CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214783Orig1s000

Trade Name:	REZUROCK oral tablets
Generic or Proper Name:	belumosudil
Sponsor:	Kadmon Pharmaceuticals, LLC
Approval Date:	July 16, 2021
Indication:	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 214783

NDA APPROVAL

Kadmon Pharmaceuticals, LLC
Attention: Michael Bui, DDS, MPH, JD
Senior Vice President, Regulatory Affairs
55 Cambridge Parkway, Suite 300E
Cambridge, MA 02142

Dear Dr. Bui:

Please refer to your new drug application (NDA) dated September 30, 2020, received September 30, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REZUROCK (belumosudil) oral tablets.

We acknowledge receipt of your major amendment dated March 5, 2021, which extended the goal date by three months.

This new drug application provides for the use of REZUROCK (belumosudil) oral tablets for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- The revised date at the end of Highlights was updated to 7/2021.
- In the first sentence of Section 6.1, adverse event was changed to adverse reaction.

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 changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 25, 2021, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214783**." 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 REZUROCK (belumosudil) oral tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature).

ADVISORY COMMITTEE

Your application for REZUROCK was not referred to an FDA advisory committee, because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 patients less than 3 months old, because necessary studies are impossible or highly impracticable. This is because it is not likely that patients in this age group would have undergone allogeneic hematopoietic

[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.

stem cell transplantation, developed chronic GVHD, and failed systemic therapy for cGVHD within 3 months from birth.

We are deferring submission of your pediatric studies for ages 3 months to less than 17 years 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 studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4106-1 Conduct a clinical trial to determine the appropriate dose of belumosudil and to assess the safety, efficacy, and pharmacokinetics of belumosudil in pediatric patients with chronic graft-versus-host disease. Include at least 20 adolescents 12 to < 17 years old, 4 children 2 to < 12 years old, and 2 infants ≥ 3 months to < 2 years old.

Draft Protocol Submission:	06/2022
Final Protocol Submission:	09/2022
Study Completion:	04/2026
Final Report Submission:	10/2026

Submit datasets with the final report.

4106-2 Conduct a pharmacokinetics trial to compare the relative bioavailability of belumosudil pediatric formulation to belumosudil tablets and develop an age-appropriate pediatric formulation of belumosudil.

Final Protocol Submission:	07/2021
Study Completion:	08/2021
Final Report Submission:	02/2022

Submit datasets and product quality information with the final report.

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 protocols to your IND 125890, with a cross-reference letter to this NDA.

[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.

Reports of these required pediatric postmarketing studies 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 these studies. 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 assess a known serious risk of infections, hypertension and other adverse events in patients receiving belumosudil.

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 these serious risks.

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

4106-3 Conduct an integrated safety analysis using data obtained from clinical trials to further characterize the safety of long-term treatment with belumosudil and determine the rate of infections, hypertension and other adverse events. The integrated safety analysis should include all adverse events, major safety events, dose-reductions, dose interruptions, withdrawals, and efficacy when all patients have completed at least three years of treatment with belumosudil or withdrew earlier.

The timetable you submitted on July 14, 2021, states that you will conduct this study according to the following schedule:

Final Analysis Plan Submission:	06/2022
Study Completion:	08/2022
Final Report Submission:	02/2023

Submit the datasets with the final report.

4106-4 Conduct an in vitro mechanism-based inhibition study (such as the two-step dilution method) estimating the inactivation parameters (k_{inact} and K_I) of CYP1A2, CYP2C19 and CYP2D6 enzymes and measuring nonspecific binding of belumosudil to assess the potential of drug interaction with

belumosudil on these enzymes in accordance with the FDA Guidance for Industry titled "In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on July 14, 2021, states that you will conduct this study according to the following schedule:

Study Completion:	01/2022
Final Report Submission:	06/2022

4106-5 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 July 14, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2022
Final Protocol Submission:	09/2022
Study Completion:	06/2023
Final Report Submission:	12/2023

4106-6 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 July 14, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2022
Final Protocol Submission:	09/2022
Study Completion:	12/2024
Final Report Submission:	06/2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of excessive drug toxicity when belumosudil is administered concomitantly with UGT1A1 substrates and on the repeat doses of belumosudil on the single dose pharmacokinetics of sensitive substrates (P-gp, BCRP and OATP1B1).

We have also determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks of cardiac toxicity and elevated drug levels in the presence of hepatic impairment; and to assess a known serious risk of grade 3 toxicities including gastrointestinal and vascular disorders in Black patients with chronic graft versus host disease receiving belumosudil.

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

4106-7 Conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single dose pharmacokinetics of a UGT1A1 substrate to assess the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on July 14, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2022
Trial Completion:	11/2022
Final Report Submission:	05/2023

Submit the datasets with the final report

4106-8 Conduct a clinical pharmacokinetic trial evaluating the effect of repeat doses of belumosudil on the single dose pharmacokinetics of sensitive substrates (P-gp, BCRP and OATP1B1) to assess the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on July 14, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2022
Trial Completion:	11/2022
Final Report Submission:	05/2023

Submit the datasets with the final report.

4106-9 Conduct a clinical pharmacokinetic trial to determine a safe and appropriate dose of belumosudil in subjects with mild, moderate, and severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." The final report should include assessment of subjects with mild, moderate and severe hepatic impairment.

The timetable you submitted on July 14, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2020
Trial Completion:	12/2021
Final Report Submission:	06/2022

Submit the datasets with the final report.

4106-10 Conduct a thorough QT/QTc trial to evaluate the effect of repeat doses of belumosudil on the QT/QTc interval to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry titled, E14 Clinical Evaluation of QT/QTc and E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3).

The timetable you submitted on July 14, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2020
Trial Completion:	02/2021
Final Report Submission:	12/2021

Submit the datasets with the final report.

4106-11 Conduct a clinical trial in a sufficient number of Black patients with chronic graft versus host disease to assess the risk of cardiac toxicities and further characterize Grade 3 toxicities including gastrointestinal and vascular disorders associated with the use of belumosudil. This study should characterize the exposure (including PK data), safety, and efficacy of belumosudil.

The timetable you submitted on July 14, 2021 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2021
Final Protocol Submission:	01/2022
Trial Completion:	06/2025
Final Report Submission:	12/2025

Submit the datasets with the final report.

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]

Submit clinical protocol(s) to your IND 125890 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 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 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4106-12 Conduct a clinical trial to assess the pharmacokinetics of belumosudil among U.S. racial and ethnic groups. This study should characterize the exposure (including PK data), efficacy, and safety of belumosudil.

The timetable you submitted on July 14, 2021, states that you will conduct this study according to the following schedule:

Study Completion:	06/2022
Final Report Submission:	12/2022

[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.

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

We remind you of your postmarketing commitment:

4106-13 Development and validation of an optimal and discriminating dissolution method for the Quality Control (QC) testing of REZUROCK™ (belumosudil mesylate) Tablets, 200 mg. Submit a Prior Approval Supplement to update the NDA to include the method in the drug product specifications.

Dissolution acceptance criterion/criteria proposal, based on the data generated from the unexpired clinical and registration batches, and the first six commercial batches, using the new dissolution method. Submit a Prior Approval Supplement to update the NDA to update the dissolution acceptance criterion in the drug product specifications. (*Note: if six commercial batches have not been manufactured at the time of final report submission, dissolution acceptance criterion will be based on the data generated from the unexpired clinical and registration batches and from all available commercial batches*).

The timetable you submitted on April 28, 2021, states that you will conduct this study according to the following schedule:

Interim Report Submission:	02/2022
Final Report Submission:	08/2022

Submit clinical protocols to your IND 125890 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 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.[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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.

If you have any questions, contact Rosa Lee-Alonzo, Senior Regulatory Health Project Manager, at rosa.lee-alonzo@fda.hhs.gov or (301) 348-3004.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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

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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/

MARC R THEORET
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