# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 219685Orig1s000

# PRODUCT QUALITY REVIEW(S)

# NDA Executive Summary

## 1. Application/Product Information

| | | | |
|---|---|---|---|
| **NDA Number.** | 219685 | | |
| **Applicant Name** | Genzyme Corporation | | |
| **Drug Product Name** | Wayrilz (rilzabrutinib) tablets | | |
| **Dosage Form.** | Tablet | | |
| **Proposed Strength(s)** | 400 mg | | |
| **Route of Administration** | Oral | | |
| **Maximum Daily Dose** | 800 mg | | |
| **Rx/OTC Dispensed** | Rx | | |
| **Proposed Indication** | • Indicated for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to (b) (4) | | |
| **Drug Product Description** | Each 400 mg film-coated tablet is orange, capsule-shaped, and debossed with “P” on one side and “400” on the other side. | | |
| **Co-packaged product information** | N/A | | |
| **Device information:** | N/A | | |
| **Storage Temperature/ Conditions** | 20°C to 25°C | | |
| **Review Team** | **Discipline** | **Primary** | **Secondary** |
| | *Drug Substance* | Daniel Jansen | Zhengfu Wang |
| | *Drug Product/ Labeling* | Rao Kambhampati | Theodore Carver |

| | | | |
|---|---|---|---|
| | *Manufacturing* | Liya Tang | Feiyan Jin and Haitao Li |
| | *Biopharmaceutics* | Kamrun Nahar | Tapash Ghosh |
| | *Microbiology* | N/A | |
| | *Other (specify):* | N/A | |
| | *RBPM* | Mikee Aguirre | |
| | *ATL* | Theodore Carver | |
| **Consults** | N/A | | |

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

**a. Expiration Dating:**

A 36-month shelf life is granted for the drug product when stored at 20℃ to 25℃.

**b. Additional Comments for Action**

None.

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

1) Background

The Applicant, Genzyme corporation, pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, has submitted a new drug application, NDA 219685, for rilzabrutinib tablets for oral use, which are indicated for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment. The NDA relies upon a Phase 3 study PRN1008-018 (EFC17093, LUNA3) and other sources of confirmatory evidence, including Phase 1/2 clinical study PRN1008-10 (DFI17124, LUNA2) Parts A and B and nonclinical pharmacological evidence. The OPQ review was conducted by

drug substance, drug product, manufacturing, and biopharmaceutics review teams.

2) Drug Substance

The drug substance is rilzabrutinib, a small synthetic molecule. The rilzabrutiib structure has been well characterized using state-of the-art methods. The drug substance is an (b) (4) solid, and the polymorphic form is adequately controlled during storage of the drug substance. The starting materials, synthesis, down-stream processes, and purification of the active substance are adequately controlled. Note that the revised specification reducing the limit of (b) (4) was submitted to the NDA after completion of the drug substance review and is captured in the drug product review (see summary in drug product section below). The drug substance review determined that the specification and analytical methods are adequate. Stability data support a retest of (b) (4) months for the rilzabrutinib drug substance when stored (b) (4) (b) (4)

3) Drug Product

The drug product is a 400 mg film-coated tablet for oral use. The drug product review determined that the composition and specification are adequately supported in the NDA. Adequate information was provided to support control of related substances and elemental impurities. Analysis of impurities carried over from the drug substance determined that an (b) (4) impurity (b) (4) (b) (4), poses a significant risk for (b) (4) during storage of the drug product. The Applicant provided test data for (b) (4) in the drug product and determined that this (b) (4) is below the Limit of Quantitation but above the Limit of Detection in three batches of the drug product. Based on these results, the Applicant agreed to lower the limit for (b) (4) in the drug substance (controlled as an unspecified impurity), to test the first six drug product batches including the process performance qualification batches for (b) (4) (b) (4), and to continue to test every other commercial batch of drug product for (b) (4). In view of the lowest estimated levels of (b) (4) in the drug product batches that were tested and low risk of (b) (4) agents in the drug product, this control strategy was deemed adequate. On the basis of the 36 months ICH long-term and 6 months accelerated stability data provided for three registration batches that were stored in the blister packs and HDPE bottles, a 36 months expiration dating period is granted when the blister packs and bottle presentations of the drug product are stored at 20℃ to 25℃.

4) Manufacturing

*Process* – The manufacturing process consists of [redacted] (b) (4). The Applicant provided adequate information to establish the comparability of drug product manufactured at the different manufacturing sites using for development and commercial manufacturing.

*Facilities* – All manufacturing facilities were determined to be approvable based on previous inspection history.

5) Biopharmaceutics

The biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Overall, the review concluded that the biopharmaceutics information and method are adequate to support approval.

6) Quality Labeling

The quality labeling review determined that the labeling is adequate from the quality perspective with final recommendations for labeling changes communicated to the Applicant.

**b. Is the overall recommendation in agreement with the individual discipline recommendations?** Yes

**Recommendation by Subdiscipline:**

| | | |
|---|---|---|
| **Drug Substance** | **-** | **Adequate** |
| **Drug Product** | **-** | **Adequate** |
| **Quality Labeling** | **-** | **Adequate** |
| **Manufacturing** | **-** | **Adequate** |
| **Biopharmaceutics** | **-** | **Adequate** |
| **Microbiology** | **-** | **N/A** |

**Environmental Assessment:** Categorical Exclusion - Adequate
**QPA for EA(s):** No

## 5. Life-Cycle Considerations

**Established Conditions per ICH Q12: No**
**Comments**: None.
**Comparability Protocols (PACMP): No**
**Comments:** None.

**Additional Lifecycle Comments:** None.

Theodore Carver

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# CHAPTER IV: LABELING
# NDA 219685

| | |
|---|---|
| **NDA Number** | 219685 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name** | WAYRILZ™ (rilzabrutinib) tablets |

**Assessment Recommendation:** Adequate

| Item | Assessment Conclusion | SDN # where labeling is adequate ("N/A" otherwise) |
|---|---|---|
| Prescribing Information Labeling (USPI) | Adequate | **eCTD Seq# 0001** |
| Patient Information (PPI) | Adequate | **eCTD Seq# 0001** |
| Container Labels | Adequate | **eCTD Seq# 0001** |
| Carton Labeling | Adequate | **eCTD Seq# 0001** |

**Brief Description of Outstanding Issues: The revised final documents will reflect all the recommended changes in this review.**

**Submissions being reviewed:**

| Document Reviewed (eCTD #, SDN #) | Date Received | Information Provided |
|---|---|---|
| NDA 219685 eCTD# 0001 | 8/30/2024 | USPI, Patient Information (PPI), and Container and Carton Labels. |
| | | |
| | | |

**Note: The following general comment was conveyed to the applicant and the applicant agreed to it:**

1) **We noticed frequent use of (b) (4) on the container and carton labels. Except when a complete description of the tablet is needed such as in Sections 3, 11 and 16 of the USPI, the (b) (4) should be removed from all other places of the labeling documents and from the container and carton labels.**

## 1.0 PRESCRIBING INFORMATION[1]

**Assessment of Product Quality Related Aspects of the Prescribing Information:**

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **Product Title in Highlights[2] [21 CFR 201.57(a)(2)]** | | |
| Established name(s)[3] | Adequate | Name: **rilzabrutinib tablets** |
| Route(s) of administration | Adequate | For oral use |
| Controlled drug substance symbol (if applicable) | N/A | |
| Initial U.S. Approval [§201.57(a)(3)] | Adequate | This is an NME and not yet approved |
| **Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]** | | |
| Dosage form(s)[4] and strength(s) in metric system[5] | Adequate | Tablet, 400 mg |
| If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6] | N/A | |

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7] | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8] | N/A | |

**Assessment:** *Adequate*

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product). | N/A | |

[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food). | N/A | |
| For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11] | N/A | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11). | N/A | |
| For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug | N/A | |
| For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs." | N/A | |

**Assessment:** *Adequate*

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | Adequate | Tablet |
| Strength(s) in metric system | Adequate | 400 mg |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement. | N/A | |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable. | Adequate | |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>). | N/A | |

**Assessment:** *Adequate*

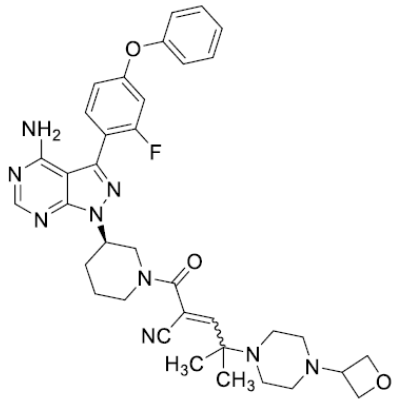
### 1.2.3 Section 11 (DESCRIPTION)[14]

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)]. | Adequate | Proposed: Tradename (rilzabrutinib) |
| Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)]. | Adequate | Tablet |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)]. | N/A | |
| List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)]. | Adequate | The inactive ingredients in the tablet core are crospovidone (Type A), microcrystalline cellulose, and sodium stearyl fumarate. The inactive ingredients in the tablet coating are FD&C yellow #6/Sunset yellow FCF aluminum lake, macrogol/polyethylene glycol (PEG), polyvinyl alcohol, talc, and titanium dioxide. |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make | N/A | |

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)]. | | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | |
| Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)]. | N/A | |
| Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)]. | Adequate | *TM* is a BTK inhibitor.<br>Note: TM will be replaced by tradename in the final USPI. |
| Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)]. | Adequate | The chemical name for rilzabrutinib is 1-Piperidinepropanenitrile, 3-[4-amino-3-(2-fluoro-4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]- $\alpha$ -[2-methyl-2-[4-(3-oxetanyl)-1-piperazinyl]propylidene]- $\beta$ -oxo-, (3*R*)-.<br>The molecular formula is $C_{36}H_{40}FN_9O_3$ and the molecular weight is 665.77. The chemical structural formula of rilzabrutinib is shown below:<br>  |

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)]. | N/A | |
| Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)]. | N/A | |
| For oral prescription drug products, include gluten statement[19] (if applicable). | N/A | |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"). | N/A | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2). | N/A | |

**Assessment:** *Adequate*

### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) [§ 201.57(c)(17)]. | Adequate | The *TM* film-coated tablets are orange, capsule-shaped, and debossed with "P" on one side and "400" on the other side. |

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| | | Note: TM will be replaced by the tradename in the final document. |
| Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement. | Adequate | 400 mg |
| Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)]. | Adequate | Bottle containing 60 film-coated tablets with a child-resistant closure.<br>Carton containing 2 blister packs, each containing 1 blister (b) (4) (58468-0251-0) with 28 film-coated tablets (b) (4). |
| Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)]. | Adequate | The *TM* film-coated tablets are orange, capsule-shaped, and debossed with "P" on one side and "400" on the other side.<br>For bottle: 58468-0251-6<br>For blister pack: 58468-0251-5<br>Note: TM will be replaced by the tradename in the final documents. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>). | N/A | |

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)] | Adequate | |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>). | Adequate | Store in original packaging between 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]. Protect from light and moisture. |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21] | N/A | |
| Include information about child-resistant packaging[22] (if chosen by manufacturer). | N/A | |

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

**Assessment:** *Adequate*

The above recommended changes were communicated to the applicant, and they will be incorporated into the final USPI.

### 1.2.5 Other Sections of Labeling: Not applicable

### 1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

| Item | Item in Proposed Labeling (choose "Adequate" or "Inadequate") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer. | Adequate | Manufactured (b) (4)<br>Genzyme Corporation<br>Cambridge, MA 02141<br>A SANOFI COMPANY |

**Assessment:** *Adequate*

Above recommended changes will be included in the final USPI.

### 2.0 PATIENT LABELING: Patient Information document was provided in the NDA submission, which is reviewed below:

### Assessment of Patient Information:

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Established name[24] | Adequate | TM (rilzabrutinib) tablets<br>Note: In the final document, applicant will replace TM with tradename. |
| Special preparation instructions (if applicable). | N/A | |
| Storage and handling information (if applicable). | Adequate | Store *TM* at room temperature between 20°C to 25°C (68°F to 77°F). |

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| | | Note: TM will be replaced by the proprietary name in the final document. |
| If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form. | N/A | |
| Active ingredient(s) (if applicable). | Adequate | rilzabrutinib |
| Alphabetical listing of inactive ingredients (if applicable). | Adequate | Inactive ingredients: Tablet core: crospovidone (Type A), microcrystalline cellulose, and sodium stearyl fumarate; Tablet coating: FD&C yellow #6/Sunset yellow FCF aluminum lake, macrogol/polyethylene glycol (PEG), polyvinyl alcohol, talc, and titanium dioxide. |
| Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer. | Adequate | Manufactured (b) (4)<br>Genzyme Corporation<br>Cambridge, MA 02141<br>A SANOFI COMPANY |

**Assessment:** *Adequate*

The above comments were conveyed to the applicant and the final Medication Guide will reflect the recommended changes.

## 3.0 CONTAINER AND CARTON LABELING[25]

(b) (4)

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[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)]. | Adequate | Yes | WAYRILZ™ (rilzabrutinib) tablets |
| Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28] | Adequate | Yes | 400 mg |
| Route(s) of administration, not required for oral use [§ 201.100(b)(3)]. | Adequate | Yes | |
| If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>]. | N/A | Yes | |
| Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29] | Adequate | Yes | Bottle and Carton: 60 tablets<br>Blister Carton: Each carton contains a total of 56 tablets containing two blister packs of 28 tablets each. |
| "Rx only" displayed on the principal display [§ 201.100(b)(1)]. | Adequate | Yes | Rx only |
| NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35]. | Adequate | Yes | Bottle and Carton: NDC 58468-0251-6<br>56-Count Blister carton: NDC 58468-0251-5<br>28-Count Blister Pack: NDC 58468-0251-0 |

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| Lot number and expiration date [§ 201.18 & 201.17]. | Adequate | Yes | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD). | Adequate | Yes | **Storage:** Store at room temperature between 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]. Store and dispense in the original package. Protect from light and moisture. |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>). | N/A | Yes | |
| Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)]. | N/A | Yes | |
| For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)]. | N/A | Yes | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | Yes | |

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| Linear Bar code [§ 201.25(c)(2)].[30] | Adequate | Yes | |
| Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55]. | Adequate | Yes | |
| Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)]. | Adequate | Yes | Manufactured (b) (4)<br>Genzyme Corporation<br>Cambridge, MA 02141<br>A SANOFI COMPANY |
| "Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)]. | N/A | Yes | |
| If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient. | N/A | Yes | |
| No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>). | N/A | Yes | |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. | N/A | Yes | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance | N/A | Yes | |

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

| Item | Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A") | Is item in Container Labels same as that of Carton Labeling? | Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate) |
|---|---|---|---|
| criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31] | | | |
| And others if space is available. | N/A | Yes | |

**Assessment of Carton Labels and Container (blister carton and blister pack) Labeling:** *Adequate*

**Above recommended changes were conveyed to the applicant and the final container and carton labels will reflect the changes.**

## 4. OUTSTANDING ISSUES AND RECOMMENDATIONS

**The comments listed in the above tables were communicated to the applicant and the final labeling documents will contain the recommended changes.**

*Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 5/23/2025*

[31] USP General Notices 3.20 Indicating Conformance

Rao Kambhampati

Digitally signed by Rao Kambhampati
Date: 5/23/2025 03:34:23PM
GUID: 508da72000029fd06e8c9283b7414189

Theodore Carver

Digitally signed by Theodore Carver
Date: 5/23/2025 03:35:01PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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# QUALITY REVIEW

**BIOPHARMACUTICS**
**NDA:** NDA 219685
**Drug Product Name / Strength:** Rilzabrutinib (Wayrilz®) tablets, 400 mg.
**Route of Administration:** Oral
**Applicant Name:** Genzyme Corporation
**Indication:** For the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.
**Submission date:** 08/29/2024
**Primary Reviewer:** Kamrun Nahar, Ph.D.
**Secondary Reviewer:** Tapash Ghosh, Ph.D.
**Recommendation: Adequate**

***BACKGROUND:***

The Applicant is seeking approval under 505(b)(1) regulatory pathways for the NDA 219685, Rilzabrutinib (Wayrilz®) tablets, 400 mg, for oral administration. Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data:

**1) Dissolution Method and Acceptance Criteria: Adequate**

Approved dissolution method and acceptance criterion for quality control testing of the proposed Rilzabrutinib (Wayrilz®) tablets, 400 mg at release and stability:

| Apparatus | Rotation Speed (rpm) | Medium | Volume (mL)/ Temperature | Dissolution acceptance criteria |
|---|---|---|---|---|
| USP Apparatus 2 (Paddle) | 50 | 0.01NHCl | 900/ 37.0°±0.5°C | Q= (b) (4)% in 45 minutes |

**2) Bridging of Formulations: Adequate**

Initial Phase 1 clinical studies were carried out with liquid and capsule formulations. Subsequently, tablets in 100 mg and 300 mg strengths were developed for early clinical trials, and the 400 mg strength was later introduced as the final dose for the immune thrombocytopenia (ITP) program. Afterwards, the tablet formulation remained unchanged during clinical development, except for the nonfunctional film coating agent and changes in tablet shape (from (b) (4) to capsule shape. These changes were shown to have no impact on the tablet release results and were implemented before clinical Phase 3 for ITP. The Applicant used proposed commercial tablet in the clinical phase 3 study, therefore, no bridging is required. During the development of 400 mg tablet, the drug substance manufacturer, tablet shape and film coating agent formulation changes were also

implemented. The Applicant compared those formulation through comparative dissolution data.

**3) Alcohol dose dumping: Not applicable**
Since the proposed product is an immediate release tablet, alcohol dose dumping study is not required.

**4) Biowaiver request: Not applicable**

***CONCLUSION AND RECOMMENDATION:***
Form a Biopharmaceutics perspective, NDA 219685 for Rilzabrutinib (Wayrilz®) tablets, 400 mg is **adequate** for approval.

**BIOPHARMACEUTICS ASSESSMENT:**

**List Submissions being reviewed:**
Sequence 0001: 08/29/2024 Orig-1

**Description and composition of the drug product:**
Rilzabrutinib tablets, 400 mg is an immediate release film-coated tablet for oral administration.

**Dissolution method development:**

(b) (4)

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(b) (4)

[redacted]

**Conclusion:**
Finally, the Applicant choose pH 2.1 buffer, 900 mL, paddle and 50 rpm as the optimum dissolution method conditions to explore the discriminatory power of the dissolution medium.

**Discriminatory ability of the method:**
The ability of the dissolution method to provide discriminatory power was evaluated with regards to drug substance (DS) particle size, tablet hardness and stressed tablets as summarized in Table 5.

**Table 3:** Studies of discriminatory ability for Rilzabrutinib dissolution method in pH 2 medium using paddle at 50 rpm

| Variation | Process changes |
|---|---|
| Drug substance particles size | (b) (4) (DS batch 17CP08M.HQ00002)<br>Untreated (DS batch 8ER-108-200001) |
| Tablet hardness | (b) (4) |
| Stressed tablets | (b) (4) |

**Figure 3:** Dissolution profiles of Rilzabrutinib film-coated IR tablets (400 mg) (b) (4) and untreated DS particle size using USP II (paddle) apparatus (n=6)

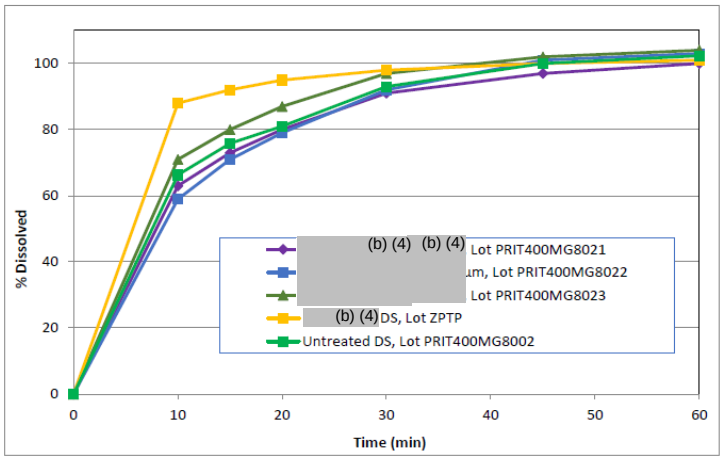


**Figure 4:** Dissolution profiles of Rilzabrutinib film-coated IR tablets (400 mg) with different tablet hardness using USP II (paddle) apparatus (n=6)

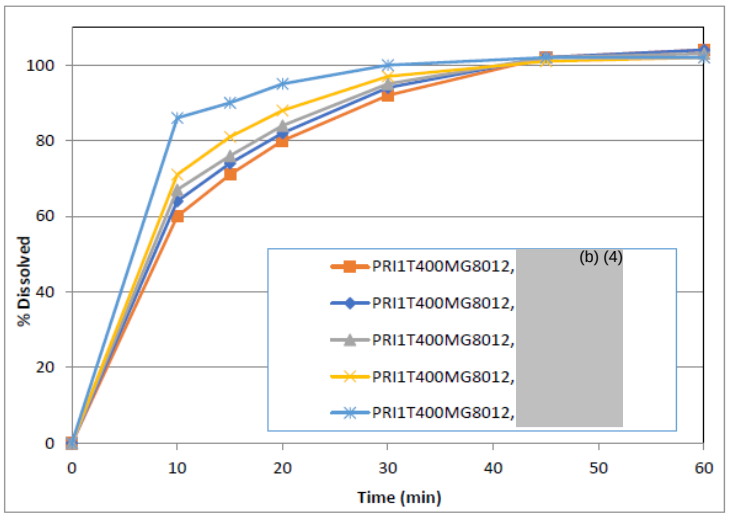
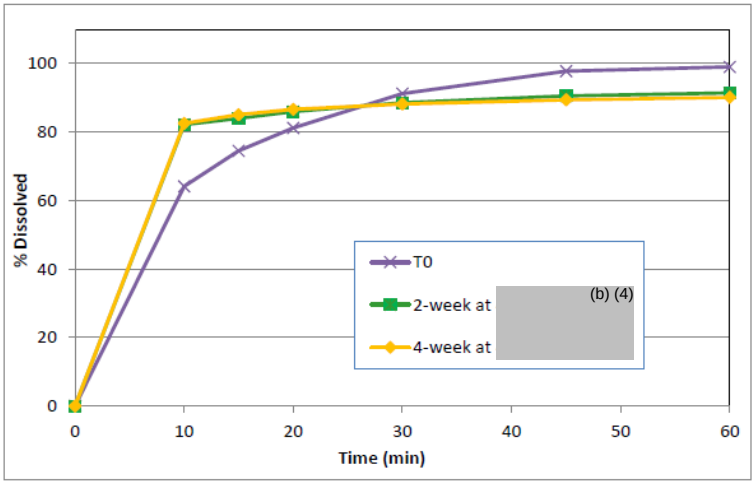



**Figure 5:** Dissolution profiles of stressed Rilzabrutinib film-coated IR tablets (400 mg) (batch# CFPBS) using USP II (paddle) apparatus (n=6)

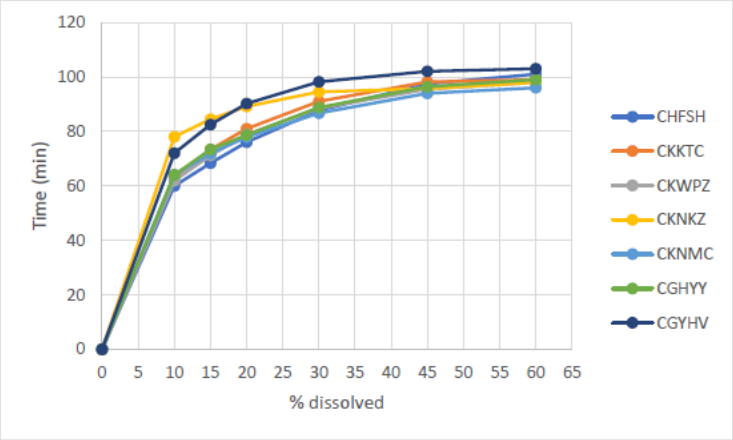



The dissolution method demonstrated some discriminatory power, revealing its ability to differentiate under stressed conditions, where the tablets were exposed to high temperature and humidity outside their primary packaging. The dissolution rate for the 400 mg tablets containing the (b) (4) drug substance was faster than those with the (b) (4) drug substance during the first 20 minutes. However, the dissolution rates became comparable thereafter, and by 45 minutes, the drug release was identical for both formulations.

**Dissolution acceptance criterion:**
The Applicant proposed the dissolution acceptance criteria as "Q= (b) (4)% in 45 minutes". Dissolution data showed (b) (4)% is released in 45 minutes. Dissolution data showed that (b) (4)% drug is released in 45 minutes. Therefore, based on the dissolution data, the Applicant's proposed

dissolution acceptance criterion is deemed adequate. Dissolution acceptance criterion is set as "Q= (b) (4)% in 45 minutes".

**Figure 6:** In-vitro dissolution profiles of the Phase 3 clinical 400 mg IR tablets



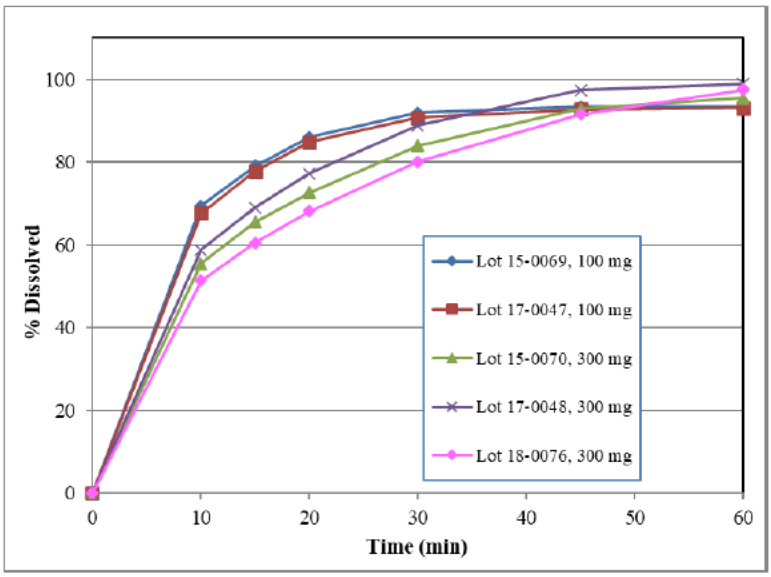

**Approved dissolution method and acceptance criteria for the proposed Rilzabrutinib (Wayrilz®) tablets, 400 mg:**

| Apparatus | Rotation Speed (rpm) | Medium | Volume (mL)/ Temperature | Dissolution acceptance criterion |
|---|---|---|---|---|
| USP Apparatus 2 (Paddle) | 50 | 0.01N HCl | 900/ 37±0.5°C | Q = (b) (4)% in 45 minutes |

**Formulation development and bridging:**
To support Phase 1 dose escalation studies (Study PRN1008-001), a liquid formulation was initially developed. To support late-stage clinical formulation selection, a hard gelatin capsule formulation, with Rilzabrutinib (equivalent to 100 mg) was developed. A relative bioavailability study (PRN1008-004) was conducted to compare a single oral dose of 300 mg Rilzabrutinib administered as an oral liquid formulation and a capsule formulation. For a more robust and manufacturable formulation at high volumes for further clinical phases and commercial development, the capsule was switched to tablet. An immediate release film-coated tablet formulation was developed in 100 mg and 300 mg strengths. Dissolution data of tablet (50 rpm) vs capsules ((b) (4) rpm) in 0.01 N HCl with paddles showed a faster release from the tablets compared to the capsule formulation. Thus, the tablet formulation was considered as an immediate release dosage form to support phase 2 and phase 3 studies. The bulk properties of the (b) (4) drug substance produced through (b) (4) showed low bulk density and a small particle size distribution (D90 < (b) (4) µm), resulting in poor powder flow properties. This required (b) (4) process was chosen. Tablets of 100 mg and 300 mg were

manufactured from (b) (4) drug substance manufactured at (b) (4) and were used in Phase 2 clinical studies for immune thrombocytopenia (ITP) indication.

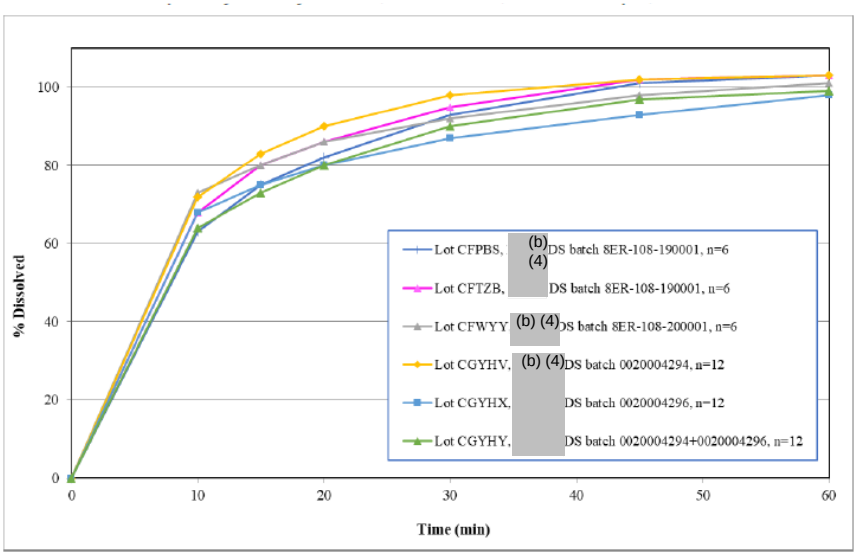
**Figure 7:** Dissolution profile for Rilzabrutinib film-coated tablet batches used in phase 1 and phase 2 studies in 0.01 N HCl pH 2), USP II at 50 rpm, n=6




As the development progressed, a human dose of 400 mg tablet twice daily was considered to provide an exposure sufficient to maintain target inhibition for full efficacy in human disease. Therefore, to support Phase 2 clinical studies (for ITP indication) and Phase 3 clinical studies (other indications than ITP), 400 mg strength tablets were introduced and manufactured using the same IR formulation as the 100 mg and 300 mg strength tablets (b) (4) During the development of 400 mg tablet, the drug substance manufacturer, tablet shape and film coating agent formulation changes were also implemented.

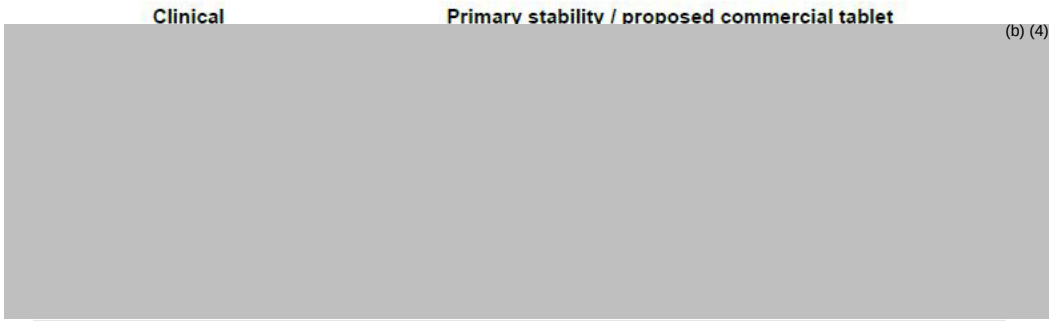
**Changes in drug substance manufacturing process and sources:**
In addition to the tablet strength change, the drug substance isolation process was changed from (b) (4) to a (b) (4) process. Initially, a (b) (4) DS source was used. The IR tablet strength was then increased up to 400 mg. However, DS was sourced at (b) (4) and (b) (4) replaced by (b) (4). DS manufactured by (b) (4) (DS source) using (b) (4) process was confirmed. Final commercial tablet of 400 mg IR tablet as well as a new DS supplier (b) (4) was introduced. (b) (4) (DS source) manufactured DS using the same (b) (4) process as (b) (4) (b) (4).

**Figure 8:** Dissolution profile for Rilzabrutinib tablet 400mg, DS from different sources, in 0.01N HCl, paddle at 50 rpm, n=6



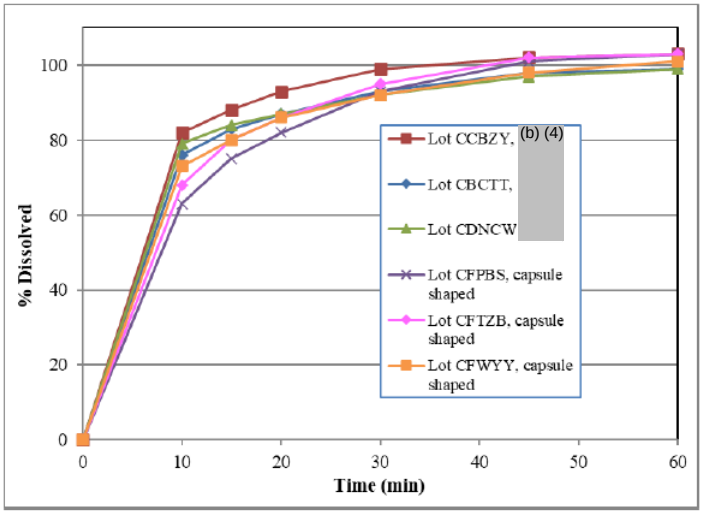

**Changes in tablet shape and film coating agent:**
The tablet shape was then changed (b) (4) to capsule and the (b) (4) in the nonfunctional film coating agent (b) (4) to fit with regulations. For the final market image, the capsule shaped tablets were debossed with "P" on one side and "400" on the other side. Afterwards, the tablet formulation and shape have remained consistent and will be used for the commercial product.

**Figure 9:** Rilzabrutinib film-coated tablet shapes and (b) (4) film coating (b) (4)



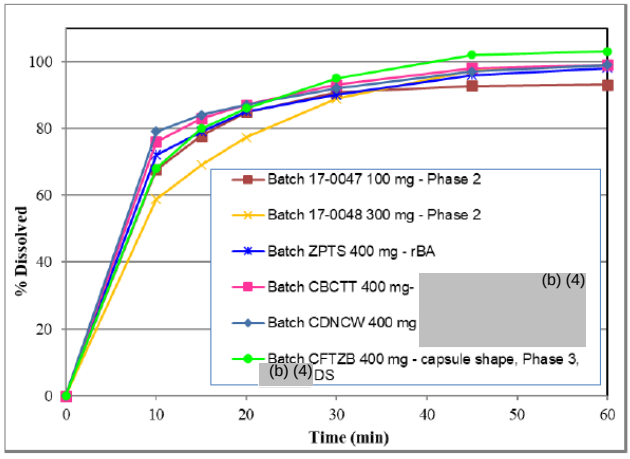

The Applicant conducted comparative dissolution between (b) (4) and capsule shaped tablets; tablets containing (b) (4) drug substance; tablets used in phase 3 studies; and tablets used in the development phase. Dissolution data between the (b) (4) and capsule shaped tablets showed similar release and >85% drug release is obtained after 45 minutes.

**Figure 10:** Dissolution profile for Rilzabrutinib tablet (b) (4) vs capsule shaped, 400 mg, in 0.01N HCl, paddle, 50 rpm, n=6




**Dissolution profiles of Rilzabrutinib tablets used during development phase:**
The dissolution profiles of the representative 400 mg tablet batches used throughout development as well as the representative 100 mg and 300 mg tablet batches used in phase 2 clinical and relative bioavailability studies (batch 17-0047 and 17-0048, respectively) are presented in Figure 16. Dissolution data showed that all these formulations are showing complete release, i.e., >85% of the drug in 45 minutes.

**Figure 11:** Dissolution profile for Rilzabrutinib tablet, 400 mg, during development in 0.01N HCl, paddle, 50 rpm, n=6



**Dissolution comparison between representative batches for (b) (4) versus Sanofi Scopitto:**

To manufacture the proposed product Rilzabrutinib tablets, 400 mg, the Applicant mentioned two manufacturers, i.e., (b) (4) versus Sanofi Scopitto. The Applicant conducted comparative dissolution test between the tablets manufactured in these two-manufacturer using QC dissolution method and at pH 1.2, 4.5 and 6.8. Dissolution profile in all these conditions showed similarity between the primary stability batches manufactured by (b) (4) and complementary stability batches manufactured by Sanofi Scopitto.

**Table 4:** Dissoluiton conditions and batches information

| Manufacturing site | Drug product batch n° | Batch use | Dissolution conditions | | | |
|---|---|---|---|---|---|---|
| | | | pH 2 (HCl 0.01N) (QC method) | pH 1.2 | pH 4.5 | pH 6.8 |
| (b) (4) | CGYHV | Primary stability batch | USP Apparatus II (paddle) | USP Apparatus II (paddle) | USP Apparatus II (paddle) | USP Apparatus II (paddle) |
| | CGYHY | Primary stability batch | 900 mL | 900 mL | 900 mL | 900 mL |
| | CGYHX | Primary stability batch | 50 rpm | 50 rpm | 50 rpm | 50 rpm |
| | | | n=12 | n=12 | n=12 | n=12 |
| Sanofi Scoppito | 3U1669 | Complementary stability batch | 10,15,20,30,45, 60 min | 10,15,20,30,45, 60 min | 10,15,20,30,45, 60 min | 10,15,20,30,45, 60 min |
| Sanofi Scoppito | 4U0869 | Complementary stability batch | | | | |
| Sanofi Scoppito | 4U0870 | Complementary stability batch | | | | |

**Figure 12:** Dissolution profiles of Rilzabrutinib tablets, 400 mg in pH 2.0:

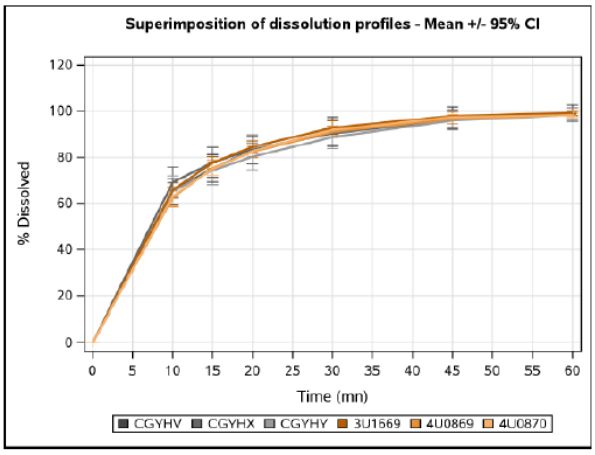


**Table 5:** Dissolution profiles of Rilzabrutinib tablets, 400 mg in pH 2.0.

| Timepoint | [redacted] (b) (4) | | | | | | Sanofi Scoppito | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CGYHV | | CGYHX | | CGYHY | | 3U1669 | | 4U0869 | | 4U0870 | |
| | Mean | RSD (%) | Mean | RSD (%) | Mean | RSD (%) | Mean | RSD (%) | Mean | RSD (%) | Mean | RSD (%) |
| 10 | 65.3 | 13.6 | 69.1 | 15.5 | 65.3 | 15.7 | 65.8 | 7.4 | 62.6 | 10.3 | 63.2 | 10.4 |
| 15 | 75.3 | 12.5 | 77.8 | 13.2 | 74.3 | 13.0 | 77.7 | 5.2 | 75.4 | 7.1 | 75.1 | 6.1 |
| **20** | 83.1 | **11.2** | 83.4 | **11.9** | 80.3 | **11.3** | 84.5 | 5.0 | 82.3 | 4.9 | 82.7 | 4.1 |
| **30** | **91.4** | **10.4** | **90.4** | 9.9 | **88.8** | 8.7 | **92.8** | 5.0 | **91.1** | 4.3 | **91.8** | 2.6 |
| 45 | 97.5 | 7.1 | 96.3 | 6.8 | 95.9 | 6.7 | 97.9 | 2.9 | 96.6 | 3.4 | 97.4 | 1.8 |
| 60 | 99.1 | 5.6 | 98.9 | 4.2 | 98.4 | 4.7 | 99.2 | 1.8 | 98.3 | 1.5 | 98.3 | 1.2 |

In bold: first time points with mean > 85% or RSD greater than 10% at time points greater than 15min

**Table 6:** Bootstrap f2 results at pH 2.0.

| Time interval | f2 observed on data | Exact Bootstrap f2 estimation (90% bias corrected percentile Confidence Interval (CI))* | Conclusion |
|---|---|---|---|
| 10 – 30 min | 85.5 | 85.5 [79.8 ; 98.7] | Similar profiles |

* Acceptance criterion: lower bound of 90% confidence interval above 50

In pH, slightly high variability in dissolution results were observed, i.e., %RSD is ~11% at 20 minutes which went down afterwards. The Applicant performed Bootstrap statistical analysis which indicates similarity in drug release between drug product batches manufactured at [redacted] (b) (4) and at Sanofi Scoppito manufacturing sites. The Bootstrap f2 (85.5) and the lower bound of the confidence interval (79.8) are above the threshold value of 50. This reviewer also analyzed the mean dissolution rate between the formulations and similarity factor f2>50, indicating similarity in drug release. From Biopharmaceutics perspective dissolution rate in two different manufacturing sites are acceptable.

In addition to the dissolution test in pH 2.0 medium, the Applicant also conducted comparative dissolution test in three additional pH conditions, pH 1.2, 4.5, 6.8 which indicates similar drug release in all three pH conditions.

In pH 1.2 medium, very rapid drug release was observed, i.e., >85% of Rilzabrutinib was dissolved within 15 min for both batches manufactured at [redacted] (b) (4) and Sanofi Scoppito. Since drug release is very rapid, similarity factor (f2) analysis was not required.

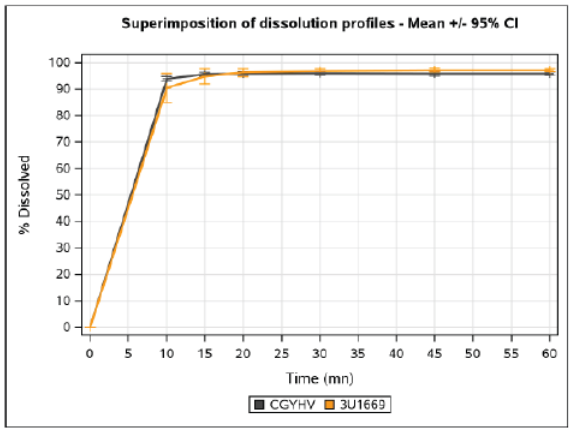
In pH 4.5 medium, since the 40-45% dissolved in 45 minutes from all the batches. Dissolution rate showed high variability at pH 4.5. Hence, the Applicant did Bootstrap f2 criteria, which showed similarity in drug release between two manufacturing sites, i.e., [redacted] (b) (4) vs Sanofi Scoppito. The Bootstrap f2 is 63.1 and the lower bound of the 90% confidence interval (56.3) are above than the threshold value of 50.

In pH 6.8 medium, less than 10% of Rilzabrutinib is dissolved up to 60 min for both batches, dissolution profiles considered as similar without statistical evaluation.

In conclusion, the dissolution profiles of production drug product batches manufactured at (b) (4) are comparable to production drug product batches manufactured at Sanofi Scoppito.

**Figure 13:** Dissolution profiles in different pH conditions:

**pH 1.2:** Batch#CGYHV (manufactured in (b) (4)) vs batch# 3U1669 (manufactured in Sanofi Scoppito)




**pH 4.5:**

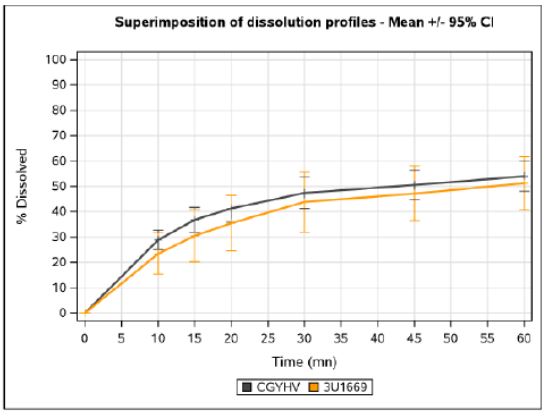



**Table 8:** Dissolution profiles of Rilzabrutinib tablets, 400 mg in pH 4.5 and bootstrap f2 results

| Timepoint | (b) (4) | | Sanofi Scoppito | |
|---|---|---|---|---|
| | CGYHV | | 3U1669 | |
| | Mean | RSD (%) | Mean | RSD %) |
| **10** | 28.9 | **20.8** | 23.5 | **54.4** |
| **15** | 36.8 | **20.9** | 30.5 | **53.4** |
| **20** | 41.3 | **20.1** | 35.5 | **48.9** |
| **30** | 47.4 | **20.3** | 43.8 | **42.2** |
| **45** | 50.6 | **18.1** | 47.2 | **35.7** |
| **60** | 54.0 | **17.2** | 51.2 | **32.6** |

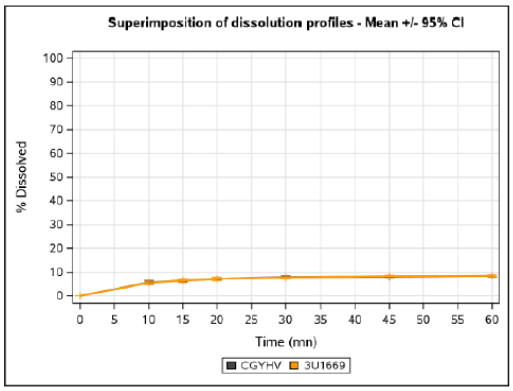
In bold: time points with RSD greater than 20% at 10min and 15min and greater than 10% at time points greater than 15min

**Bootstrap f2 results at pH 4.5.**

| Time interval | f2 observed on data | Exact Bootstrap f2 estimation (90% bias corrected percentile CI)* | Conclusion |
|---|---|---|---|
| All | 63.1 | 63.1 [56.3 ; 87.9] | Similar profiles |

* Acceptance criterion: lower bound of 90% confidence interval above 50

**pH 6.8:**




**Conclusion:**

In conclusion, Rilzabrutinib is a low soluble compound. The Applicant provided dissolution method development and validation report. The Applicant optimized the dissolution method conditions; dissolution method showed some discriminating ability due to the change in stress conditions, i.e., tablets were exposed to high temperature and humidity conditions out of their final primary packaging and (b) (4) DS vs untreated DS in the drug products. Therefore, based on the totality of the information, dissolution method and acceptance criterion as described below is adequate.

**Approved dissolution method and acceptance criteria for the proposed Rilzabrutinib (Wayrilz®) tablets, 400 mg:**

| Apparatus | Rotation Speed (rpm) | Medium | Volume (mL)/ Temperature | Dissolution acceptance criterion |
|---|---|---|---|---|
| USP Apparatus 2 (Paddle) | 50 | 0.01N HCl | 900/<br>37±0.5°C | Q = (b) (4)% in 45 minutes |

**Appendix 1. Dissolution Data**

**Dissolution data:** **\\CDSESUB1\EVSPROD\nda219685\0001\m3\32-body-data\32p-drug-prod\rilzabrutinib-film-coated-tablet\32p2-pharm-dev\pharmaceutical-development-04.pdf**

**\\CDSESUB1\EVSPROD\nda219685\0001\m3\32-body-data\32p-drug-prod\rilzabrutinib-film-coated-tablet\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses-individual-dissolution-data.xls**

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Kamrun Nahar

Digitally signed by Kamrun Nahar
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Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 4/08/2025 03:47:07PM
GUID: 508da7230002a2433ddcef616ca190df

Theodore Carver

Digitally signed by Theodore Carver
Date: 6/06/2025 08:56:10PM
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