Human validation packet

50 FDA Complete Response Letter deficiency segments

Data vintage	2026-08-07
Review sample	Fixed random sample of 50 letters
Reviewer	_____
Review dates	_____

Reviewer instructions

This review provides an independent human check of the primary and secondary deficiency categories assigned to a fixed random sample of 50 FDA action letters. The packet shows the same extracted deficiency segments supplied to the original classifier. It does not show model classifications, prior validation labels, approval outcomes, or study results.

Complete all 50 reviews before looking at the existing classifications. Save the completed review as a blinded version before any comparison is made.

What to code

A substantive or approval-blocking deficiency is a problem that FDA says prevents approval in the application's present form and must be fixed. Code only those problems. Do not code standard language about future labeling review, resubmission procedures, safety updates, or proprietary-name review unless the letter makes the item an actual reason for nonapproval.

For every letter

1. Select every category that is a substantive reason for nonapproval.

2. Select exactly one primary category. The primary category is the problem most directly responsible for the action, based on FDA's decision language and required remedy. It is not automatically the first heading or the longest section.

3. Complete the three additional fields and the text-quality status.

4. Write a short rationale identifying the decisive language or remedy.

Use only the text printed in the packet. Do not research the product, sponsor, later approval, or other FDA records. Do not fill gaps from memory or inference.

Category definitions

1. Clinical efficacy

The evidence does not establish effectiveness, or the benefit is too small or uncertain.

2. Clinical safety

A specific safety signal, inadequate safety database, or unfavorable benefit-risk balance prevents approval.

3. Trial design and conduct

A new or materially redesigned trial is needed, or FDA cites data-integrity, GCP, endpoint, statistical-design, site, or conduct problems. If failed efficacy evidence also requires a new adequate trial, code both 1 and 3; category 1 is normally primary when lack of effectiveness is the stated reason.

4. Chemistry and manufacturing controls (CMC)

Formulation, specifications, analytical methods, process validation, manufacturing controls, sterility assurance, container-closure information, or other product-quality information in the application is inadequate.

5. Facility inspection

An inspection, Form 483, CGMP compliance finding, or facility acceptability is an approval-blocking problem. Code both 4 and 5 only when the letter states a distinct product- or process-information deficiency.

6. Stability and shelf life

Stability evidence, expiration dating, storage, degradation, or shelf life is independently deficient.

7. Bioequivalence and bioavailability

Bridging, comparative exposure, food effect, pharmacokinetic equivalence, or bioavailability evidence is inadequate.

8. Nonclinical toxicology

Animal, in-vitro, carcinogenicity, genotoxicity, or other nonclinical safety evidence is inadequate.

9. Labeling and proprietary name

Labeling, instructions for use, carton or container labels, or a proprietary name is itself a reason for nonapproval. Do not code standard language reserving comment on labeling.

10. Administrative and procedural

The submission is incomplete or procedurally defective; required datasets or documents are missing; patent certification is defective; or a REMS or similar administrative requirement blocks approval.

Additional fields

New clinical trial required: Yes only when the letter explicitly requires or recommends a new or additional clinical trial as necessary to resolve a deficiency.

Third-party manufacturer: Yes only when the deficient manufacturer or facility is clearly external to the applicant. Use Unclear when ownership cannot be determined from the displayed text.

Otherwise approvable: Yes only when FDA explicitly says the application is otherwise approvable or adequate except for the identified problem. Do not infer this from a letter listing only one deficiency.

Text-quality status

OK: The displayed text is sufficient to classify.

Uncertain - redaction: Removed confidential text prevents a confident classification.

Uncertain - OCR: Scanning or OCR damage prevents a confident classification.

Unable to classify: The approval-blocking reason cannot be determined from the text.

Visible redaction or OCR errors do not by themselves make a letter uncertain. Use an uncertain status only when the missing or damaged material affects the classification.

Review workflow

Work through the packet in numbered order and read each complete displayed deficiency segment before coding. Give a one- to three-sentence rationale and quote only a short decisive phrase if useful.

Record answers in the companion Excel workbook. Choose the primary category first, use the optional additional-category dropdowns only when needed, and do not repeat a category. Resolve any row that is not marked Complete. Save the completed workbook as a blinded copy. Do not open classification_validation_sample_v20260807.csv, the classified panel, or prior validation tables until all 50 records are complete.

Source-text note

The packet uses the frozen deficiency segments originally supplied to the classifier, so the human and model see the same information. One sampled record was later found to be affected by the known segment-boundary correction. For classifier agreement, code only the text shown here; keep the segmenter correction as a separate sensitivity check.

Worked example (not part of the 50-letter sample)

The complete extracted letter below illustrates the coding rules. Read the letter first, then compare your judgment with the answer that follows it. This letter is not included in the validation sample and does not affect the agreement calculation.

Application: NDA210649 Letter date: 2018-09-12
Example ID: crl_efaca4c48347fb5b Source file: 210649_2019_Orig1s000OtherActionLtrs.pdf

Complete extracted letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210649
COMPLETE RESPONSE

AB Pharmaceuticals, LLC

U.S. Agent for Macleods Pharmaceuticals Limited, India
Attention: Andrej Gasperlin, President

17471 Highland Way Drive

Chesterfield, MO 63005

Dear Mr. Gasperlin:

Please refer to your New Drug Application (NDA) dated and received September 14, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

> Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg

We acknowledge receipt of your amendment dated March 15, 2018, which constituted a complete response to our March 13, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot tentatively approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During a recent inspection of the Macleods Pharmaceuticals Limited (FEI # 3007517881) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

PRESCRIBING INFORMATION

2. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

Reference ID: 4319870

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If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "RESUBMISSION" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590541.

The drug product is not eligible for procurement under the President's Emergency Plan for AIDS Relief (PEPFAR) program until you have been notified in writing that this application is approved.

If you have any questions, please call Monica Zeballos, Program Coordinator, at (301) 796-0840.

Sincerely yours,
{See appended electronic signature page}

Jeffrey Murray, M.D., M.P.H.

Deputy Director

Division of Antiviral Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Reference ID: 4319870

Signature Page 1 of 1

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.

JEFFREY S MURRAY
09/12/2018

Reference ID: 4319870

Correct coding

Primary category	5. Facility inspection
Secondary categories	None
New clinical trial required	No
Third-party manufacturer	Yes
Otherwise approvable	No
Text-quality status	OK

Why this coding is correct

The approval-blocking problem is the completed inspection of the Macleods Pharmaceuticals facility, where FDA observed objectionable conditions and required satisfactory resolution before approval. Facility inspection is therefore the only substantive category and the primary category.

Do not add CMC: the letter identifies no separate problem with the product, process, specifications, analytical methods, or manufacturing information in the application. Do not add labeling: FDA says that it reserves comment on labeling until the application is otherwise adequate, which is standard future-review language rather than a reason for nonapproval.

The deficient Macleods facility is external to the applicant, AB Pharmaceuticals, so the third-party-manufacturer field is Yes. No new clinical trial is requested. The application is not coded as otherwise approvable because FDA does not explicitly say that it is adequate apart from the inspection problem. The text is clear enough to classify, so its status is OK.

Letter 01 of 50

Application: NDA200655 Letter date: 2013-10-22
Packet ID: crl_41b7fa5a07cc4bac Source file: 200655_2019_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

_____

_____

Displayed deficiency segment

CLINICAL / STATISTICAL

Your application contains no data from adequate and well controlled clinical trials. Significant deficiencies have been identified in the referenced literature studies and in the studies you have conducted in support of this application. The data submitted in your application are not sufficient for evaluating the diagnostic effectiveness and usefulness of Fluorodopa F 18 PET in the proposed patient population.

1. The following deficiencies have been identified with clinical Study #15, which was conducted at the Feinstein Institute of Medical Research:

a. The study is a retrospective, single center study.

b. The study was not conducted according to a pre-specified protocol, and hence, definitions of the primary efficacy endpoint and the standard of truth that would normally be specified by a protocol, are not well-defined for the study.

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Page 2

c. The study used each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. We do not find such a standard to be clinically meaningful and do not agree with the cited diagnostic performance measurements of Fluorodopa F 18 as 100% for sensitivity and 100% for specificity.

d. Of the 185 study patients, 158 patients had a pre-imaging clinical diagnosis of Parkinson's disease and were responding to Parkinson's disease medications. For these patients a Fluorodopa F 18 PET scan provides no additional clinically useful information. Deficiencies concerning the remaining 27 study patients are discussed below (Study #16).

e. You have provided no documentation that Fluorodopa F 18 PET images have been read independently by three readers blinded to clinical information. Furthermore, inspection of the study site revealed that none of the 47 audited cases contained documentation that each patient's images were read by three blinded readers.

2. Study #16 is a publication with the follow-up results of 27 Fluorodopa F 18 PET negative patients enrolled in Study #15. Study #16 has the following major deficiencies:

a. Per your amendment dated April 5, 2013, only 8 of the 27 Fluorodopa F 18 PET negative patients from Study #15 were followed for 2 to 4 years to obtain the patient's final clinical diagnosis. Clinical data from such a small number of patients do not provide a reliable assessment of the performance characteristics of Fluorodopa F 18 PET. Furthermore, inspection of the study site revealed that none of the subject files contained documentation (clinical follow-up confirmation) of the continued absence of classical Parkinson's Disease symptoms and signs.

b. The reasons for not obtaining follow up on the remaining 19 patients are not provided.

3. Among the remaining literature publications in your application (Studies #17-23), only the publication by Eshuis et al. (Study #21) provides clinical data for the assessment of the efficacy of Fluorodopa F 18 as a diagnostic radiopharmaceutical. However, Study #21 does not provide substantial evidence of efficacy for the following reasons:

a. The study is a small single center study and is exploratory in design.

b. All study patients had a diagnosis of Parkinson's disease at the time of enrollment. The study excluded patients with atypical signs and patients not responding to Parkinson's disease medication. Therefore, the study does not evaluate a patient population that might benefit from a diagnostic imaging test.

c. The definition of positive scans (mean standard uptake value in patients below two

standard deviations of the mean in healthy controls) is an exploratory quantitative measure and its threshold is arbitrarily set.

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d. It is unclear how specificity was calculated, as all patients included in the analysis of

the study had confirmed Parkinson's disease.

To address these deficiencies, we recommend the following:

1.

Conduct an adequate and well-controlled clinical trial which might
evidence of effectiveness of Fluorodopa F 18 in the intended patient
encourage you to develop such a study using a pre-defined standard

rovide substantial
population. We
of reference for

measuring the performance characteristics (sensitivity and specificity) of Fluorodopa F 18, a

pre-specified statistical analysis plan, and image interpretations mai

le by independent readers

blinded to clinical information. Note in order to measure the sensitivity and specificity of Fluorodopa F 18, you need to obtain the standard of reference (follow-up clinical diagnosis)

in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18
You should use as a standard of reference the clinical diagnosis ma
disorder specialist at a predefined time interval following the Fluoro

The study population must include subjects who might benefit from
PET scan. Such patients could include those in whom Parkinsonian
could not be differentiated on clinical grounds, those with suspecte
Parkinsonian syndrome, and/or those not responding to a Parkinson

To facilitate the interpretation of the study's results, we recommen:

exclusion of subjects with features suggestive of multiple system atroy

supranuclear palsy, response to Parkinson's disease medication, a c:

PET negative patients.
le by a movement
lopa F 18 PET scan.

the Fluorodopa F 18
and essential tremor
early onset of
disease medication.

that you consider
hy or progressive
inical history

exceeding five years, and concomitant medication known or suspected of interacting with

striatal uptake of Fluorodopa F 18.

We reference the Good Clinical Practice (GCP) deficiencies identifi

ed during our

inspection of your clinical study site and communicated to you on March 22, 2013.
These deficiencies call into question the reliability of the clinical data in your application.
It is necessary to conduct a study in compliance with GCP standards to ensure the quality

and integrity of the data.

GOOD CLINICAL PRACTICE (GCP) INSPECTION

A GCP inspection was performed at the clinical site where Studies #15 and #16 were conducted.

As noted during the inspection, a prospective study protocol and case report forms were not used and important study records (including source records) were not available for inspectional review. Additionally, the adequacy of clinical safety monitoring could not be determined. As a retrospective documentation of the clinical experience at a single center, these studies do not appear to have been performed under adequate GCP standards sufficient to support a regulatory submission.

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During the inspection of your clinical study site, deficiencies were conveyed to you for failure to prepare and maintain adequate case histories and for inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects. The following is a detailed description of these deficiencies:

1.

Referral diagnoses were not adequately documented as part of subject case records. The subject files did not contain the physician referral letter in 15 of the 47 files audited. The files typically lacked documentation of the presence of the cardinal features of Parkinsonian syndrome and/or responsiveness to Parkinson's disease drugs.

The case records for the control subjects did not include evidence of an adequate neurological examination by a qualified neurologist.

For all the subjects audited, the case records lacked evidence of PET scan interpretation by three separate blinded readers.

Study treatment and procedures were not adequately documented. For example, there was no documentation of carbidopa administration prior to Fluorodopa F 18 in a total of 18 of the subject files audited and the use of concomitant medication was inconsistently documented.

For Study #16, none of the subject files contained documentation (clinical follow-up confirmation) of continued absence of classical Parkinson's disease symptoms and signs.

For Study #15, the available study records indicated that the PET scan procedure was discontinued in one subject due to an undocumented adverse event. This observation is inconsistent with your claim of no adverse events in the study.

PRODUCT QUALITY

You have not adequately responded to our requests for information dated December 28, 2012 and May 31 and July 2, 2013. The following issues remain outstanding:

1.

Regarding specifications for the precursor of the drug substance, add a test method and acceptance criteria to establish the chiral identity of the precursor (i.e., the L-isomer only). Provide experimental and characterization data including optical rotation measurements for the precursor to the drug substance adequate to justify the proposed acceptance criteria.

Provide the revised drug product specifications, in tabular format, in the appropriate drug product section of your NDA (Section 3.2.P.5.1 Specifications). A separate discussion of drug substance specifications in the drug substance section of the NDA is not necessary. Describe all analytical methods in the drug product section 3.2.P.5.2 Analytical Procedures. Provide a revised document with tracked changes identified.

Reference ID: 3394281

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Page 5

4. Provide validation data in the drug product section of your application for the drug product HPLC chemical and chiral purity method establishing the limit of detection and quantitation, accuracy, precision, linearity and robustness. This data was not included in your August 21, 2013 amendment, as stated in your cover letter.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise the labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)()] in structured product labeling (SPL) format as described at:
http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Letter 02 of 50

Application: NDA208564 Letter date: 2017-05-05
Packet ID: crl_16d7ff26442a7eb9 Source file: 208564_2018_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

_____

_____

Displayed deficiency segment

CLINICAL SAFETY

1. Your application does not provide long-term endometrial safety data for the 4, 10)" meg estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product. In making this determination, we have considered the following:

e Treatment of moderate-to-severe dyspareunia, due to menopause, involves a chronic duration.

e Unopposed estrogen use in a postmenopausal woman with a uterus increases the risk of endometrial hyperplasia/cancer.

e 12-week safety data from Trial TXV14-01 are inadequate to assess long-term endometrial safety of your estradiol vaginal insert.

Reference ID: 4094584
Reference ID: 4271237

NDA 208564
Page 2

e Long-term endometrial safety data with your product are necessary to ensure its safe use.

= Clinical practice allows the chronic treatment of local vaginal symptoms related to menopause, such as dyspareunia, with vaginally administered estrogen without opposing progestin therapy to mitigate the risk of endometrial hyperplasia and cancer in women with a uterus.

= Proliferative changes of the endometrium were seen with your product in some women at 12 weeks of treatment compared to none on placebo. Based on these 12-week endometrial changes, it is unclear, without long-term data, whether your product could be used without an opposing progestin even if it is intended for local vaginal use.

- Long-term endometrial safety information with your product in labeling is essential to guide prescribers' decisions regarding endometrial surveillance and the need for progestin therapy with the chronic use of your product in a woman

with a uterus.

- If long-term endometrial data are not reassuring and indicate that your product must be co-administered with a progestin for adequate endometrial protection, then the safety and efficacy of the co-administered drugs will need to be demonstrated.

2. The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize the pattern of drug-related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.

To address the aforementioned deficiencies, you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. This trial should also collect and characterize the long-term general safety profile of your product. You are encouraged to request a meeting with us to discuss the details of such a trial.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of

Reference ID: 4094584
Reference ID: 4271237

labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Letter 03 of 50

Application: NDA209128 Letter date: 2017-10-11
Packet ID: crl_a1d2b881b375795d Source file: 209128Orig1s000OtherActionLtr.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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_____

Displayed deficiency segment

SAFETY

The safety database, while suitable in number of patients, did not contain a sufficient number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of Dsuvia. This is particularly important as there is a nearly 4-fold increase in the exposure and a more than 2-fold increase in the maximum concentration when Dsuvia is dosed at steady state.

To address this deficiency:

Collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of Dsuvia for a period following the maximum dosing proposed.

HUMAN FACTORS

We have determined that the human factors (HF) validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments. Failures that result in dropped sufentanil tablets pose a risk for accidental exposure, improper dosing, and diversion. Overall, we do not find the risk acceptable and note that you did not propose any additional measures to further mitigate the risk.

Reference ID: 4165764

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Page 2

To address this deficiency:

Develop mitigation strategies to address the risk of dropped sufentanil tablets. Conduct another HF validation study to demonstrate the effectiveness of the recommended mitigation strategies in addressing the use-related errors that were observed in your validation study and to ensure that the changes do not introduce new risks. We recommend incorporating the following changes to the user interface:

A. Directions for Use (DFU)
1. Revise step 6 of the DFU: "Depress the green Pusher to deliver the tablet to the patient's

sublingual space and confirm tablet placement" into two separate steps such as the following:

"Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space."

"Step 7: Visually confirm tablet placement in the sublingual space."
2. Modify the figures that depict the patient's mouth by labeling parts of the mouth so they represent a more accurate representation of human anatomy. Labeling parts of the mouth

within the graphics will help guide users in the proper administration technique.

3. Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written instructions (e.g. "see Figure 1").

B. Pouch Package

1. Replace the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL)

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format as described at
http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, March 30, 2017, which addresses the proposed proprietary name, DSUVIA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

RISK EVALUATION AND MITIGATION STRATEGY REQUIRE

TS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks[section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated December

12, 2016, which contains elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for DSUVIA (sufentanil sublingual tablet), if it is approved, to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from

accidental exposure.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

Letter 04 of 50

Application: NDA206610 Letter date: 2017-12-06
Packet ID: crl_5ac16c195d0e8fec Source file: 206610_2021_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

_____

_____

Displayed deficiency segment

NONCLINICAL

You have not provided an fe assessment of the ence of
leachable compounds from the

drug product formulation. An adequate safety justification was not
leachable/extractable compounds that includes

Reference ID: 4191451

NDA 206610
Page 2

© Include a dosing regimen that mimics the clinical dosing regimen. The study design must define a NOAEL for the levels of each of these compounds. Calculate the safety margin for human exposure for these NOAELs based on body surface area (mg/m?). The study report must also include quantitative analysis of the above compounds with an identification of the i compound in the solutions administered to the animals to ensure that the safety of the compounds leached from the | have been adequately qualified for safety in the study.

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Letter 05 of 50

Application: BLA761073 Letter date: 2018-05-25
Packet ID: crl_af782e5ba918ec04 Source file: 761073_2019_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

During a recent inspection of the © manufacturing facility
for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the draft FDA Guidance for Industry, "Labeling for Biosimilar Products," March 2016 at:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at:
http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Reference ID: 4268735

BLA 761073
Page 2

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated March 6, 2018.
PROPRIETARY NAME

Please refer to correspondence dated, September 25, 2017, which addresses the proposed proprietary name, Kanjinti. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

Letter 06 of 50

Application: NDA209510 Letter date: 2018-10-05
Packet ID: crl_e61aa4806bf55148 Source file: 209510_2020_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

_____

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Displayed deficiency segment

PRODUCT QUALITY/FACILITY INSPECTION DEFICIENCIES

During a recent inspection of the ow
manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility at the close of the inspection. Satisfactory resolution of these observations is required before this NDA may be approved.

PRESCRIBING INFORMATION

1. Submit a revised PI, based on the version appended to this letter.

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:
e The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
e The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
e Regulations and related guidance documents

Reference ID: 4331444

NDA 209510
Page 2

e Asample tool illustrating the format for Highlights and Contents, and

e The Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

e FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

CARTON AND CONTAINER LABELING

2. Submit draft carton and container labeling based on the version appended to this letter.
PROPRIETARY NAME

3. Please refer to correspondence dated, May 24, 2018, which addresses the proposed proprietary name, Barhemsys. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

Letter 07 of 50

Application: NDA210735 Letter date: 2019-01-15
Packet ID: crl_9db525bd09871d8a Source file: 210735_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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_____

Displayed deficiency segment

PRODUCT QUALITY

1. In the resubmission, the presence of visible particles at the 24-month timepoint for the 1 lg configuration is reported that you attribute to
The observed particles could be present but not detected at release and at earlier stability timepoints due to inadequate inspection procedure. Provide the following information to demonstrate that this issue has been satisfactorily resolved:

a) Detailed analytical procedures for the proposed and the original inspection methods for visible particulate matter in English. Identify the differences between these two methods and provide evidence to demonstrate that the detection capability of the proposed method is sufficient to detect all the visible particulate matter in the filled vials.

b) Any non-compliant observations or results from 100% visual inspection of the filled placebo (trial batch FE-17-005) and drug product vials manufactured with aa ©® should be included. In CAPA-16-015 you indicate tha |

after filling one Cyclophosphamide Placebo batch. This indicates that there

Reference ID: 4376130

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Reference ID: 4376130

are quality issues with © The rejected vials were found to contain particles oo]

. Propose your approach to resolve this issue and demonstrate that visible particulate matter will not be an issue for the proposed commercial product.

c) Acopy of CAPA-15-006.
d) Results of investigations on stoppers as a possible source of visible particles.

e) Status and results of the corrective and preventive actions you proposed on Page 28 - 30 of the quality event report Req-16-117, req-16-119, req-16-123 in the amendment dated 12/13/2017 (Sequence 0007).

f) Data to demonstrate that visible particles are not observed for the 500 mg configuration. If the results show that 500 mg strength vials do not have visible particulates, provide your rationale for the observation an aed tification of not manufacturing three registration batches using If visible particulates were observed for the 500 mg configuration, see 2(a) below.

Based on the information you provided, we determined that the detection capability of the original inspection method for visible particulate matter is not sufficient to detect all the particulate matter in the stability and batch release samples, which made the release and stability data for visible particulate matter at time 0, 3, 6, 9, 12 and 18 months invalid. Since all three registration batches for the 1 g configuration, 000663, 000664 and 000665, failed the visible particulate matter test, you should:

a. Manufacture three new registration batches for the 1 g strength as well as the 500 mg strength (if visible particulates are not observed, see 1(f) above) with aa which is compatible with the drug product and provide adequate batch release and stability data as recommended in ICH Q1A. Provide the executed batch records and revised master batch records.

b. If stoppers are potential source of visible particles, the registration batches should be manufactured using the new stopper that will not cause particulates in the filled vials (see 2(a) above). Ifa change to the stopper is proposed and the proposed stopper dimensions do not significantly overlap with or fall within the critical (i.e., at the stopper/vial interface) dimensions of the previously validated stopper, then container-closure integrity validation data should be provided for the proposed container closure system. A change in the stopper should be supported. oe

validation information or a Letter or Authorization (LOA) authorizing access to the Agency to review the associated DMF for the processes used by the manufacturer of the rubber stoppers.

c. Inspect! after each batch and provide pictures of the OM filling operation. Note any) deterioration or leak and take appropriate action (e.g., © replacement).

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3. Revise the quantitative statement of the immediate container and carton labels to include the amount of dehydrated alcohol, as described in Section 11 of the Package Insert.

FACILITY INSPECTIONS

During a recent inspection of the © manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. Upon resubmission of your application, you must submit a revised proposed label that is current with any revisions in the reference listed drug. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www. fda.gov/ForIndustry/DataS tandards/StructuredProductLabeling/default.htm.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling with your resubmission. We reserve comment on the proposed labeling until the application is otherwise adequate.

Letter 08 of 50

Application: NDA211988 Letter date: 2019-04-30
Packet ID: crl_d6896c685d861fe2 Source file: 211988_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

1. The limited data provided on leachables in the drug product, |
© is not adequate to assure that the leachables
remain within permitted daily exposure limits through the end of shelf-life. |

is not sufficient to establish the safety of
leachables present in HTX-011.

Information needed to address this deficiency:

Provide test data for all potential leachables, identified through the various extraction studies, monitored at release and at multiple timepoints during the stability testing of HTX-011 batches using validated analytical methods. Further refer to the Additional Nonclinical Comment 5 regarding study design considerations.

2. During a recent inspection of the © (FEI: ©®) manufacturing

facility for this application, our field investigator conveyed deficiencies to the representative of the facility.

Reference ID: 4496538

NDA 211988

Page 2

Information needed to address this deficiency:

Satisfactory resolution of these deficiencies is required before this application may be approved.

NONCLINICAL

3. You have not provided adequate data to support the safety of the DMSO or triacetin, in

Reference ID: 4426880

your drug product. The levels in the product exceed the maximum potency listed in the CDER Inactive Ingredient Database (IID) and are, therefore, considered novel. Specifically, your NDA did not include any discussion of the impact of these two

excipients on the standard reproductive and developmental battery of studies.

Information needed to address this deficiency:

Submit adequate data to fully characterize the impact of the proposed doses of DMSO.

and triacetin on all endpoints normally characterized via the standard battery of reproductive and developmental toxicology studies. Should you elect to address this via literature, justify the adequacy of the literature based on current standard study protocols and provide copies of all referenced literature. In the absence of adequate published data, GLP nonclinical toxicology studies should be completed.

Your toxicological risk assessment for the excipient maleic acid, which exceeds the maximum potency listing in the CDER Inactive Ingredients Database (IID), does not address the potential impact of maleic acid on embryo-fetal development in a second species (typically rabbit).

Information needed to address this deficiency:

Submit adequate justification for the safety of the proposed maximum daily dose of maleic acid, specifically with respect to the effects of this compound on rabbit embryo-fetal development.

You have not provided adequate data to qualify the proposed drug product degradant ©® which exceeds the ICH Q3B(R2) qualification threshold.

Information needed to address this deficiency:

Either tighten the drug product specification © to NMT"% or
provide adequate qualification in accordance with ICH Q3B(R2) as follows:

a. Complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

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6.

7.

Reference ID: 4496538

b. In addition, conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

c. Alternatively, provide adequate data to support your position oo]

However, we note that if you elect to pursue this option, the data may not address the local safety concerns via this drug product's proposed dosing regimen.

You have not provided adequate data to support the safety of the drug product specification ©® The proposed specification of NMT9®%
exceeds the appropriate qualification threshold of NMT®®o% or) ©® whichever is lower, for a drug product with a maximum recommended human dose of greater than 2 grams as outlined in the ICH guidance for industry: 03B(R2) Impurities in New Drug Products.

We also acknowledge that "" was detected in the clinical HTX-011 lot
that was tested in the pivotal 28-day toxicology studies in dogs and rats; however, the level detected in these stability batches do not support the proposed specification.

Information needed to address this deficiency:

Either tighten the specification ® to be within the qualification threshold of NUT
0% or provide adequate qualification in accordance with ICH Q3B(R2) as follows:

a. Complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

You have not provided adequate leachable data to permit substantive toxicological evaluation of the safety of the container closure system ® for this drug product. Specifically:

a. You have not tested at least three drug product stability batches over the entire course of the stability protocol (e.g., 0, 3, 6, 12 months) in order to identify trends for leachables over the course of stability.

b. You have not tested your drug product, for extractable compounds detected above the safety concern threshold (SCT) of @mcg/day ® in Extractable Study 3 (RPT-694).

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Reference ID: 4496538

c.

You have not fully identified all of the compounds above the SCT in your extraction studies.

In your risk assessment ©® you have not provided adequate

justification for the use of the O@ asa surrogate for the eo]

The variability of ©® present in the existing leachable data do not identify

any clear trends and suggest the potential for these compounds to be derived from ® As such, the maximum levels potentially in the

product cannot be ascertained for risk with an adequate degree of certainty.

Information needed to address this deficiency:

Conduct new leachables studies based on all of the extractables identified in Extractable Study 3 identified above the safety concern threshold (SCT) of @mcg/day |

® according to USP <1663> and <1664>. In

addition, since Extractable Study 3 did not address non-volatile compounds, conduct new leachable studies based on the non-volatile compounds identified in Extractable Studies 1 (RPT-701) and 2 (RPT-693). As you design these studies, note the following comments intended to guide your efforts:

a.

Include at least three to-be-marketed drug product batches, each tested over the entire course of the stability protocol (0, 3, 6, 12 months) to identify trends for leachables over the course of stability. The three drug batches should be stored in the planned commercial container closure.

Of note, you used a conservative SCT of OM meg presumably based on genotoxic concerns. However, for acute products (duration of < 1 month) an SCT of 120 mcg/day can be used for genetic toxicity assessment. However, for general toxicity concerns, employ a SCT of 5 mcg/day in the leachable study. The leachable study should use an AET that accurately reflects the potential total daily intake of potential leachables from the drug product and how the product will be dosed. For example, if multiple vials are to be used to deliver a dose, this could affect the AET calculation. In addition, as you have proposed multiple drug product packaging presentations, the AET and toxicological risk assessment must be based on the worst-case clinical use of the product, which may result in

the use of more than one packaging configuration per procedure, unless adequately justified otherwise.

Multiple compounds were not fully identified from your extraction/leachable studies. This included the leachable identified in the final drug product samples from Leachable Study 3 as ® Provide descriptions of the methods and procedures used to attempt to identify these compounds and justify why these compounds could not be identified or provide further data supporting identification of these chemicals.

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d. Provide adequate justification to support that use of 8 is appropriate to represent the potential toxicity of ©© either by providing literature references or performing adequate QSAR analysis.

e. Provide a root-cause analysis to identify the source of the ©® or confirm that the © present are derived from either |

©® If they are derived from a ow

©® justify how you intend to adequately control © to ensure product consistency and quality. In addition, submit a detailed discussion of the extractables leachables correlation and specifically discuss any discrepancy between the compounds identified in the leachable studies compared to those that were predicted to be potentially present based on the extractable data.

CENTER FOR DEVICES AND RADIOLOGIC HEALTH

8.

Reference ID: 4496538

You provided shelf-life and package integrity summary results for the syringe tip cap. However, you did not provide enough information to ensure that the tip cap will be provided sterile and will remain sterile throughout its shelf-life. This information should be provided to ensure that your device is safe for use. Provide the following:

a. A description of the sterilization method | as well as the sterilization site.

b. Incase of ©® sterilization |

c. For ©® the maximum levels ©® and an explanation

why these levels are acceptable.

d. A description of the sterilization validation method with a citation of the relevant standard(s), but not the validation data itself.

e. The sterility assurance level.

f. Pyrogenicity testing, including a description of the test method, the chosen endotoxin test limit, and your testing frequency. Alternatively, you may provide a scientific justification for why endotoxin testing is not required.

g. A description of the packaging used to maintain the sterility of the device and a description of the test methods, but not the package integrity test data itself. Please note that the Agency recommends seal strength and a package integrity test after accelerated (and/or real time) aging and visual inspection and a package integrity test after simulated shipping and distribution.

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Page 6

PRESCRIBING INFORMATION

9. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

PROPRIETARY NAME

10. Please refer to correspondence dated, January 25, 2019, which addresses the proposed proprietary name, ZYNRELEF. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

Letter 09 of 50

Application: BLA761082 Letter date: 2019-06-11
Packet ID: crl_85fdb55a3e955336 Source file: 761082_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

We also acknowledge receipt of an amendment to a supportive DMF, which was not reviewed for this action. You may cite the DMF by specific reference as part of your response to the deficiencies cited in this letter.

FACILITY INSPECTIONS:

1. During a recent inspection of the Kashiv BioSciences, LLC (FEI 3011289655) manufacturing facility for this BLA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

U.S. Food and Drug Administration

Silver Spring, MD 20993
www.fda.gov

Reference ID: 4962624

BLA 761082

Page 2

PRODUCT QUALITY:

2.

Reference ID: 4962624

A pre-license inspection of the drug substance (DS) manufacturing facility identified significant deficiencies regarding quality control (QC) documentation that may have negatively impacted the accuracy and reliability of the analytical data provided to demonstrate that Theragrastim is highly similar to US-licensed Neupogen. Furthermore, the data provided in the submission do not support process validation and DS and drug product (DP) quality at release and on stability. In addition, the Agency is concerned about the repeated Quality Assurance (QA) failures at Kashiv Biosciences manufacturing site. For the Agency to make a meaningful assessment of the application, it is critical that product quality information provided in the BLA be accurate, reliable, and complete. In the absence of an adequately functioning QA unit, the Agency does

not have sufficient assurance that the Applicant will be able to perform an appropriate retrospective review of all analytical data to ensure their accuracy. The retrospective review is necessary to support a determination that Theragrastim is highly similar to U.S.-licensed Neupogen and the adequacy of process validation, release, and stability data. To address this deficiency, identify an appropriately qualified, external third party to perform an independent and thorough audit of all the product quality data provided in your 351(k) BLA for accuracy and completeness. The Agency recommends that, prior to initiating the external third party audit, you submit a detailed audit protocol with the following information to obtain Agency's agreement on the protocol design and content:

a. Purpose and scope of the audit,

b. Adescription of the qualifications and experience of audit team members with regards to the intended purpose and scope of the audit,

c. Roles and responsibilities of the external third party and Kashiv Biosciences,

d. | Adescription of how the external third party and Kashiv Biosciences would address any disagreements or differences in opinion that may arise during the audit process, and

e. Adescription of the nature and extent of information that will be included in the final audit report.

Depending on the final audit results, as appropriate, additional studies may be needed to generate new information and data to support the product quality content in your 351(k) BLA resubmission. The Agency will not be able to perform a meaningful review of your 351(k) BLA until the final audit report provides assurance that all analytical similarity and other product quality information provided in the 351(k) BLA application is accurate and complete.

BLA 761082

Page 3

4.

Reference ID: 4962624

Analytical Similarity

The CEX-HPLC analytical similarity data indicate differences in charge variants between Theragrastim and US-licensed Neupogen. For example,

a.

Figure 19 from report RPT-1076 "Analytical Testing Report to Demonstrate Similarity of Theragrastim (Adello Product) to Neupogen (Reference Product)" shows that out of the 8 Theragrastim DP lots, lots 180136, 170086, 3-FIN2479, and 3-FIN-2897 have total charge impurity variants levels of 1.0-1.3%, which exceed the US-licensed Neupogen range of < 1.0% for total charge impurity variants levels.

. Figure 4 from the new forced degradation report PTL-2169-R "Force

Degradation Study Report of Theragrastim and Neupogen" shows peaks eluting at ~ 12.5 min and ~18.5 min by CEX-HPLC for Theragrastim. These peaks were not observed in US-licensed Neupogen under the same light-induced stress conditions. In addition, data provided in Figure 15 show that Theragrastim has lower purity than US-licensed Neupogen (~82% vs. ~95%) after 2 cycles of light exposure for 0.3 mg/mL vial presentation.

In the absence of additional data and appropriate justification, these differences preclude a determination that Theragrastim is highly similar to US-licensed Neupogen. To address this deficiency, provide appropriate information in your 351(k) BLA resubmission to demonstrate why these differences do not preclude

a determination that Theragrastim is highly similar to US-licensed Neupogen.

We noted several deficiencies in the impurity characterization report RPT-1055

provided in Section 3.2.S.3.2. For example,

a. The labels for chromatographic plots in the report indicate that the study was performed in August 2018. It appears that some study samples, e.g., US-licensed Neupogen lot 1062643 with an expiration date of April 2018, were tested after expiry in this study. In addition, you did not provide the storage conditions and dating periods for samples from Hydrophobic Interaction Chromatography (HIC) load and Tangential Flow Filtration (TFF) retentate + rinse. Therefore, it is not clear whether samples from HIC load and TFF retentate + rinse were of good quality when tested in this study. It is not appropriate to use expired products in the impurity characterization studies because the impurity results from expired products may not be representative of the impurities profiles from unexpired material. To address this deficiency, provide the ages of the Theragrastim materials used in the study and the study execution dates in your report. Ensure that Theragrastim and US-licensed Neupogen lots

used in this study are within expiry dates. As appropriate, perform additional studies to characterize the impurities in Theragrastim and compare against US-licensed Neupogen.

It is not clear whether you used the baseline drop integration method to quantify the chromatographic peaks observed in the RP-HPLC and CEX-HPLC chromatograms. Clarify the peak integration method used to quantify RP-HPLC and CEX-HPLC chromatographic peaks for Theragrastim and US-licensed Neupogen. Integration of RP-HPLC and CEX-HPLC chromatograms should be conducted using the baseline drop integration method because the original valley-to-valley peak integration method resulted in underestimation of impurities. Reanalyze any peaks not analyzed using the baseline drop integration method and provide the updated results.

We do not agree with your statement that "All species are product-related substances". For example, several CEX-HPLC peaks have < 50% potency, indicating that these peaks likely represent product-related impurities. Per ICHQ6b "Test Procedures and Acceptance Criteria for Biotechnological/Biological Products" product-related substances have "properties comparable to those of the desired product with respect to activity, efficacy, and safety...". Provide a rationale for designating the various charge variants observed by CEX-HPLC as product-related substances or product-related impurities.

You did not state whether the Theragrastim peaks separated by RP-HPLC are product-related substances or product-related impurities. In addition, you did not provide potency values for Theragrastim peaks separated by RP-HPLC. Clarify which variants observed by RP-HPLC are product related substances and which are product related impurities and explain your rationale for those categorizations.

You stated that the peak CEX-4 is characterized as primarily comprised of a pentose adduct species when Theragrastim is stored under the recommended storage conditions, and is primarily comprised of an M127 oxidized species in oxidation-stressed materials. The difference in CEX-4 species identified for material stored under recommended and stress conditions suggests that the identity for fractions enriched under stressed conditions may not represent the species existing under recommended

storage conditions. Provide data on the identity of species in corresponding chromatography peaks observed by CEX-HPLC, RP-HPLC, and SE-HPLC, for Theragrastim and US-licensed Neupogen samples stored at the recommended and stressed storage conditions.

BLA 761082

Page 5

5.

f. The Theragrastim lot used for characterization of SEC-P1 aggregate peak was not listed in the material table in RPT-1055. The Theragrastim lot used for characterization of SEC-P2 dimer peak was also not listed. Provide a description of the identity and suitability of the Theragrastim samples used in characterization of SEC-HPLC fractions.

g. You did not characterize some chromatographic peaks observed by RP-HPLC and CEX-HPLC in US-licensed Neupogen samples, for example, RP-2, RP-4, and CEX-3. Clarify whether the identity of the species in the uncharacterized peaks from US-licensed Neupogen is the same as in the same peaks observed in Theragrastim samples.

In your 351(k) BLA resubmission, you stated that the conditions used in the original forced degradation study under protocol PTL-1192-R were too extreme. For this reason, you performed a new forced degradation study under protocol PTL-2169 and provided the relevant data in the report PTL-2169-R in the 351(k) BLA resubmission. However, you did not provide a justification for the stress conditions and the time points used in this new forced degradation study. To address this deficiency, provide detailed information in your 351(k) BLA resubmission to justify how these study conditions are appropriate to help evaluate meaningful degradation rates for Theragrastim and US-licensed Neupogen.

Regarding analytical similarity report RPT-1076 for Theragrastim and US-licensed Neupogen, it is not clear whether you used the baseline drop integration method to quantify the chromatographic peaks observed in the RP-HPLC and CEX-HPLC chromatograms, refer to comment 4b. Reanalyze any peaks not analyzed using the baseline drop integration method and provide the updated results.

Control Strategy

BLA 761082

Page 12

23.

Reference ID: 4962624

Stability Protocol

In your response to CR item #52 regarding annual stability protocol, you proposed to place (i) one lot from each of all four presentations on stability in the first year of commercialization, and (ii) one lot of vials and one lot of PFSs on stability each year following the first year of commercialization, with alternating high and low dose forms for the vial and PFS presentations. Your proposed approach for annual stability program is not acceptable because you did not provide sufficient stability data to demonstrate that the high and low dose forms in vials versus PFSs have the same stability profiles. For example, data provided in Figure 26 in report PTL-2169-R "Force Degradation Study Report of Theragrastim and Neupogen" show differences in the degradation rates between high and low dose forms of Theragrastim DP. Moreover, the proposed stability strategy carries the inherent risk that changes to product quality will go undetected for 2 years because you will not test the low and high dose products in both container closure systems every year. To address this deficiency, revise

your annual stability protocol to place one lot from each of all four presentations on stability at the intended storage condition of 5°C after commercialization.

Stability

24.Real time stability data provided in the BLA submission do not support the proposed 24 months dating period for Theragrastim PFS and vial presentations. Specifically:
a. DP stability data show many out-of-specification (OOS) results by RP-HPLC.

For examp!
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vi. Loi

e,

Lot 400-16014 (vial): Multiple OOS failures for purity by RP-HPLC occurred at 6 months, 12 months, and 18 months inverted; as well as 12 months, 18 months, and 24 months upright.

Lot 400-16015 (vial): OOS for purity by RP-HPLC happened at 24 months upright; as well as 12 months, 18 months, and 24 months inverted.

450-16017(vial): OOS for purity by RP-HPLC at 24 months.
Lot 300-16009 (PFS): OOS for purity by RP-HPLC at 18 months.
Lot 300-16011(PFS): OOS for purity by RP-HPLC at 6 months.
350-16012(PFS): OOS for purity by RP-HPLC at 18 months.

You did not provide a scientifically sound justification for proposing a 24-month dating period for Theragrastim DP despite the above-mentioned stability failures

for multiple lots.
b.

Therefore, these data are insufficient to support tl
period for DP PFS and vial presentations when s
conditions of 5°C. To address this deficiency, pro}

In addition, there are missing data at many stabi
specifications. For example, missed testing for p;

ity timepoints for various
articulate matter at 6 months

or 12 months, as well as missed testing for polysorbate 80 at 6 month and 12

months for several lots. Justify these missing da

'a. You should follow the

stability protocol to test particulate matter and polysorbate 80 at all proposed

timepoints.

several lots by UV absorbance and was tested b:

. Protein concentration was not tested at 18-month and 24-month timepoints for

y RP-HPLC instead. Provide

appropriate information to demonstrate that the two different methods will produce comparable results for protein concentration.

he proposed 24-month dating
'ored at recommended storage
pose a revised dating period

that is supported by appropriate real-time stability data for Theragrastim DP along with a scientifically sound justification to support the proposed dating period.

BLA 761082
Page 14

Shipping Validation

25.We noted the following deficiencies in shipping performance qualification protocols PTL 2079 and PTL-2080:

a. You did not fully address CR item #30(a) with regards to assessment of the qualification of the shipping container to maintain the product temperature when exposed to worst-case conditions of temperatures (e.g., different climatic zones and seasons).

b. You did not fully address CR item #30(b) with regards to a description of the batches used in the study and criteria for selection.

c. The proposed product quality assessment strategy for shipping qualification does not include a test for appearance. Include appearance testing in your assessment to help evaluate changes in product quality before and after shipping.

Provide appropriate information in your 351(k) BLA resubmission to address the

above deficiencies.

PRODUCT QUALITY MICROBIOLOGY:

26. Your application referenced the Drug Master File (DMF)! This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on May 16, 2019. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this CR letter, include the date the DMF holder amended their DMF to address the deficiencies.

27.Numerous discrepancies were noted between the media fill reports, the media fill summary report (CMO-1041), and Section 3.2.P.3.5 of the BLA (Tables 67 and 68). Clarify these discrepancies and provide the corrected information in the BLA resubmission.

CMC STATS:

28.Regarding the biological potency results of the M-NFS-60 cell proliferation assay, we found inconsistencies in the reported potency values and the Theragrastim DP lots included in the analysis between multiple submissions. Refer to Exhibit III of the report RPT-0987 in response to IR received by FDA on 01/23/2018 and Table 3 of the report PRT-1077 in current submission. Specifically, differences are found for:

e The relative potency data provided for DP lots 35-15013-RND, 40-15046, 3-FIN-2897 and 45-14042 are different in RPT-0987 and PRT-1077.

Reference ID: 4962624

BLA 761082
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e Lots 30-15018, 30-15019 and 45-15025 are not included in report PRT-1077 while they were included in report RPT-0987.

e DP lots 17-0086 and 180136 are included in report PRT-1077 while these two lots were not in report RPT-0987.

To allow for a proper evaluation of the results, provide scientific justifications or explanations for these differences and any other differences identified during the audit described in CR item #2 above.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the draft guidance for industry Labeling for Biosimilar Products.°

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.*

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that are identical to the carton and immediate container labels submitted on March 20, 2019.

PROPRIETARY NAME

Please refer to correspondence dated, March 13, 2019, which addresses the proposed proprietary name, Releuko. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

1 http://www.fda.gov/Drugs/GuidanceComplianceRegulatory|nformation/LawsActsandRules/ucm084159.htm

2 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

3 When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Reference ID: 4962624

BLA 761082
Page 16

Letter 10 of 50

Application: NDA211950 Letter date: 2019-10-18
Packet ID: crl_93e408cdb3f69560 Source file: 211950_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

COMPLETE RESPONSE

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing and holding of the drug substance and the drug product must comply with the current good manufacturing practice (CGMP) regulations in 21 CFR 210 and 211. During the pre-approval inspection of

manufacturing facility for this
NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved or alternative manufacturing facilities which are in compliance with cGMPs must be included in the application.

2. There is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling. Clinical use data should be submitted to support the use of the final to-be-marketed SCS Microinjector Delivery System. The final to-be-marketed configuration should be evaluated by at least three physicians and in at least 30 patients.

Reference ID: 4507848

NDA 211950

Page 2

3.

Please provide data generated from three new registration batches

using the proposed commercial process to demonstrate process robustness and product meeting quality standards of efficacy, stability, and safety. Please provide at least one registration batch with 3 months stability data at long term storage and 3 months stability data at accelerated condition.

One or more amendments to your pending application does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6,

2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

To add a new indication or other condition of use;

To add a new strength;

To make other than minor changes in product formulation; or
To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, you must verify that the proposed change described in the amendment is not one of the types of amendments described above.

Please provide a list of your amendments submitted to FDA on or after December 5, 2016, clearly referencing each amendment by submission date, and either:

i. state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

ii. verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

The cover letter for your Complete Response and all future amendments to your unapproved 505(b)(2) application should continue to address the requirements under 21 CFR 314.60(f).

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Reference ID: 4507848

NDA 211950
Page 3

ADDITIONAL COMMENTS

In addition, we have the following comments/recommendations that are not approvability issues:

5. The drug product is an ophthalmic suspension. We recommend that for quality control purposes, you develop an in vitro drug release method and include the dissolution test in the specifications of the product. We recommend that you submit the development and validation report for the proposed in vitro drug release method including justifications and enough data supporting the selection of the dissolution testing conditions (equipment/apparatus, in vitro drug release media, agitation/rotation speed, pH, sink conditions, use of surfactant if applicable, etc.). Please provide data/information supporting the discriminating ability of the method with respect to the most relevant critical material attributes (CMAs, e.g., PSD), critical formulation variables, and critical process parameters (CPPs).

6. Update manufacturing process flow diagram to include all individual process step enhancements described below.

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Reference ID: 4507848

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PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

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Application: NDA208574 Letter date: 2019-11-04
Packet ID: crl_ab80a221e7214739 Source file: 208574Orig1s000,Orig2s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

During a recent inspection of the TEVA PARENTERAL MEDICINES, INC. (FEI 2027158) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR

1 We update guidance's periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https:/www.fda.gov/Regulatory|Information/Guidances/default.htm.

Reference ID: 4576302

NDA 208574
Page 2

Requirements for Prescribing Information? and Pregnancy and Lactation Labeling Final

Rule' websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.*

FACILITY INSPECTIONS

During a recent inspection of the TEVA PARENTERAL MEDICINES, INC. (FEI 2027158) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Letter 12 of 50

Application: NDA210852 Letter date: 2019-11-20
Packet ID: crl_ca8406cfae8a219a Source file: 210852_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

During a recent inspection of the O° (FEI oe and
Dr. Reddy's Laboratories Limited (FEI 3006549835) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION
Your proposed Prescribing Information (PI) must conform to the content and format

regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR

Reference ID: 4522753

NDA 210852
Page 2

Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final Rule? websites, which include:

e The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

e The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

e Regulations and related guidance documents

e Asample tool illustrating the format for Highlights and Contents, and

e The Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

e FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.%

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised, as attached, based on our proposed revisions.

Letter 13 of 50

Application: NDA205394 Letter date: 2020-03-24
Packet ID: crl_f4366f3c85221805 Source file: 205394_2023_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

1) With respect to the manufacturing process:

Reference ID: 4580538

NDA 205394
Page 2

2) With respect to drug product stability:

We acknowledge the out of specification (OOS) investigations submitted in response to the September 26, 2019, action letter. However, due to the manufacturing process deficiencies described in Item 1 above, we have determined that stability data obtained from testing of the existing exhibit batches cannot be used as primary data for establishment of product shelf life. Therefore, we recommend the following:
a) Submit 12 months of long-term stability data for exhibit batches manufactured as recommended in Comment 1. Stability testing should be performed using fully validated methods and the suitability of analytical equipment should be verified prior to use. The product shelf life assigned will be based on review of this stability data.
b) If you intend to use the 2017 or 2018 batch stability results as supportive data, provide the raw HPLC data for all corrected analytical results. Additionally, regarding INV-2019-017, in order to support disqualification of the OOS stability results obtained using © for analysis of this
product, further investigation is needed to identify the root cause.

FACILITY INSPECTIONS

3) During a recent inspection of the a
drug substance manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

4) During the recent inspections of IntelGenx Corp. (FEI 3005721224) for oral film products, our field investigator observed objectionable conditions at the drug product manufacturing facility. In addition, during the review of the submission dated 09/26/2019, we are recommending manufacture of new exhibit batches tested in accordance with cGMPs. Please note that that this information will be reviewed by the Agency during the review of the application and a follow up Pre approval inspection may be needed to verify that the facility has taken necessary corrective actions to ensure oral film product quality.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final

1 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

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Reference ID: 4580538

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Page 3

Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items rom labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) 'ormat as described at FDA.gov.?

CARTON AND CONTAINER LABELING

If you resubmit this application, include draft carton and container labeling revised as ollows:

General Comments (Container labels and Carton Labeling)

e The usual dose statement can be improved to ensure consistency with the Physician Labeling Rule (PLR) formatted prescribing information labeling. We recommend you revise the usual dose statement:

to read "Recommended Dosage: See prescribing

(4)

information."

e The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. Ensure that the degree symbol and temperature scale follow each numeric value denoting temperature ranges to increase clarity. For example, revise "59° - 77°F (15° - 25°C)" to read "59°F to 77°F (15°C to 25°C)".

Container Labels

e As currently presented, the format for the expiration date is "YYYY MM." However, it is unclear whether the month (that is, MM) will be displayed using numerical (for example, 06) or alphabetical (for example, JU) characters. Therefore, we were not able to assess the appropriateness of the proposed expiration date format from a medication safety perspective. Please clarify whether you propose to use only numerical characters for the expiration date, or whether you propose to use alphabetical characters for the month. Additionally,

to minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day, if space permits. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

2 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330Zhtm
3 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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www.fda.gov

Reference ID: 4580538

NDA 205394
Page 4

numerical characters are used or in YYYY-MMNM-DD if alphabetical characters are used to represent the month.

Carton Labeling

e It is unclear what information will be contained within the "Serialization Area." Therefore, we are unable to assess the acceptability of the information. Please clarify the specific information you intend to display in the "Serialization Area."

e As currently presented, there is no product identifier on the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The draft guidance is available from: https:/Awww.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044 pdf

e We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

e We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the carton labeling. The lot number and expiration date are required per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively. Ensure that the lot number and expiration date are present on the carton labeling in accordance with 21 CFR 10(i)(1) and 21 CFR 211.137.

e We note the statement

(b) (4)

which could lead to confusion.
Consider relocating this statement to the back panel, deleting the statement altogether, or address this concern by other means.

PROPRIETARY NAME

Please refer to correspondence dated, January 29, 2020, which addresses the proposed proprietary name, RizaFilm. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA211964 Letter date: 2020-11-06
Packet ID: crl_03513dfd21bbac21 Source file: 211964_2021_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

During a review of records requested under FD&C act section 704(a)(4) provided by Supernus (FEI: 3005209462) manufacturing facility, FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection or adequate facility responses addressing these conditions) before this application may be approved.

If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-quidance-documents-industry-fda-staff-and-other-stakeholders.

Reference ID: 4698727

NDA 211964
Page 2

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.°

CARTON AND CONTAINER LABELING

The Office of Pharmaceutical Quality (OPQ) finds the label attached to your November 5, 2020, email correspondence not acceptable from a Chemistry, Manufacturing, and Controls perspective, and we recommend the label be revised as follows:

Each capsule contains:
Viloxazine..... 150 mg
(equivalent to 173 mg of viloxazine hydrochloride)

For more information, you may refer to the FDA Guidance Naming of Drug Products Containing Salt Drug Substances.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

Please refer to correspondence dated, November 5, 2020, which addresses the proposed proprietary name, Qelbree. This name was found acceptable, pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

1 http://www.fda.gov/Drugs/GuidanceComplianceRegulatory|nformation/LawsActsandRules/ucm08415 9.htm
2 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm
3 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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Application: NDA211413 Letter date: 2021-01-08
Packet ID: crl_fc1e15a2630b3958 Source file: 211413_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

NONCLINICAL

Unless otherwise justified, nonclinical studies conducted to qualify the safety of leachables should be designed such that the identified leachables are administered in a clinically relevant manner at levels that are equivalent to or greater than what patients would be administered when incorporating interspecies allometric scaling. The information provided in your complete response does not adequately qualify the safety of the identified leachables with your drug product. Specifically:

1. The 14-day toxicity study in rats does not achieve clinically relevant leachables exposures, with animals receiving <_™ of the leachables/day when compared with the maximum estimated daily leachables exposure in patients. While the evaluation of analyzed concentrations in leachable study TE190276 in comparison with the 14-day toxicity study TE192771 based on the GC/MS analysis is informative, it does not address the observed differences in daily exposures to the animals versus maximum estimated daily exposures in humans when accounting for interspecies allometric scaling.

2. You have proposed an acceptable intake of' mcg/day for the identified

™® leachables (Toxicological Assessment
Annex 5). As previously communicated to you, while it is recognized that PQRI-

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NDA 211413
Page 2

PODP has proposed higher qualification threshold levels for leachables, the FDA recommends 5 mcg/day as the qualification threshold for non-genotoxic

leachables. a)

3. You applied ©® on the PQRI limit of __mcg/day to calculate acceptable intake for the © that would allow for sufficient safety margins. However, this approach is not considered adequate as the application ©® has not been considered for regulatory decisions on the qualification of leachables (or impurities) for safety.

4. You applied ©®to estimate that the total exposure of the API and

related leachables to the rats during the 14-day toxicity study is approximately times higher than what a patient would receive following administration of 8 g in a single day and proposed a change in labeling |

©® Given the unknown toxicity of the identified leachables, it cannot be assumed that lower daily doses of API and related leachables over the 14-day study in rat would adequately address the safety concerns of the higher leachables exposures associated with an 8 g dose in a single day.

5. The surrogates chosen for use in your read-across analysis with worst-case scenario substances (submitted December 8, 2020), do not contain sufficient toxicology information to qualify the identified leachables for safety. The

© surrogates included in the read-across assessment
are not considered acceptable and there are insufficient toxicity data available for to
predict any potential leachables toxicity. Because the]
cannot be fully characterized, there is considerable uncertainty regarding the structural similarity of the chosen surrogate compounds (i.e., active pharmaceutical ingredient [API] and
which further limits the utility of the read-across approach.

(4)

Information needed to resolve the deficiencies

Given the absence of sufficient toxicity information surrounding the identified leachables, and the feasibility issues precluding adequate structural characterization of the ©@ 'you will need to conduct an additional general
toxicity study, in an appropriate animal species, for any leachable that exceeds the safety qualification threshold of 5 mcg/day. Such a study should be designed to achieve leachables exposures that are clinically relevant. The potential challenges of the API masking potential toxicity associated with the leachables exposure are acknowledged, but we believe it is feasible to design a nonclinical study that will allow for an adequate safety assessment of the leachables and/or identify any leachables-related shifts in the toxicity profile associated with the API. For example, you may consider conducting a toxicity study of 14-day duration in a larger animal species that would allow for a larger volume of the drug product containing leachables from the ©@ rubber
stopper to be administered. As indicated in the teleconference held on November 30, 2020, we strongly recommend that you submit a draft study protocol for the Agency to review and provide feedback prior to initiating any additional nonclinical studies. Providing a draft protocol for comment will help you to design a study that can best

inform on the safety of the identified leachables when administered at clinically relevant exposures.

Submit a leachables assessment plan and/or justification that the leachables in the drug product to be administered to the animals are qualitatively and quantitatively similar to the identified leachables described in Study Report TE190276. If any additional leachables are characterized on further testing, or if there are any revised structures and/or identification of any new structures of leachables compared with those identified in your previous leachables assessment (TE 190276), plan to conduct additional (Q)SAR evaluation(s) for bacterial mutagenicity. A follow-up Ames test (bacterial reverse mutation assay) is recommended to qualify leachables that exceed

120 mcg/day with identified structural alerts for genotoxic potential.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.3

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Application: NDA214439 Letter date: 2021-04-22
Packet ID: crl_294397bf9e47126d Source file: 214439_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

During a recent inspection of the oO (FEI: om)
manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by oO FEI: ;

© 'manufacturing facility, the FDA noted objectionable
conditions. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and adequate facility responses addressing these conditions) before this application may be approved. The FDA will communicate the outstanding issues to the facility no later than 10 business days from issuing this complete response letter. Please contact , FEI: © manufacturing
facility for additional information.

(b) (4)

An inspection of the O FEI a we

, facility is required before the application can be approved. FDA must
assess the ability of that facility to conduct the listed manufacturing operations in

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Page 2

compliance with CGMP. Because of restrictions on travel we have been unable to conduct an inspection of the © (FEI: ©) facility.

We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID-19.!

ADDITIONAL PRODUCT QUALITY COMMENT

We acknowledge you added © testing as part of the |
commercial production. You stated in Section 3.2.P.3.4 that the acceptance criteria {
®® will be established based on results from first three commercial batches. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process Validation: General Principles and Practices (2011)), rather than to develop and finalize the commercial manufacturing process. Therefore, propose acceptance criteria ®® based on data collected
from development and registration batches. Proposed ranges should take into account scalability issues for any scale-dependent parameters.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information? and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.4

1 https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-gquidance-documents-industry-fda-staff-and-other-stakeholders

2 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

3 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

4 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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PROPRIETARY NAME

Please refer to correspondence dated, January 8, 2021, which addresses the proposed proprietary name, NORLIQVA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA215000 Letter date: 2021-04-30
Packet ID: crl_e6238fc0872f60e1 Source file: 215000_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

1

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2.

. Conduct a leachable study using the conditions that represent the worst case scenario, i.e., aged samples under the long term and accelerated

conditions.

. Justify the proposed AET and PDE.

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PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.$

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Application: NDA213972 Letter date: 2021-07-23
Packet ID: crl_b74cbd31a180bf39 Source file: 213972_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL and STATISTICAL

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21CFR §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (21 CFR §314.125(b)(5)). The clinical data submitted from Study 301 do not provide substantial evidence of effectiveness of sulopenem etzadroxil and probenecid tablets for the proposed indication of treatment of adult women with uncomplicated urinary tract infections (uUT1) caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The reasons for reaching this conclusion are as follows:

1. Although statistical significance was demonstrated for the difference in overall response rate by treatment arm in the ciprofloxacin-resistant (MMITT-R) population, the results are not sufficient as a single trial without a second adequate and well-controlled trial.

2. The other trials conducted with sulopenem failed to meet their primary endpoint, and therefore, could not provide evidence of effectiveness. In addition, these negative trials call into question the effectiveness of sulopenem for the treatment of uUTI. In Study 301, significantly inferior results were observed in the overall response rate for

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sulopenem compared to ciprofloxacin in the ciprofloxacin-susceptible (mMITT-S) population. Significantly inferior results for sulopenem were also observed in the complicated urinary tract infections trial (Study 302) and there was a lack of noninferiority of sulopenem in the complicated intra-abdominal infections trial (Study 303).

To address these deficiencies, we recommend you conduct at least one additional adequate and well-controlled study in uUTI and consider using a different active comparator drug in the study(ies) that is more reflective of currently recommended treatment for uUTI. Additionally, we recommend that you conduct further investigation to determine the optimal sulopenem dosing regimen for the proposed treatmen

indication(s) (see Additional Comments below).

We look forward to working with you on the design of the clinical trial(s) you plan to conduct to address the deficiencies noted above.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.?

CONTAINER LABELS AND CARTON LABELING

Submit draft container labels and carton labeling revised as follows:

Container Labels and Carton Labeling

e To ensure consistency with the Prescribing Information, we recommend revising the recommended dosage statement, _
Prescribing Information" to read "Recommended Dosage: See prescribing information."

' https//www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
3 http://www. fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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Container Labels

Ensure that a linear barcode is included on the 10- and 30-count bottle labels in accordance with 21 CFR 201.25(c)(2). Additionally, we recommend that the container label linear barcode be oriented in a vertical position, as a barcode placed in a horizontal position may be difficult to scan due to the curvature of the bottle.

Furthermore, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

Ensure that a linear barcode is included on the blister cell. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

Carton Labeling

Add the linear barcode to your proposed | {i}-count unit-dose carton labeling. Additionally, when determining placement of the linear barcode, consider that the barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

Ensure that the human-readable and machine-readable product identifier is included on each carton labeling. We recommend you include the intended

location of the machine-readable (2D data matrix barcode) product identifier, near the human-readable portion of the product identifier information. For more information, see draft guidance, Product Identifiers Under the Drug Supply Chain Security Act.

Additionally, we recommend you ensure there is sufficient white space between he linear barcode and 2-D matrix barcode to allow barcode scanners the ability '0 correctly read each barcode.

PROPRIETARY NAME

Please refer to correspondence dated, April 12, 2021, which addresses the proposed proprietary name, Orlynvah. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: BLA761082 Letter date: 2021-08-02
Packet ID: crl_a5ddce1474406b6e Source file: 761082_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

1. Aninspection of the Kashiv Biosciences LLC DS manufacture facility (FEI 3011289655), Chicago, Illinois, is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to conduct an inspection of the Kashiv Biosciences LLC facility during the current review cycle, and the application cannot be approved until the required FDA inspection is conducted and the findings are assessed with regard to this application. We will continue to monitor the public health situation as well as travel restrictions.

Please see the FDA's "Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/148197/download). Please also see the FDA guidances related to COVID 19. These guidances can be found at

' Your proposed proprietary name, Releuko, and proposed proper name, filgrastim-ayow, are conditionally accepted until such time that the application is approved. In this document, we refer to your proposed biosimilar product by using the descriptor Theragrastim, a developmental code name.

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https:/Awww.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-quidance-documents-industry-fda-staff-and-other-stakeholders.

2. During inspection of the manufacturing facility from , the FDA field investigation team conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

3. In-House Reference Standards

a. In response to FDA Item #4, you updated the stability protocols PTL-1981

"Stability Protocol for Theragrastim Primary Reference Standard Lot
"Stability Protocol for Theragrastim Workin
eference Standari r the working reference standards (WRS)

to include a trending strategy and the acceptance criterion to control for EC50 values in the potency testing. However, there are deficiencies in both stability protocols.

b. You provided PTL-2306-R "Summary Report for Qualification of Theragrastim In-House Working Reference Standard Lot " as an update to the information request response #3 dated October 08, (BLA 761082/0053). However, the Agency noted multiple out of specification results (OOS) in this report. Specifically,

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(b) (4)

Because of the above OOS results, we do not agree that the current in-house |

has been qualified appropriately.

To address the above issues, update the stability protocols for the in-house primary and working reference standards to:

i. Provide adequate trending analysis strategies for the EC50 values of the RSs. You should evaluate whether there is a EC50 value drift based on the absolute values generated in the potency assay.

ii. Provide an updated qualification report for the adequately qualified in-house WRS. You should use an adequately qualified WRS as the standard in the stability testing for the PRS.

Establish a stability acceptance criterion for the EC50 for the WRS based ona trend analysis of the EC50 values of the WRS obtained during routing release and stability testing.

4. Analytical methods

In section "Additional information related to Module 3", you revised the potency method (STM-0118) based on the change control CC-20-036. However, the summary information you provided to justify the changes made to the potency assay was inadequate because no supporting data were provided to allow assessment of the appropriateness of the proposed change. To ensure that the proposed change has no impact on the potency assay method validation and test article data, provide adequate information to support the proposed change.

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PRESCRIBING INFORMATION

5. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling

Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry Labeling for Biosimilar Products.

CARTON AND CONTAINER LABELING

6. Submit draft carton and container labeling.
PROPRIETARY NAME

7. Please refer to correspondence dated, February 2, 2021, which addresses the proposed proprietary name, Releuko. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: BLA761148 Letter date: 2021-08-03
Packet ID: crl_22fbea9c63fa9d90 Source file: 761148_2022_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY
Facility Inspections

1. During a recent inspection of the © (FEI: oy
manufacturing facility, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. During a recent inspection of the © (FEI wa)

manufacturing facility for this application, our field investigator conveyed

deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION
We reserve comment on the proposed labeling until the application is otherwise

adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final

1 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

Reference ID: 4835934

BLA 761148
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Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.3

CARTON AND CONTAINER LABELING

We acknowledge receipt of your proposed container label and carton labeling dated July 22, 2020. We reserve comment on the proposed container label and carton labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated January 21, 2020, which addresses the proposed proprietary name, Rolontis. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA215352 Letter date: 2021-10-22
Packet ID: crl_812bafa061f6206f Source file: 215352_2023_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211, and the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. During a recent inspection of the

©® drug product manufacturing
facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Stability data collected from a facility that is not compliant with current Good Manufacturing Practices may not be sufficient to support the stability of your product.

2. The investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

a. The © microbial ingress container closure integrity testing
(CCIT) performed oy]

is acknowledged. However, your proposed

system has yet to demonstrate the ability to withstand a worst-case

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microbial challenge. Please consider the following options to demonstrate the integrity of the assembled device:

b. It is acknowledged that the Alcami facility has performed

hold time study.

c. The validation information for
is acknowledge lease address
e following:

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(b) (4)

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For

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further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination

Products (January 2017), available at
http:/www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

In your submission, you have stated that the aa

Please clarify the electrical component of
your device.

In your submission, you have stated that the device is a

Please clarify the reusability of the device in order to determine if additional testing is needed.

In your submission, you have provided a table of planned validation testing. However, no testing has been included and the list of planned testing does not state specifically what is to be tested. Please perform the following validation testing:

a. You have mentioned conducting transit testing. However, there is no transit testing data included in the submission. Please perform shipping and transit testing mentioned in your submission (ASTM D4169). This is needed in order to ensure a viable product after shipping has consistent performance. Variability of the device after shipping and transit impacts the safety and effectiveness.

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b. Actuation force testing should be conducted to demonstrate that the amount of force needed is not excessive as it could impede the ability of the user to deliver the drug formulation and lead to improper dosage which is critical for safety and effectiveness.

c. Leak testing should be performed a

d. Performance testing to confirm that the device does deliver' of fluid with each actuation and that there is a low variance of volume delivered.

e. Further performance testing to demonstrate consistent performance of the device over the product lifetime. It is important that the device not suffer fatigue over the recommend use life and deteriorate in performance. The deterioration of the device may result in improper or no dosage of the drug formulation.

f. You mention conducting accelerated aging (ASTM F1980). However, there is no testing data included. Furthermore, there is no real-time aging data or real-time aging protocol as well. This is essential to demonstrate consistent performance and stability of the device over the shelf life. The testing to confirm the viability of the device should be a comparison of the previously mentioned performance tests at time point zero and compare it to the testing for devices at the end of the shelf life after undergoing real-

time and accelerated aging, sterilization, and transit testing.

8. You have not submitted human factors validation study data to demonstrate that your user interface supports the safe and effective use of your product by the intended users, for intended uses, and in the intended use environment. We recommend you include a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. You can consider submitting your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments

on the HF validation study protocol. Note that submission of a protocol for review is not a requirement. Guidance on human factors procedures to follow can be found in the following guidance documents: Applying Human Factors and Usability Engineering to Medical Devices Guidance on Safety Considerations for Product Design to Minimize Medication Errors.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.?

CARTON AND CONTAINER LABELING
We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME
Please refer to correspondence dated, March 15, 2021, which addresses the proposed proprietary name, MYDCOMBI. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA213976 Letter date: 2021-12-17
Packet ID: crl_862d3509a3d02ed3 Source file: 213976_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL/ STATISTICAL:

As was conveyed in the Filing Communication - Filing Review Issues Identified Letter dated December 14, 2020, and subsequently communicated in the Discipline Review Letter dated March 19, 2021, our review identified deficiencies with the ability of the submitted data to demonstrate the short- and long-term efficacy of BOS for the treatment of EoE. We have completed our review of NDA 213976, and have determined that neither the data submitted in the NDA, nor the data submitted to the NDA during review of the application, are adequate to support the demonstration of efficacy of BOS for the treatment of EoE in adult and adolescent patients 11 years and older.

1. The results from the evaluation of the symptomatic coprimary endpoint in trial SHP621-301, while statistically significant, were not representative of clinically meaningful change. Throughout the conduct of the development program and the course of the review, we expressed our concerns with the selection of the 230 percent Dysphagia Symptom Questionnaire (DSQ) responder threshold and cautioned you that evidence was needed to support its clinical meaningfulness. The anchor-based analyses that you provided, conducted using the data from the

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12-week initial treatment phase 3 trial SHP621-301, do not support that the selected threshold constituted a clinically meaningful within-patient change.

In addition, although a statistically significant response was observed on the histologic coprimary endpoint in trial SHP621-301, the contribution of that finding to support a determination of benefit is unclear due to the lack of sustained histologic response observed in subjects maintained on treatment with BOS in trial SHP621-302. Further, there are inadequate data to demonstrate that short-term improvement in histologic response predicts improvement in meaningful clinical outcomes.

The evaluation of the key secondary efficacy endpoint of absolute change from baseline in 14-day DSQ combined score for trial SHP621-301 did not demonstrate that subjects treated with BOS had meaningful benefit compared to

those treated with placebo. Although statistically significant results were reported on this prespecified alpha-controlled symptomatic secondary endpoint, the treatment difference between BOS and placebo groups was small, and the assessment period was not supported by the 7-day Patient Global Impression of Severity (PGIS). A treatment difference was not observed on evaluation of the change in 7-day DSQ absolute combined score (conducted to match the 7-day assessment period of the PGIS).

As EoE is a chronic relapsing condition, data to establish the benefit of long-term treatment for a candidate therapeutic is needed to support a determination of durability of effect. The need for long-term efficacy data to support your application has been emphasized throughout the development program, and we refer you to the following communications under IND 103173:

e November 12, 2014 Type B End-of-Phase 2 meeting (meeting minutes

finalized on November 30, 2014)

e July 13, 2015 Type C meeting (meeting minutes finalized on July 15,

2015)

e November 2, 2016 'Initial Comprehensive Multidisciplinary Breakthrough

Therapy Type B Meeting' (meeting minutes finalized on November 4,

2016)

e June 25, 2019 Type B Pre-NDA face-to-face meeting (meeting minutes finalized on June 27, 2019)

e May 20, 2020 Type B Pre-NDA teleconference (meeting minutes finalized on June 2, 2020)

On review of your submitted phase 3 trial SHP621-302 efficacy data, the benefit of long-term treatment with BOS for patients with EoE was not established. The trial did not yield statistically significant results on the pre-specified long-term efficacy endpoint of relapse on both histology and symptoms in the individual

subject.

4. The data submitted to the NDA during review of the application from post hoc

subgroup analyses of subjects without prior history of dilation for the 12-week initial treatment period are inadequate to support the demonstration of efficacy for BOS or the treatment of patients with EoE. Dilation status was collected during screening for eligibility criteria, and dilation-naive status was identified as a subgroup of interest for efficacy analyses only after data unblinding and completion of the SAP-specified analyses. The variable (i.e., dilation status) used '0 identify the subpopulation in trial SHP621-301 is not reliable, as a substantial portion of these subjects were identified by self-report, and it was not possible to confirm the dilation status for these subjects from medical records. On analysis of he 7-day DSQ combined score (to match the 7-day PGIS anchor) in subjects with medical record confirmation of dilation status, minimal separation between reatment groups over the 12-week treatment period was observed.

Information needed to resolve the deficiencies:

To resolve the above-noted deficiencies, we recommend you leverage the existing data to inform the design of a new adequate and well-controlled study including adolescent

and adult subjects with EoE in a prespecified subpopulation (e.g., subjects without a prior history of dilation, subjects with more severe dysphagia symptoms at baseline) to support chronic administration of BOS. If subjects with a prior history of dilation are to be included for analysis, medical record documentation of the procedure should be available for these subjects.

We recommend a treatment period of at least 24 weeks' duration to assess efficacy for both clinical and histologic endpoints, followed by an extension period to provide a total treatment period of at least 52 weeks' duration to ensure adequate exposure to allow for characterization of the safety profile and the durability of response in the intended population.

This new study should assess prespecified symptomatic and histologic coprimary endpoints. To aid in the interpretation of the DSQ results, an appropriate range of within-patient score change that patients consider to be clinically meaningful should be proposed using anchor-based methods (e.g., patient global impression scale as an anchor), supplemented with empirical cumulative distribution function (eCDF) curves using data pooled across treatment arms. You should complete this study before resubmitting the application.

We look forward to engaging with you as you consider the study design and population selection for a future trial of BOS in patients with EoE and advise you to continue to benefit from the frequent interactions with FDA available to you under your granted breakthrough therapy designation. This application may need discussion at an advisory committee meeting during the next review cycle.

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ADDITIONAL COMMENTS:

We have the following additional comments/recommendations that are not approvability issues:

1. You did not conduct a food effect study with either the phase 3 formulation or the to-be-marketed (TBM) formulation of your proposed product. Therefore, the effect of food on the pharmacokinetics (PK) and safety of your drug product to inform dosing instructions in relation to meal intake is unknown. We have determined that the potential effect of food on budesonide exposure from BOS cannot be predicted based on available data/rationale, and a dedicated food effect study is needed. Your product is an oral suspension of corticosteroid budesonide, where adverse events including hypercortisolism and adrenal axis suppression have been shown to be concentration dependent. Considering this, assessing any factor that could potentially increase budesonide exposure is critical. Therefore, you should conduct a dedicated food effect study to inform the prescribing information for BOS and include the results of this study in the resubmission.

2. In the current submission, you provided limited dissolution data with the proposed dissolution method collected at the time of batch release. If approval of your proposed product needs manufacturing any new batch to resolve the deficiencies, provide full-profile dissolution data (n= 12) from that newly manufactured batch collected at the time of batch-release in the next submission. If no new batch manufacturing is required for approval of your product in terms of resolving the deficiencies, only upon approval of the proposed drug product, collect full-profile dissolution data (n= 12) for the first six commercial batches at the time of batch-release and provide these data to the FDA in your annual report.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

1 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, November 25, 2020, which addresses the proposed proprietary name, Eohilia. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA215192 Letter date: 2022-03-29
Packet ID: crl_6261457fac7b308d Source file: 215192_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL AND STATISTICAL

Your submitted data do not support a favorable benefit-risk assessment of vadadustat for the proposed indication of treatment of anemia associated with chronic kidney disease (CKD) in adults not on dialysis and on dialysis. Our determination that the benefits of vadadustat do not outweigh the risks applies to both the non-dialysis-dependent (NDD) and dialysis-dependent (DD) populations of patients with anemia associated with CKD.

With regard to the benefits of vadadustat, you have met the efficacy endpoint of hemoglobin (Hb) response by demonstrating that the change from baseline in Hb with vadadustat is non-inferior to that of darbepoetin alfa, an erythropoietin stimulating agent (ESA), in both the NDD and DD populations of patients with anemia associated with CKD. However, there was higher use of rescue therapy for worsening anemia with vadadustat compared to darbepoetin alfa, particularly for ESA rescue in the NDD-CKD population and for ESA and red blood cell (RBC) transfusion rescue in the DD-CKD population. Some of these differences in rescue therapy are striking. For example, in DD-CKD Trial 0016, ESA rescue for worsening anemia was reported in 22% of vadadustat-treated patients compared to 5% of darbepoetin alfa-treated patients. The corresponding rates in DD-CKD Trial 0017 were 35% and 14%. In addition, in the DD-CKD trials there was a higher incidence of RBC transfusion rescue therapy for worsening anemia with vadadustat, which could potentially impact alloreactivity, a risk factor for renal allograft rejection in patients who undergo kidney transplantation.

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As an oral therapy, vadadustat may offer convenience compared to the intravenous route of ESAs, especially in the NDD-CKD population and the minority of dialysis patients who receive peritoneal dialysis. However, the convenience of an oral drug in the DD-CKD population is less clear for most DD-CKD patients in the United States (U.S.), who receive hemodialysis and are administered ESA at the time of hemodialysis.

The trials established no other benefits of vadadustat in the NDD-CKD or DD-CKD populations.

We have identified the following major safety concerns with vadadustat that outweigh these benefits:

1.

In the NDD-CKD population primary analysis, you did not establish non-inferiority for vadadustat compared to darbepoetin alfa on the primary safety endpoint of adjudicated major adverse cardiac events (MACE) - a composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke - with a hazard ratio (HR) of 1.17 (95% confidence interval 1.01, 1.36). The upper bound of this 95% confidence interval excluded the prespecified non-inferiority margin of 1.25. Furthermore, the lower bound excluded the value of no effect. The risk of MACE with vadadustat was seen in comparison to darbepoetin alfa, an ESA with an established increased risk of non-fatal MI, non-fatal stroke, and all-cause mortality. In addition, each component of the adjudicated MACE endpoint had a numerically unfavorable HR for vadadustat compared to darbepoetin alfa.

Your conclusion that vadadustat is safe in the U.S. population is not supported by the data. In the U.S. subgroup, the estimated hazard ratio for adjudicated MACE was 1.06 (95% CI, 0.87, 1.29); the upper bound of 1.29 does not provide assurance of an absent safety signal for MACE occurrence in the U.S. Furthermore, there was an increased hazard ratio for the non-fatal MI component of MACE in the vadadustat arm in the U.S. population (HR, 1.49, 95% CI, 0.97, 2.30), comparable to that of the overall population.

In the DD-CKD population, there was a concerning signal for adjudicated thromboembolic (TE) events with vadadustat compared to darbepoetin alfa, an ESA with an established increased risk of TE events. The HR was 1.20 (95% CI 0.96, 1.50) for the overall population and appeared more concerning in the U.S. subgroup, which had an estimated HR of adjudicated TE of 1.46 (95% CI 1.13, 1.89).

Furthermore, over 80% of adjudicated TE events were vascular access thromboses. The estimated HR for adjudicated vascular access thrombosis events was 1.28 (95% CI 1.00, 1.63). This result is particularly concerning in the DD-CKD population given the critical need for vascular access for these patients.

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3. Your submitted data raise concerns for a clinically significant risk for drug-

induced liver injury (DILI) with the use of vadadustat in patients with CKD. This conclusion is based on one Hy's Law case, at least seven cases of probable drug-induced liver injury (DILI) with significant elevation in alanine aminotransferase (ALT) without jaundice, and an imbalance in ALT elevations with vadadustat compared to darbepoetin alfa (e.g., ALT >3x ULN in 0.47% of patients treated with vadadustat compared to 0.35% of patients treated with darbepoetin alfa; ALT >5x ULN in 0.31% of patients treated with vadadustat vs. 0.25% of patients treated with darbepoetin alfa). The elevation in alkaline phosphatase in the Hy's Law case does not preclude a conclusion of hepatocellular DILI. Using the new R-value (nR value) criterion, this subject had hepatocellular DILI with at least 10% mortality risk, fulfilling Hy's Law.

Furthermore, we have concerns that the risks seen in the clinical trials where patients were closely monitored (e.g., with liver tests), may underestimate the risks with real-world use of vadadustat, if approved. Given that ESAs are typically administered by health care providers, hemoglobin and patient monitoring is fairly well assured. With the convenience of an orally administered drug such as vadadustat, there is the potential for inadequate patient monitoring (e.g., hemoglobin, liver tests) that could lead to worse

outcomes in some settings as well as the potential to prescribe vadadustat to patients with anemia and decreased creatinine clearance who presently do not receive ESAs. Some of these patients, particularly the elderly, would be at greater risk of MACE. We could not identify a risk mitigation strategy that can adequately mitigate the risks of vadadustat with the proposed dosing regimen to ensure that the benefits of vadadustat outweigh its risks.

Potential Path Forward:

1.

Conduct new clinical trial(s) that establish a favorable benefit/risk assessment of vadadustat in a specific patient population or with a different dosing regimen. In your new clinical trial(s) also assess the following:

e The occurrence of ESA and RBC transfusion rescue therapies, as key secondary efficacy endpoints.

e Rhabdomyolysis as an adverse event of interest, with appropriate clinical and laboratory assessments. We noted numerical imbalances in the incidence of rhabdomyolysis, a rare event, in your NDD population (10 cases with vadadustat vs. 4 cases with darbepoetin alfa) and DD population (5 cases with vadadustat vs. 3 cases with darbepoetin alfa). Vadadustat has a known drug-drug interaction potential with some statins, but the role of this drug-drug interaction in the development of rhabdomyolysis is unclear.

e Seizures as an adverse event of interest. The risk of seizure with vadadustat appears comparable to the known seizure risk associated with ESAs.

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2. You will also need to propose and assess a strategy that successfully mitigates the risk of hepatotoxicity with the use of vadadustat in patients with CKD. Note that even if you are able to mitigate the risks of MACE and TE in a specific population or with a different dosing regimen, we have significant concerns regarding the ability to mitigate the risk of DILI given that this DIL] appears idiosyncratic, and patients are not as closely monitored in the real-world setting compared to clinical trials. DILI can cause acute liver failure, the need for liver transplantation, or death. Even if rare, it is not clear that the convenience of oral dosing could outweigh such risks.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(I)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.3

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Refer to correspondence dated, June 11, 2021, which addresses the proposed proprietary name, Vafseo. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

3 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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Application: BLA761240 Letter date: 2022-04-29
Packet ID: crl_91ff2b834a8e838b Source file: 761240_2023_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY
1. We have determined that manufacturing control strategy for toripalimab manufacturing at © does not

align with current industry standards and ICH QS5A guidelines. Specifically, no adventitious virus testing is performed for unprocessed bulks (UPBs) in the manufacturing process to produce toripalimab and other product(s) for non-US market. Those processes share common equipment and/or materials with toripalimab manufacturing for the US market. ICH guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin recommends that "Appropriate testing for viruses should be performed at the unprocessed bulk level [...]" and "the safety of these products [biotechnology products derived from cell lines] with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process [...]" through "testing the product at appropriate steps of production for absence of contaminating infectious viruses," as well as requires "manufacturers develop programs for the

Reference ID: 4976394

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ongoing assessment of adventitious viruses in production batches." The lack of an adventitious virus testing program for non-US manufacturing processes poses

a risk

of adventitious virus cross-contamination of toripalimab batches for the US

market manufactured using the same equipment and materials, as well as risk of manufacturing facility disruptions that could risk patient supply.

To address the deficiency, provide the following information on control strategy and measures implemented to assure that all toripalimab batches are produced per current industry standards and aligned with ICH Q5A guidelines:

a.

You committed to implement virus testing for UPB for every batch of all products which share equipment or materials or any other product-contacting surface with toripalimab intended for the US market. Submit change control report(s) demonstrating implementation of the virus testing for UPB for all products manufactured on the same equipment as toripalimab drug substance.

The materials and equipment used downstream of the UPB testing point carry risk of being contaminated by unknown adventitious virus from previously untested production batches. To mitigate this risk, implement the following and submit applicable documentation demonstrating implementation:

i. Replace the multi-use materials in manufacturing that harbor the greatest risk of contamination, such as «
with new materials. Submit qualification and implementation reports of these multi-use materials.

ii. Sterilize shared product-contact equipment that is amenable to sterilization using methods sufficient for removal or inactivation of viruses. Submit reports of the sterilization activities that assure a virus-free process, including documentation of the method(s) used and scientific justification for their suitability for removing or inactivating virus.

Due to the risk of potential contamination of toripalimab batches produced prior to the implementation of adequate viral safety measures, toripalimab batches manufactured prior to implementation of these measures should not be distributed for human use in the US. To fulfill 21 CFR 601.20(b) requirements, confirm that toripalimab drug product produced from drug substance manufactured after implementation of the corrective measurements described in items a and b will be available within the review timeline of the re-submitted application.

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d. Submit a comprehensive rationale on how the revised BLA control strategy aligns with current industry standards and ICH Q5A guidelines.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.3

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

Please refer to correspondence dated, October 6, 2021, which addresses the proposed proprietary name, ©® This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

3 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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Application: BLA761151 Letter date: 2022-05-12
Packet ID: crl_a7dc7930884c4cd6 Source file: 761151_2023_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

During a recent inspection of the UCB Pharma SA (FEI: 3003909356) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PROPRIETARY NAME
Please refer to correspondence dated, October 14, 2020 which addresses the proposed proprietary name, Bimzelx. This name was found acceptable pending approval of the

application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

Reference ID: 4983101

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Page 2

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Application: NDA212905 Letter date: 2022-05-23
Packet ID: crl_a44d3759849e311a Source file: 212905_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

(b) (4)

for this application, our field
investigator conveyed deficiencies to the representative of the facility.
Satisfactory resolution of these deficiencies is required before this application
may be approved.

PRESCRIBING INFORMATION

(1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources7 and Pregnancy and Lactation Labeling Final Rule2 websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include

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updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

CARTON AND CONTAINER LABELING

(2) We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, March 23, 2021, which addresses the proposed proprietary name, Ycanth. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: BLA761299 Letter date: 2022-12-20
Packet ID: crl_89da1b7f9b961c13 Source file: 761299_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

Following inspection of the Alvotech hf, Reykjavik, Iceland facility (FEI: 3013702557) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected

1 This Complete Response letter takes no position on whether this application would be eligible for or blocked by any exclusivity if it were otherwise eligible for approval.

2 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

3 https:/Awww.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

Reference ID: 5098083

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Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry Labeling for Biosimilar Products.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient

is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

Please refer to correspondence dated, March 11, 2022, which addresses the proposed proprietary name, Simlandi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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Application: NDA204311 Letter date: 2023-01-13
Packet ID: crl_1fe400ba00112e18 Source file: 204311_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS

(1) Following surveillance inspection of Mylan Laboratories Limited Unit-8, a Viatris Company (FEI # 30002785310, Vizianagaram, Andhra Pradesh, India) manufacturing facility listed in this application, FDA conveyed deficiencies to the representatives of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.

PRESCRIBING INFORMATION

(2) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the

Reference ID: 5109697

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CARTON AND CONTAINER LABELING

Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.?

(3) We reserve comment on the proposed labeling until the application is otherwise

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Application: NDA215721 Letter date: 2023-01-13
Packet ID: crl_2c22f57579146a8c Source file: 215721_2024_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

Considering that
provide updated release and stability speci
unidentified © 'provide the anal

©® are likely present in the drug product,

ications to include any identified and
lytical methods and respective validations,

and release and stability data on at least three batches of drug product to demonstrate

that the levels of any potential

©® in all drug

product batches have not and will not exceed the allowable daily intakes stated in FDA

Guidance
monitoring such © "from release
studies for all the commercial batches.

PRESCRIBING INFORMATION

© Commit to continue
'0 the end of shelf-life during the stability

We reserve comment on the proposed label!
adequate. We encourage you to review the
Prescription Drug Labeling Resources! and

ing until the application is otherwise
labeling review resources on the
Pregnancy and Lactation Labeling Final

Rule? websites, including regulations and related guidance documents and the Selected

1 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-

final-rule

Reference ID: 5109885

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Page 2

Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.?

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

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Application: BLA761303 Letter date: 2024-03-22
Packet ID: crl_1b841b4e93b4f3bd Source file: CRL_BLA761303Original2_20240322.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL

(1) The Agency has determined that a confirmatory trial is required to be underway for odronextamab for large B-cell lymphoma (LBCL) prior to approval.' However, a confirmatory trial in LBCL with odronextamab is not considered to be underway. oe , you had enrolled |) patients in the dose-finding portion of OLYMPIA-3, and a patients have been enrolled in the confirmatory portion of the trial. Additionally, the current conduct of OLYMPIA-3 and projected

1 Federal Food, Drug, and Cosmetic Act (FD&C Act) sections 506(c)(2)(A)(i) and (D)

Reference ID: 5352255

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completion date do not provide sufficient assurance of timely completion of the rial.

To support resubmission of the BLA, you must address this deficiency. After enrollment and analysis of Part 1 (dose-finding) is completed, we recommend hat you request a meeting with the Agency to discuss trial benchmarks (e.g., enrollment goals, site activation, proportion of primary endpoint events accrued, rial completion date) to allow measurement of the progress of the trial. You should demonstrate in your submission that your milestones are appropriate and hat, prior to approval, you will demonstrate sufficient progress in the conduct of he confirmatory portion of the confirmatory trial to provide sufficient assurance of imely completion of the trial.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.4

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

We reserve comment on the proposed Medication Guide until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, , which addresses the proposed proprietary name, -_. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the

(b) (4)

2 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

3 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

4 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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Application: BLA761147 Letter date: 2024-04-05
Packet ID: crl_1834aa9f67635437 Source file: CRL_BLA761147_20240405.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS
Following pre-license inspection of oe

, listed in this application, FDA conveyed deficiencies to the representative of the facility. Your complete response should include the date of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

PRODUCT QUALITY (Microbiology)

(&) (4)

Reference ID: 5359825

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Page 2

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry Labeling for Biosimilar Products.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, oe , which addresses the proposed proprietary name, |. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the

proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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Application: BLA125807 Letter date: 2024-04-16
Packet ID: crl_18c50132e64d115b Source file: CRL_BLA125807_20240416.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

1. You did not demonstrate adequate suitability of the microbiological test methods listed below for your final drug product, prademagene zamikeracel (PZ).

a. Sterility Test Method: You proposed to conduct (1b) (4)

(b) (4) rapid
sterility testing (b) (4) on final drug product (DP) samples using
the (1b) (4) However, data to demonstrate the

suitability of these C8) sterility methods were not provided. Without

adequate validation of the sterility methods, the sterility of your PZ DP is not assured. To demonstrate that each method can reproducibly detect appropriate levels of microbial contamination, you should provide a report that includes the (1b) (4)

as well as acceptance criteria (AC) with justification, for at least
(b) (4) DP lots. The impact of any deviations that occurred during testing should be described in the report. In addition, method validation should be performed in accordance with (1b) (4). To demonstrate your rapid sterility test methods provide assurance of effectiveness equal to or greater than the assurances provided by the (b) (4) sterility test

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method under the actual condition of use, you should provide data from comparability studies.

b. Mycoplasma Test Method: The data you provided does not demonstrate the suitability of your mycoplasma test method because assay specificity and equivalency to (1) (4) methods were not adequately demonstrated. To complete demonstration of assay specificity, you should

conduct a specificity study for the (6) (4) method using your(b) (4)

(b) (4)

To demonstrate
comparability/equivalency of the (b) (4) _ and the proposed (6) (4)
(b) (4) system, data from a comparability study must be
provided to assure that the sensitivity of the (©) (4) method is equal to or
greater than the (b) (4) method (1b) (4) under the actual condition
of use.

c. Bacterial Endotoxin Test: The test sample dilution (6) (4) you proposed for
determining endotoxin concentration is not acceptable because it is at the
limit of the test, i.e., the (b) (4) Testing at the
() (4) may detect endotoxin in the sample at the specification limit;
however, testing at the (®) (4) should only be performed if dilutions ©
(b) (4) do not provide valid test results. To identify the appropriate
sample dilution to use in the endotoxin test, you need to provide data from
a test for interfering factors that show positive product control recoveries
for a series of test dilutions (1b) (4) As per (b) (4) the
dilution equation must include the media volume. You should use this
information to identify the dilution that provides optimal recovery and use
as the sample dilution in release assays.

d. Supporting (6) (4) Studies: You did not provide adequate
evidence of endotoxin or microorganism recovery in media that has been
in (6) (4) with DP after assembly of the P1 packaging (i.e.,
clamshell inside (1) (4) bag). Data should be provided for (1b) (4)
studies for all assays that will utilize this media as a test sample, including
endotoxin, (6) (4) -, and all sterility tests. The (6) (4) tests
should be designed to demonstrate that the proposed (1) (4) time allows
for adequate detection and recovery of appropriate levels of contaminants
in the DP and use an (6) (4) volume that is appropriate for the
intended test method. The (b) (4) studies for bacterial endotoxin must
comply with (1b) (4) for bacterial endotoxin (1) (4) volume and

process. A full test report including a description of the test
methods, acceptance criteria (AC) with justification, and sensitivity of the
evaluated assays with the media samples, is needed to demonstrate your
endotoxin, (b) (4) and rapid sterility testing methods are appropriate

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for their intended use.

4. You proposed to conduct additional identity testing on your final DP as part of lot
release testing to assess and confirm the cell populations in your DP. You
propose to utilize a (1) (4) (16) (4)) to "detect the presence of
keratinocytes" in your product. However, you did not provide an adequate
method description, protocol, or validation report for your proposed identity
assay. In order to ensure the identity and purity of your final DP, a validated
identity assay is necessary. Please submit a method validation report
demonstrating that your proposed method can adequately detect and identify the
cell populations present in your DP. The report should include the AC, with
justification, description of the test method, including test sample and sample
size, discussion of results, and deviations, if any.

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5. As part of the final product lot release testing, you conduct (1b) (4)
(b) (4) visual inspection on the DP. You indicate that these
methods are qualified and operators are adequately trained to conduct these
visual tests. However, you did not provide adequate validation reports for these
methods to demonstrate that these assays can be consistently and accurately
performed. Specifically, we identified the following issues in the method

validation reports provided in Amendment 45, received on March 28, 2024:

a. (b) (4) identified a contaminant (hemoclip) in the DP during visual inspection that the other operators missed during the (6) (4) validation run. The discrepancy described resulted in out-of-specification results of the visual inspection.

b. (b) (4) that identified the contaminant (hemoclip) did not perform (6) (4) "as the) tests were performed concurrently. This resulted in (°) 4) (b) (4) the visual inspection validations to be conducted on only peal

DP validation runs.

c. A discrepancy was described where all operators missed a tear in the cell sheet during visual inspection.

To address these issues, you indicated that you intend to make additional protocol changes for the visual inspection validation protocol, after which you

plan to manufacture (1b) (4) to complete the ©) validation run that did not pass specifications. However, with a revised visual inspection protocol, (4) is inadequate to sufficiently validate

() (4) visual testing methods. Therefore, please utilize at (b) (4) DP lots to validate the final validation protocols for the (6) (4) | visual inspection test. Please provide validation reports including the AC, with justification, description of the test methods, including test sample and sample size, discussion of results, and deviations, if any. Please also provide a justification for the changes implemented in the protocols.

6. You manufacture several media and reagents at your manufacturing facility which are used in the aseptic manufacturing of PZ DP. \°) @) of the reagents,

(b) (4)

However, as
this proposed change was made after completion of your process performance qualification (PPQ), you did not provide adequate data to support the change in reagent. Therefore, in order to replace the (1b) (4) reagent with a (b) (4) alternative, please submit data to demonstrate that the reagent change does not impact the final DP.

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7. You describe your control of materials in Section 3.2.S.2.3, indicating that as part of your raw material qualification program, all incoming reagents are, a (b) (4) Additionally, you perform
material qualification and requalification testing of the incoming materials to ensure that they meet the QC requirements. Regarding these activities, we have the following comments:

a. You state that (6) (4) testing is conducted on all incoming materials. However, you did not provide a list of these (6) (4) tests and did not provide information to demonstrate the testing is performed using appropriately qualified or validated assays. In order to assess the (b) (4)

of your reagents, you should utilize (6) (4) tests which are appropriately qualified or validated to (b) (4) of all incoming materials. Please provide a list of all (O) (4) assays performed as part of your raw material qualification program, including a description of the assay/method, as well as the validation method protocols and reports. If using (b) (4) methods, then providing qualification protocols and reports would be sufficient.

b. In Table 2 of Section 3.2.S.2.3, you state that certain testing is conducted on incoming materials as part of the material qualification requirements, including minimum incoming QC tests and (6) (4) re-qualification testing

performed (6) (4) lot to verify the reagent's certificate of analysis (CoA). However, you did not specify the methods or assays used to perform hese qualifications/re-qualifications. Per 21 CFR 211.82(d)(2), you should establish "the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." Therefore, you should provide additional details regarding your raw material qualification program, including the methods or assays used 'o perform these qualifications/re-qualifications, and how you are validating the reagents' CoA at appropriate intervals.

8. Your corrections to FDA's inspectional observations issued to you at the conclusion of the inspection conducted between February 19 and March 1, 2024, of your Cleveland, OH facility are still ongoing.

9. (b) (4)

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1 page has been determined to be not releasable: (b)(4)

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12.To support the container closure integrity of the PZ drug product, you performed

a(b) (4) test per (6) (4)

The integrity of the container closure should be demonstrated to ensure sterility is maintained and to prevent contamination of the drug product (21 CFR 211.94b Drug Product Containers and Closures). The studies provided do not satisfy the requirement of ensuring the final drug product packaging is integral.

We requested additional CCIT studies through an information request (IR) on March 11, 2024. In your response to the IR submitted on March 27, 2024, you

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indicated that this study will be performed. However, the studies could not be provided in sufficient time to review prior to the action due date.

Please provide a CCIT study for the PZ DP primary containers per (©) (4) (6) (4) © and include details of the test method performed with an established sensitivity of the method (1b) (4)

(b) (4)

ADDITIONAL COMMENTS

In addition to the deficiencies that were the basis for not granting approval, we have identified the following comments:

LABELING

13.We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

14.In your BLA submission, you provided stability data in support of a proposed shelf-life of 84 hours for the PZ DP. However, the data you provided is insufficient to support your proposed shelf-life. Specifically, you did not provide adequate data to demonstrate robust viability and sheet integrity in a sufficient number of samples. For example, you indicated that cell viability results were not

available for (1b) (4) out of (6) 4) tested DP lots at the 60 hour timepoint due to equipment failure. In addition, the AC you proposed for (®) (4) is that (6) (4) However, at
some timepoints you tested (b) (4) per" Thus, thel) (4)
acceptance criterion is not adequate because you did not demonstrate you have enough product (b) (4) to treat a patient from a (6) (4) ®" at all

timepoints. Therefore, to demonstrate the stability of your product, we recommend the AC for the (®) (4) be revised to show that at (1b) (4)

at any given timepoint remain intact. Please also refer to comment 5 above related to the validation of (6) 4)

way

15.In response to information requests (IRs) during the review cycle, you proposed modified AC for (6) (4) lot release testing. Please note that AC for lot release testing will be finalized upon review of your complete response. We reserve comment on your proposed AC until the application is otherwise acceptable.

16.In response to IRs during the review cycle, you changed criticality designations for several process parameters in (1b) (4) manufacturing. Please note that criticality designations for in-process parameters and AC for in-process

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testing of your (1b) (4) will be finalized upon review of your complete response.

17.In section 3.2.8.7 of your BLA submission, you propose a shelf-life of (1b) (4) for your LZRSE-Col7A1 RVV. Your proposed LZRSE-Col7A1 RVV shelf-life is still under review, pending FDA receipt of additional stability data. In your resubmission, please include any stability data collected prior to the resubmission date, including but not limited to the following:

a. Data collected from (1b) (4) stability studies you proposed in amendment 33 received on March 1, 2024, which was expected to be submitted to the FDA by June 30, 2024.

b. Any additional long-term stability data collected according to your stability protocols STA-DS-000001 and STA-DS-000003.

18.In amendment 21 received on January 22, 2024, you noted that a report of (b) (4) testing of your (6) (4) r
(b) (4) for (b) (4) would be submitted to the FDA by April 30, 2024. Please include this report in your resubmission.

Letter 33 of 50

Application: NDA216987 Letter date: 2024-05-10
Packet ID: crl_91f0d15039616325 Source file: CRL_NDA216987_20240510.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY AND FACILITY INSPECTIONS
1. Following surveillance inspection of oe
manufacturing
facilities for this application, our field investigator conveyed deficiencies to the representatives of the facilities. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

1 https:/Awww.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

Reference ID: 5379228

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Page 2

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)]in structured product labeling (SPL) format as described at FDA.gov.3

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

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Application: BLA761326 Letter date: 2024-07-10
Packet ID: crl_c8d5856b8a008299 Source file: CRL_BLA761326_20240710.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

_____

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Displayed deficiency segment

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BLA 761326/Original 2
Page 2

Deficiencies for both BLA 761326/Original 1 AND BLA 761326/Original 2

FACILITY INSPECTIONS

1. Following the pre-license inspection 0
oo . listed in this application, conveyed deficiencies to the

representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to submission of your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies will be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

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BLA 761326/Original 1
BLA 761326/Original 2
Page 3

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BLA 761326/Original 1
BLA 761326/Original 2
Page 4

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Silver Spring, MD 20993
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BLA 761326/Original 1
BLA 761326/Original 2
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Reference ID: 5411302

BLA 761326/Original 1
BLA 761326/Original 2
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Reference ID: 5411302

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BLA 761326/Original 2
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Reference ID: 5411302

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Reference ID: 5411302

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BLA 761326/Original 2
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Deficiency for BLA 761326/Original 1 ONLY
CLINICAL

Our assessment of the data submitted to support use for glycemic control in adults with type 1 diabetes is that the benefit-risk balance is unfavorable due to an unacceptably higher risk (vs. daily basal insulin comparator) of clinically meaningful hypoglycemia without evidence of any relative improvement in hemoglobin a1c reduction or other benefit (e.g., better adherence or patient satisfaction) versus available therapy. In ONWARDS 6, conducted in a type 1 diabetes population, there was a 50% higher incidence and 80% higher event rate of level 2 or level 3 hypoglycemia reported in the NNC0148-0287 arm compared to the insulin degludec arm using self-measured blood glucose (SMBG) data, and the risk of hypoglycemia was consistently higher regardless of method of data capture (SMBG or continuous glucose monitoring (CGM)). Our conclusion is that NNC0148-0287, when used in a type 1 diabetes population

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BLA 761326/Original 1
BLA 761326/Original 2
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following the ONWARDS 6 protocol, results in excess hypoglycemia that is likely a consequence of the dosing and titration algorithm used in ONWARDS 6 in the context of the time action profile of NNC0148-0287. Level 2 and 3 hypoglycemia are clinically significant events that have the potential to result in morbidity and mortality. Although NNC0148-0287 allows for fewer weekly injections for patients over daily basal insulin products, this feature on its face does not offset the observed difference in clinically meaningful hypoglycemia in ONWARDS 6.

As a path forward, provide new clinical data to demonstrate favorable benefit-risk for NNC0148-0287 in subjects with type 1 diabetes. We recommend that you request a post-action meeting to discuss a potential new glycemic control clinical study in participants with type 1 diabetes that would optimize the dosing and titration algorithm and assess other outcome(s) important to patients such as the patient experience with NNC0148-0287.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.4

PROPRIETARY NAME

Please refer to correspondence dated, oe , which addresses the proposed proprietary name, oe . This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

Letter 35 of 50

Application: NDA217433 Letter date: 2024-07-15
Packet ID: crl_eda140dc3ef99053 Source file: CRL_NDA217433_20240715.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

DEVICE
(1) In your response to our Information Requests (IR) sent on oe , you indicate that the final finished version of your device is not considered in your verification, reliability, stability and shipping verification tests. The following two differences between the tested versions of your device and the intended commercial version of your device were noted:

0) (4)

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Page 3

PRODUCT QUALITY

HUMAN FACTORS

(3) Based on the evaluation of the human factors (HF) validation study results, the user interface does not support the safe and effective use of the proposed product. The results of the HF validation study demonstrated several use errors, close calls, and use difficulties with the critical task of depressing the plunger to administer the dose. Specifically, results of your HF validation study demonstrated that several participants failed to depress the plunger, some of whom thought they had successfully administered a dose. These use errors led to administration of no doses which would likely negatively impact patient care and could increase the risk for mortality in this patient population.

As conveyed in the a: Discipline Review letter, we note that many of the participants who failed to depress the plunger provided subjective feedback

indicating that early clicking sounds and plunger counterpressure after being approximately halfway depressed led the participants to believing they had successfully administered a dose when they had not.

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Information needed to resolve the deficiency:

Implement user interface revisions and design modifications to promote the safe and effective use of the proposed product, and provide data demonstrating that, with these mitigations, the product user interface can be used safely and effectively to deliver the intended dose of drug substance.

Prior to conducting an assessment to evaluate the impact of any mitigation strategies, we recommend submitting your HF validation study protocol, along with the redesigned user interface, for our review and feedback.

It is critically important for a product to be safe, effective, and easy-to-use in the proposed indication and population. As described above, you should provide data demonstrating the revised proposed product can be used safely and effectively to deliver the intended dose.

PRESCRIBING INFORMATION

(4) We reserve comment on the proposed labeling until the application is otherwise

adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources® and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

(5) We reserve comment on the proposed labeling until the application is otherwise

adequate.

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Application: NDA218772 Letter date: 2024-08-19
Packet ID: crl_d993b1bc38d26beb Source file: 218772_2025_Orig1s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

Reference ID: 5431920 (SEN ong bie pane

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Page 5

(4) Given the outstanding product quality deficiencies, the acceptability of the drug product lot used in the relative bioavailability study (Study 14323/21-22) and food effect study (Study 14324/21-22) will be assessed after you have resubmitted your NDA.

PRESCRIBING INFORMATION

We acknowledge your draft labeling submitted on August 5, 2024. We reserve further comment on your proposed labeling until your application is otherwise approvable. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING
We acknowledge your proposed carton and container labeling submitted on

August 5, 2024. We reserve further comment on the proposed labeling until the application is otherwise adequate.

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2

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PROPRIETARY NAME

Refer to our correspondence dated January 22, 2024, which addresses the proposed proprietary name, Arbli. This name was found conditionally acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 37 of 50

Application: BLA761338 Letter date: 2024-09-30
Packet ID: crl_a4715609d213355b Source file: 761338Orig1Orig2s000OtherActionLtrs.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY MICROBIOLOGY

(1) The bacterial retention study is inadequate
for the CT-P43 drug product, 130 mg/26 mL (5 mg/mL) single-dose vial for IV

Repeat the bacterial

retention study of the

(2) The container closure integrity test (CCIT) dye ingress method used for stability testing of CT-P43 drug product, 130 mg/26 mL (5 mg/mL) single-dose vial for IV use is not validated to ensure reproducibility of results between different analysts. The validation summary for the dye ingress method in Table 3.2.P.5.3-59 includes results for sensitivity, specificity, and robustness, however the reproducibility of the visual detection method between different analysts is not addressed. According to FDA guidance for industry "Analytical Procedures and Methods Validation for Drugs and Biologics (2015)", for non-compendial method, validation data are needed to support the reproducibility of the method. Provide evidence of the reproducibility of the visual inspection method to detect breach sizes at the limit of detection with multiple analysts. Alternatively, measure all

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Page 2

samples by spectrophotometry and provide an updated method description with acceptance criteria and submit additional method validation data accordingly.

PRODUCT QUALITY

(3) The proposed release and stability specifi ication for clarity of

for CT-P43 drug product (DP) [SCS] is
not acceptable because it is not justified by your clinical and manufacturing experience. In your response to information request (IR), received on May 13, 2024, you proposed not to tighten this release and stability specification based on ®® for Lot No. 2NGPO1
as justification. The proposed justification is not acceplable as it is not clinically

relevant. Results from should not be used to
support the release and long-term stability acceptance criteria. In addition, this specification is not supported by the updated full term (36 months) stability data from the primary stability (non-PPQ) batches provided in the same amendment in SN 0027, which consistently showed results are below{NTU at all timepoints throughout the product shelf life. Tighten the release and stability acceptance criteria for clarity for CT-P43 [SCS] DP based on the historical release and long-term stability results to ensure consistent quality of CT-P43 DP [SCS].

(4) The proposed shelf-life limit of ©® in CT-P43 45 mg/0.5 mL

and 90 mg/mL PFS and 130 mg/26 mL (5 mg/mL) Vial DP is not supported by your clinical and manufacturing experience. In the IR response received on May 13, 2024, you proposed not to tighten, this shelf-life limit based on |

You described that the ey
(b) (4) we

wren

are associated with an

However, the proposed shelf-life limit does not reflect the clinical and manufacturing experience and is not supported by the updated full term stability results (all data points < (3%) from the primary stability batches (non-PPQ) for both 45 mg/0.5 mL and 90 mg/mL PFS and 130 mg/26 mL (5 mg/mL) vial DP presentations provided in the same amendment in SN 0027. Tighten the shelf-life acceptance criteria for ®® based on long term stability data to ensure
the consistent CT-P43 DP quality over the shelf-life.

PRESCRIBING INFORMATION

(5) We reserve comment on the proposed labeling until the application is otherwise

adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling

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Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry "Labeling for Biosimilar Products".

CARTON AND CONTAINER LABELING

(6) We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

(7) Please refer to correspondence dated, September 29, 2023, which addresses the proposed proprietary name, Steqeyma. This name was found conditionally acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 38 of 50

Application: NDA212271 Letter date: 2024-12-11
Packet ID: crl_b80f4ff14840a1c1 Source file: CRL_NDA212271_20241211.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY/ FACILITY INSPECTIONS
Following a pre-approval inspection of ow

listed in this application, FDA conveyed deficiencies to the representative of the facility. The FDA conducted an expedited, risk-based review of the available information from the inspection and determined that the deficiencies represent significant issues that adversely impact the facility's ability to perform the designated functions described in your application. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response resubmission. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. If the FDA determines the deficiencies are resolved following a full review of the inspection and 483 responses after this Complete Response Letter, the facility will be informed. Otherwise, further assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies. Satisfactory resolution of these deficiencies is required before this application may be approved.

Reference ID: 5494134

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Page 2

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.®

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated oe , which addresses the proposed proprietary name, | This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 39 of 50

Application: NDA219357 Letter date: 2024-12-23
Packet ID: crl_6e6d91b2a5e3b2d4 Source file: CRL_NDA219357_20241223.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

Reference ID: 5501502

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Page 2

-PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, oe , which addresses the proposed proprietary name). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 40 of 50

Application: NDA215644 Letter date: 2025-06-25
Packet ID: crl_0f4fb128982cadf9 Source file: CRL_NDA215644_20250625.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

PRESCRIBING INFORMATION

(1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the

Reference ID: 5614685

NDA 215644
Page 2

Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.?

CARTON AND CONTAINER LABELING

(2) We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

(3) Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

(4) Please refer to correspondence dated, om which addresses the proposed proprietary name). This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

(5) Following a Current Good Manufacturing Practice (CGMP) inspection and

preapproval inspection of oe

, listed in this application, FDA
conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Our determination that the facility's responses are satisfactory will depend on a finding that the facility has come into compliance with CGMP and has addressed any deficiencies specific to your application. You should coordinate with the facility for timely resolution of all inspection deficiencies, as well as to determine if

1 https:|www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

3 http://www. fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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Reference ID: 5614685

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Page 3

any deficiencies may require updates to your application. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on postinspection activities specific to CGMP compliance evaluation. FDA may determine that a CGMP reinspection and/or additional pre-approval inspection (PAI) is needed to confirm satisfactory resolution of inspection deficiencies before this application can be approved. If both CGMP and PAI reinspection are needed, the PAI coverage will generally occur following a determination that the facility is in compliance with CGMP.

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Application: BLA125842 Letter date: 2025-07-09
Packet ID: crl_09e7f2fd8abed3cd Source file: CRL_BLA125842_20250709.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

Clinical and Biostatistics

1. Your application provides data from the HOPE-2 and HOPE-2-OLE studies as the proposed primary and supportive evidence of effectiveness, respectively, for your product, deramiocel. The HOPE-2 study failed to demonstrate efficacy for its prespecified primary efficacy endpoint, which was change from baseline to Month 12 in the mid-level (elbow) dimension of the Performance of Upper Limb version 1.2 (PUL 1.2), a neuromuscular outcome assessment. Additionally, HOPE-2 failed to demonstrate efficacy on its prespecified secondary endpoints. To support your proposed indication for treatment of cardiomyopathy in patients with Duchenne muscular dystrophy (DMD), you have presented post hoc analyses of HOPE-2 and HOPE-2-OLE. However, as outlined below, these post hoc analyses are not sufficient to provide substantial evidence of effectiveness to support approval of deramiocel.

a. As stated in your response to an FDA information request (dated)))(6)(4)), the HOPE-2 study was intended to evaluate the effectiveness of deramiocel on neuromuscular function and was not designed to assess effectiveness for the treatment of cardiomyopathy in patients with DMD. Thus, HOPE-2 was not an adequate and well-controlled study with a clear statement of the objectives of the investigation and without sufficient

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Page 2 - BLA 125842/0 - Margaret Kayo, PhD, MBA

prespecified collection of essential baseline clinical data to assess effectiveness for the treatment of cardiomyopathy in patients with DMD.

b. The data submitted in this BLA to support the proposed indication include 50 secondary and exploratory endpoints, including post hoc analyses of 26 endpoints of cardiac MRI assessments. These 50 secondary and exploratory endpoints were not prespecified for hypothesis testing, and no prespecified multiplicity adjustment strategy was employed for control of the overall Type 1

error rate. As such, these analyses are exploratory and hypothesis-generating only and cannot provide evidence of effectiveness. No overall consistency in treatment effect was evident across a large number of exploratory cardiac endpoints in the primary HOPE-2 study, suggesting that the few nominally significant findings could be spurious. Similarly, the post hoc and exploratory analyses of cardiac function from the nonrandomized HOPE-2-OLE study are subject to potential unmeasured confounding and inflation of Type 1 error.

The Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 505(d), 21 Code of Federal Regulations (CFR) § 314.126, and Section 351 of the Public Health Service Act (PHS Act) require substantial evidence of effectiveness from adequate and well-controlled studies to support a marketing application of a drug or biological product. Your BLA does not meet the statutory requirement for substantial evidence of effectiveness. If you wish to seek approval of deramiocel for treatment of cardiomyopathy in patients with DMD, we recommend that you conduct adequate and well-controlled study(ies), whose primary objective is evaluation of cardiac outcomes in deramiocel-treated patients with DMD cardiomyopathy, compared to a randomized, concurrent control group over an appropriate duration of follow up.

Chemistry, Manufacturing, and Controls (CMC)

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Page 4 - BLA 125842/0 - Margaret Kayo, PhD, MBA

CMC [Facility and Equipment]

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ADDITIONAL COMMENTS

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13.We acknowledge receipt of your proposed labeling and anticipate conducting a detailed labeling review once the above concerns have been fully addressed.

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Application: BLA761303 Letter date: 2025-07-30
Packet ID: crl_f91e6bb32eb0d7fc Source file: CRL_BLA761303_20250730.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS
(1) Following a CGMP inspection of oe
, listed in this application, FDA conveyed deficiencies to the

representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a pre-license inspection (PLI) of the facility. Satisfactory outcomes of both the PLI and the CGMP surveillance inspections will be needed prior to an approval of the application.

Reference ID: 5633550

BLA 761303
Page 2

PRESCRIBING INFORMATION

(2) Submit draft labeling that is responsive to our electronic communication dated c

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.'

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling Final Rule? websites, which include:

e The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

e The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

e Regulations and related guidance documents

e Asample tool illustrating the format for Highlights and Contents, and

e The Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

e FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

e Additional resources for the PI, patient labeling, and carton/container labeling.

1 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

2 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

3 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
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Reference ID: 5633550

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Page 3

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling dated oe

MEDICATION GUIDE

(3) Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

Please refer to our correspondence dated, om , Which addresses the proposed proprietaryname, ©® . This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 43 of 50

Application: NDA209531 Letter date: 2025-09-22
Packet ID: crl_d23b12bf287d8a6c Source file: CRL_NDA209531_20250922.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

NONCLINICAL AND PRODUCT QUALITY

Reference ID: 5663424

NDA 209531/S-016
Page 2

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated nl which may be a resubmission of your draft labeling provided in an electronic response communication also dated 88

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition,

submit updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov."

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources? and Pregnancy and Lactation Labeling Final Rule? websites, which include:

¢ The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

¢ The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

1 http:/Awww.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

2 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

3 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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Reference ID: 5663424

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Page 3

e Regulations and related guidance documents
e Asample tool illustrating the format for Highlights and Contents, and

e The Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

e FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

e Additional resources for the PI, patient labeling, and carton/container labeling.
CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on your carton and container labeling submission dated omy

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Application: BLA761461 Letter date: 2025-11-26
Packet ID: crl_fd111ab1b3267727 Source file: CRL_BLA761461_20251126.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS
(1) Following pre-license inspection of oe
, listed in this application, FDA conveyed deficiencies to the

representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA Form 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

PRESCRIBING INFORMATION
(2) We reserve comment on the proposed labeling until the application is otherwise

adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling

1 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

Reference ID: 5702234

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Page 2

Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry Labeling for Biosimilar Products.

CARTON AND CONTAINER LABELING

(3) We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

(4) Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

PROPRIETARY NAME

Please refer to our correspondence dated me, which addresses the proposed proprietary name, me) . This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

Letter 45 of 50

Application: BLA761458 Letter date: 2025-12-16
Packet ID: crl_bf59a91e60e9053c Source file: CRL_BLA761458_20251216.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL/STATISTICAL

The submitted data do not provide adequate evidence to support approval of depemokimab || lili ul lum ll lilt. 0 ll

Reference ID: 5712877

BLA 761458/Original 2
Page 2

Efficacy for depemokimab was evaluated in two, replicate, randomized (1:1), double-blind, placebo-controlled trials (ANCHOR-1 and ANCHOR-2) in n= adults with inadequately controlled CRSwNP. Participants were followed for 52 weeks to assess the co-primary endpoints of change from baseline on endoscopic nasal polyp score and self-reported symptoms on a nasal obstruction mean score. The results from the nasal obstruction score are especially important for assessing benefit-risk because they are a direct reflection of the clinically meaningful effects for patients.

The co-primary endpoints of nasal polyp score and nasal obstruction score were statistically significant in ANCHOR-1 & 2. However, the nasal obstruction scores were not robust to sensitivity analyses for missing data and handling of intercurrent events. In addition to the statistical deficiencies, the effect sizes for both co-primary endpoints were numerically small and, specifically for the nasal obstruction score, of uncertain clinical meaningfulness.

The review team also considered secondary endpoints for evidentiary support, including additional patient reported symptom scores, the need for nasal sinus or polyp surgery, and oral corticosteroid use. Despite trends favoring depemokimab, no secondary endpoint met statistical significance based on the pre-specified hierarchical testing strategy.

The 100 mg dose was selected based on a modeling and simulation approach informed by PK/PD data from the first-in-human single-dose trial in subjects with mild-to-moderate asthma. No phase 2 dose-ranging trials in participants with CRSWNP were conducted. Exposure response analyses of ANCHOR-1 & 2 demonstrated a trend that higher exposure is generally associated with greater placebo-adjusted treatment effects in reduction of total endoscopic nasal polyp score and nasal obstruction score in CRSwNP participants, especially in CRSwNP participants with comorbid asthma. This

indicates that a higher dose of depemokimab may provide a greater treatment effect.

While the every 6 month dosing interval has advantages for adherence, non-responders would either have to wait six months to switch to a more effective therapy, or initiate a second biologic therapy while depemokimab is still present systemically, potentially causing an associated increase in risk of dual biologic therapies. Given the small effect size for depemokimab with lack of robustness on tipping point analysis, the benefit-risk in the setting of a six-month duration of action is not favorable.

Information Needed to Resolve the Deficiency

Provide new evidence demonstrating a treatment effect of sufficient magnitude to establish that depemokimab will provide a statistically persuasive and clinically meaningful benefit to patients with CRSWNP.

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Reference ID: 5712877

BLA 761458/Original 2
Page 3

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule' websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.?

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

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Application: NDA219624 Letter date: 2025-12-23
Packet ID: crl_73361a3ed966fcf2 Source file: CRL_NDA219624_20251223.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

A favorable benefit-risk profile could not be established for any patient subpopulation

We acknowledge Study EFC16645 demonstrated positive results in a population that you have defined as non-relapsing secondary progressive multiple sclerosis (nrSPMS). However, we have determined that a serious risk of severe drug-induced liver injury (DILI), which was identified during the conduct of your clinical trials, cannot be adequately mitigated by the proposed risk evaluation and mitigation strategy (REMS). Given the gravity of this serious and potentially fatal risk, the review of your application focused on attempting to identify a population in whom the benefit-risk assessment is favorable to support approval, such as a population of patients with multiple sclerosis (MS) that has the greatest unmet need because there are no approved therapies. We considered your proposed indication of nrSPMS, as well as the subgroups of subjects with active SPMS and non-active SPMS in Study EFC16645, to conduct benefit-risk

Reference ID: 5717409

NDA 219624
Page 2

assessments. However, we were unable to identify a population for which the benefit could be clearly established and for which that benefit would be anticipated to outweigh the serious risk of severe DILI to support approval. We outline our reasons for this determination below.

1. Serious risk of severe (including fatal) DILI

The risk of severe DILI (i.e., requiring transplant or fatal) with tolebrutinib is substantial and unusually high for drug development programs in general, and specifically for MS therapies. Our review of your premarket development program '0 date has identified 6 cases meeting Hy's Law criteria in the tolebrutinib Phase 3 development program out of approximately 2700 subjects, including one subject who died after requiring a liver transplant, which indicates a high level of hepatotoxic risk with tolebrutinib. Per the guidance document, Drug-induced Liver Injury: Premarketing Clinical Evaluation (July 2009), the presence of even a single case meeting Hy's Law criteria in the premarket development program of a drug is a signal of a high level of hepatotoxicity. Most of the drugs withdrawn

rom the market for hepatotoxicity have caused death or transplantation at rates so low (i.e., $1 per 10,000) that severe hepatotoxicity is not typically identified in he premarket development program.

Additionally, per the guidance document referenced above, another major indicator of the potential for severe DILI is an excess of aminotransferases greater than 3 times the upper limit of normal (i.e., Temple's Corollary). In the irst 6 months of double-blind treatment of Study EFC16645, 3.6% of tolebrutinib-reated subjects versus 1.9% of placebo-treated subjects experienced aminotransferases greater than 3 times the upper limit of normal.

Therefore, based on the DILI cases (which included both fatal and non-fatal Hy's Law cases) reported in the tolebrutinib development program to date, the predicted postmarket rate of severe DILI associated with tolebrutinib is high. The predicted rate of severe DILI with tolebrutinib is at or above that of drugs which were either not approved due to the risk of DILI or were removed from the market due to DILI. The risk of DILI with tolebrutinib is idiosyncratic and greatly exceeds hat observed with all other therapies approved for multiple sclerosis. Additionally, we acknowledge that DILI is a class effect of BTK inhibitors discussed in current approved labeling, but the risk of fatal DIL] associated with olebrutinib appears to be among the highest in the class. There is therefore a significant and unusually high risk of severe DILI associated with tolebrutinib.

We considered whether the risk of DILI could be mitigated through your proposed REMS, but have determined, based on the available data, that the proposed REMS would not adequately mitigate the risk of severe DILI. We acknowledge that you changed your monitoring strategy to weekly liver monitoring following

1 https://www.fda.gov/media/116737/download

identification of Hy's Law cases, including the fatal case of DILI, and that there have been no additional cases of DILI resulting in death or transplant following that change to date. However, additional DILI cases, including a Hy's Law case, have occurred in this limited dataset after weekly monitoring was initiated. These cases included a Hy's Law case with a rapid rise in aminotransferases, and other cases with a substantial rise in aminotransferases (greater than 10 to 60 times the upper limit of normal), some with hyperbilirubinemia. These cases predict that severe liver injury will occur in a larger population of exposed patients in a potential postmarketing setting, even with the mitigation measures described in the proposed REMS.

Therefore, even with the implementation of weekly monitoring, the predicted postmarket rate of severe DILI associated with tolebrutinib remains substantial. The benefit-risk assessment must assume that there will be severe and potentially fatal cases of DILI in the postmarketing setting, even with a REMS requiring weekly laboratory monitoring.

Uncertainties regarding benefit in disease subpopulations

Your enrollment criteria defined the targeted population for the proposed indication of nrSPMS, which does not align with the current multiple sclerosis (MS) course descriptor paradigm. Enrolled subjects could have either non-active SPMS (i.e., no clinical relapses and no inflammatory MRI activity) for which there are no approved therapies, or active SPMS (i-.e., no clinical relapses but evidence of inflammatory MRI activity) which is considered a relapsing form of MS (RMS) and for which there are approved therapies.

Because of the lack of historical MRI data collection in the study, we were unable to retrospectively determine whether the subjects enrolled in Study EFC16645 had active or non-active SPMS based on the information included in your submission. We acknowledge that you attempted to retrospectively obtain historical MRI data to characterize enrolled subjects, which was submitted in a response to information request dated ™®. However, these data are of limited interpretability due to selection bias, as the data were only able to be collected from subjects who elected to enroll in and remained in the open-label extension study (Study LTS17043), and reflected <40% of the enrolled population in Study EFC16645. The lack of historical MRI data collection during the study limits this assessment to the baseline MRI, which is a single timepoint that is not likely to adequately characterize a subject's recent clinical course and disease activity. Nonetheless, we conducted additional analyses to better characterize a potential treatment effect of tolebrutinib in subjects based on their baseline MRI.

? Lublin FD, et al. Neurology. 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560. Epub 2014 May 28.

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Subgroup analyses of Study EFC16645 indicate that the observed treatment effect was greater in subjects who had T1 gadolinium-enhancing (GdE) lesions at baseline (i.e., active SPMS), which comprised 13% of the enrolled population. For subjects with GdE lesions at baseline, the hazard ratio (HR) (95% confidence interval [CI]) for the primary endpoint was 0.346 (0.183, 0.656), and without GdE lesions at baseline was 0.777 (0.601, 1.006). This subgroup analysis suggests that the treatment effect is largely driven by the small group of subjects with active SPMS based on their baseline MRI scan, a population for which there are approved therapies.

Additionally, the observed treatment effect in Study EFC16645 was greater in subjects who had not received a prior MS therapy, which comprised approximately 25% of the study population. The treatment effect was substantially diminished in subjects who had tried two or more prior MS therapies. For the primary endpoint, the HR (95% CI) based on number of prior MS therapies is as follows: subjects with no prior MS therapies 0.392 (0.241, 0.638); subjects with one prior MS therapy 0.649 (0.407, 1.034); subjects with two or more prior MS therapies 0.902 (0.643, 1.265). These observations raise concerns regarding the consistency of any potential benefit across all patients with nrSPMS, which needs to be weighed against the known substantial risk of DILI. We also note that patients with SPMS in the United States would typically have been treated with at least one approved MS therapy for RMS prior to reaching the secondary progressive phase of MS.

We acknowledge that these analyses do not allow definitive conclusions about efficacy in these subgroups; however, the analyses raise substantial uncertainties about the SPMS population that is more likely to benefit from tolebrutinib. Given the serious and unusually high risk of severe DILI, it is critical to have certainty about efficacy in a population in whom this level of DILI risk could be considered acceptable.

Insufficient evidence of effects on slowing disability accumulation independent of relapse activity

Additionally, there are uncertainties about the analyses that you have provided to support the claim included in your proposed indication statement regarding

slowing disability accumulation independent of relapse activity.

We acknowledge the data submitted as confirmatory evidence, including post hoc analyses of disability accumulation independent of relapse activity from two Phase 3 studies in the RMS population (Studies EFC16033 and EFC16034) that did not meet their primary endpoint. Though the concept of disability accumulation independent of relapse activity is of interest, it remains an emerging construct with multiple limitations. There are no widely accepted criteria for defining disability accumulation independent of relapse activity. There are

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also limitations in both the analysis methods and the interpretability of the

submitted post hoc analyses.

Additionally, it is unclear whether this concept

represents the same pathophysiology or has the same clinical implications for both nrSPMS and RMS, especially in later stages of the disease.

There are also significant limi

ations in the understanding of the underlying

pathophysiology of progression in MS and the potential for BTK inhibitors to

address this pathophysiology,

which limit the ability of a mechanistic rationale to

provide confirmatory evidence for this application.

These limitations are highligh
Study EFC16035 in primary pi
to demonstrate a benefit of to

ied by the recent negative topline results from
rogressive multiple sclerosis (PPMS), which failed
lebrutinib on the primary endpoint of 6-month

composite confirmed disability progression (CCDP).

The Division has determined that the data are insufficient to support a claim of slowing disability accumulation independent of relapse activity, particularly in the context of the significant risk of DILI, because of the reliance on post hoc analyses; the uncertainties regarding the concept of disability accumulation independent of relapse activity; the limitations of the mechanistic rationale; and he negative results of Study EFC16035 on cCDP.

No study subpopulation was identified with a favorable benefit-risk profile

The Division considered the issues cited above in the benefit-risk assessment for he proposed indication of nrSPMS. As previously noted, the nrSPMS population

includes both active and non-active SPMS. The bene
hese SPMS subpopulations differ due to the availabi
or RMS that is inclusive of active SPMS. Because of

The Division considered the benefit-risk assessment

it-risk assessments for
ity of approved therapies
the heterogeneity of the

broader population defined in the clinical trials as nrSPMS, we determined that he benefits did not outweigh the risk of severe DILI in this population.

'or the active SPMS

population. We acknowledge that this subgroup was not pre-defined in the enrolled population; however, the population of enrolled subjects with baseline GdE lesions would be considered to have active SPMS. There were much larger

treatment effects in the population with baseline GdE

lesions than in those

without baseline GdE lesions. We also acknowledge

hat there are limitations to

this subgroup analysis due to lack of historical MRI data to more fully

characterize an active SPMS population compared to

a non-active SPMS

population. However, given the availability of approved therapies for RMS that do not have the same magnitude of DILI risk, the Division determined that the

benefits would not be anticipated to outweigh the risk

of DILI for the general

population of active SPMS. The Division also considered whether there was a population within the active SPMS population that may have an unmet need,

such as those that have experienced disability progression despite treatment with approved therapies, that could potentially support a favorable benefit-risk assessment. However, Study EFC16645 was not designed to assess the benefit of tolebrutinib in active SPMS in patients who experienced disability progression despite treatment with approved MS therapies. Furthermore, the data showed diminished treatment effects in subjects who had been on one or more prior MS therapies than in those who had not received any prior MS therapies.

The Division then considered whether the data could support approval for non-active SPMS, for which there are no approved therapies and therefore different benefit-risk considerations. We acknowledge that this subpopulation was not pre-defined in the enrolled population; however, the Division was willing to show flexibility to consider narrowing the indication to a population for which there are no FDA-approved therapies, and for which there is a significant unmet medical need. However, even when applying flexibility, the Division considered the data (described under item 2 above) insufficient to establish substantial evidence of effectiveness for non-active SPMS given the uncertainties raised by the diminished treatment effects in the subgroup analysis of subjects without baseline GdE lesions; the inability to rely on the post hoc analyses from the two negative Phase 3 studies in RMS; and the negative topline results from Study EFC16035 in PPMS. As discussed in the FDA draft guidance document, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019),° therapies with greater risks may require a greater magnitude and certainty of benefit to support approval. The Division determined that, given the substantial uncertainties regarding efficacy, the potential for benefit in this population was inadequate to overcome the identified tisk of severe DILI.

Overall, substantial evidence of effectiveness has not been established in a clinically identifiable population for whom the benefits potentially outweigh the risks.

Potential next steps

To address the deficiencies in your application, we are open to having further discussion with you to identify a population for whom the potential benefits of your drug may outweigh the serious risk of severe DILI. This discussion would need to be supported by additional analyses of the safety data from the recently completed Study EFC16035 and the ongoing extension Study LTS17043 to characterize the impact of weekly liver safety monitoring on the incidence of severe DILI.

3 https://www.fda.gov/media/133660/download

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PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final Rule® websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.®

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) OR FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1 (a)].

We acknowledge receipt of your proposed REMS included in your submission dated

, and amended on om , which contains a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for!" (tolebrutinib), if it is approved, to ensure that the benefits of the drug outweigh the risks of DILI. The REMS, should it be approved, will create enforceable obligations.

We have determined that your proposed REMS does not adequately mitigate the risk of DILI. Because your application cannot be approved without an approved REMS, you must revise your proposed REMS and submit it as part of your response to the deficiencies cited in this letter. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

4 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

5 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

6 https://www.fda.gov/industry/fda-data-standards-advisory-board/structured-product-labeling-resources
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Reference ID: 5717409

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PROPRIETARY NAME

Please refer to our correspondence dated, oe , which addresses the proposed proprietary name, |) This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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Application: NDA220304 Letter date: 2026-04-23
Packet ID: crl_2e03df187e0e8302 Source file: CRL_NDA220304_20260423_Redacted.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

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NONCLINICAL

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Reference ID: 5785855.

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Page 3

FACILITY INSPECTIONS

4. Following a current good manufacturing practice (CGMP) inspection of
eran rel listed in this application, F
conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA Form 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a pre-approval inspection (PAI) of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to approval of the application.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final

1

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Page 4

Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.°

CARTON AND CONTAINER LABELING

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Reference ID: 5785855.

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PROPRIETARY NAME

Please refer to our correspondence dated, February 3, 2026, which addresses the proposed proprietary name, exummant This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that

have been identified in this letter.

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Application: NDA220283 Letter date: 2026-05-29
Packet ID: crl_72a21c9cbe6b2c34 Source file: CRL_NDA220283_20260529_Redacted.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

PRODUCT QUALITY

Reference ID: 5806800

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Reference ID: 5806800

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FACILITY INSPECTIONS

Following pre-approval inspection 0 ee
an. listed in this application, conveyed deficiencies to the

representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA Form 483 prior to your complete response to your application. Your complete response should include the date(s) of the facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

1 https:/Awww.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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PROPRIETARY NAME

Please refer to our correspondence dated, October 2, 2025, which addresses the proposed proprietary name, |"). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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Application: NDA220138 Letter date: 2026-06-15
Packet ID: crl_6888176f0ed6736c Source file: CRL_NDA220138_20260615_Redacted.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

CLINICAL/CLINICAL PHARMACOLOGY

The Agency finds that the scientific bridge between oxybate ER C OS and the listed drugs (LDs), Xyrem and Xywav, is inadequate for the
Although the systemic exposures
of the oe of the proposed product are within the range of those observed for the LDs (Xyrem and Xywav), the shape of pharmacokinetic (PK) profiles is different from the LDs, as they are approved as twice-nightly regimens for the treatment of cataplexy or EDS in adults with narcolepsy. The exposure-response (E-R) analysis submitted by the Applicant relied on aggregated exposures (e.g., AUCinf, Cmax, and dose), assuming that the shape of PK profile has no effect on clinical response. However, this analysis itself does not demonstrate that differences in PK shape will not lead to different clinical outcomes. You have not submitted adequate and well-controlled clinical studies that support me of the LDs for
. In the absence of an adequate and well-controlled efficacy and

safety study, the E-R analysis alone is insufficient to justify that the PK shape difference would not impact the efficacy or the safety of oxybate ER OS for

. Therefore, the proposed product, oxybate
ER OS, cannot rely solely on the Agency's previous findings of effectiveness of the LDs for the treatment of cataplexy and EDS in narcolepsy.

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Additional information will be necessary to resolve these deficiencies and support the safety and effectiveness of oxybate ER OS Ce
| (e.g., additional bridging studies to a product with similar

shape and/or results from at least one adequate and well-controlled trial in patients with

narcolepsy).

NONCLINICAL/PRODUCT QUALITY

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling, other than the Additional Comments below, until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources' and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling, other than the Additional Comments below, until the application is otherwise adequate.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1 (a)].

We acknowledge receipt of your proposed REMS, included in your submission dated August 20, 2025, and amended on November 10, 2025, and January 30, 2026, which contains elements to assure safe use, an implementation system, and a timetable for

1 https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

2 https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for oxybate for extended-release oral suspension, if it is approved, to ensure that the benefits of the drug outweigh the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse,

abuse, and diversion. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

For administrative purposes, designate all submissions related to the proposed REMS "PROPOSED REMS for NDA 220138-AMENDMENT."

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms or website screenshots, are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, submit the REMS document in Structured Product Labeling (SPL) format as described in the guidance for industry Providing Regulatory Submission in Electronic Format - Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the deficiencies with the application as described in this letter. Please resubmit the

proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter. If you do not have a conditionally acceptable proprietary name, you may submit a Request for Proprietary Name Review to your IND.

Letter 50 of 50

Application: NDA216586 Letter date: 2026-07-09
Packet ID: crl_8c7cb99c0b70f3af Source file: CRL_NDA216586_20260709_Redacted.pdf

Read the complete displayed segment, including continuation pages, before completing this form or the matching workbook row.

[ ] 1	Clinical efficacy	[ ] Primary
[ ] 2	Clinical safety	[ ] Primary
[ ] 3	Trial design and conduct	[ ] Primary
[ ] 4	Chemistry and manufacturing controls (CMC)	[ ] Primary
[ ] 5	Facility inspection	[ ] Primary
[ ] 6	Stability and shelf life	[ ] Primary
[ ] 7	Bioequivalence and bioavailability	[ ] Primary
[ ] 8	Nonclinical toxicology	[ ] Primary
[ ] 9	Labeling and proprietary name	[ ] Primary
[ ] 10	Administrative and procedural	[ ] Primary

New clinical trial required	[ ] Yes [ ] No
Third-party manufacturer	[ ] Yes [ ] No [ ] Unclear
Otherwise approvable	[ ] Yes [ ] No [ ] Unclear
Text-quality status	[ ] OK [ ] Redact. [ ] OCR [ ] Unable

Rationale / decisive language

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Displayed deficiency segment

FACILITY INSPECTIONS
1. Following a CGMP inspection of me)
listed in this application, FDA

conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a PAI of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to an approval of the application.

Reference ID: 5830543

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PRESCRIBING INFORMATION

2. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources! and Pregnancy and Lactation Labeling Final Rule? websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

3. We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our January 23, 2026, correspondence which addresses the proposed proprietary name, |). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed

proprietary name when you respond to all of the application deficiencies that have been identified in this letter.