

NDA 219685

**NDA APPROVAL**

Genzyme Corporation  
Attention: Antonia Martinez, MSc, MBA  
Strategist, Global Regulatory Affairs  
55 Corporate Drive  
Bridgewater, NJ 08807

Dear Antonia Martinez:

Please refer to your new drug application (NDA) received August 29, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Wayrilz (rilzabrutinib) tablets.

This NDA provides for the use of Wayrilz (rilzabrutinib) tablets for treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

### **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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert) 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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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 enclosed carton and container 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 219685.**” 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 Wayrilz (rilzabrutinib) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C.

## **ADVISORY COMMITTEE**

Your application for Wayrilz was not referred to an FDA advisory committee because the clinical trial design is acceptable, the evaluation of the clinical data did not raise significant safety or efficacy issues, and the application did not raise significant public health questions or have controversial issues that would benefit from advisory committee discussion.

## **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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## **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 an unexpected serious risk of pregnancy complications, maternal mortality, and adverse

effects on the developing fetus and neonate related to the use of rilzabrutinib during pregnancy, and adverse effects on infants exposed to rilzabrutinib via breast feeding.

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:

4878-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Wayrilz (rilzabrutinib) during pregnancy to assess the risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on June 27, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2026
Final Protocol Submission:	12/2026
Interim study report #1:	12/2029
Interim study report #2:	12/2032
Interim study report #3:	12/2035
Study Completion:	12/2036
Final Report Submission:	09/2037

4878-2 Perform a milk-only lactation study in lactating women who have received rilzabrutinib to measure concentrations of Wayrilz (rilzabrutinib) in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

The timetable you submitted on July 9, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2026
Final Protocol Submission:	12/2026
Study Completion:	12/2029
Final Report Submission:	06/2030

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.<sup>3</sup>

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the signals of serious risk of potential interaction of rilzabrutinib with substrates of P-gp, BCRP, OATP1B1, and OATP1B3 transporters, and serious risk of increased exposures in subjects with severe renal impairment.

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

4878-3 Conduct a clinical drug interaction study to evaluate the effect of Wayrilz (rilzabrutinib) on the pharmacokinetics of P-gp, BCRP, OATP1B1, and OATP1B3 transporter substrates in adult healthy volunteers. The study will assess the magnitude of exposure change of the transporter substrates and inform appropriate drug interaction management strategy for coadministration of rilzabrutinib with these transporter substrates in adult patients with persistent or chronic immune thrombocytopenia. This study should be designed and conducted in accordance with the ICH Guideline on Drug Interaction Studies M12 (August 2024).

The timetable you submitted on June 27, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2026
Final Protocol Submission:	06/2026
Trial Completion:	03/2027
Final Report Submission:	09/2027

4878-4 Conduct a dedicated renal impairment study to evaluate the effect of severe renal impairment (eGFR <30 mL/min) on Wayrilz (rilzabrutinib) pharmacokinetics compared to subjects with normal renal function. The study will assess the magnitude of exposure change of rilzabrutinib and inform appropriate dosing instructions for patients with severe renal impairment. This study should be designed and conducted in accordance with Guidance for Industry: *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing* (March 2024).

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<sup>3</sup> 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>.

The timetable you submitted on June 27, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2026
Final Protocol Submission:	06/2026
Trial Completion:	09/2027
Final Report Submission:	03/2028

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.<sup>4</sup>

Submit clinical protocol(s) to your IND 132668 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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.

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<sup>4</sup> 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>.

## **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*.<sup>5</sup>

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.<sup>6</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>7</sup>

## **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 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<sup>8</sup>.

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<sup>5</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>6</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>7</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>8</sup> <https://www.uspnf.com/>

If you have any questions, please contact Rolanda Bailey, Regulatory Project Manager, at (240) 402-5631 or email at [Rolanda.Bailey@fda.hhs.gov](mailto:Rolanda.Bailey@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Lisa Yanoff, MD  
Deputy Director  
Office of Cardiology, Hematology,  
Endocrinology, and Nephrology  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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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.**  
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/s/  
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