-controlled, parallel group, multiple dose study in healthy subjects. The highest dose evaluated was 450 mg (once daily for 14 days), which covers two-times the worst-case exposure scenario (hepatic impairment, section 3.1) and therefore supports waiving the requirement for inclusion of a positive control as per ICH E14 Q&A (R3) 5.1.

The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that berotralstat is associated with significant QTc prolonging effect at the therapeutic doses (refer to section 4.5) – see Table 1 for overall results.

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

ECG Parameter	**Treatment**	**Concentration** (ng/mL)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Berotralstat 150 mg*	158.2	3.4	(0.1 to 6.6)
QTc	Berotralstat 450 mg*	591.0	15.9	(8.3 to 23.5)
QTc	Supra-therapeutic Exposure	240.0	5.7	(2.0 to 9.5)

**Administered orally as once daily for 14 days; For further details on the FDA analysis please see section 4.*

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

The sponsor submitted data from 2 clinical studies conducted in healthy subjects (Studies # BCX7353-101 and BCX7353-106). Study # BCX7353-106 was adequately designed and offered ~2-fold margin over the highest clinically relevant exposures satisfying the requirement of separate positive control. For this purpose, the exposure response analysis using the data from study # BCX7353-106 was utilized for labeling (see Section 3.1.1). Nevertheless, the data from study # BCX7353-101 was also utilized for conducting categorical analysis and safety analysis.

Oral administration of berotralstat was associated with dose- and concentration- dependent increases in the PR interval (see Sections 4.5.2 and 4.3.3). Based on a linear concentration-response relationship, the effect on PR interval was predicted to be 4.4 msec at the therapeutic dose (150 mg once daily for 14 days) and 11.3 msec at the supratherapeutic dose (450 mg once daily for 14 days) evaluated in Study # BCX7353-106. In this study, however, none of the subjects had PR values > 220 ms (see Section 4.4.3).

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology

(b) (4)

At the recommended dose of 150 mg once daily, <TRADENAME> does not prolong the QT interval to any clinically relevant extent. At 3-times the recommended dose, the mean (upper 90% confidence interval) increase in QTcF was 15.9 msec (23.5 msec). The observed increase in QTcF was concentration-dependent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

BioCryst Pharmaceuticals, Inc. is seeking approval for berotralstat (Orladeyo) to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients (NDA-214094 / IND-135058). The product is also being developed for the treatment of angioedema attacks in adult and adolescent patients with hereditary angioedema (IND-142879). Berotralstat (BCX7353, MW: 635.48 dihydrochloride and 562.56 free base) is an inhibitor of human plasma kallikrein. The product is formulated as immediate-release hard gelatin capsule formulation containing 150 mg berotralstat (equivalent to (b) (4) mg of berotralstat dihydrochloride) for oral administration. The proposed dose is 150 mg once daily and the peak concentrations of 158 ± 38 ng/mL (Racc: ~3.25) are expected at steady-state with the proposed therapeutic doses (Day 14; Study # 106). Population pharmacokinetic analyses indicated that exposures of berotralstat are slightly higher in pediatric patients 12 to <18 years of age (≥ 40 kg).

Previously, the IRT reviewed the sponsor's BCX7353-101 study protocol as a potential substitute for a thorough QT study (Dt: 10/24/2017). This was a phase 1, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of BCX7353 in healthy subjects. Subjects received single doses from 10 to 1000 mg and multiple doses from 125 to 500 mg (once daily for 7 days and 350 mg once daily for 14 days). ECGs with time-matched PK samples were collected (in Parts 1 and 2 of the study) at timepoints from pre-dose to 24 hours post-dose, at either 7 days (Part 2: BCX7353 125, 250, 500 mg once daily; or Part 3 Japanese subjects: 250 mg once daily) or 14 days (Part 2: BCX 350 mg once daily) post-dose. The sponsor's exposure-response analysis indicated a positive relationship between BCX7353 concentration and ΔΔQTcF or subinterval ΔΔTpTe. In addition, the sponsor claimed a non-statistically significant negative relationship between BCX7353 concentration and ΔΔJTpc. However, in the absence of final therapeutic dose, the exposures achieved in the study were not considered reflective of steady state exposures due to long half-life (~80 h) of BCX7353.

Subsequently, the sponsor proposed to characterize the QT effects of BCX7353 in healthy subjects. This was a phase 1, randomized, double-blind, placebo-controlled, parallel group, multiple dose, QT study evaluating the effects of BCX7353 on cardiac repolarization in healthy subjects (Study # BCX7353-106). Study included 2 cohorts – cohort 1) therapeutic dose (n=14 + 6 placebo; 150 mg once daily for 14 days; n = 12 + 6 placebo) and cohort 2) supratherapeutic dose (n=14 + 6 placebo; 450 mg once daily for 14 days; n = 12 + 6 placebo). ECGs with time-matched PK samples were collected at predefined timepoints on Day 1 and Day 14. The sponsor selected 450 mg once daily dose as the supratherapeutic dose which was expected to offer ~3.4-fold margin over therapeutic exposures (Cmax,ss: 150 ng/mL vs 517 ng/mL) and ~2.75-fold margin over worst-case scenario due to drug interaction (i.e. cyclosporin; Cmax,ss: 188 ng/mL vs 517 ng/mL). The IRT reviewed the sponsor's study protocol and concluded that the study design and analysis plan is adequate to characterize the QT effects of BCX7353 and offered recommendation on the data modeling and submission (Dt: 11/08/2018). Recently, the sponsor submitted the data for the IRT's review.

Sponsor claims that berotralstat is metabolized by CYP2D6 and CYP3A4 and highlights that it has a low drug interaction potential as a victim drug. Studies also indicate that berotralstat is a P-gp and BCRP substrate. The drug interaction study (Study # 105) indicated that the exposures of berotralstat are increased (Cmax: ~25% and AUCinf: ~70%) upon concomitant administration with cyclosporine (an inhibitor of P-gp and BCRP). The renal impairment study (Study # 107) indicated that the exposures of berotralstat are increased (Cmax: ~39% and AUCinf: no effect) in subjects with severe renal impairment. The hepatic impairment study (Study # 107) indicated that the exposures of berotralstat are increased (Cmax: ~50% and AUCinf: ~38%) in subjects with moderate to severe hepatic impairment. However, the sponsor indicated no dose adjustment during concomitant administration of P-gp inhibitors or in patient with severe renal or hepatic impairment.

The peak concentrations of 158 ng/mL and 473 ng/mL were observed at steady state with 150 mg once daily and 450 mg once daily doses (Day 14, Study # 106; PK/PD dataset). Higher exposures of berotralstat (Cmax: ~1.5-fold) are expected in subjects with severe hepatic impairment and are considered as the highest clinically relevant exposures (Study # 108). Thus, the QT study offers ~2-fold margin over the highest clinically relevant exposure at steady state following maximum therapeutic dose (473 ng/mL vs. 240 ng/mL) and is adequate to waive the requirement of positive control.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to previous IRT reviews dated 10/24/2017 and 11/08/2018 under IND-135058 and dated 06/17/2019 and 09/18/2019 under IND-142879 in DARRTS.

In in vitro ion channel assays, BCX7353 caused a concentration-related inhibition of the potassium channel (hERG) with a 50% inhibitory concentration (IC50) of 0.29 μM, and also inhibited sodium (hNav1.5) and calcium (hCav1.2) channels, with IC50 of 4.79 and 1.29 μM, respectively.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for berotralstat was based on exposure-response analysis, please see section 3.2.3 for additional details. The sponsor performed parametric descriptive statistics for study BCX7353-101 and linear mixed model for study BCX7353-106. However, by-time analysis of study BCX7353-101 and study BCX7353-106 are not interpretable due to small sample size. The reviewer performed non-parametric statistics to show the by-time trends.

Reviewer's comment: *Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not Applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *FDA reviewer's categorical analysis results are similar to the sponsor's analysis results. FDA reviewer could not locate categorical analysis for PR and HR intervals for study BCX7353-101. HR categories in study BCX7353-106 are different compared to the FDA analysis. Results are not directly comparable. There were no significant outliers in both sponsor's and FDA analysis. Please see section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor's analysis included linear mixed effects modeling exploring the relationship between the baseline-adjusted, placebo-correct ECG intervals of interest and concentration of berotralstat as the primary endpoints. The model included ΔQTcF as the dependent variable, berotralstat plasma concentration as a continuous covariate, time (combined days and hours) and treatment (any dose level of berotralstat and placebo) as categorical factors, and random subject effects for both intercept and slope.

In addition, as a co-primary endpoint, the sponsor evaluated the effect of berotralstat on the QT subintervals - the relationship between the concentration of berotralstat and each of the ΔΔ intervals from the end of QRS to J-Tp (J-Tpc) and Tp-Te and the concentration of berotralstat. The sponsor's exposure-response analysis indicated a statistically significant relationship ($p < 0.001$) between ΔQTcF and concentration with a positive slope of 0.044 msec/(ng/mL). The intercept for the ΔΔQTcF vs. concentration regression equation was -3.611 msec (90% confidence intervals are (-6.694, -0.528); $p = 0.0559$).

Reviewer's comment: Concentration dependent increase in QTc interval was observed. The conclusion of the reviewer's analysis was in agreement with the sponsor's analysis. Please see section 4.5 for additional details.

3.2.4 Cardiac Safety Assessment

Study BCX7353-106

40 subjects were enrolled; 14 subjects received 14 days of berotralstat 150 mg or 450 mg, and 12 subjects received 14 days of placebo.

There were no deaths, SAEs or severe AEs. One subject in the berotralstat 450 mg group discontinued due to an AE of non-cardiac chest pain and after he was administered the prohibited medication (ondansetron), which is known to prolong the QT interval, for concomitant nausea.

Subject (b) (6), a 22-year-old white male randomized to berotralstat 450 mg, experienced non-cardiac chest pain on Day 9 leading to discontinuation on Day 10. In addition to the non-cardiac chest pain, he also experienced nausea. He was discontinued because he was administered the prohibited medication ondansetron, which is known to prolong the QT interval. The event of non-cardiac chest pain was moderate in severity and probably related to study drug. The subject recovered from the event.

Study BCX7353-101

There were no deaths or SAEs. In part 2 (MAD), two subjects randomized to BCX7353 discontinued due to TEAEs prior to completion of the study: 1 due to an unacceptable toxicity (Subject (b) (6)) and 1 due to an intercurrent illness (Subject (b) (6)). Subject (b) (6) (BCX7353 500 mg for 7 days) experienced Grade 2 abdominal pain and diarrhea.

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 the studies.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which 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 (# 106) appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

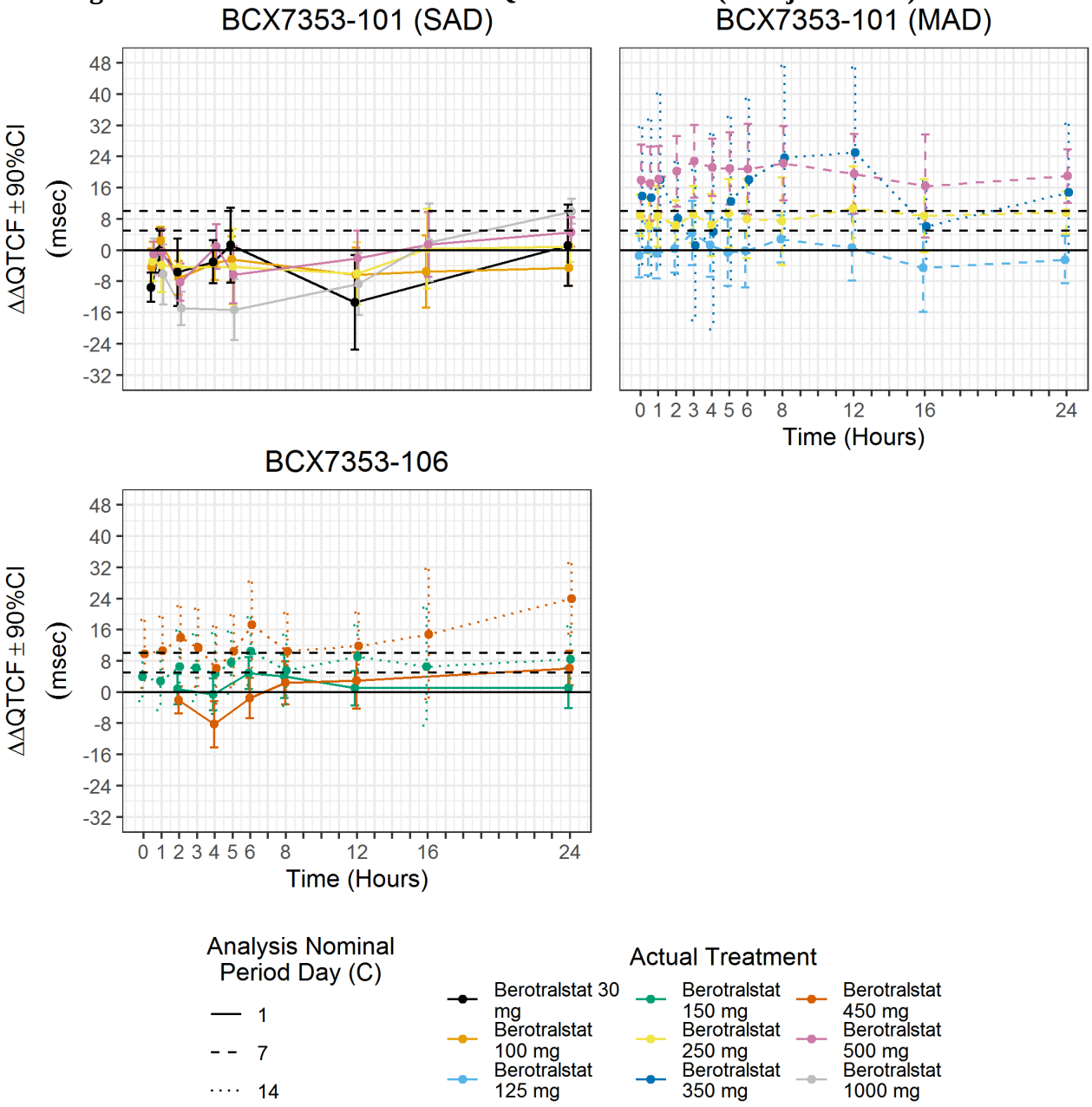
The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics. Data sets from two studies were analyzed. By time analysis of study BCX7353-101 and study BCX7353-106 are not interpretable due to small sample size.

4.3.1 QTcF

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).



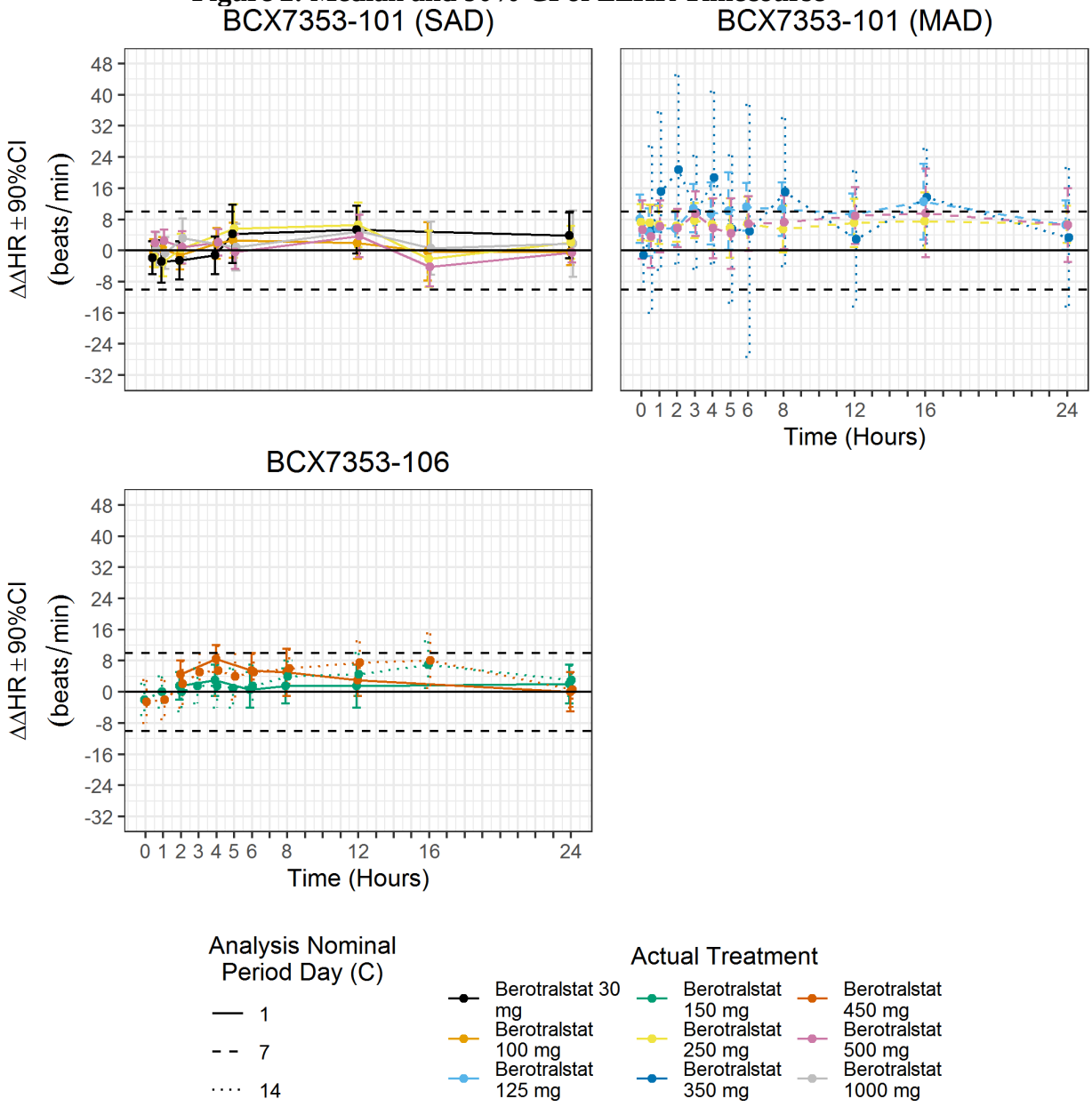
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

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

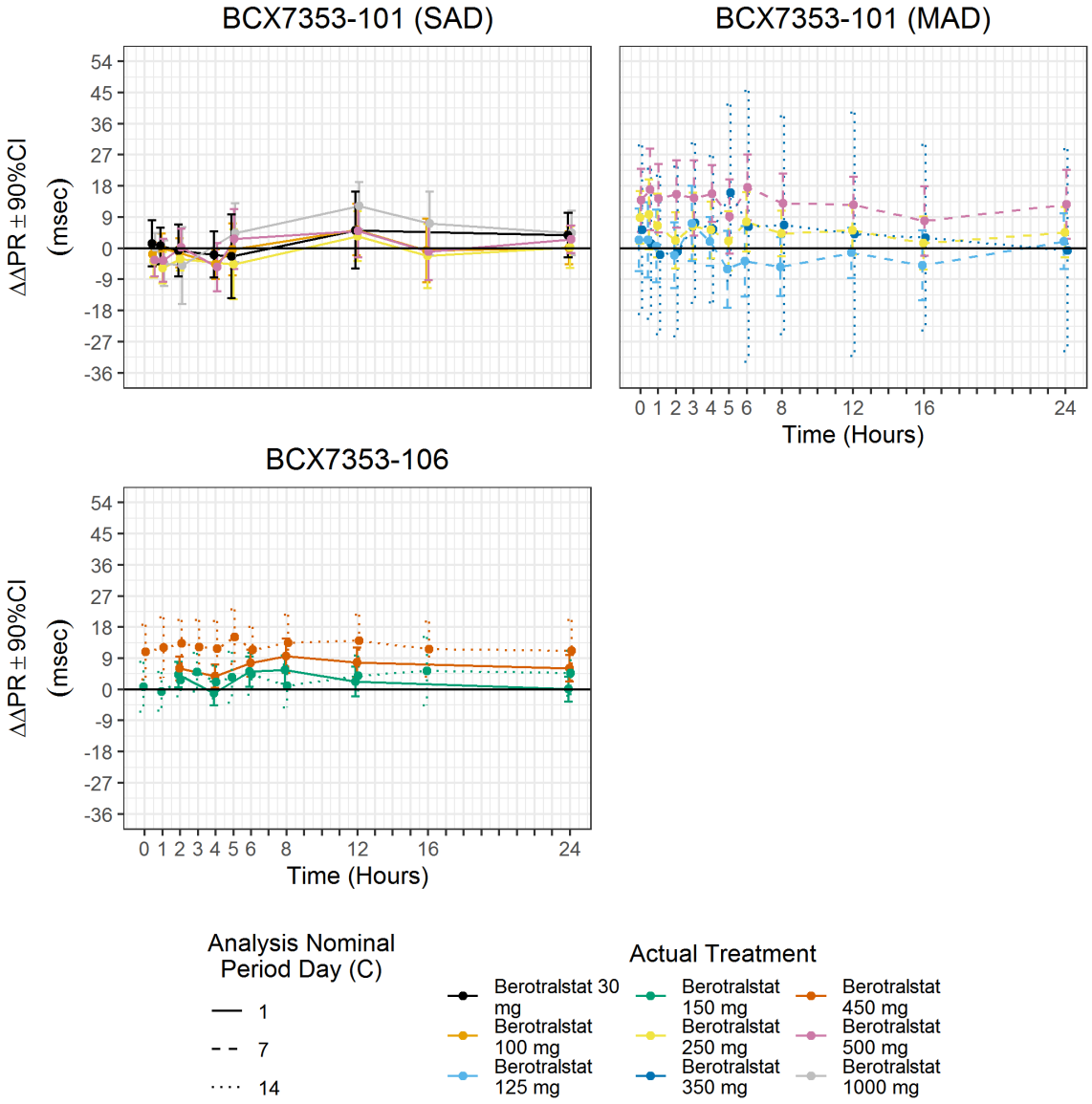
Figure 2: Median and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

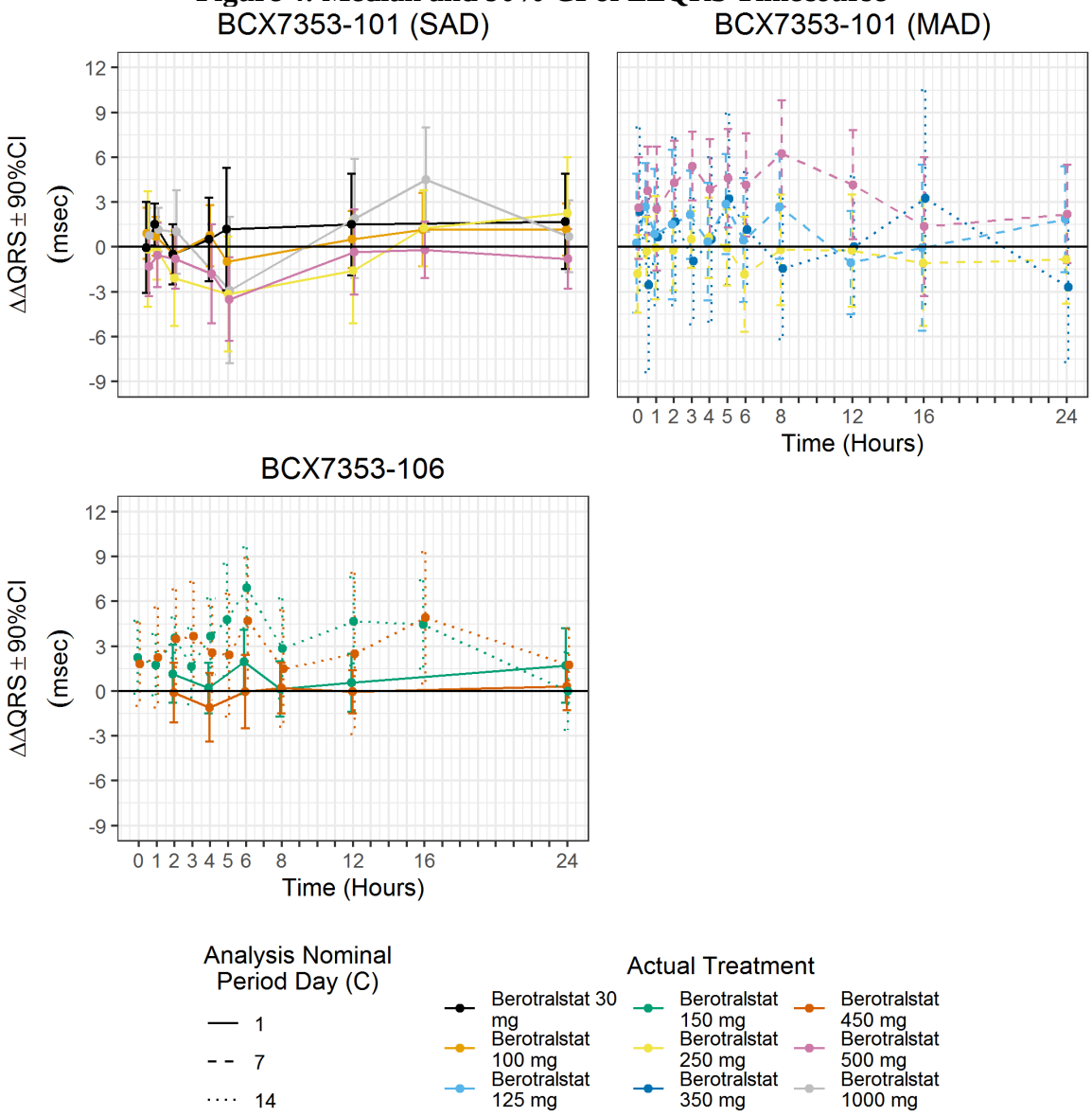
Figure 3: Median and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

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

Figure 4: Median and 90% CI of ΔΔQRS Timecourse



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 of two studies (BCX7353-101 and BCX7353-106) and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 480 msec in different dosing groups of berotralstat. Similarly, none of the subjects experienced ΔQTcF greater than 60 msec in different dosing groups of berotralstat.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in different dosing groups of berotralstat.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec and 25% increase over baseline in different dosing groups of berotralstat.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec with or without 25% increase over baseline in different dosing groups of berotralstat.

4.5 EXPOSURE-RESPONSE ANALYSIS

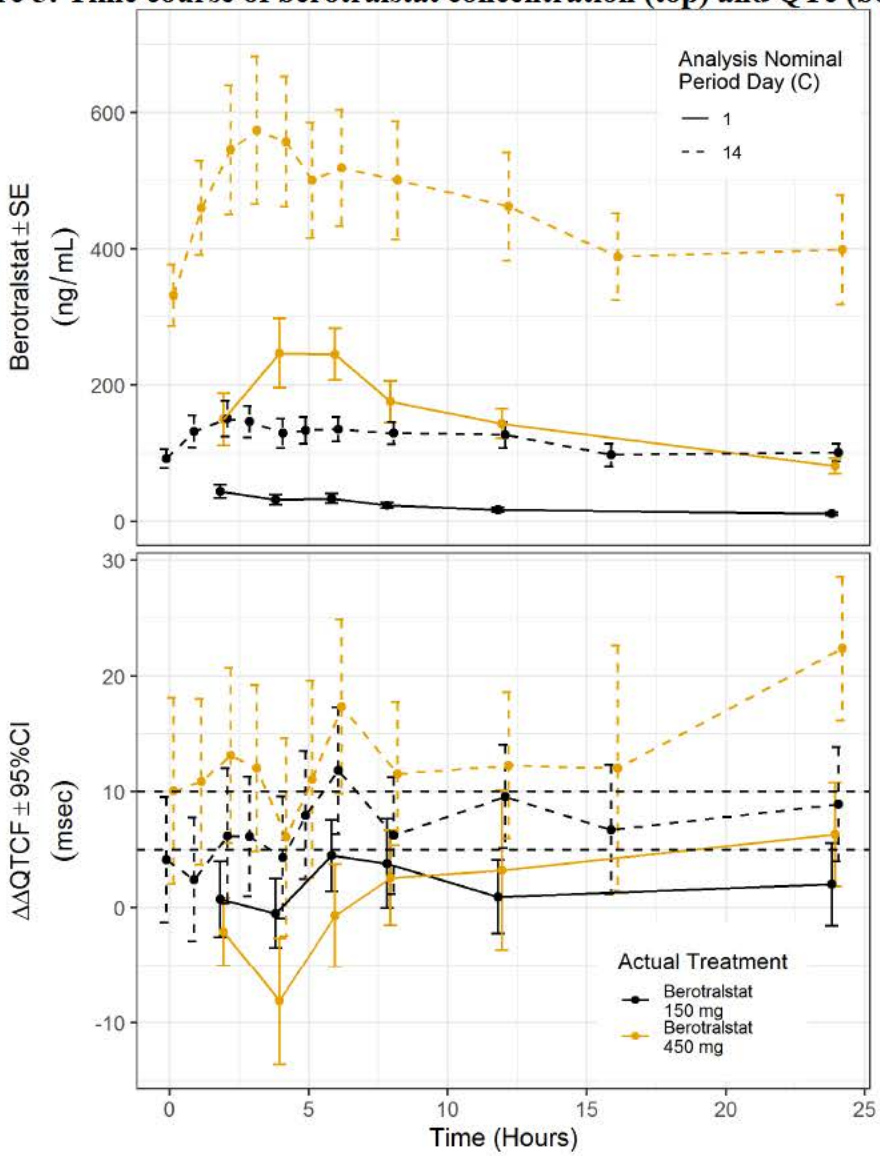
The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and concentration of berotralstat. Due to limited sample size and magnitude of signal, the subinterval analysis was not conducted for this study. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (Study # 106).

4.5.1 QTc

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were 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 concentration of berotralstat and ΔQTcF; and 3) presence of non-linear relationship.

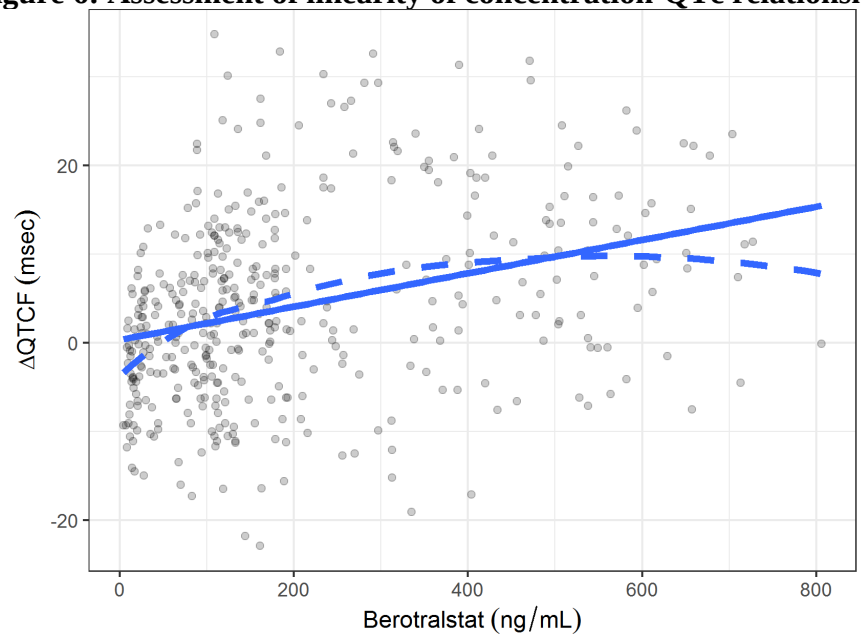
An evaluation of the time-course of berotralstat concentration and changes in ΔΔQTcF is shown in Figure 5, which do not appear to show significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which suggests an absence of significant ΔΔHR changes (see Section 4.3.2 and 4.4.2).

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



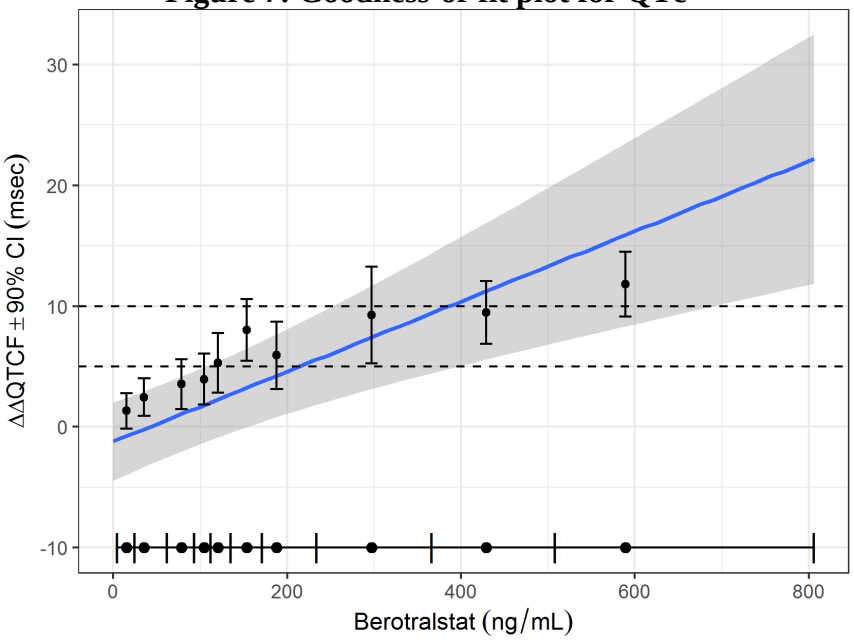
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between berotralstat concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between berotralstat concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7.

Figure 7: Goodness-of-fit plot for QTc



Predictions from the concentration-QTc model are provide in Table 1. Since one subject receiving 450 mg dose did not have baseline ECG data, the PK/PD dataset did not include this subject. However, the subject was included in PK summary which resulted in higher observed peak concentrations (Cmax: 591 ng/mL; n=11) on Day 14. For this purpose, the Table 1 describes the predicted QT effects at Cmax of 591 ng/mL (450 mg dose, Day 14).

4.5.2 PR

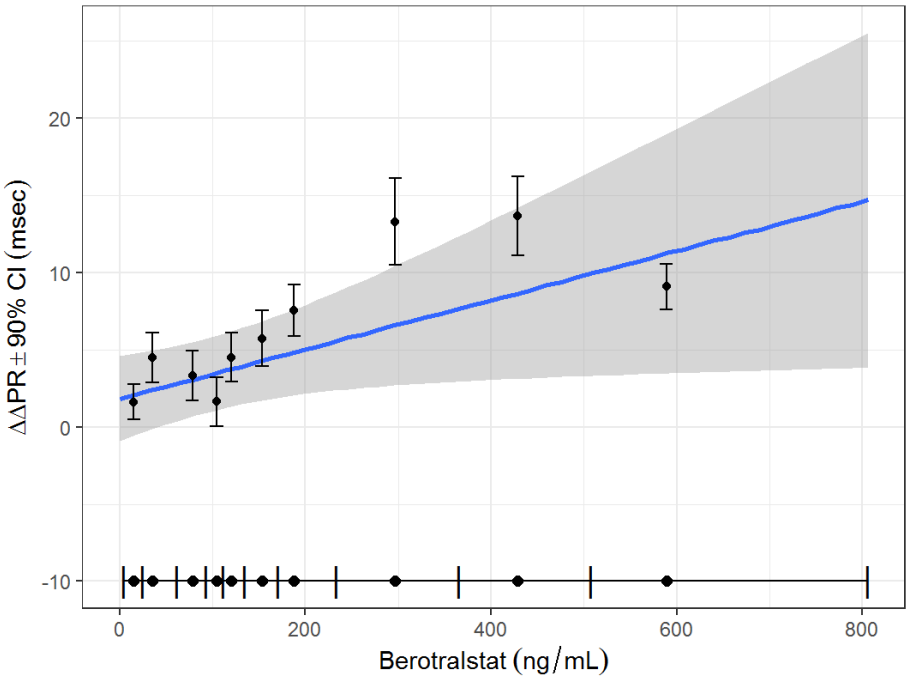
Concentration-response analysis indicated a positive slope in the relationship between ΔΔPR and berotralstat concentration (Figure 8). Based on a linear relationship, the model predicted ΔΔPR were 4.4 msec and 11.3 msec for the peak berotralstat concentrations at 150 mg and 450 mg once daily doses, respectively (Table 2). These findings were in agreement with the by-time analysis. Thus, oral administration of berotralstat was associated with dose- and concentration-dependent increases in the PR interval. However, none of the subjects in this study had PR values > 220 msec (see Section 4.4.3).

Table 2: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Concentration** (ng/mL)	**ΔΔPR** (msec)	**90% CI** (msec)
PR	Berotralstat 150 mg*	158.2	4.4	(1.8 to 6.9)
PR	Berotralstat 450 mg*	591.0	11.3	(3.5 to 19.0)

**Administered orally as once daily for 14 days.*

Figure 8: Goodness-of-fit plot for PR



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