NDA 217779

NDA APPROVAL

Geron Corporation
Attention: Sherrie Pettiford, MS, RAC
Senior Director, Regulatory Affairs
919 E. Hillsdale Boulevard, Suite 250
Foster City, CA 94404

Dear Sherrie Pettiford:

Please refer to your new drug application (NDA) dated June 16, 2023, received June 16, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RYTELO (imetelstat) for injection.

This NDA provides for the use of RYTELO (imetelstat) for injection for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on May 23, 2024 (container label) and June 3, 2024 (carton labeling), as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217779**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for RYTELO (imetelstat) for injection shall be 24 months for the 188 mg strength and 12 months for the 47 mg strength from the date of manufacture when stored at refrigerated conditions: 2ºC-8ºC (36ºF-46ºF).

Results of ongoing stability should be submitted throughout the dating period in your annual report, as they become available, including the results of stability studies from the first three production lots.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages to birth to <1 year of age because necessary studies are impossible or highly impracticable. This is because of the rare incidence of myeloid malignancies in this age range.

We are deferring submission of your pediatric study for ages 1 year to <17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4631-1 Evaluate a minimum of 25 pediatric patients, including a minimum of 6 patients to <12 years of age, enrolled in one or more molecularly targeted pediatric cancer investigations to evaluate dosing, pharmacokinetics, safety, and preliminary efficacy of imetelstat, in combination with fludarabine and cytarabine, in pediatric patients 1 year to <17 years of age with relapsed/refractory acute myeloid leukemia, myelodysplastic syndromes, or juvenile myelomonocytic leukemia.

Final Protocol Submission:	12/2028
Study Completion:	06/2032
Final Report Submission:	12/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 147027, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4631-2 Conduct a rodent carcinogenicity study in mice to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on May 23, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	03/2026
Study Completion:	01/2027
Final Report Submission:	09/2027

4631-3 Conduct a rodent carcinogenicity study in rats to evaluate the potential for carcinogenicity. Submit a carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on May 23, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2027
Final Protocol Submission:	05/2028
Study Completion:	08/2030
Final Report Submission:	08/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks of neutropenia, thrombocytopenia, infections, and bleeding in adults with transfusion-dependent lower-risk MDS and to assess a signal of a serious risk of QT prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4631-4 Complete the randomized part of trial MDS3001 to assess the long-term safety of imetelstat including the incidence of known serious risks of neutropenia, thrombocytopenia, infections, and bleeding in adults with transfusion-dependent lower-risk MDS. Include an integrated report to summarize the safety, overall survival, and efficacy when all patients on the Phase 3 Study MDS3001 have completed at least 5 years of treatment

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

with imetelstat or have 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or have withdrawn from the study, to demonstrate long term safety of imetelstat.

The timetable you submitted on May 23, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	10/2026
Final Report Submission:	04/2027

Submit the datasets with the final report submission.

4631-5 To potentially minimize the serious risks of imetelstat treatment including neutropenia and thrombocytopenia and other serious adverse events and improve tolerability, conduct a randomized trial comparing at least 2 dosages of imetelstat in patients with low or intermediate-1 risk myelodysplastic syndromes (LR-MDS) to evaluate alternative dosing regimens such as different dose levels, dosing frequencies, and duration of treatment. The study should include sufficient clinical pharmacokinetic sampling to analyze the exposure-response (ER) relationships. Update the current population pharmacokinetics (PopPK) and ER analysis with this clinical trial data. The trial should enroll sufficient representation of U.S. racial and ethnic minorities to ensure that the results are reflective of the U.S. population. Additionally, the study should follow subjects for a sufficient time after end of dosing to establish the time required to return to baseline grade for neutrophil and platelet count, in the absence of disease progression or subsequent therapy.

The timetable you submitted on May 23, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Trial Completion:	12/2030
Final Report Submission:	06/2031

Submit the datasets with the final report submission.

4631-6 Conduct a QT assessment and include results from the QT substudy under the Phase 3 portion of Study MDS3001, to further assess and characterize signals of serious risk of QT prolongation with use of

imetelstat in patients with low or intermediate-1 risk myelodysplastic syndromes (LR-MDS).

The timetable you submitted on May 23, 2024, states that you will conduct this trial according to the following schedule:

Final Report Submission: 10/2024

Include the clinical study report and datasets for the QT substudy under Study MDS3001 in the final report submission.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit clinical protocol(s) to your IND 147027 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4631-7 Conduct exploratory analyses aimed at identifying predictors of response to imetelstat using patient samples for cytogenetic and mutational analyses collected at baseline from patients treated with imetelstat in Study MDS3001. Conduct an analysis to characterize genetic markers, demographics, or other characteristics that predict long term transfusion independence (at least >24 weeks and >1 year) to imetelstat.

The timetable you submitted on May 23, 2024, states that you will conduct this study according to the following schedule:

Study Completion: 10/2026
Final Report Submission: 04/2027

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4631-8 Provide sufficient batch data, justification, and propose final quantitative acceptance criteria for the release specifications for (b) (4)

The timetable you submitted on April 19, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/06/2025

4631-9 As additional batch and stability data are obtained, submit a CBE-0 supplement annually (over the next five years) to report interim results that reviews this new data and tighten specification limits for product related substances by the LC-UV/MS method. Provide a final report of efforts to tighten specification limits for the product related substances and analytical method improvements for the LC-UV/MS method at the end of this five-year period as a CBE-0.

The timetable you submitted on April 19, 2024, states that you will conduct this study according to the following schedule:

Interim Report Submissions: 06/06/2025; 06/06/2026; 06/06/2027; 06/06/28

Final Report Submission: 06/06/2029

Submit clinical protocols to your IND 147027 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[6]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

If you have any questions, contact Saumya Nathan, Senior Regulatory Project Manager, at 301-348-1963 or saumya.nathan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[9] https://www.uspnf.com/

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/

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