CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761082Orig1s000

OTHER ACTION LETTERS

BLA 761082

COMPLETE RESPONSE

Kashiv BioSciences, LLC
Attention: John Pakulski
Senior VP, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Mr. Pakulski:

Please refer to your biologics license application (BLA) dated July 8, 2017, received July 10, 2017, submitted under section 351(k) of the Public Health Service Act for Theragrastim[1].

We acknowledge receipt of your amendment dated February 2, 2021, which constituted a complete response to our December 22, 2020, action letter.

We have completed our review of this application, as amended, and have determined that we cannot 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. An inspection 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

[1] 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.

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

2. During inspection of the [redacted] (b) (4) manufacturing facility from [redacted] (b) (4), 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 [redacted] (b) (4) "Stability Protocol for Theragrastim Working Reference Standard" for the working reference standards (WRS) [redacted] (b) (4) 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.

   [redacted] (b) (4)

   b. You provided PTL-2306-R "Summary Report for Qualification of Theragrastim In-House Working Reference Standard Lot [redacted] (b) (4)" as an update to the information request response #3 dated October 08, 2020 (BLA 761082/0053). However, the Agency noted multiple out of specification results (OOS) in this report. Specifically,

Because of the above OOS results, we do not agree that the current in-house (b) (4) 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 on a 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.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.

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[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

- Present tabulations of the new safety data combined with the original BLA data.

- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

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

(b) (4)

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

(b) (4)

3. You have not provided stability data for deliverable volume to support the proposed shelf life of 24 months (accelerated or real time) for your drug product. As stated in our February 7, 2017 BPD Type 4 meeting to discuss the content of format of the BLA, we stated that you should include expellable volume testing at the end of your proposed shelf life. We recommend that you provide results for this essential performance requirement testing to support the proposed 24-month shelf life for your drug product.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call May Zuwannin, Regulatory Project Manager, at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Deputy Division Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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

/s/

ALBERT B DEISSEROTH
08/02/2021 09:59:50 AM

BLA 761082

COMPLETE RESPONSE

Kashiv BioSciences, LLC
Attention: John Pakulski
Senior VP, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Mr. Pakulski:

Please refer to your biologics license application (BLA) dated July 8, 2017, received July 10, 2017, submitted under section 351(k) of the Public Health Service Act for Theragrastim.[1]

We acknowledge receipt of your amendment dated June 24, 2020, which constituted a complete response to our June 11, 2019, action letter.

We have completed our review of this application, and have determined that we cannot 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. An inspection 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 restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. While you may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect, please note that the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application.

For more information, please see the FDA guidances related to the Coronavirus Disease 2019 (COVID-19) public health emergency.[2]

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[1] 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.

[2] https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

APPEARS THIS WAY ON ORIGINAL

PRODUCT QUALITY

Audit Completeness and Data Traceability

2. We understand that you identified [redacted] as the third-party to audit your quality data and systems to support BLA 761082. However, it is unclear whether the [redacted] audit reviewed all the quality data submitted in the BLA because the [redacted] audit covered data mainly generated during the years 2015-2017 and the clinical DP lots 40-13013 and 45-14042 were manufactured on November 9, 2013 and July 19, 2014, respectively. Also, it is not clear whether there are source data traceability issues in the comparative analytical assessment including lots used in clinical studies submitted in the BLA. The audit team reported (see pages 596-7 of "Response to Retrospective Review of the GMP Systems and Product Quality Data of Theragrastim by [redacted]"):

    a. some HPLC raw data and UV data were not traceable to the source, and

    b. SDS-PAGE data for the clinical lot 45-14042 manufactured on July 19, 2014 were not available for review during the audit.

The Theragrastim lots for which source data are not traceable should not be included in the comparative analytical assessment. To address this deficiency:

    a. Provide a table listing all lots, tests performed with those lots, and the dates of testing that were retrospectively reviewed during the [redacted] audit.

    b. Identify results that were included in the comparative analytical assessment but cannot be traced back to the source.

    c. Remove untraceable data from the comparative analytical assessment. If the source of the data is known but the source is unavailable for FDA inspection, then the data are considered untraceable.

Depending on the impact of removing untraceable data from the comparative analytical assessment you may need to conduct additional comparative analytical studies, repeat clinical studies, or both.

Sequence Variants

3. In your response to the June 11, 2019, complete response (CR) item # 3, you reported the detection of two sequence variants, S77-R77 and G101-R101 from a peak (CEX-P6) separated using the CEX-HPLC method. However, you did not provide an explanation for the etiology of the sequence variants or whether the sequence variants impact the conclusions reached in your comparative analytical assessment. To address this deficiency, provide an explanation for the sequence

variants, and whether the variants impact a determination that Theragrastim is highly similar to US-licensed Neupogen. Depending on the etiology of the sequence variants and their impact on a determination that Theragrastim is highly similar to US-licensed Neupogen, you may need to develop a strategy to control or remove these sequence variants in Theragrastim.

In-House Reference Standards

4. The stability protocols PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard [redacted] (b) (4) "Stability Protocol for Theragrastim Working Reference Standard" are deficient because there are no acceptance criteria established to control for EC50 values. To address this deficiency, update the stability protocols for in-house primary and working reference standards to include adequate control over EC50. Because you have not established a working reference standard (WRS) and you have been using the primary reference standard (PRS) in QC testing, you should perform a trending analysis of the EC50 values obtained during routine release and stability testing to establish a stability acceptance criterion for the PRS. After a WRS has been established and used in QC testing, you may use a similar strategy to establish a stability acceptance criterion for the WRS. Provide a detailed description of how you propose to perform this trend analysis and how the acceptance criterion is going to be defined.

Post-Approval Stability Protocol

5. We noted deficiencies in your stability specifications and stability protocols for Theragrastim DP. The DP stability protocols listed in section 3.2.P.8.2. indicate to test for syringe break loose and glide force determination and follow specifications per SPC-0031 "Theragrastim Drug Product (DP) Specification". However, we noted that SPC-0031 does not list stability specifications for this quality attribute. Also, we noted you schedule to test container closure integrity (CCI) only at the 12-month time-point but not at the 24-month time-point. To address these deficiencies:

    a. update the DP stability specifications to assess for syringe break loose and glide force, and

    b. modify the DP post-approval stability protocols to include CCI testing at the 24-month time-point.

Shipping Validation Protocol

6. We noted the following deficiencies in the shipping performance qualification protocols PTL 2079 and PTL-2080 for the DP in vials and pre-filled syringes:

    a. You proposed to use the lower filling volumes in the shipping validation studies without providing adequate justification that the lower filling volumes

represent worst-case scenarios, and it is inconsistent with your response to June 11, 2019, CR item # 25, that the higher filling volumes will be used in the shipping validation studies.

b. There is no test to examine the primary and secondary packaging systems to ensure that there is no physical damage to the packaging systems after shipment.

To address the above deficiencies, revise the DP shipping validation protocols to:

a. provide adequate justification that the lower filling volumes represent worst-case scenarios,

b. update the protocols to include examination of the primary and secondary packaging systems for physical damage.

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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*.

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.[5]

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that are identical to the carton and immediate container labels submitted on September 11, 2020.

[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, September 29, 2020, 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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.

    - Present tabulations of the new safety data combined with the original BLA data.

    - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Additional Comments

In addition, there are several comments that are not approvability issues, but need to be addressed.

1. You did not provide appropriate information to support that there is no impact on the RP-HPLC (STM-0076) and CEX-HPLC (STM-0042) method validation after replacing the United States Pharmacopeia reference standard (USP RS), FOL526, with in-house (b) (4) as a reference standard for the methods. Specifically,

    a. Figure 6.6b in PTL-1193-R indicates that USP RS FOL526 and in-house (b) (4) showed differences in RP-HPLC chromatographic patterns, specifically, the reduced peaks did not align.

    b. We cannot locate data showing that CEX-HPLC chromatogram profiles for USP RS FOL526 and in-house (b) (4) are comparable.

To address this concern, provide appropriate information supporting the suitable performance of in-house (b) (4) in these methods.

2. We noted deficiencies in the stability protocols for the in-house reference standards:

    a. PTL-1981 "Stability Protocol for Theragrastim Primary Reference Standard (b) (4)" does not include adequate replicate runs to robustly test potency. For the primary reference standard, a sufficient number of tests should be performed at the time of stability testing to achieve a statistically significant mean EC50 value. To address this deficiency, update the stability protocol to include sufficient replicates for potency testing.

    b. In PTL-2305 "Stability Protocol for Theragrastim Working Reference Standard", your Table 11.1a is entitled "Theragrastim in-house Primary Reference Standard (b) (4) Stability Specifications". It is our

understanding that Table 11.1a refers to WRS rather than PRS. Provide the correct reference standard for that table.

3. We noted deficiencies in the protocols for qualification of new cell banks.

   a. We noted the following deficiencies in protocol PTL-2168 "Protocol for generation and characterization of new Theragrastim master cell bank and working cell bank":

      i. The protocol does not include alert limits, action limits, or criteria for trend analysis of quantitative in-process and release data from the Theragrastim DS lots produced using the new working cell banks (WCB) against historical DS lots manufactured using previous WCBs.

      ii. The protocol does not include acceptance criteria for cell growth kinetics from fermentation process, including doubling time, growth rate, age at harvest, and percent cell viability and viable cell concentration; and productivity, such as titer.

To address these deficiencies, update the protocol to include adequate acceptance criteria to ensure that new WCB perform comparably to previous WCBs.

(b) (4)

4. In your response to June 11, 2019, CR item #24c, you concluded that methods STM-0078 (UV) and STM-0076 (RP-HPLC) produce comparable results for protein concentration by showing a difference of less than (b) (4) in protein concentration values measured by these two methods in the real-time stability studies. However, your justification is not adequate because the stability data in report file PTL-1088-R for the previous in-house (b) (4) indicate that protein concentration values measured by these two methods showed up to (b) (4) difference: (b) (4) using STM-0076 (RP-HPLC) at the 26-month time-point vs. (b) (4) using STM-0078 (UV) at the 49-month time-point. To address

this deficiency, provide an appropriate justification to demonstrate that the two methods STM-0078 (UV) and STM-0076 (RP-HPLC) will produce comparable results for protein concentration.

5. We acknowledge that you provided data to support that the removal of kanamycin in the (b) (4) fermentation processes does not have an impact on manufacturing process and product quality. However, the final conclusion will be made after the review of the final report that you committed to submit.

(b) (4)

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). You may also request an extension of time in which to resubmit the application.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call May Zuwannin, Regulatory Project Manager, at 301-796-7775.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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

/s/

ALBERT B DEISSEROTH
12/22/2020 12:18:04 PM

BLA 761082

COMPLETE RESPONSE

Kashiv BioSciences, LLC
Attention: John Pakulski
Senior, Vice President, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Mr. Pakulski:

Please refer to your biologics license application (BLA) dated July 8, 2017, received July 8, 2017 and your amendments, submitted under section 351(k) of the Public Health Service Act for Theragrastim.

We acknowledge receipt of your amendment dated December 11, 2018, which constituted a complete response to our May 10, 2018, action letter.

We also refer to our complete response letter dated June 11, 2019, which contained the following errors: The company name and FEI number on page 1 under FACILITY INSPECTIONS is incorrect.

This replacement complete response letter incorporates the correction of the error. The effective complete response date will remain June 11, 2019, the date of the previous complete response letter.

We have completed our review of this application, as amended, and have determined that we cannot 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.

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.

PRODUCT QUALITY:

2. 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. A description 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. A description 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. A description 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.

Analytical Similarity

3. 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.
   b. 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.

4. 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.

b. 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.
c. 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.
d. 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.
e. 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.

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.

5. 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.

6. 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

(b) (4)

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Stability Protocol

23. 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 example,
        i. 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.
        ii. 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.
        iii. Lot 450-16017(vial): OOS for purity by RP-HPLC at 24 months.
        iv. Lot 300-16009 (PFS): OOS for purity by RP-HPLC at 18 months.
        v. Lot 300-16011(PFS): OOS for purity by RP-HPLC at 6 months.
        vi. Lot 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. In addition, there are missing data at many stability timepoints for various specifications. For example, missed testing for particulate 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 data. You should follow the stability protocol to test particulate matter and polysorbate 80 at all proposed timepoints.
    c. Protein concentration was not tested at 18-month and 24-month timepoints for several lots by UV absorbance and was tested by RP-HPLC instead. Provide appropriate information to demonstrate that the two different methods will produce comparable results for protein concentration.

    Therefore, these data are insufficient to support the proposed 24-month dating period for DP PFS and vial presentations when stored at recommended storage conditions of 5°C. To address this deficiency, propose 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.

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) (b) (4) 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:

    - 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.

- Lots 30-15018, 30-15019 and 45-15025 are not included in report PRT-1077 while they were included in report RPT-0987.
- 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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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*.[3]

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

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.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/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

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.
- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

(3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

(6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). 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 601.3(c). 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 should 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 guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ALBERT B DEISSEROTH
06/11/2019 12:00:00 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761082

COMPLETE RESPONSE

Adello Biologics, LLC
Attention: Joel Brittain, PhD
Senior Associate, Global Regulatory Affairs
20 New England Avenue
Piscataway, NJ 08854

Dear Dr. Brittain:

Please refer to your Biologics License Application (BLA) dated July 8, 2017, received July 10, 2017, and your amendments, submitted under section 351(k) of the Public Health Service Act for Theragrastim.[1]

We have completed our review of this application, as amended, and have determined that we cannot 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 Adello Biologics manufacturing facility (FEI: 3011289655), our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

Analytical Similarity

2. The analytical similarity data for CEX-HPLC indicate that the species contributing to charge variants are different for Theragrastim and US-licensed Neupogen and that charge variant levels in the proposed commercial Theragrastim lots are higher than in US-licensed Neupogen. Specifically, we note:

    a. Commercial DS Theragrastim lots 20-17001, 20-17002, and 20-17003 and DP Theragrastim lots 170086, 170087, and 170088 have total charge impurity levels outside the US-licensed Neupogen quality range.

[1] 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, which was the name Adello used to refer to this product during development.

b. In Theragrastim, the predominant charge variant species elutes as a shoulder to the main peak (RRT = 0.95). This species is absent in US-licensed Neupogen lots under non-stressed conditions but is enriched in both products under forced degradation conditions of oxidative stress, suggesting this species may be also present in US-licensed Neupogen but in levels undetectable under non-stress conditions.
c. A basic variant species eluting at RRT = 1.17 is consistently present in Theragrastim lots but absent in US-licensed Neupogen lots.
d. Results from a photostability study (Table 8 of report PTL-1192-R) showed high levels of charged variants eluting around RRT =1.10-1.15 in Theragrastim following one cycle of light exposure. These species are not seen in US-licensed Neupogen.

Without additional data and an appropriate justification, these differences preclude a determination that Theragrastim is highly similar to US-Neupogen. To address these differences, you should conduct a comparative analysis of individual charge species between Theragrastim and US-licensed Neupogen and address the differences in the levels and type of charge variants observed between these products. In addition, you should justify why these differences do not preclude a determination that Theragrastim is highly similar to US-licensed Neupogen. Provide data and information in your 351(k) BLA resubmission.

3. RP-HPLC data included in your analytical similarity assessment was originally evaluated using the valley to valley integration method. This integration method resulted in an underestimation of the impurities in Theragrastim. You re-analyzed the RP-HPLC data using a baseline drop integration method and submitted the data in Table 2 of your response to our IR dated February 28, 2018. You proposed to exclude lots 45-15025, 30-15018 and 30-15019 from the analyses because they were formulated using (b) (4) You also propose to exclude clinical lot 45-14042 because you state that it was tested beyond the proposed shelf life. We agree with your proposal to exclude the referred three lots manufactured with (b) (4) because you proposed a strategy to control (b) (4) However, we disagree with your proposal to exclude from the analysis clinical lot 45-14042 because you did not provide evidence that lot 45-14042 was within the RP-HPLC US-licensed Neupogen quality range at release and within the proposed shelf life when RP-HPLC data are analyzed using the baseline drop peak integration method. The analytical similarity data for RP-HPLC indicate that the level of individual species contributing to total impurities is different in Theragrastim and US-licensed Neupogen and the total impurities by RP-HPLC is higher in Theragrastim compared to US-licensed Neupogen. To address these deficiencies, provide the following in your 351(k) BLA resubmission:

a. Data and information to support that the level of total impurities in lot 45-14042 are due to its age. The RP-HPLC data should be integrated using the baseline drop method.
b. Conduct a comparative analysis of individual species between Theragrastim and US-licensed Neupogen and address the differences in the levels of individual and total impurities observed between these products. You should also justify why these differences do not preclude a determination that Theragrastim is highly similar to US-licensed Neupogen.

4. The characterization data of product-related species provided in your original 351(k) BLA were limited with regards to the spectra of species identified and were insufficient to establish a conclusive identification of individual species. For example, you did not provide data and information on whether product related species known to occur in therapeutic protein products such as sequence variants, formylate methionine species, succinimide species, norleucine species, acetylated species, and truncated species are present in Theragrastim. You explain that additional product-related species were not detected by the intact mass or peptide mass methods in ten-fold concentrated Theragrastim samples. However, it is unclear whether these species are absent in Theragrastim or whether the material used for the characterization studies was inadequate. In addition, it appears that your characterization data correspond to chromatography fractions, which may include various product-related species, instead of individual species eluting as single peaks in the chromatography methods. This information is needed to support the safety profile of your product and to support that the species present in Theragrastim are the species also identified in US-licensed Neupogen.

   Provide characterization data of individual product-related species of Theragrastim, including low abundance species and determine whether they are product related substances or product-related impurities. You may consider using in your characterization studies, process intermediates or accelerated stability Theragrastim and US-license Neupogen samples containing higher levels of these species. The characterization data are needed to support analytical similarity and inform the control strategy for your product. Submit the data and information in your 351(k) BLA resubmission.

5. Table 16 of PTL-1192-R shows the RP-HPLC results of the comparative forced degradation study under oxidation conditions. We note that Theragrastim lot 3-FIN-2475 shows high levels of impurities eluting at RRT = 0.96-97 and RRT=0.97-0.99 compared to other Theragrastim and US-licensed Neupogen lots. You did not provide an explanation for these data and did not provide an evaluation of how these results may impact the comparative assessment. In your 351(k) BLA resubmission, provide an explanation for the results and a justification as to why they do not impact the comparative assessment of forced degradation under oxidation conditions. Furthermore, clarify whether RP-HPLC data from the forced degradation study under oxidation conditions were generated using the baseline drop integration method or the valley to valley integration method. If valley to valley integration was used, we request that you provide these data reanalyzed using the baseline drop integration method.

6. In Table 28 in PTL-1192-R showing mass balances for CEX-HPLC, the results for 3 hours of oxidative stress are listed to have mass balances significantly different than 100%. Notably, the Theragrastim samples are listed below 100% (at around 77%), while the US-licensed Neupogen lots are above 100% (at around 174-226%). Furthermore, it appears there might be errors in the data shown in table 28. In your 351(k) BLA resubmission, provide:

   a. An updated table 28 with corrected values for mass balances, as needed.

b. A justification for the use of data where the mass balance data provided are significantly different from 100%, and for any data where Theragrastim has a different range of mass balance values than US-licensed Neupogen in the same studies. Clarify whether the area of the sample and standard used in the mass balance calculation is based on area under all peaks or only area under the main peak. Clarify the method of peak integration for mass balances.

Reference standard or materials

7. The reference standard (RS) program for Theragrastim is inadequate. Specifically,

a. The qualification of your current Theragrastim in-house primary reference standard Lot [redacted] is inadequate because its potency and protein concentration were not accurately assigned. The potency and protein concentration of this RS was assigned based on release testing results from [redacted]. This approach is inadequate because your potency and protein concentration release testing uses three replicates, which are insufficient for an accurate determination of potency and protein concentration for RS qualification. Potency and protein concentration of a RS should be determined using sufficient replicates and appropriate statistical methods to ensure an accurate and precise potency and protein concentration values are assigned to the RS. This determination is critical to prevent drift in potency of your product. You state that you qualified your in-house reference standard against a USP filgrastim reference standard Lot # F0L526. You also noted that in addition to USP filgrastim RS Lot # F0L526 and in-house [redacted] other reference standards were used during development. These include Theragrastim lots [redacted]. It is unclear how these reference standards are related because you did not provide data and information to establish a bridge between the RS lot [redacted], the RS used in the analytical similarity assessment, and the RSs used for release and stability testing of DS and DP lots during development. Provide these data and information.

b. You indicate that stability testing of reference standard lot [redacted] is redundant with the stability program for [redacted], because they are the same drug substance material. For this reason, you used stability testing data from [redacted] to support the stability of reference standard lot [redacted]. You also state that "retest of the RS will be performed [redacted] While [redacted] lot was developed from [redacted], the container closure systems are different. *Section 3.2.S.5 Reference Standards or Materials*, indicates that the container closure system for [redacted] is [redacted] and that the container closure for reference standard lot [redacted] is [redacted] The RS requalification approach used for [redacted] lot is inadequate because you did not provide data and information to demonstrate that the stability data collected from DS lot [redacted] is relevant to support that [redacted] remains stable over time.

Therefore, your proposed [redacted] (b) (4) lot is not adequately qualified to be used for release of commercial lots of Theragrastim. To address this deficiency, provide the following data and information in your 351(k) BLA resubmission:

a. Implement a adequately qualified in-house reference standard for release and stability testing of Theragrastim DS and DP (refer to item a above).The RS should be representative of production and clinical materials, and the material used in analytical similarity. As per ICH Q6B, your in-house reference standards should be calibrated against an international or national standard (if available) and be bridged with the RS used in the analytical similarity assessment and throughout development.
b. Describe the procedures used to determine the potency and protein concentration of the Theragrastim in-house reference standard.
c. Describe the procedures you use to declare the biological activity of Theragrastim in-house reference materials, e.g. the potency range within which a reference standard will be assigned a potency of 100%.
d. Provide data to support the stability of your in-house RS and a protocol for requalification of your in-house RS. The protocol should incorporate the considerations discussed above regarding qualification for potency and protein concentration.
e. If you propose to qualify a RS other than [redacted] (b) (4) be aware that you will need to bridge the new RS, [redacted] (b) (4) and the RS lot used in analytical similarity and throughout development.

8. In Section 3.2.S.5 Reference Standards or Materials you describe the development of your current in-house reference standard lot [redacted] (b) (4) prepared from PPQ lot [redacted] (b) (4). In that section, you also state that reference standard lot [redacted] (b) (4) had been previously used during drug development. However, in section 2 of document PTL-1193-R "Qualification Report of Theragrastim In-House Primary Reference Standard Lot [redacted] (b) (4) you state that the USP reference standard has been used during process development for release, stability, characterization and similarity, and in-process testing. The information provided in Document PTL-1193-R is inconsistent with information provided in Section 3.2.S.5 Reference Standards or Materials. To address these inconsistencies, provide the following information in your 351(k) BLA resubmission:

   a. Clarify whether reference standard lot [redacted] (b) (4) were used for release and stability testing of drug substance and/or drug product. If so, provide qualification data for each RS used for the control of DS and DP and explain how content and potency were assigned for each reference material used.

   b. Clarify whether primary reference standard lot [redacted] (b) (4) has been used for release and stability testing of Theragrastim DS and/or DP. Provide a list of the lots tested using this RS material, as appropriate.

9. We note that in the description of the analytical methods used for in process, release and stability testing and characterization, you state that reference standard material could be USP

RS, in-house RS or US-licensed Neupogen. As per ICH Q6B, reference standards should be representative of production and clinical lots. USP filgrastim reference standard and US-licensed Neupogen are not appropriate reference standards for Theragrastim because they are not representative of your production and clinical lots. For commercial manufacturing and control of Theragrastim, you should only use an adequately qualified Theragrastim reference standard that has been developed, characterized, and qualified in-house. In addition, you should revise your analytical method description and SOPs to only use an adequately qualified in-house reference material. Provide this information in your 351(k) BLA resubmission.

Drug substance process description and validation

(b) (4)

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Drug substance container closure system

Drug product

18. In 3.2.P.3.3, 3.2.P.3.4 and, 3.2.P.3.5 you use the terms specifications, acceptance criteria, and limits interchangeably to describe the acceptable ranges for Theragrastim DP in-process controls (IPC) critical process parameters (CPPs) and non-CPPs. Note that the disposition of lots that fail specifications acceptance criteria are different from the disposition of lots that fail alert or action limits. For example, lots failing specifications acceptance criteria should be rejected whereas lots failing action limits should trigger an investigation. Therefore, it is

unclear what each of these terms mean and what actions will be taken when results fall outside the specifications acceptance criteria or limits. To address this deficiency, revise your 351(k) BLA to clearly define whether the ranges described for DP IPCs, CPPs and non-CPPS are specifications with acceptance criteria or whether they are limits. Specify the actions that are taken when acceptance criteria or action limits fail for IPCs, CPPs and non-CPPs. Indicate whether failure of acceptance criteria or action limits will trigger lot rejection or a deviation with product quality impact assessment and batch disposition evaluation. Ensure these terms are used consistently in your 351(k) BLA application.

19. In your response to our IR dated February 12, 2018, you explain that visual inspection is performed on all Theragrastim DP vials and syringes manufactured in a lot. Your proposed rejection limits for visual inspection are (b) (4) for particulate matter rejects and (b) (4) for overall rejects. These limits were not exceeded for any of the PPQ and PV lots. However, you do not explain the actions you will follow if visual inspection failures are above (b) (4) for particulate matter rejects or above (b) (4) for overall rejects. Likewise, you do not explain the actions you will follow if the lot fails AQL inspection. In your 351(k) BLA resubmission, explain your control strategy for particulate matter by visual inspection including a description of the conditions that would result in rejection of the lot.

20. To comply with 21 CFR 610.14, you propose to test DP identity by SDS-PAGE after the primary container closure labeling activities have been completed. This is not sufficient because SDS-PAGE does not assess a unique characteristic of your product. This limitation is not overcome by including a rhG-CSF reference standard because showing that the RS and the Theragrastim have the same apparent molecular weight does not unequivocally demonstrate the identity of Theragrastim. To address this deficiency, implement a suitable identity assay, to comply with 21 CFR610.14, such as peptide mapping and include the assay results in the CoA. Provide data and information to support the identity assay in the 351(k) BLA resubmission.

21. Theragrastim DP is manufactured at a CMO, (b) (4), where other products may also be manufactured. Therefore, having an identity test that unequivocally distinguishes Theragrastim from other products manufactured at the facility is critical. To address this deficiency, implement identity testing for incoming Theragrastim DS at (b) (4) that evaluates a unique characteristic of your product. Include the information in your 351(k) resubmission.

22. In the initial steps of the DP manufacturing process (b) (4) Provide the information in your 351(k) BLA resubmission.

23. In Figure 4, section 3.2.P.3.3 Description of Manufacturing Process and Process Controls you describe the DP manufacturing process and in process parameters and controls for each

step of the manufacturing process. [redacted] (b) (4) To address this deficiency, implement an upper limit for [redacted] (b) (4) and provide the information in your 351(k) BLA resubmission.

Stability protocols

24. We identified the following deficiencies regarding your annual stability testing protocol for IP, DS, and DP:

    a. You propose to test for stability of IP, DS, and DP every 6 months. This testing program does not allow adequate monitoring of the stability of your product. ICH Q5C recommends testing at least every three months the first year, every six months the second year and annually thereafter. In your 351(k) BLA resubmission, provide revised stability protocols that include the 3 months and 6 months testing timepoints.

    b. You propose to monitor pH and concentration yearly. Testing for concentration and pH does not allow adequate monitoring of the stability of your product. Revise your protocol to monitor pH and concentration for IP, DS and DP in all stability timepoints recommended in ICHQ5C. Provide the revised stability protocol in your 351(k) BLA resubmission

    c. Testing for Theragrastim protein concentration at DS release is performed using UV absorbance-based method STM-0078 whereas testing for DS stability testing is performed using RP-HPLC based method STM-0076. Clarify whether you intend to use two different methods to monitor protein concentration at release and during stability. Explain how you plan to compare protein assay results at release with stability results when using methods with different read outs, and provide information and scientific justification in your 351(k) BLA resubmission to support the use of the two different protein concentration methods for release and stability testing.

    d. The DP annual stability protocol does not include testing for extractable volume for vials and syringes. This testing is needed to ensure that your product meets label claim over the shelf life. Include extractable volume and deliverable volume in the annual stability protocol. You are not expected to test for this attribute in all stability timepoints. However, you should provide a justification for the testing points selected. Provide the revised stability protocol and justification in your 351(k) BLA resubmission.

Analytical methods

25. You describe updates to several analytical methods; however, no data or information were provided to describe the nature of the changes and to assess their impact on assay performance and testing results. To address this deficiency, in your 351(k) BLA

resubmission, provide the following information regarding all analytical methods used for control of DS and DP:

a. Date of full validation.
b. The change history of the method and an assessment of the changes on the validation status of the analytical method, with a justification as to why the change was determined to be acceptable.
c. The version of the analytical procedure proposed to test commercial material and how it differs from the version provided in the 351(k) application.
d. Update the relevant sections of your 351(k) BLA with the proposed commercial version of each analytical method.

Control strategy

26. Your proposed release and stability specifications are inadequate to support consistent product quality. Revise your release and stability specifications for drug substance (DS) and drug product (DP) to address the following deficiencies:

(b) (4)

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Shipping validation

30. To support DP shipping validation, you performed simulated shipping studies with Theragrastim DP packaged in vials and syringes and the results for those studies were submitted in your 351(k) BLA submission. In addition, you propose to conduct shipping performance qualification studies. However, your submission lacks an adequate shipping performance qualification protocol or data from real time shipping studies using the proposed modes of transportation, and the shipping conditions that will be used for shipping of commercial product. To address this deficiency, provide results from real time shipping qualification studies in your 351(k) BLA resubmission. Alternatively, submit a shipping

performance qualification protocol. This protocol should include, but not limited to, the following information:

a. 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) and to the maximum storage and transport duration that the product may encounter during shipping, using minimum and maximum shipping loads for each shipping container.

b. Description of the batches used in the study and criteria of selection. For shipping container qualification, representative mock-filled (e.g., water) container closure systems may be used, as appropriate.

c. Assessment of product quality of the fully packaged batch before and after shipping to evaluate the effect of shipping conditions.

d. Pre-defined acceptance criteria for evaluation of product quality and to support shipping container qualification.

Drug product container closure system

31. In section 3.2.P.2.6 you describe the leachable studies you performed on DP aged in vials and in syringes. You state that (b) (4) was detected at (b) (4) ppm from aged vials and syringes after 24 hr extraction. (b) (4)
You did not provide information to demonstrate that the levels of (b) (4) detected in these studies do not impact product quality and stability of the drug product stored at long-term conditions up to the proposed expiry date. Likewise, you did not assess the impact on product quality and stability of (b) (4) known to leach from syringes. To address these deficiencies, provide the following information in your 351(k) BLA resubmission:

a. Specify the maximum levels of (b) (4) present in the container closures system.

b. Provide a risk assessment for the impact of (b) (4) on the quality, stability and safety of your drug product.

c. Provide a justification for why the levels of (b) (4) detected in the leachables studies are acceptable.

d. Describe your strategy to control the levels of (b) (4) that could leach into your product from the container closure system.

32. In section 3.2.P.2.6 you state that contract laboratory [redacted] (b) (4) performed an assessment of all product contact materials and equipment used in the manufacturing process of Theragrastim at Adello and at [redacted] (b) (4). You provided a summary of the result in assessment Report CMO-0034 Theragrastim. The report identified five high risk materials used in the manufacture of Theragrastim based on the lack of extractable data and the direct, long-term contact of these materials with the product. You explain that these high-risk materials were used in extractable studies and refer to report CMO-0039 for the study results. However, report CMO-0039 could not be located in your 351 (k) BLA submission. In your 351(k) BLA resubmission, provide the results of the studies you performed to assess the risk on product quality and safety of leachates from these materials.

Stability

[redacted] (b) (4)

34. You request a shelf life of 24 months for the Theragrastim DP vial presentations when stored at 5°C. To support the proposed shelf life, you submitted stability data for up to 36 months from one vial lot of the 300µg/1.0 mL strength and two vial lots of the 480µg/1.6 mL strength. These data are insufficient to support the requested 24-month shelf life for the Theragrastim DP vial presentations. In your 351(k) BLA resubmission, provide stability data under the recommended storage conditions of 5°C for at least one additional vial lot of the 300µg/1.0 mL strength. Alternatively, provide data to support that the stability and rate of degradation of Theragrastim DP in the 480µg/1.6 mL strength vial presentation are informative of those of Theragrastim DP in the 300µg/1.0 mL strength vial presentation.

Microbiology

35. The end of the fermentation production does not include a bacterial purity test to monitor for possible contamination. Include a bacterial purity test at the end of each [redacted] (b) (4) production bioreactor [redacted] (b) (4) and provide bacterial purity acceptance criterion.

36. Critical manufacturing steps of Theragrastim drug substance are not routinely monitored for bioburden and endotoxin to verify continued microbial control of the process. Additional monitoring samples proposed in BLA Amendment 0033 were not updated in the BLA. Include in the BLA resubmission bioburden and endotoxin monitoring sampling [redacted] (b) (4)

[redacted] In addition, include a description of the test methods and test method qualification.

37. Maximum hold times for the [redacted] are not supported by microbial data. [redacted] The microbial study included in the BLA was not representative of the commercial process and therefore does not support the proposed hold times. Provide microbial data to support the maximum hold times for [redacted]. Alternatively, reduce the maximum hold times [redacted]

[redacted]

ADDITIONAL COMMENTS

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

Application Organization

41. Overall, Module 3 of your original 351(k) BLA submission is not well prepared. There were many inconsistencies in the information and data provided in different sections of the BLA as well as missing information. For example, in your narratives you frequently refer to reports that were not included in the submission (e.g. refer to comment 10 above). In addition, reports are not adequately labeled to allow for an efficient review process. Further, tabular data has not been consistently rounded or there are discrepancies between the primary data and the results reported in the submission narratives. Conduct an evaluation of your application and revise the submission as appropriate. Clearly identify all revisions in your 351(k) BLA resubmission

Reference standard or materials

42. Based on the data provided in Section 3.2.S.5 Reference Standards or Materials, it appears that you have a one-tier reference material system. You should develop a two-tier in-house reference material system consisting of primary and working reference materials. Each subsequent working or primary reference material should be calibrated against an in-house primary material appropriately characterized that is representative of production and clinical materials and of material used in the analytical similarity assessment. Calibrating against a single primary reference material assures that the bioactivity determined for the test samples is consistent over time and limits the potential drift in product potency that may occur when each new standard is compared to the current working standard. In your 351(k) BLA resubmission, provide a timeline for development of a two-tier RS system. Incorporate the recommendations provided in previous comments in the implementation of the two-tier RS system. Note that in the absence of a suitable protocol for qualification of primary and secondary reference standard, qualification of a new RSs will require the submission of a Prior Approval Supplement.

Drug substance manufacturing

(b) (4)

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Reference ID: 4263275

(b) (4)

Analytical methods

49. We note in PTL-0568-R for the validation report for CEX-HPLC method, you use Theragrastim DP syringe lot 350-16012. This lot number is not listed in your DP batch analysis section. We also note the impurity value by CEX-HPLC is higher than the other lots used and would not pass current specifications for purity by CEX-HPLC. In your 351(k) resubmission, provide the disposition of this lot, the CoA for this lot, how this lot was used, and explain why this lot was chosen for use in the method validation protocol.

Control strategy

50. In section 3.2.S.2.4, you provide the release and stability specifications for Theragrastim IP. (b) (4) In your 351(k) BLA resubmission,

    a. Specify the actions that are taken when potency investigational limit is not met.
    b. Explain whether this limit applies to both release and stability specifications.

Cell Banks

51. Your original 351(k) BLA submission lacks a protocol for qualification of new MCB and WCB. Submit a protocol for qualification of new MCB and WCB in your 351(k) BLA resubmission. Note that in the absence of a suitable protocol for qualification of new MCB and WCB, qualification of new cell banks will require the submission of a Prior Approval Supplement.

Stability

52. You propose to place one batch of Theragrastim DP from each presentation on stability every year. Specify the strength(s) of the products you intend to place on annual stability and provide a justification for the selection of lots in your 351(k) BLA resubmission.

53. We note that you are using the ELISA kit from [redacted] (b) (4) to measure host cell proteins (HCP) [redacted] (b) (4). The HCP antiserum and other reagents in the kit are critical reagents that when changed could affect the performance of the HCP ELISA. Therefore, you should have adequate control over these critical reagents. Be aware that when changes to the [redacted] (b) (4) critical reagents occur you should requalify your method to ensure it performs as expected. In particular, you should qualify new lots of the HCP kit to confirm comparable antibody coverage using two dimensional (2D) SDS-PAGE and western blot or a similarly sensitive and discriminating assay. The best approach is that you develop an in-house HCP antiserum and qualify it as described above. In your 351(k) BLA resubmission, clarify your plans to address this issue.

Analytical Similarity

54. In Table 2 of PTL-1192-R, you describe the stress conditions evaluated in the comparative forced degradation study. You indicate that studies under oxidation conditions were performed for 0, 3, 6, and 24 hours of treatment. Your submission, however, includes results for only a 3-hour treatment timepoint for some analytical methods. You indicate that samples may be over-stressed and data are not interpretable. In your 351(k) BLA resubmission, provide an explanation as to why these data are not interpretable and an evaluation of whether the missing data impact the comparative degradation assessment of Theragrastim and US-licensed Neupogen.

55. Figures 38 and 39 in report PTL-0618-R (Rev 02) show the results of isoelectric focusing point for Theragrastim and US-licensed Neupogen lots. In Figure 39, we note the presence of a small peak to the left of the "Filgrastim peak" at approximately 6.05 minutes in lots for both products. This peak is absent in the results shown in Figure 38 in both Theragrastim and US-licensed Neupogen lots. In your 351(k) BLA resubmission, provide an explanation for the presence of the small peak at approximately 6.05 minutes and information on the identity of this peak.

56. You did not specify the presentation and strength of Theragrastim and US-licensed Neupogen lots used in the comparative stability studies described in Report PTL-0618-R. In your 351(k) BLA resubmission, provide a summary table identifying presentation and strength of each lot used in the comparative stability studies and a rationale for the selection of lots included in the studies.

57. In PTL-1192-R, Figure 15 "Impurity Profiles by RP-HPLC of Theragrastim and Neupogen under Oxidation for 3 hrs" and Figure 16 "Comparative Charge Variant Profile of Theragrastim and Neupogen under Oxidation for 3 hrs", you provide expanded chromatogram of the lots tested in the study. However, this expanded view does not allow comparative assessment of the results. In your 351(k) BLA resubmission, provide an overlay of the expanded chromatograms to allow for comparison of all peaks in the chromatographic profile observed after 3 hours of oxidative stress.

58. Figure 20 in PTL-1192-R shows peptide mapping results of forced degradation studies under oxidative stress. Based on other peptide mapping data submitted in the original 351(k) BLA submission, some peak identities are incorrectly labeled (e.g. multiple G1 peaks are labeled). In your 351(k) BLA resubmission, provide an updated image with correctly labeled peaks.

Microbiology

59. Bioburden reduction filters are not in place to ensure microbial control at critical steps of the Theragrastim drug substance manufacturing process. [redacted] (b) (4) . Implement bioburden-reduction filtration [redacted] (b) (4) and include this information in the BLA resubmission.

60. The endotoxin test results for [redacted] (b) (4) samples are reported per mg. It is not clear whether that refers to mg of unpurified protein or to mg of Theragrastim. Report endotoxin limits in EU/mL and readjust the reported endotoxin values accordingly.

61. Describe how bioburden control is maintained and controlled [redacted] (b) (4) during routine operations.

62. Include a study protocol to demonstrate microbial control [redacted] (b) (4)

63. Provide summary shipping validation report to support shipping of the drug substance to the drug product manufacturing facility. Include temperature limits, results, and allowable excursions based on stability data.

64. Clarify whether in-process and/or release methods for bioburden and endotoxin are conducted at Adello and [redacted] (b) (4) and provide method descriptions and qualification summary reports for each site as applicable.

65. Implement an in-process endotoxin monitoring test with an appropriate limit prior to sterile filtration and provide the information in the BLA resubmission.

66. Provide the number of vials and syringes that were tested for container closure integrity in the shipping simulation studies.

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

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that are identical to the carton and immediate container labels submitted on February 28, 2018.

PROPRIETARY NAME

Please refer to correspondence dated, September 20, 2017, 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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
   - Present tabulations of the new safety data combined with the original BLA data.
   - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). 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 601.3(c). 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 Biosimilar Biological Product Sponsors or Applicants," November 2015 at https://www.fda.gov/downloads/drugs/guidances/ucm345649.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
05/10/2018