CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219685Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Review

Date: May 28, 2025 **Date consulted:** January 6, 2025

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Division of Nonmalignant Hematology

Drug: WAYRILZ (rilzabrutinib)

NDA: 219685

Applicant: Genzyme Corporation

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of adult patients with persistent or chronic immune thrombocytopenia who have an insufficient response (b) (4) [redacted] to a previous treatment.

Materials Reviewed:

- DPMH consult request, dated 1/6/2025. DARRTS Reference ID: 5506693
- Applicant's background package and proposed labeling for NDA 219685, Sequence Number (SN) 0001, dated 8/30/2024.

- Applicant's response to DPMH Information Request (IR) dated 5/15/2025, SN 0039, submitted 5/19/2025.

Consult Question: "Review PLLR Labeling text."

I. INTRODUCTION AND BACKGROUND

On August 30, 2024, the Applicant, Genzyme Corporation, submitted a 505(b)(1) New Drug Application (NDA) for Wayrilz (rilzabrutinib) for the treatment of adult patients with persistent or chronic immune thrombocytopenia who have an insufficient response [redacted] (b) (4) to a previous treatment. The Division of Nonmalignant Hematology (DNH) consulted the Division of Pediatrics and Maternal Health (DPMH) on January 6, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

<u>Relevant Regulatory History</u>

- Rilzabrutinib was submitted under Investigational New Drug (IND) 132668 on April 12, 2017.
- Rilzabrutinib received Orphan Drug designation on October 15, 2018, for the treatment of immune thrombocytopenia purpura (ITP), also referred to as immune thrombocytopenia.
- Rilzabrutinib was granted Fast Track designation for ITP on October 15, 2020.

<u>Drug Characteristics</u>[1]

Drug Class	Bruton's tyrosine kinase inhibitor
Proposed mechanism of action	Mediates its therapeutic effect for ITP through: 1. Inhibition of B cell activation and 2. Interruption of antibody-coated cell phagocytosis by Fcγ Receptor (FcγR) in spleen and liver. *In vitro*, rilzabrutinib reduced autoantibody signaling mediated through the FcγR pathway, blocked B cell signaling, and decreased autoantibody generation through effects on B-cell activation.
Proposed dosage form and administration	400 mg tablets 400 mg taken orally twice daily
Molecular weight	665.77 g/mol
Half-life	[redacted] (b) (4)
% protein bound	97.5%
Bioavailability (BA)	4.7%

[1] NDA 219685, draft Annotated Labeling with DNH review team edits, review ongoing.

Immune Thrombocytopenia (ITP) and Pregnancy

Immune thrombocytopenia is an acquired autoimmune disorder characterized by persistent thrombocytopenia resulting from platelet destruction and impaired platelet production. The pathogenesis of ITP is incompletely understood. Platelet destruction occurs primarily through autoantibody-mediated (typically IgG, most often directed against platelet membrane glycoproteins) clearance by the reticuloendothelial system and/or T-cell-mediated lysis. Impaired platelet production results from autoantibodies targeting megakaryocytes and a disruption of megakaryopoiesis and thrombopoiesis. ITP in adults is more frequently found in females, with a female/male ratio of 1.7 overall and a female/male ratio of 2.8 for patients between 18 and 49 years of age. About two-thirds of adult ITP patients are likely to develop a chronic form. Chronic ITP is defined as ITP persisting for more than 12 months since diagnosis.[2,3,4,5]

ITP occurs in approximately 1 to 3 in 10,000 pregnancies. This is approximately 10-fold greater than the incidence of ITP in the general population, estimated to be 3 in 100,000 adults. While the exact reasons for the increased incidence of ITP during pregnancy are not fully understood, several factors likely contribute to this. These include an immune system shift from Th2 to Th1 cytokines which may play a role in the development of ITP, a tendency for mild, asymptomatic thrombocytopenia to be unmasked during gestation and increased blood testing during pregnancy leading to the detection of ITP. ITP is the most common medical cause of thrombocytopenia in pregnancy.[5]

ITP may occur during any trimester, or the diagnosis may be known prior to pregnancy. ITP is identified for the first time during pregnancy in approximately 10% of pregnant women with ITP in the U.S. The severity of thrombocytopenia is variable, and the platelet count will decrease during the pregnancy, as it does in all pregnancies as part of normal physiology. The thrombocytopenia is often more severe in the third trimester and post-partum period, with over 50% of ITP patients having a platelet count $< 80 \times 10^9$/L.[5,6]

Significant bleeding symptoms are the first indication for ITP treatment. Incidence of bleeding events among pregnant women with ITP is only somewhat higher than that among those with ITP who are not pregnant (hazard ratio, 1.83; 95% CI 0.91 to 3.65) and severe bleeding is rare.

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[2] Won YW, Moon W, Yun YS, Oh HS, Choi JH, Lee YY, Kim IS, Choi IY, Ahn MJ. Clinical aspects of pregnancy and delivery in patients with chronic idiopathic thrombocytopenic purpura (ITP). Korean J Intern Med. 2005 Jun;20(2):129-34. doi: 10.3904/kjim.2005.20.2.129. PMID: 16134767; PMCID: PMC3891381.

[3] Wyszynski DF, Carman WJ, Cantor AB, Graham JM Jr, Kunz LH, Slavotinek AM, Kirby RS, Seeger J. Pregnancy and Birth Outcomes among Women with Idiopathic Thrombocytopenic Purpura. J Pregnancy. 2016;2016:8297407. doi: 10.1155/2016/8297407. Epub 2016 Mar 22. PMID: 27092275; PMCID: PMC4820621.

[4] Grimaldi-Bensouda L, Nordon C, Michel M, Viallard JF, Adoue D, Magy-Bertrand N, Durand JM, Quittet P, Fain O, Bonnotte B, Morin AS, Morel N, Costedoat-Chalumeau N, Pan-Petesch B, Khellaf M, Perlat A, Sacre K, Lefrere F, Abenhaim L, Godeau B; Group for the PGRx-ITP Study. Immune thrombocytopenia in adults: a prospective cohort study of clinical features and predictors of outcome. Haematologica. 2016 Sep;101(9):1039-45. doi: 10.3324/haematol.2016.146373. Epub 2016 May 26. PMID: 27229715; PMCID: PMC5060020.

[5] McIntosh, JJ, Perez Botero, J. Thrombocytopenia in pregnancy. In:UpToDate, Connor RF (Ed), Wolters Kluwer. (Accessed 3/26/2025)

[6] Beltrami-Moreira M, Sharma A, Bussel JB. Immune thrombocytopenia and pregnancy: challenges and opportunities in diagnosis and management. Expert Rev Hematol. 2024 Sep;17(9):595-607. doi: 10.1080/17474086.2024.2385481. Epub 2024 Aug 6. PMID: 39105265.

In the absence of significant bleeding symptoms, treatment is only advised if platelets are less than 20-30 x 10^9/L until preparation for delivery. As the degree of thrombocytopenia progresses through pregnancy, treatment becomes more frequently required. Platelet counts of 50-80 x 10^9/L are needed for delivery to allow for a safe Caesarean section if required, to facilitate the safe administration of neuraxial anesthesia, and to minimize the risk of major postpartum hemorrhage.[6,7,8]

First-line therapy in pregnancy includes corticosteroids and intravenous immunoglobulin (IVIG). When delivery is not imminent, prednisone, given at the lowest effective dose, is preferrable because there is less fetal exposure compared to dexamethasone. Dexamethasone or betamethasone given antenatally can serve to treat ITP and reduce the incidence and severity of Respiratory Distress Syndrome (RDS) and mortality associated with preterm birth.[5,6]

Neonatal thrombocytopenia occurs in 12-28% of children born to mothers with ITP, due to the transplacental passage of maternal autoantibodies. The strongest predictor of neonatal thrombocytopenia is a previously affected sibling. There is no correlation between the maternal and neonatal platelet count at the time of delivery. Maternal treatment with IVIG or corticosteroids does not appear to affect the neonatal platelet count. Significant neonatal thrombocytopenia with platelets below 30 x 10^9/L is uncommon, occurring in 1-5% of newborns, and the rate of intracranial hemorrhage secondary to neonatal thrombocytopenia is estimated to be less than 1%.[8]

The approved labeling for fostamatinib, the one FDA-approved drug for the treatment of chronic ITP, cites an estimated background risk of miscarriage and major birth defects for the chronic ITP population. During this review, DPMH identified two publications which provided information on pregnancy outcomes among women with ITP. Wyszynski et al (2016)[9] provided a claims-based and chart-based evaluation of pregnancy outcomes among women with ITP and chronic ITP in the U.S. With respect to pregnancy outcomes among the women with chronic ITP (n=84), spontaneous or elective terminations and stillbirths were reported collectively (11/84 = 13.1%). However, the article did not include data to allow for determining the rate of miscarriage for the chronic ITP group specifically. The prevalence of congenital anomalies in chronic ITP was reported as 10.3% (7/68) in claims-based results and 6.1% (4/66) in chart-based results. Among the 346 infants of mothers with claims-based ITP (all ITP, including those with chronic ITP), 27 infants had a claim for at least one major malformation (27/346 = 7.8%). Although the Wyszynski et al article provides a potential range for congenital anomalies (6.1 to 10.3% depending on whether it was chart-based or claims-based data), this range is based on limited data from a small sample size in which the diagnosis of chronic ITP was not clinically validated. In addition, confounding factors such as maternal medical conditions other than ITP and concomitant medical treatments received for ITP or other conditions were not captured, so their potential effects on pregnancy and infant outcomes were not evaluated or accounted for by

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[7] Bussel JB, Hou M, Cines DB. Management of Primary Immune Thrombocytopenia in Pregnancy. N Engl J Med. 2023 Aug 10;389(6):540-548. doi: 10.1056/NEJMra2214617. PMID: 37590449.
[8] Eslick R, McLintock C. Managing ITP and thrombocytopenia in pregnancy. Platelets. 2020;31(3):300-306. doi: 10.1080/09537104.2019.1640870. Epub 2019 Jul 11. PMID: 31296105.
[9] Wyszynski DF, Carman WJ, Cantor AB, Graham JM Jr, Kunz LH, Slavotinek AM, Kirby RS, Seeger J. Pregnancy and Birth Outcomes among Women with Idiopathic Thrombocytopenic Purpura. J Pregnancy. 2016;2016:8297407. doi: 10.1155/2016/8297407. Epub 2016 Mar 22. PMID: 27092275; PMCID: PMC4820621.

the study. The French prospective cohort study by Guillet et al (2023)[10] also discussed pregnancy outcomes in women with ITP. In this cohort study, 5.2% (9/171) of pregnancies resulted in miscarriage/stillbirth and 3.9% resulted in early and late miscarriages (n=7) alone. This study did not provide pregnancy outcome data for women with chronic ITP, so the data is not specific to the target population for the current NDA. This study did not capture infant outcomes. No additional publications were located to further validate the miscarriage or major birth defect data for the chronic ITP population.

II. REVIEW

PREGNANCY

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:

Embryofetal development studies were conducted in rats and rabbits. Rilzabrutinib given to pregnant rats by oral gavage at 50, 150 or 300 mg/kg/day during the period of organogenesis (Gestation Day 7 to 17) did not cause adverse effects on embryofetal development at exposures approximately 10-times the clinical exposure at the maximum recommended human dose (MRHD) based on AUC.

Rilzabrutinib given to pregnant rabbits by oral gavage at 10, 30 or 100 mg/kg/day during the period of organogenesis (Gestation Day 7 to 19) did not cause adverse effects in embryofetal development at exposures approximately 4-times the clinical exposures at the MRHD based on AUC.

In the Pre- and Postnatal Development (PPND) study, pregnant rats were given rilzabrutinib by oral gavage at doses of 50, 150, or 300 mg/kg/day during the periods of gestation, parturition, and lactation (Gestation Day 7 to Lactation Day 21). Developmental delay (reduced body weight) was observed in pups in the presence of maternal toxicity at 300 mg/kg/day, at exposures approximately 18-times the MRHD based on AUC. There were no effects of rilzabrutinib on the ability of F_1 offspring to reproduce or on subsequent F_2 development at any dose.

The reader is referred to the full nonclinical review by C M Sabbir Ahmed, Ph.D.

> ***Reviewer Comment:***
> *No adverse effects on embryofetal development were observed in the rat or rabbit at the highest doses tested, resulting in safety margins of 10-fold in the rat and 4-fold in the rabbit. DPMH discussed the animal reproduction studies with the nonclinical team. The nonclinical team considered the 4-fold safety margin in the rabbit EFD study to be reasonable given there were no adverse effects observed.[11] The animal reproduction studies do not identify any potential safety signals.*

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[10] Guillet S, Loustau V, Boutin E, Zarour A, Comont T, Souchaud-Debouverie O, Costedoat Chalumeau N, Pan-Petesch B, Gobert D, Cheze S, Viallard JF, Morin AS, Sauvetre G, Cliquennois M, Royer B, Masseau A, Terriou L, Fieschi C, Lambotte O, Girault S, Lioger B, Audia S, Sacre K, Lega JC, Langlois V, Benachi A, Orvain C, Devidas A, Humbert S, Gambier N, Ruivard M, Zarrouk V, Ebbo M, Willems L, Segaux L, Mahevas M, Haddad B, Michel M, Canoui-Poitrine F, Godeau B. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. Blood. 2023 Jan 5;141(1):11-21. doi: 10.1182/blood.2022017277. PMID: 36054922; PMCID: PMC10644036.

[11] Personal communication with C M Sabbir Ahmed, Ph.D., Nonclinical Review Team, dated 4/15/2025.

Review of Pharmacovigilance Database

The Applicant reported two pregnancy cases during the rilzabrutinib clinical development program as follows[12,13]:

1) Participant PRN [redacted] (b) (6): A 32-year-old female with a medical history of ITP and obesity completed both the double-blind and open-label treatment periods receiving 400 mg rilzabrutinib orally twice daily. The participant entered the long-term extension treatment period on Day 365 of the study. On Day 410 of the study, "pregnancy was reported". The study participant's LMP was [redacted] (b) (6). The last urine pregnancy test performed for the study on [redacted] (b) (6) was negative. Rilzabrutinib was discontinued on Day 410 [redacted] (b) (6) of the study due to the pregnancy. Concomitant medications included paracetamol (Day 320 to Day 348), ketorolac (Day 327 to Day 337), and acetylsalicylic acid; caffeine; paracetamol (Day 348). The participant did not consent for information related to the "pregnancy or its outcome" be recorded for the study; thus, the pregnancy outcome is unknown. No further details were reported.

2) Participant PRN [redacted] (b) (6): A 23-year-old female had a positive pregnancy test on Day 394 of the study. The participant's last menstrual period (LMP) was not reported. The participant had been in the treatment group, receiving 400 mg rilzabrutinib orally twice daily. Rilzabrutinib was discontinued on Day 394 due to the pregnancy. On Day 427 of the study, the participant had elective termination of pregnancy. No further details were reported.

   Reviewer Comment:
   Study participant PRN [redacted] (b) (6) received rilzabrutinib 400 mg orally twice daily for 410 study days. Based on the timing of the pregnancy during active participation in the long-term extension treatment period, rilzabrutinib exposure during pregnancy occurred. However, the pregnancy outcome is unknown. The second pregnancy case resulted in an elective termination for unknown reasons. There are insufficient pregnancy data from the clinical development program to inform the safety of rilzabrutinib use in pregnancy.

Review of Literature

Applicant's review:

The Applicant performed a cumulative literature search with the following strategy:

- Databases: Ovid MEDLINE and Embase;
- Search terms: BTK inhibitors (tolebrutinib, ibrutinib, acalabrutinib, and zanabrutinib) or rilzabrutinib or PRN1008 or SAR444671 or thiocyanate and embryotoxicity or fetotoxicity or reprotoxicity or use in pregnancy and lactation.
- Limits: April 23, 2015, to April 22, 2024

[12] NDA 219685, Module 2.7.4, Summary of Clinical Safety and 8.3.3 Participant narratives – Adverse Events leading to discontinuation.
[13] NDA 219685, SN 0039, Applicant's response to DPMH IR, dated 5/15/2025.

The Applicant's literature search did not identify any published clinical literature related to rilzabrutinib use during pregnancy[14].

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "rilzabrutinib" and "pregnancy", "pregnancy outcomes", "pregnant", "major birth defects", "birth defects", "congenital malformations", "congenital anomalies", "teratogenicity", "miscarriage", "spontaneous abortion", "elective abortion", "pregnancy loss", "stillbirth", "fetal loss", "fetal demise", and "fetotoxicity". No relevant publications were found.

In addition, DPMH conducted a search for rilzabrutinib in Micromedex[15], Reprotox[16], TERIS[17], Shepard's[18], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[19]. No information was found.

> ***Reviewer comment:***
> *The Applicant's review is adequate.*

LACTATION

Nonclinical Experience

The nonclinical team reviewed the Applicant's submission and provided the following information:
In the PPND study conducted in rats, the F_1 neonatal/developmental toxicity NOAEL was 150 mg/kg/day, because developmental delay (reduced body weight) was observed in pups in the presence of maternal toxicity at 300 mg/kg/day (exposures approximately 18-times the MRHD based on AUC).

The reader is referred to the full nonclinical review by C M Sabbir Ahmed, Ph.D.

> ***Reviewer Comment:***
> *There are no animal data to indicate rilzabrutinib is present in animal milk. Reduced pup body weights and body weight gains were observed throughout the preweaning period (PND1 to PND 21) at exposures approximately 18-times the MRHD based on AUC. The effects on pup development could be due to in utero exposure, however, the presence of maternal toxicity at the same dose confounds the interpretation. Given the presence of rilzabrutinib in rat milk is unknown, it is difficult to determine whether lactational exposure to rilzabrutinib contributed to the findings observed during the lactation period.*

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[14] NDA 219685, Module 2.7.4 Summary of Clinical Safety, p 196.
[15] Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 1/8/2025.
[16] Reprotox Website: www.Reprotox.org. Accessed 1/8/2025.
[17] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 1/8/2025.
[18] Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 1/8/2025.
[19] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

Review of Pharmacovigilance Database
The Applicant did not report any cases related to rilzabrutinib exposure in lactating individuals during the clinical development program.

Review of Literature
Applicant's review:
Refer to the Pregnancy section of this review for the Applicant's literature search parameters. The Applicant did not identify any published clinical literature related to rilzabrutinib use in lactating women[14].

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "rilzabrutinib" and "lactating", "lactation", "nursing", "breastfeeding", "breastfed", "breast fed", "neonates", and "infants". No relevant publications were found.

In addition, DPMH conducted a search for rilzabrutinib in Micromedex[15], Reprotox[16], Hale's *Medications and Mothers' Milk*[20], the Drugs and Lactation Database (LactMed)[21], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[19]. No information was found.

> ***Reviewer Comment:***
> *The Applicant's review is adequate.*
>
> *Rilzabrutinib has an oral bioavailability of 4.7%, is 97.5% bound to plasma proteins and has a short half-life of 1.4 hours. These physiochemical properties suggest decreased transfer of rilzabrutinib into human breast milk. However, physiochemical characteristics alone are not sufficient to determine the transfer of a drug into breastmilk. While rilzabrutinib is a BTK inhibitor, it differs from others in class in that it has a high selectivity for BTK inhibition and is reversible. Based on discussion with the Clinical team, increased infections were observed in the rilzabrutinib-treated group in the LUNA-3 study. The most common infection-related adverse reactions were COVID-19 infections and nasopharyngitis. Grade-3 infections included complicated acute otitis media, covid-19 infection, kidney abscess, sepsis, pelvic inflammatory disease and urinary tract infections, as well as a single death due to pneumonia. In addition to infections, adverse reactions associated with other BTK inhibitors include hemorrhage, cytopenias, secondary primary malignancies, cardiac arrythmias, and hepatotoxicity. These adverse reactions have either not been appreciated or are not considered significant issues with rilzabrutinib. Due to their associated adverse reactions, other BTK inhibitors advise lactating women to refrain from breastfeeding. Although rilzabrutinib does not seem to have the same adverse reaction profile as others in class, there is a concern for increased infections, some of which are serious bacterial infections in an*

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[20] Hale, Thomas W. Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 1/8/2025.
[21] Drugs and Lactation Database (LactMed). Accessed 1/8/2025.

infant (pneumonia, UTI, sepsis). The clinical impact on the infant exposed via breastmilk is unknown, however, there is potential for a significant safety concern for an infant should a serious infection-related adverse reaction occur following exposure via breastmilk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Rilzabrutinib was not mutagenic in an *in vitro* bacterial reverse mutagenicity (Ames) assay, was not clastogenic in an *in vivo* human peripheral lymphocyte chromosomal aberrations assay, nor was it clastogenic in an *in vivo* bone marrow micronucleus assay in rats.

The fertility studies in male and female rats did not identify any adverse effects on fertility at doses up to approximately 18-times the clinical exposure at the MRHD. Rilzabrutinib had no effect on mating, estrous cycle, fertility, sperm parameters, or any ovarian and uterine parameters at any dose.

The reader is referred to the full nonclinical review by C M Sabbir Ahmed, Ph.D.

Review of Pharmacovigilance Database

The Applicant did not report any cases related to effects of rilzabrutinib on female or male fertility during the clinical development program.

Review of Literature

Applicant's review:

Refer to the Pregnancy section of this review for the Applicant's literature search parameters. The Applicant did not identify any published clinical literature with relevant safety information related to females and males of reproductive potential[14].

DPMH review:

DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "rilzabrutinib" and "fertility", "infertility", "decreased sperm count", "contraception", "oral contraceptives", "effects on fertility", and "reproduction".

In addition, DPMH conducted a search for rilzabrutinib in Micromedex[15], Reprotox[16], and TERIS[17]. No relevant publications or additional information on the effects of rilzabrutinib on human fertility or interactions with hormonal contraceptives were found in the literature search.

Reviewer comment:

The Applicant's review is adequate.

III. DISCUSSION AND CONCLUSIONS

<u>Pregnancy</u>
The animal reproduction studies did not identify any potential safety signals.

Although there were two case reports of exposure during pregnancy from the clinical studies conducted during the drug development of rilzabrutinib, information regarding the pregnancy outcomes was lacking. Thus, the data on rilzabrutinib use in pregnancy are of insufficient quantity and quality to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

ITP occurs commonly in women of reproductive age, and consequently, co-occurrence of ITP and pregnancy is not rare. Rilzabrutinib would not be used as first-line treatment in pregnant women as its proposed indication is for the treatment of adult patients with persistent or chronic ITP who have an insufficient response [redacted] (b) (4) to a previous treatment. Although animal reproduction studies did not identify any potential safety signals, animal findings do not always predict findings in humans, therefore, there is a need to collect data in humans exposed. It is anticipated that rilzabrutinib may be used in a small population of pregnant patients. Thus, to obtain safety information related to the use of rilzabrutinib in pregnancy, DPMH recommends issuing a postmarketing requirement (PMR) for a descriptive pregnancy safety study.

<u>Lactation</u>
There are no data on the presence of rilzabrutinib or its metabolites in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. There are no available data to inform the risks related to the use of rilzabrutinib during lactation. Although rilzabrutinib does not seem to have the same adverse reaction profile as others in class, there is a concern for increased infections, some of which are serious bacterial infections in an infant (pneumonia, UTI, sepsis). The clinical impact on the infant exposed via breastmilk is unknown, however, there is potential for a significant safety concern for an infant should a serious infection-related adverse reaction occur following exposure via breastmilk. Therefore, DPMH recommends avoiding breast milk feeding while a mother is taking rilzabrutinib and for [redacted] (b) (4) after the final dose. DPMH recommends issuing a postmarketing requirement (PMR) for a clinical milk-only lactation study to determine the amount of rilzabrutinib in breast milk.

<u>Females and Males of Reproductive Potential</u>
There are no available clinical data to inform labeling related to rilzabrutinib effects on human fertility. Animal fertility studies do not indicate any adverse effects at clinical exposures. Given there is no evidence of embryo-fetal toxicity or genotoxicity, pregnancy testing or contraception in conjunction with rilzabrutinib use are not recommended. [redacted] (b) (4)

POSTMARKETING REQUIREMENTS (PMR) SUGGESTED LANGUAGE

- **Descriptive Pregnancy Safety Study**: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Wayrilz (rilzabrutinib) during pregnancy to assess risk of pregnancy and maternal complications, adverse effect on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

- **Lactation Study**: Perform a milk-only lactation study in lactating women who have received rilzabrutinib to measure concentrations of rilzabrutinib in breast milk using a validated assay.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on 3/26/2025. DPMH recommendations are below and reflect the discussions with DNH. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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

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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/

KERRY R SHAAB
08/26/2025 01:10:43 PM

TAMARA N JOHNSON
08/26/2025 02:14:11 PM

LYNNE P YAO
08/26/2025 03:21:21 PM

CLINICAL INSPECTION SUMMARY ADDENDUM

Date	July 29, 2025
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kristen Snyder, M.D., Physician Margaret C. Thompson, M.D., Medical Team Leader Rolanda Bailey, Regulatory Health Project Manager Tanya Wroblewski, M.D., Deputy and Acting Division Director, Division of Nonmalignant Hematology Office of Cardiology, Hematology, Endocrinology and Nephrology
NDA	NDA 219685
Applicant	Genzyme Corporation, A Sanofi Company
Drug	Rilzabrutinib
NME	Yes
Classification	Inhibitor of Bruton's tyrosine kinase
Proposed Indications	Treatment of adult patients with persistent or chronic immune thrombocytopenia who have had an insufficient response [redacted] (b) (4) to a previous treatment
Review Type	Standard
Consultation Request Date	November 19, 2024
Summary Goal Date	August 1, 2025 (extension)
Action Goal Date	August 5, 2025
PDUFA Date	August 29, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This review is an **addendum to the original clinical inspection summary dated May 27, 2025,** and covers the inspection of Wojciech Homenda, M.D. (Site 61609) in Poland, for Study PRN1008-018 that was submitted to the Agency in support of a New Drug Application (NDA) for rilzabrutinib.

Based on the inspection results of Dr. Homenda, no significant regulatory violations were identified. The clinical data generated by Dr. Homenda's site are verifiable and appear acceptable in support of the respective indication.

II. RESULTS

Wojciech Homenda, M.D./ Site 61609
Hubalczykow 1
SLUPSK, 76-200
Poland

Inspection dates: July 21 - 25, 2025

At this site, nine subjects were screened, and seven study subjects enrolled in this study. Seven subjects completed the double-blind treatment portion of the study (from Day 1 to Week 24). Five subjects completed the open label extension phase (from Weeks 25 to Week 53). Three study subjects are currently in the long-term extension phase. All enrolled seven subjects' records were reviewed during the inspection.

This comprehensive inspection covered the following areas: ethics committee and consent documents, adverse events, treatment with the investigational product, laboratory results, selected questionnaire results and source data for subject visits, communication with the sponsor, and selected monitoring activities. Source records were a combination of hard copy paper records and printed electronic medical records.

The primary efficacy endpoint data of durable platelet response were verified. No data discrepancies were observed.

All adverse events appeared to be reported and no underreporting were observed.

Based on this preliminary inspectional result, no significant Good Clinical Practice (GCP) violations were found.

A follow-up summary report will be amended if there are any significant changes in the final establishment inspectional results.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D., F.A.C.P.
FDA Senior Physician
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Medical Team Leader
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Jenn Sellers, M.D., Ph.D., F.A.A.P.
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MIN LU
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JENN W SELLERS
07/31/2025 11:09:59 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memorandum for Pregnancy Safety Concerns
Version: 2024-09-13

Date:	July 29, 2025
Product Name:	WAYRILZ (rilzabrutinib)
Application Type/Number:	NDA 219685
Sponsor/Applicant:	Genzyme Corporation
NEXUS Task Tracking Tool ID #:	2025-14896
Reviewer:	Kate Gelperin, MD, MPH Division of Epidemiology I
Team Lead:	CDR Steven Bird, PhD, PharmD, MS, USPHS Division of Epidemiology I
Division Leadership:	Kira Leishear White, PhD, MS Division of Epidemiology I
Sub-Office Director:	David Moeny, RPh, MPH Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Sarah Dutcher, PhD Regulatory Science Staff Office of Surveillance and Epidemiology

1. BACKGROUND INFORMATION

1.1. Medical Product

Rilzabrutinib is an oral, reversible covalent inhibitor of Bruton's tyrosine kinase (BTK). The proposed indication is "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." ITP is a rare autoimmune disorder characterized by autoantibody-mediated platelet destruction and impaired platelet production, leading to thrombocytopenia and an increased risk of life-threatening bleeding episodes (e.g., intracranial hemorrhage), severe bleeding and fatigue.

Two exposed pregnancies were reported during the rilzabrutinib clinical development program: 1) Pregnancy was reported in a 32-year-old female after 410 days of rilzabrutinib therapy 400 mg twice daily in a clinical trial; however, the patient did not consent to provide information on the pregnancy or its outcome and no further details were available; 2) A positive pregnancy test was reported in a 23-year-old female after 394 days of rilzabrutinib therapy 400 mg twice daily. Rilzabrutinib therapy was discontinued and elective termination of the pregnancy was done on Day 427. No further details about the pregnancy were provided.[1]

The current rilzabrutinib draft labeling relevant to pregnancy states:[2]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

Animal Data

Rilzabrutinib given to pregnant rats by oral gavage at 50, 150 or 300 mg/kg/day during the period of organogenesis (gestation day 7 to 17) did not cause adverse effects on embryo-fetal development at exposures approximately 10-times the clinical exposure at the maximum recommended human dose (MRHD), based on AUC. Increased incidence of post-implantation loss (25%), delayed ossification associated with a markedly lower (24%) mean fetal weight, and increased skeletal (scoliosis) and visceral malformations (abnormalities of major vessels, urogenital tract, and kidney) occurred in a preliminary study in rats at a maternally toxic dose of 500 mg/kg/day that resulted in exposures 22-times the clinical exposure at the MRHD, based on AUC.

Rilzabrutinib given to pregnant rabbits by oral gavage at 10, 30 or 100 mg/kg/day during the period of organogenesis (gestation day 7 to 19) did not cause adverse effects on embryofetal development at exposures approximately 4-times the clinical exposures at the MRHD, based on AUC.

In a pre- and postnatal developmental toxicity study, pregnant rats were given rilzabrutinib by oral gavage at doses of 50, 150 or 300 mg/kg/day during the periods of gestation, parturition, and lactation (gestation day 7 to lactation day 21). Decreased body weight was observed in pups in the presence of maternal toxicity at 300 mg/kg/day, at exposures approximately 18-times the MRHD based on AUC. There were no effects of rilzabrutinib on the ability of F1 offspring to reproduce or on subsequent F2 development at any dose.

[1] Shaab KR. DPMH Review; WAYRILZ (rilzabrutinib) NDA 219685; dated May 28, 2025; DARRTS Ref ID #5598898.
[2] Draft labeling for WAYRILZ (rilzabrutinib) tablets, for oral use. Updated as of July 21, 2025.

1.2. Describe the Safety Concern

The need for a PMR study to evaluate the safety of rilzabrutinib during pregnancy was described in the DPMH review[3] as follows:

> Although there were two case reports of exposure during pregnancy from the clinical studies conducted during the drug development of rilzabrutinib, information regarding the pregnancy outcomes was lacking. Thus, the data on rilzabrutinib use in pregnancy are of insufficient quantity and quality to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. ITP occurs commonly in women of reproductive age, and consequently, co-occurrence of ITP and pregnancy is not rare. Rilzabrutinib would not be used as first-line treatment in pregnant women as its proposed indication is for the treatment of adult patients with persistent or chronic ITP who have an insufficient response (b) (4) to a previous treatment. Although animal reproduction studies did not identify any potential safety signals, animal findings do not always predict findings in humans, therefore, there is a need to collect data in humans exposed. It is anticipated that rilzabrutinib may be used in a small population of pregnant patients. Thus, to obtain safety information related to the use of rilzabrutinib in pregnancy, DPMH recommends issuing a postmarketing requirement (PMR) for a descriptive pregnancy safety study.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Ensure that the selected purpose(s) is consistent with the other PMR documents in DARRTS. More than one purpose may be chosen.

- ☐ Assess a known serious risk
- ☐ Assess signals of serious risk
- ☒ Identify unexpected serious risk when available data indicate potential for serious risk

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☒ No approved indication in pregnant women, but practitioners may use product off-label in pregnant women
- ☒ No approved indication in pregnant women, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication in pregnant women, but use in women of childbearing age is a general concern

[3] Shaab KR. DPMH Review; WAYRILZ (rilzabrutinib) NDA 219685; dated May 28, 2025; DARRTS Ref ID #5598898.

2.2. Regulatory Goal[4]

- ☐ Signal evaluation of specific outcome(s) – *implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest*.
- ☐ Signal refinement of specific outcome(s) – *further investigation of an identified potential safety signal to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome*.
- ☒ Signal identification – *detection of new and unexpected potential medical product safety concerns and may be for a* ***targeted or multiple*** *safety concern(s)/health outcome(s)*.
  - ☐ Targeted evaluation of specific safety concern
  - ☒ Simultaneous identification of multiple unspecified adverse outcomes

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Descriptive pregnancy safety study

2.4. Identify the epidemiologic domain(s) where ARIA is not sufficient and provide a rationale on ARIA insufficiency for those epidemiologic domain(s). Then, provide an assessment of the overall ARIA sufficiency.

Epidemiologic Domain	Explanation on ARIA insufficiency
☒ Study Population	The population of interest includes both pregnant women and their offspring. Algorithms are available for both; however, ARIA lacks the capacity to identify exposed pregnancies from countries outside the US where rilzabrutinib is approved, as required for a worldwide descriptive study.
☐ Exposures (and Comparators)	ARIA is sufficient for the exposure.
☒ Outcomes	This study requires collection of outcomes in both the pregnant women and the resultant offspring. ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess

[4] Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

	exposure-outcome temporality, and conduct causality assessments.
☒ Covariates	ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors, prenatal supplement use, and over the counter medication use.
☐ Analytic Tools	ARIA is sufficient for the analytic tools.
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	

2.5. If ARIA is deemed insufficient, include the PMR language to be included in the approval letter.

As of July 18, 2025, the PMR language is:

Descriptive Pregnancy Safety Study: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Wayrilz (rilzabrutinib) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

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/s/

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CLINICAL INSPECTION SUMMARY

Date	May 27, 2025
From	Anthony Orencia, M.D., Ph.D., F.A.C.P., Senior Physician Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kristen Snyder, M.D., Physician Margaret C. Thompson, M.D., Medical Team Leader Rolanda Bailey, Regulatory Health Project Manager Tanya Wroblewski, M.D., Deputy and Acting Division Director, Division of Nonmalignant Hematology Office of Cardiology, Hematology, Endocrinology and Nephrology
NDA	NDA 219685
Applicant	Genzyme Corporation, A Sanofi Company
Drug	Rilzabrutinib
NME	Yes
Classification	Inhibitor of Bruton's tyrosine kinase
Proposed Indications	Treatment of adult patients with persistent or chronic immune thrombocytopenia who have had an insufficient response (b) (4) to a previous treatment
Review Type	Standard
Consultation Request Date	November 19, 2024
Summary Goal Date	May 30, 2025
Action Goal Date	July 29, 2025
PDUFA Date	August 29, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study PRN1008-018 were submitted to the Agency in support of a New Drug Application (NDA) for rilzabrutinib, 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.

Two of the three clinical investigator (CI) inspections have been completed for the study: Lei Zhang, M.D. and Howard Liebman, M.D. The inspection of Wojciech Homenda, M.D. in Poland is postponed for late July. The Contract Research Organization (CRO) inspection of (b) (4) was also completed. Based on the results of the completed inspections, the study data derived from the above inspected clinical investigator sites are considered acceptable. The CRO's monitoring for the study appear adequate.

In general, the clinical data submitted to the Agency for assessment appear to be acceptable in support of the proposed indication.

An addendum to this clinical inspection summary will be filed when the inspection of Dr. Homenda is completed, and the inspection report is reviewed.

II. BACKGROUND

Immune thrombocytopenia is characterized by autoantibody-mediated platelet destruction and impaired platelet production, resulting in an increased risk of bleeding and thrombosis, and increased mortality.

Rilzabrutinib is an oral small molecule, ATP competitive, covalent-reversible inhibitor of Bruton’s tyrosine kinase (BTK).

Rilzabrutinib was granted fast track designation (FTD) for immune thrombocytopenic purpura (ITP) on October 15, 2020.

In this application, the Sponsor submitted clinical data from a single Phase 3 study PRN1008-018 (EFC17093, LUNA3) to support the proposed indication of rilzabrutinib 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.

<u>Study PRN1008-018 (EFC17093, LUNA3)</u>

Study PRN1008-018 (EFC17093, LUNA3) was a randomized, double-blind, placebo-controlled, parallel-group multicenter trial to evaluate the efficacy and safety of oral BTK inhibitor rilzabrutinib (PRN1008, SAR444671) in participants with immune thrombocytopenia who had a response to either intravenous immunoglobulin (IVIg) or corticosteroid that was not sustained. The clinical study consisted of three periods including a double-blind treatment period of up to 24 weeks in (which participants were randomized 2:1 to rilzabrutinib 400 mg BID or placebo) followed by a 28-week open label period.

The primary study objective was to demonstrate the efficacy of rilzabrutinib versus placebo in participants with refractory/relapsed ITP, based on the durability of platelet response during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy.

The primary efficacy endpoint during the blinded treatment period was durable platelet response. Response was defined as the proportion of participants (a) able to achieve platelet counts at least 50,000/µL for two-thirds or greater of at least eight non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period (b) in the absence of rescue therapy, and (c) provided that at least 2 non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period.

This study was conducted at 92 centers that randomized adult participants in 25 countries. The first patient enrolled on December 14, 2020, to March 14, 2024 (last participant last visit for the double-blind period). The analyses presented in this report were based on a database lock on April 16, 2024 (last adult completed blinded treatment period).

III. RESULTS

1. **Lei Zhang, M.D./ Site #15602**
   Institute of Hematology and Blood Diseases Hospital
   Chinese Academy of Medical Sciences, Jinghai District
   Tianjin, 300020
   China

   Inspection dates: February 24 - 28, 2025

   The site enrolled and randomized 9 adult study subjects. Nine subjects completed the study. All subject records were reviewed.

   This comprehensive inspection covered the following areas: documentation of informed consent, eligibility criteria, adverse events, treatment with the investigational product, laboratory results, selected questionnaire results and source data for subject visits, ethics committee approvals, communication with the sponsor, and selected monitoring activities. Source records were a combination of hard copy paper records and printed electronic medical records.

   The primary efficacy endpoint data of durable platelet response were verified. No data discrepancies were observed.

   No safety issues or under-reporting of adverse events were observed at this principal investigator clinical site.

   In general, no significant Good Clinical Practice (GCP) deviations were reported.

2. **Howard Liebman, M.D./ Site # 84024**
   1441 Eastlake Ave
   Los Angeles, CA 90033

   Inspection dates: February 3 - 6, 2025

   A total of seven adult subjects were screened; five study subjects enrolled. Three study subjects completed the treatment phase of the study. The data for all the enrolled subjects were reviewed.

   This comprehensive inspection covered the following areas: protocol adherence; inclusion and exclusion criteria; informed consent; adverse event reporting; serious adverse event reporting; source documents; delegation logs; case report forms; financial disclosure forms; data listings verification; monitoring procedures; monitoring logs; study site trainings; investigational product accountability; investigator agreements; IRB submissions, approvals and correspondence, and sponsor correspondence.

The primary efficacy endpoint was verifiable. There were no discrepancies between the source records and the submitted data listings.

No under-reporting of serious adverse events or adverse events were found.

The clinical data derived from Dr. Liebman's site are considered acceptable.

3. [redacted] (b) (4) CRO

[redacted] (b) (4)

Inspection dates: [redacted] (b) (4)

[redacted] (b) (4) was responsible for study monitoring.

Under the Transfer of Regulatory Obligations (TORO), sponsor outlined the transfer of responsibilities from Genzyme Corporation to [redacted] (b) (4).

FDA inspection reviewed records including standard operating policies and procedures, task orders, monitoring plans, medical monitoring plans, safety management plans, data management plans, site corrective and preventive action plans, monitoring visit reports, Interactive Response Technology (IRT) subject listings, user access reports for IRT, protocol deviation listings, and vendor listings.

Specifically monitoring files for Sites #15602, 61609, and 84024 were reviewed and found to be adequate.

Study site monitoring by [redacted] (b) (4) was considered adequate.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D., F.A.C.P.
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Branch Chief
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Office of Scientific Investigations

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 20, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 219685
Product Name, Dosage Form, and Strength:	Wayrilz (rilzabrutinib) tablet, 400 mg
Applicant Name:	Genzyme Corporation (Genzyme)
FDA Received Date:	May 8, 2025
TTT ID #:	2024-10742-2
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Genzyme Corporation (Genzyme) submitted revised container labels and carton labeling received on May 8, 2025 for Wayrilz. We reviewed the revised container labels and carton labeling for Wayrilz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Genzyme Corporation (Genzyme) implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Black, S. Review of Revised Label and Labeling for Wayrilz (NDA 219685). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 24. TTT ID: 2024-10742-1.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 9, 2025

To: Rolanda Bailey, Regulatory Project Manager,
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Melissa Khashei, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for WAYRILZ (rilzabrutinib) tablets, for oral use

NDA: 219685

Background:
In response to DNH's consult requests dated September 11, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for WAYRILZ (rilzabrutinib) tablets, for oral use.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 29, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 9, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on April 29, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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/s/

MELISSA KHASHEI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 9, 2025
To:	Rolanda Bailey Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer Position Title **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	WAYRILZ (rilzabrutinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 219685
Applicant:	Genzyme Corporation

1 INTRODUCTION

On August 29, 2024, Genzyme Corporation submitted for the Agency's review an original New Drug Application (NDA) 219685 for WAYRILZ (rilzabrutinib) tablets 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on September 11, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for WAYRILZ (rilzabrutinib) tablets.

2 MATERIAL REVIEWED

- Draft WAYRILZ (rilzabrutinib) tablets PPI received on August 29, 2024, and received by DMPP and OPDP on April 29, 2025.
- Draft WAYRILZ (rilzabrutinib) tablets Prescribing Information (PI) received on August 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 29, 2025.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MELISSA KHASHEI
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BARBARA A FULLER
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 24, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 219685
Product Name, Dosage Form, and Strength:	Wayrilz (rilzabrutinib) tablet, 400 mg
Applicant Name:	Genzyme Corporation (Genzyme)
FDA Received Date:	April 14, 2025
TTT ID #:	2024-10742-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Genzyme Corporation submitted revised container labels and carton labeling received on April 14, 2025 for Wayrilz. We reviewed the revised container labels and carton labeling for Wayrilz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Genzyme Corporation implemented most of our recommendations. Genzyme clarified the barcode at the top of the principal display panel (PDP) is the linear barcode and relocated it to ensure that it easily readable. In addition, Genzyme clarified that the blister container label is not visible on the samples as it is sealed in between the inner front and back card and contains product information as part of normal operational practice and to allow for traceability if the blister is ever separated from the inner sleeve/tray and/or blister pack. Genzyme also informed that an additional panel was added to the outer sleeve to enhance the blister pack's robustness and improve overall child-resistance to prevent unintended openings and will be positioned internally within the component and is not visible to the user. The container labels and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Genzyme Corporation in Section 3.

3 RECOMMENDATIONS FOR GENZYME CORPORATION

A. General Comments (Container Labels and Carton Labeling)

1. We note the placement of the graphic above the proprietary name was relocated; however it continues to compete with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. Placing a graphic immediately before, within, or after the proprietary name can lead to misinterpretation because graphics may look like an additional letter in the proprietary name or detract from legibility. We continue to recommend deleting, moving, and/or decreasing the prominence of the graphic above the proprietary name.
2. We note the manufacturer information (e.g., manufacturer name "Sanofi" on principal display panel) continues to compete in prominence with critical product information (e.g., proprietary name, established name, strength). Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel (PDP) in accordance with 21 CFR 201.15. We continue to recommend decreasing the manufacturer information (e.g., manufacturer name

[a] Black, S. Label and Labeling Review for Wayrilz (NDA 219685). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAR 27. TTT ID: 2024-10742.

"Sanofi" on principal display panel) in size and prominence so it does not compete with the prominence of important product information on the PDP.

3. The Dosage and Administration statement includes a specific dose, (b) (4) As the dosage statement "Recommended Dosage: see Prescribing Information." is already present on the side panel and users can refer to the Prescribing Information for dosing information, we recommend removing the Dosage and Administration statement (b) (4) (b) (4)

B. Bottle Carton Labeling

1. As currently presented, the side panel (b) (4) (apart from the location of the NDC number and Rx only statement), (b) (4) may lead to confusion (b) (4). We recommend removing information on the side panel (b) (4) to decrease clutter and redundancy.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024346
NDA#/Referenced IND for NDA:	NDA 219685/Referenced IND 132668
Applicant:	Genzyme Corporation
Established Name/Trade Name:	rilzabrutinib tablets
Indication:	Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment. ☒Rare Disease/Orphan Designation
PDUFA Goal Date:	August 29, 2025
Review Division:	Division of Non-Malignant Hematology (DNH)
Clinical Reviewer:	Kristen Snyder
Clinical Team Leader (TL)	Margaret Thompson
Regulatory Project Manager:	Rolanda Bailey
COA Reviewer:	Sarah Rosenberg
COA Deputy Director:	Selena Daniels
COA Division Director:	David Reasner
Instruments reviewed:	1. Immune Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ) Please select COA Type(s): ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of rilzabrutinib tablets for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response [redacted] (b) (4) to a previous treatment. The specific COA [redacted] (b) (4) is improvement in physical fatigue, which is derived from a single randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 study (Study PRN1008-018, also referred to as LUNA 3). The primary objective of this review is to evaluate from a COA perspective [redacted] (b) (4)

The secondary efficacy COA endpoint [redacted] (b) (4) is:

- Change from baseline on Item 10 of the Immune Thrombocytopenic Purpura Patient Assessment Questionnaire (ITP-PAQ) (i.e., physical fatigue) in adult participants (≥18 years) at Week 13.

The data from the LUNA 3 Study demonstrated that rilzabrutinib had statistically significant improvement in the ITP-PAQ item 10 score compared to placebo between baseline and Week 13.

Despite achievement of statistical significance, from a COA perspective, [redacted] (b) (4) (refer to the Key Issues Identified section).

2 REVIEW CONCLUSIONS

The Applicant submitted an evidence dossier for the ITP-PAQ. The ITP-PAQ item-10 (physical fatigue) was reviewed for content validity, other measurement properties, and score interpretability (i.e., meaningful with-in patient change).

Review Summary

- Fatigue appears to be a clinically relevant and important symptom to some patients with ITP. However, it is unknown what aspects of fatigue are most relevant to the target population.
- There is insufficient evidence to support that ITP-PAQ item 10 is fit-for-purpose for the context of this development program. Refer to the Key Issues Identified section.
  - There is insufficient evidence to support the content validity of the ITP-PAQ item-10.
  - Given issues surrounding the content validity and data interpretability of the ITP-PAQ item 10 score, the other measurement properties of the ITP-PAQ item 10 score were not fully reviewed.

Key Issues Identified

<u>Issue 1: Content validity</u>

- There is insufficient evidence to support that physical fatigue is the most important and relevant aspect of the fatigue experience in patients with ITP.

- While we recognize that fatigue may be an important symptom to some patients with ITP, it is unclear whether physical fatigue reflects a meaningful aspect of health to patients' experience with ITP.
  - The qualitative data submitted shows that the majority of participants spontaneously reported experiencing fatigue (n=17/18, 94.4%), however, only a small proportion of participants reported experiencing the physical aspect of fatigue based on the qualitative coding (n=5/17, 29%).
- The concept of physical fatigue may not be well-understood, as the qualitative data shows it was interpreted differently across respondents (e.g., general fatigue/weakness (n=9/17, 53%), low energy (n=7/17, 41.2%), lack of drive (n=6/17, 35.3%), drowsiness of body (n=1/17, 5.9%)).
  - Note that general fatigue may not necessarily equate to physical fatigue.
  - Lack of drive may be a result of many factors, including physical and/or mental fatigue.
- The ITP-PAQ item 10 is a double-barreled question (measures more than one concept, e.g., it asks, "In the past 4 weeks, how often did ITP or its treatment cause you to feel physically fatigued?"). Combining these concepts into one question makes it unclear what is being measured.
- The recall period is lengthy (i.e., 4 weeks) and may be susceptible to recall error.

<u>Issue 2: Data Interpretability</u>

- Because ITP-PAQ item-10 is double-barreled, there may be unwanted variability in the data. [redacted] (b) (4) it is impossible to know what concept is being improved (i.e., ITP-related symptom or treatment-related symptom).
- The threshold for meaningful change in the ITP-PAQ item 10 score is unknown due to issues surrounding content validity. Further, the anchors used in the anchor-based analyses had limitations (refer to Section 5.5.6 of this review).

3 Recommendations for Future Studies

For future clinical trials in this indication, Sponsors should consider the following:

1. Sponsors should engage with FDA early (e.g., Pre-IND) and throughout drug development to discuss their COA measurement strategy to ensure the selected instruments are fit-for-purpose and the studies are designed appropriately for the context of use prior to initiation of pivotal studies.
2. Qualitative studies should be designed to provide a complete understanding of the disease and/or treatment including presentation of symptoms and associated impacts in the target population, as well as establish the appropriateness (content relevance) and comprehensiveness of the assessment, (e.g., conceptual coverage). Specifically, Sponsors should understand which dimensions of fatigue are relevant and important in the target population to inform the trial endpoints. It is important that the concepts selected to measure are based on aspects of the condition that are likely to demonstrate meaningful and interpretable changes on how patients feel or function in daily life.
3. Once concepts have been identified that measure the important aspects of the fatigue experience, Sponsors should provide evidence of validity that the COA is fit-for-purpose

for the specified context of use. Refer to Draft FDA Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders Patient- Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments[1] for the types of evidence to support a COA.

4. Sponsors should select a sufficiently impaired population for their studies or otherwise plan for stratification or appropriate statistical analyses.
    a. Based on literature[2-3], fatigue it is not considered a core symptom of ITP and may vary across patients. This may result in patients having an insufficient level of symptomatology at baseline.

4 Background and Correspondence on Clinical Outcome Assessment(s)

<u>Regulatory Background</u>:
There were previous communications regarding the COA measurement strategy during the IND stage, which include the following:

- <u>FDA Advice/Information Request email communication dated February 10, 2021.</u>
    - Requested clarification on which items comprise the ITP-PAQ Fatigue domain score and would be analyzed as part of the secondary PRO endpoint.
    - Disagreed with combining fatigue and sleep disturbance concepts within a domain score.
    - Disagreed that a single item, such as ITP-PAQ item 10, could sufficiently measure fatigue; recommended use of a multi-item fatigue instrument (b) (4) [redacted]
    - Reiterated concern regarding the instrument's susceptibility to recall error due to the 4-week recall period.
    - Identified limitations with anchor scales.

- <u>FDA Advice/Information Request email communication dated August 27, 2021</u>
    - Requested details on rater instructions and administration of the Immune Thrombocytopenia Bleeding Scale (IBLS) assessment, including training materials.
    - Requested evidence of content validity and other measurement properties (e.g., reliability, construct validity, ability to detect change) for the IBLS.
    - Requested the IBLS scoring algorithm(s) and corresponding information on how the instrument's scores would be analyzed as part of an endpoint, including what constituted meaningful within-patient score changes.

- <u>Type B (End of Phase 2) Meeting Minutes dated June 17, 2020</u>

[1] Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments, https://www.fda.gov/media/159500/download. When this guidance is published it will reflect FDA's current thinking on the topic.
[2] Kohli R, Chaturvedi S. Epidemiology and Clinical Manifestations of Immune Thrombocytopenia. Hamostaseologie. 2019;39(03):238-249. doi:10.1055/s-0039-1683416
[3] Platelet Disorder Support Association. The Voice of the Patient: Immune Thrombocytopenia. A Report on the Externally Led Patient Focused Drug Development Meeting.; 2020. https://pdsa.org/images/voice-of-the-patient.pdf

- Concluded there was insufficient information to comment on the adequacy of the ITP-PAQ (b) (4) [redacted]
- Encouraged collection of patient input to inform COA measurement strategy.

Previous COA Reviews:

- For previous COA reviews, refer to Appendix A.

Disease Background:
Immune thrombocytopenic purpura (ITP) is characterized by autoantibody-mediated destruction of platelets and impaired platelet production (transient or persistent decrease of platelet counts), which result in thrombocytopenia and a predisposition to bleeding associated with morbidity and mortality (i.e., increased risk of bleeding).

Investigational Product:
Rilzabrutinib is a reversible covalent, small molecule, high affinity inhibitor of Bruton's tyrosine kinase (BTK) that has the potential to target multiple pathways and cell types involved in inflammation and autoimmunity; these include B-cell receptor-mediated B-cell pathways, FcγR-induced cytokine release from monocytes and macrophages, FcεR-induced mast cell degranulation and granulocyte migration and mediator release. Pertinent to the treatment of ITP, rilzabrutinib treatment in vitro profoundly inhibited human B-cell activation and blocked antibody (IgG, IgE) mediated activation of immune cells via Fc receptor signaling. Rilzabrutinib is orally administered as a film-costed oral tablet at 400 mg twice daily (BID).

Materials reviewed:
For materials reviewed, refer to Appendix A.

5 Clinical Outcome Assessment Review

5.1 Clinical Trial Population

The target population for Study PRN1008-018 were participants with primary ITP for a duration of >6 months in pediatric participants[4] aged 12 to <18 years and duration of >3 months in adults aged ≥18 years. Eligible participants must have had a response (achievement of platelet count ≥50,000/μL) to IVIg/anti-D or corticosteroids (CS) that was not sustained and who had documented intolerance, insufficient response or any contraindication to any appropriate courses of standard of care ITP therapy.

A complete list of the inclusion and exclusion criteria is summarized in Section 5 of Protocol PRN1008-018 (EFC17093; SDN 1, received date August 24, 2024).

Reviewer's comment(s):

The demographic characteristics in the adult randomized population were generally similar between the treatment groups with the exception of sex. Overall, 75 (37.1%) males and 127 (62.9%) females with ITP were included in the study. The majority of participants

[4] Pediatric participants aged 10 to <12 years will be enrolled in the EU [EEA countries] only; refer to Appendix 10.2, Appendix 10.3, and Appendix 10.7 of Protocol PRN1008-018 (EFC17093) for country-specific requirements.

were White (61.9%) or Asian (31.7%), with no differences in race distribution between treatment groups. The adult participants were aged between 18 and 80 years, with a mean (standard deviation [SD]) age of 46.9 (17.4) years. The mean (SD) body mass index was 27.541 (6.144) kg/m^2. Participants were balanced across treatment groups with regard to geographic regions.

5.2 Clinical Trial Design

Study PRN1008-018 was a global, randomized, parallel-group, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of oral rilzabrutinib in patients with primary ITP who had a response to either Intravenous immunoglobulin (IVIg) or CS that was not sustained.

The study consisted of the following periods:

- Screening period (28 days; up to 4 weeks)
- Blinded treatment period (12 to 24-weeks),
- Open-label (OL) period (28-weeks),
- Follow-up period (4 weeks) or long-term extension (LTE)[5].

Total study duration was up to 60-weeks.

Participants were randomized6 in a 2:1 allocation ratio to one of two study arms:

- Rilzabrutinib 400 mg twice a day (BID) or
- Placebo

Reviewer's comment(s): *Approximately 202 adult participants were randomized (2:1), including 133 who received rilzabrutinib 400 mg BID and 69 who received placebo.*

At the end of 12 weeks of blinded treatment (Week 13), participants[7] were assessed for achieving a platelet response defined as a) platelet count of ≥50,000/µL OR a platelet count of between ≥30,000/µL and <50,000/µL and at least doubled from baseline[8] at any time during the first 12 weeks and; b) absence of rescue medication in the 4 weeks prior to the elevated platelet count that met platelet response criteria.

For more details regarding the study design, refer to Section 4 of Protocol PRN1008-018 (EFC17093).

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[5] For adult participants, the maximum duration of the long-term extension (LTE) period will be 12 months from the date of the last adult participant to enter the LTE. For pediatric participants, the maximum duration of the LTE period will be 12 months from the date of the last pediatric participant to enter the LTE.
[6]Randomization was carried out separately for the two age groups of adult and pediatric participants.
[7] Participants who met this definition of response continued the blinded treatment period for a total of 24 weeks before entering the OL period. Participants who did not meet this definition of response (including participants who received rescue medication after 8 weeks of treatment) were to discontinue from the study or enter the 28-week OL period at the end of 12 weeks of blinded treatment (Week 13), receiving treatment with rilzabrutinib 400 mg BID. Initial study medication assignment remained blinded.
[8]Baseline is defined as the average of the participant's pre-dose platelet counts (Screening and Study Day 1).

5.3 Endpoint Position, Definition, and Assessment Schedule

The placement of the COAs in the endpoint hierarchy (for the US), including the endpoint APPEARS THIS WAY ON ORIGINAL

definition and assessment schedule for Study PRN1008-018 is summarized below.

Primary efficacy endpoint

- Proportion of participants able to achieve platelet counts at or above 50,000/µL for ≥ two thirds of at least eight non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least two non-missing weekly scheduled platelet measurements are at or above 50,000/µL during the last 6 weeks of the 24-week blinded treatment period.

Secondary efficacy COA endpoint (*multiplicity controlled*)

- Change from baseline on Item 10 of the ITP-PAQ (i.e., physical fatigue) in adult participants (≥18 years) at Week 13.

Reviewer's comment(s): *For the secondary efficacy COA endpoint, the change from baseline analysis used the ITP-PAQ Item 10 transformed score. Refer to Section 5.5.3 of this review.*

For a complete list of the study endpoints, refer to the Protocol PRN1008-018 (EFC17093; SDN 1, received date August 24, 2024).

The ITP-PAQ was administered at Screening, during the blinded treatment period every four weeks (Weeks 1 through 21), and then every four weeks during the OL period (Weeks 25 through 53) until end of study or early termination/discontinuation.

5.4 Targeted Clinical Outcome Assessment [redacted] (b) (4)

The Applicant has proposed the following specific targeted COA [redacted] (b) (4)

[redacted] (b) (4)

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(b) (4)

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

5.5.1.1 Immune Thrombocytopenia Patient Assessment Questionnaire (ITP-PAQ) Item 10

The ITP-PAQ Item 10 is a single item within the ITP-PAQ, a 44-item patient-reported outcome (PRO) instrument. This item is designed to assess physical fatigue using a 5-point verbal rating scale (VRS) ranging from “Never” to “All of the time.” The recall period is the previous 4-weeks (“in the past 4 weeks”). A copy of the instrument is in Appendix B.

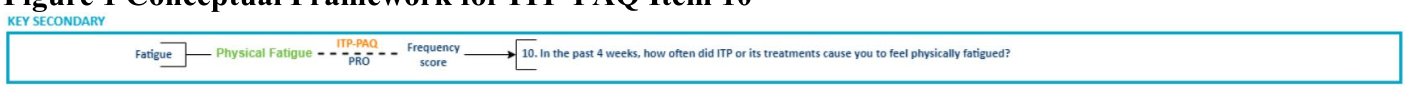
Reviewer’s comment(s):

- *The Applicant assessed fatigue to support a secondary endpoint using only item 10 from the ITP-PAQ instrument (“In the past 4 weeks, how often did ITP or its treatments cause you to feel physically fatigued”).*
- *On p. 22/881, the Applicant specifies that COA-based endpoints were electronically administered during the LUNA 3 (PRN1008-018) study.*

5.5.2 Conceptual Framework(s)

The conceptual framework for the ITP-PAQ Item 10 is shown in Figure 1.

Figure 1 Conceptual Framework for ITP-PAQ Item 10



Source: COA Dossier, Figure 2, page 32 of 811, SDN 1, received date August 29, 2024.

5.5.3 Scoring Algorithm

<u>ITP-PAQ Item 10</u>

The ITP-PAQ item 10 score is transformed to a 0 to 100 continuum using the formula below, with a higher score indicating less physical fatigue and changes of positive value indicating improvement.

$$\text{transformed item score} = 100 * \frac{(possible\ maximal\ item\ score - item\ score)}{range}$$

A multiple imputation approach was used to impute missing Week 13 value, using all data during the double-blind on treatment period up to Week 13 from participants who did not take rescue medication (after eight weeks of double-blind treatment), nor discontinued before Week 13 due to related adverse events or lack of response, assuming missing at random and multivariate normal distribution. The imputation model included treatment group, randomization stratification factors and geographic region as classified variables and baseline item score as a covariate. If the baseline score was missing for a participant, the pooled mean of baseline scores was used.

5.5.4 Content Validity

5.5.4.1 ITP-PAQ Item 10

The Applicant completed the following activities to evaluate the content validity of the ITP-PAQ item 10:

- Targeted literature review
- Patient input (hybrid concept elicitation and cognitive interviews in adult patients with ITP)

A summary of the results for each activity is described below. Refer to the Applicant's COA evidence dossier (SDN 1, received date August 29, 2024) for further details regarding the methodology and results of each activity.

Reviewer's comment(s):
On p. 18/881 of the COA Dossier, "ITP-PAQ will only be completed by adult participants in the LUNA 3 trial, this PRO dossier will focus on evidence relating to an adult ITP population only."

5.5.4.1.1 Targeted Literature Review

The Applicant conducted a targeted literature review to understand the patient experience of ITP and identify what key symptom and impact concepts are important to measure in the rilzabrutinib development program.

- The review identified 19 PRO instruments, of which 8 were analyzed in depth to compare their contents to the original conceptual model developed by the Applicant (for further details, refer to the Sponsor's COA evidence dossier listed in Appendix A).
- From the literature findings, fatigue was highlighted as a core symptom and reported by patients to be the most bothersome.
- The Voice of the Patient report (dated August 26, 2020) reported that 20% of respondents (n=44/225) reported fatigue as one of the symptoms from ITP that has the most significant impact on one's life.
- Per the Applicant, the results of the literature review helped to (1) inform the conceptual framework, and (2) identify existing instrument that may be suitable for assessing symptoms in ITP; specifically, the ITP-PAQ.

5.5.4.1.2 Patient input

<u>Hybrid concept elicitation and cognitive) interviews in adults (ages ≥18 years)</u>
The Applicant conducted qualitative hybrid concept elicitation and cognitive interviews (n=18) via telephone in patients with ITP in the US. The participants were predominantly White (n=13/18, 72.2%), female (n=14/18, 77.8%), with a mean age of 42.7 years (range: 20-66 years) and at least some college education or higher (n=16/18, 89%). Time since

diagnosis ranged between 1 to 5 years or more than 10 years in most participants (n=7/18, 38.9%; n=6/18, 33.3%, respectively). Most participants reported having received three or more treatments for ITP (n=12/18, 66.7%).

Concept Elicitation Phase

The results for the concept elicitation phase of the interviews are summarized below:

- The most commonly reported ITP-related signs/symptoms were fatigue (n=17/18, 94%), bruising (n=15/18, 83%), bleeding[9] (n=15/18, 83%), and petechiae (n=13, 72%).
- The top three most frequently endorsed symptoms with corresponding bothersomeness ratings ('0'=least bothersome to '10'=most bothersome") included: fatigue (n=17, mean bothersomeness rating: 8.2), bruising (n=15, mean bothersomeness rating: 6.4), and petechiae (n=13, mean bothersomeness rating: 6.3) respectively.
  - Over half of participants endorsed fatigue as the most bothersome symptom (n=10/18, 56%).
- The patients' definition of fatigue was categorized by the Applicant as physical (inability to complete physical tasks due to lack of energy, drive, general weakness), or mental fatigue (short term memory loss, brain fog, confusion, inability to find words or form sentences, difficulty to think clearly, loss of concentration/focus).
- Based on the Applicant's qualitative coding, those who spontaneously reported experiencing fatigue (n=17), a small proportion of participants reported experiencing the physical aspect of fatigue (n=5/17, 29%). Four participants (n=4/17, 24%) reported experiencing both mental and physical aspects of fatigue.

Reviewer's comment(s):

- *Most participants who experienced fatigue attributed it to their ITP (n=12/17, 71%).*
- *Per the Applicant, "The codebook captured all symptoms and impacts identified in the conceptual model developed by Mathias et al (2008)." (p. 768/881, COA Dossier). Mathias et al. (2008) identified a theme of fatigue, and the sub-themes included "inability to get out of bed" and "limits daily activities." The Applicant did not provide a final copy of their codebook with their final report, so this reviewer was unable to assess how "physical fatigue" was categorized from participant responses.*
- *This reviewer reviewed several interview transcripts (n=5/18, 27.8%) to corroborate the findings reported by the Sponsor in their COA Dossier. Based on review of the transcripts, this reviewer has the following concerns:*
  - *Physical fatigue was described by participants to include many aspects which may produce variable results. For instance, on page 815 of 881 of the COA Evidence Dossier, the Sponsor reported that patients said that item 10 is relevant "because ITP and its treatments make them feel tired, drained, exhausted, sluggish, their arms, shoulders and legs are heavy or, they are not able to move or go running."*
  - *The ITP-PAQ item-10 is double-barreled in which it asks patient to reflect on their experiences with ITP-related symptoms or treatment-related symptoms, which led to confusion by respondents. For example, on pg. 25 of 561 (Interview Transcripts):*

[9] Bleeding episode included: bleeding gums, nose bleeds, bleeding episodes, blood blisters, and heavy menstrual cycles.

> *Moderator: All right. Would you have answered differently when thinking about when you're on prednisone versus when you're Rituxan?*
>
> *ID* (b) (6) *Yes, definitely. Yeah. I would say when I was on prednisone, I was physically fatigued probably most of the time. Rituxan I would say some of the time.*

For another example (pg. 110/561, Interview Transcripts):

> *Moderator: Okay. All right. Do you feel like other than, you know, you said when you're on steroids the physical fatigue was more, do you feel like other than that that the fatigue, either the mental or the physical, has it changed over time?*
>
> *ID* (b) (6)*: Yes. It definitely has. I think that the physical fatigue I think has lessened, and that's why I attribute a lot of that to the steroids because since I've been off of those I do feel better physically. Actually, emotionally too because I feel like there were a lot of emotional side effects from those as well.*

- *In some interview, the moderator appeared to lead respondents using probing questions. Specifically, the moderator appeared to probe more about symptoms related to fatigue after the respondent indicated that other symptoms were of greater relevance (i.e., petechiae, bruising, emotional impact, etc.). For instance, interview with Patient ID* (b) (6)

> *Moderator: The fatigue that you experience now either mentally or emotionally...sorry, mental or physical, do you associate it with the ITP?*
>
> *ID* (b) (6)*: No, I really don't.*
>
> *Moderator: Okay. When you experience fatigue either from the medications or from the ITP, did you need someone else's help to carry out daily activities at all?*

Another example in which the moderator continues to lead with probes about fatigue (pg. 233/561 interview transcripts):

> *Moderator: Okay. All right. Again, you don't experience any type of fatigue because of your ITP?*
>
> *Patient ID* (b) (6)*: No.*
>
> *Some interview participants reported that mental fatigue was of greater relevance than physical fatigue to their experience with ITP. Patient ID* (b) (6) *indicated that mental fatigue was more relevant than the physical fatigue, "I would also say the mental." (pg. 109/561). This patient also indicated that the mental fatigue would be most important to treat between physical and mental fatigue.*

- *In response to an Information Request dated February 4, 2025, the Applicant provided the number of participants who spontaneously reported each concept used to define fatigue: general fatigue/weakness (n=9/17, 53%), low energy (n=7/17, 41.2%), lack of drive (n=6/17, 35.3%), drowsiness of body (n=1/17, 5.9%).*

<u>*Cognitive Debriefing Phase*</u>
The results for the cognitive debriefing phase of the interviews are summarized below:
- Eighteen (n=18) participants were cognitively debriefed on ITP-PAQ items 7 through 10.
- All participants (n=18/18, 100%) indicated that item 10 (physical fatigue) was relevant to their experience with ITP, the item wording was clear, and all response options were relevant.
- Seventeen participants (n=17/18, 94%) reported that the response options were clear. All participants (n=18) were able to answer item 10 of the ITP-PAQ.
- Four participants recommended changes to item 10, including incorporating examples, or better defining "physically" as this term is broad, or rewording to show "tired" or "low energy" instead of "physical fatigue."
- All patients who were asked (n=10/10, 100%) about the 4-week recall period of item 10 (N=10), indicated that this was appropriate to capture their experience with ITP-related fatigue.
    - No participant reported the need for a shorter or longer recall period for item 10 (physical fatigue).

Reviewer's comment(s):
- *Forty (n=4/10, 40%) of participants recommended changes to ITP-PAQ item-10 wording to include examples to better define "physically" as this term is broad or rewording to show "tired" or "low energy" instead of "physical fatigue." These suggestions made by respondents suggests that there may have been differences in interpretation as to the meaning, thus leading to variability in responses across respondents.*
- *Respondents seemed to have difficulty in responding to the double-barreled nature of the ITP-PAQ Item 10. Refer to Reviewer's comment in the Concept Elicitation Section for further details and examples. Of note, the Applicant did not directly debrief participants on the double-barreled nature of the item 10 stem wording. Upon review of some of the interview transcripts, it appeared that some respondents had difficulty responding to the*

item since it asks participants to reflect on their experiences with ITP-related symptoms or treatment-related symptoms.

Overall, this reviewer concludes the following:

- *There is insufficient evidence to support that physical fatigue is the most important and relevant aspect of the fatigue experience of patients with ITP.*
- *While we recognize that fatigue may be an important symptom to some patients with ITP, it is unclear whether physical fatigue reflects a meaningful aspect of health to patients' experience with ITP.*
- *The qualitative data submitted shows that the majority of participants spontaneously reported experiencing fatigue (n=17/18, 94.4%), however, only a small proportion of participants reported experiencing the physical aspect of fatigue based on the qualitative coding (n=5/17, 29%).*
- *The concept of physical fatigue may not be well-understood, as the qualitative data shows it was interpreted differently across respondents (e.g., general fatigue/weakness (n=9/17, 53%), low energy (n=7/17, 41.2%), lack of drive (n=6/17, 35.3%), drowsiness of body (n=1/17, 5.9%)).*
    - *Note that general fatigue may not necessarily equate to physical fatigue.*
    - *Lack of drive may be a result of many factors, including physical and/or mental fatigue.*
- *The ITP-PAQ item 10 is a double-barreled question (measures more than one concept, e.g., it asks, "In the past 4 weeks, how often did ITP or its treatment cause you to feel physically fatigued?"). The Applicant did not provide summary statistics for the number of respondents who thought about ITP versus treatment in the final report. Combining these concepts into one question makes it unclear what is being measured.*
- *The recall period is lengthy (i.e., 4 weeks) and may be susceptible to recall error.*

5.5.5 Other Measurement Properties

The Applicant conducted psychometric analyses on the ITP-PAQ item-10 using blinded data from Study PRN1008-018. However, given the surrounding content validity issues, the other measurement properties (reliability, construct validity, and ability to detect change) were not fully reviewed. Testing other measurement properties, while important, will not replace or address problems with content validity.

Reviewer's comment(s):

- *The proportion of patients who reported 'rarely' (n=35/202, 17.5%) or 'never' (n=37/202, 18.5%) experiencing physical fatigue at baseline remained relatively consistent to week 13 (n=40/188, 21.9% for 'rarely' and n=38/188, 20.8% for 'never').*

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

The Applicant conducted anchor-based analyses for interpreting the ITP-PAQ item-10-based endpoint scores, however, given the surrounding issues related to content validity and data interpretability, the Applicant's proposed threshold for meaningful within-patient score change could not be fully reviewed.

A description of the anchors is summarized in the following section.

5.5.6.1 Anchor scales

Patient Global Impression of Severity (PGIS) Fatigue

The PGIS scale is a single-item patient-reported outcome (PRO) instrument designed to assess severity of fatigue using a 5-point verbal rating scale (VRS) ranging from "None" to "Very severe." The recall period is "over the past week." A copy of the instrument is in Appendix C.

The PGIS Fatigue was administered at Screening, during the blinded treatment period every four weeks (Weeks 1 through 21), and then every four weeks during the open-label period (Weeks 25 through 53) until end of study or early termination/discontinuation.

Patient Global Impression of Severity (PGIS) Disease-related symptoms

The PGIS scale is a single-item PRO instrument designed to assess disease-related symptoms using a 5-point verbal rating scale (VRS) ranging from "None" to "Very severe." The recall period is "over the past week." A copy of the instrument is in Appendix C.

The PGIS Disease-related symptoms was administered at Screening, during the blinded treatment period every four weeks (Weeks 1 through 21), and then every four weeks during the open-label period (Weeks 25 through 53) until end of study or early termination/discontinuation.

Patient Global Impression of Change (PGIC)

The PGIC is a single-item PRO instrument designed to assess overall change in disease-related symptoms using a 7-point VRS ranging from "Very much better" to "Very much word." The recall period is "since you started taking the study medication." A copy of the instrument is in Appendix C.

The PGIC was collected starting after Screening (Day 1), during the blinded treatment period every four weeks (Weeks 1 through 21), and then every four weeks during the open-label period (Weeks 25 through 53) until end of study or early termination/discontinuation.

Reviewer's comment(s):

Global Scales:

- *PGIS-Fatigue: All participants (n=18/18, 100%) were able to answer the PGIS-Fatigue and reported the item was relevant to their experience with ITP. Most reported that the item wording was clear (n=16/18, 89%), and the response options were relevant (n=15/18, 83%) and clear (n=14/18, 78%), respectively.*
    - *Most participants (n=16/18, 89%) indicated that a 1-point categorical change on the PGIS-Fatigue would be a minimum meaningful improvement.*
    - *Five participants were asked to reflect on the one week recall period. Four indicated it was appropriate (n=4/5, 80%) and one patient suggested a longer time frame (n=1/5, 20%)*
- *PGIS disease-related symptoms: Most participants were able to answer the item (n=17/18, 94%). Most participants reported that the item was relevant (n=17/18, 94%),*

the wording was clear (n=13/18, 72%), and the response options (n=17/18, 94%) were relevant and clear (n=17/18, 94%).
  - *Most participants (n=12/18, 71%) indicated that a 1-point categorical change on the PGIS would be a minimum meaningful improvement.*
  - *Only two participants provided feedback regarding the "past week" recall period, and both found it appropriate (n=2/2, 100%)*
- *<u>PGIC disease-related symptoms</u>: All participants (n=18/18, 100%) were able to answer the item and found it relevant to their experience with ITP. Most participants found the item wording clear (n=14/18, 78%), and the response options relevant (n=17/18, 94%) and clear (n=14/18, 78%).*
  - *Most participants (n=15/18, 83%) indicated that a 1-point categorical change on the PGIC would be a minimum meaningful improvement.*
  - *Two participants provided feedback regarding the "past week" recall period. One (n=1/2, 50%) found the time period appropriate and one (n=1/2, 50%) suggested a longer recall period (i.e., a few weeks).*
- *The majority of patients indicated that a 1-point categorical change in worsening overall on the PGIS-Fatigue (n =16/18, 89%), PGIS (n=12/18, 71%), and PGIC (n=15/18, 83%) would be meaningful.*

This reviewer notes that that the anchors had limitations, which would have impacted the interpretability of the results of the anchor-based analyses. For example,

- *Four (n=4/18, 22%) participants reported issues with PGIC wording noting that clarification on which symptoms to reflect- those symptoms related to ITP or those including symptoms related to study medication. For instance, patient ID* (b) (6) *had difficulty understanding the PGI-C disease-related symptoms question, "For the most part I understand this question, but I think it was maybe a little harder to understand. Again, really just different shading between are we talking about symptoms related to ITP, or including symptoms related to ITP treatment."*
- *The concept measured in the PGIS and PGIC items is generic (disease-related symptoms; disease-related fatigue) and is not fully aligned with the concept of the ITP-PAQ item 10 (physical fatigue). Further the concept of the ITP-PAQ item 10 is measuring fatigue related to ITP and its treatments. We generally recommend that an anchor scale measures the same concept (i.e., the aspect of the disease specified in the endpoint, as opposed to global status of the disease) of the target instrument to the extent possible to provide the most direct evidence.*
- *The recall period of the PGIS item ("past week") does not align with the assessment time period of the prespecified ITP-PAQ item 10-based endpoint (previous 4 weeks). We generally recommend that the anchor scale's recall period should be consistent with the assessment time period of the pre-specified endpoint to the extent possible.*
- *The PGIC item may be misinterpreted as having two different recall periods since it includes language referencing a "past week" recall and an earlier time period ("since you started the study medication"). Generally, global impression of change scales assesses the overall change in the measurement concept from the current state to an earlier time period.*

- *Patients may be unable to distinguish between some of the response categories in the PGIS and PGIC items (e.g., "severe" and "very severe;" "moderately improved" and "very much improved;" "moderately worse" and "very much worse") due to the high number of response categories. Anchor scales should be plainly understood by respondents in the context of use.*

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SELENA R DANIELS
03/27/2025 12:30:07 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 27, 2025
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 219685
Product Name, Dosage Form, and Strength:	Wayrilz (rilzabrutinib) tablet, 400 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Genzyme Corporation (Genzyme)
FDA Received Date:	August 29, 2024
TTT ID #:	2024-10742
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Wayrilz (rilzabrutinib) tablet, we reviewed the proposed Wayrilz Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of NDA 219685.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Information Request	D

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Wayrilz Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the carton labeling contains a statement to dispense in original package; however, this information is missing from the Prescribing Information. In addition, we note the net quantity statement on the container labels and carton labeling contains (b) (4) [redacted] rather than the actual dosage form "tablets." In addition, we note that the net quantity statement on the outer carton labeling contains the package type term "blister pack" (b) (4) [redacted] We reached out to the Office of Pharmaceutical Quality (OPQ) to clarify if the product should be stored and dispensed in the original package for both bottle and blister pack presentations, if the net quantity statement should only include the proposed dosage form "tablet", and what the appropriate package type terms are. OPQ confirmed that based on light and moisture precautions, they agree with storing and dispensing the product in the original container for both bottle and blister pack presentations and the net quantity statement should contain the dosage form "tablet" only. In addition, OPQ also suggested revising the net quantity on the outer carton labeling to state "Each carton contains a total of 56 tablets in two blister packs of 28 tablets each.".

4 CONCLUSION

The proposed Wayrilz Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Non-Malignant Hematology (DNH) in Section 5 and for Genzyme Corporation in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. General Comment
    a. As currently presented, the proprietary name is denoted by the placeholder “*TM*”. We reference our December 9, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Wayrilz, was found conditionally acceptable. We recommend replacing the placeholder “*TM*” with the conditionally acceptable proprietary name, Wayrilz.
2. Highlights of Prescribing Information
    a. As currently presented in the *Dosage and Administration* section, administration information is presented (b) (4). To increase readability, we recommend placing the administration information (b) (4) (b) (4) and revising to “Recommended dosage: 400 mg orally twice daily; swallow whole with water, with or without food. Do not cut, crush, or chew tablets. (2.1)”.
3. Section 2 Dosage and Administration
    a. As currently presented, the frequency of administration contains (b) (4) (b) (4). Error prone (b) (4) may lead to misinterpretation and medication error. We recommend removing the (b) (4).
4. Section 16 How Supplied/Storage and Handling
    a. The strength is not provided in Section 16. The strength is required per 21 CFR 201.57(c)(17). Add the strength in Section 16 in accordance with 21 21 CFR 201.57(c)(17).
    b. We note the carton labeling states to dispense in original package; however, this information is also missing in the storage statement in Section 16. For consistency between the labels and labeling and to minimize the risk of deteriorated drug medication errors, we recommend revising the storage statement to “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.”.
    c. As currently presented, the “How Supplied” table contains the package type terms “blister pack” and (b) (4) OPQ confirmed the appropriate package type term is “blister pack”. Therefore, we recommend revising the content statement to “Carton containing 2 blister packs. Each blister pack (58468-0251-0) contains 28 film-coated tablets”.
5. Section 17 Patient Counseling
    a. Section 2.1 *Recommended Dosage* states to take the product at the same time each day but this information is missing in Section 17 *Administration Instructions*. For consistency with the Section 2.1, we recommend

revising the Section 17 *Administration Instructions* to "Instruct patients to take Wayrilz orally twice daily at approximately the same time each day with or without food. Advise patients that Wayrilz tablets should be swallowed whole, and not to cut, crush or chew the tablets. *[see DOSAGE AND ADMINISTRATION (2.1)]*.".

b. Section 2.1 *Recommended Dosage* states not to take an extra dose but this information is missing in Section 17 *Missed Dose*. For consistency with the Section 2.1, we recommend revising the Section 17 *Missed Dose* to "Advise patients that if they miss a dose of Wayrilz, they should still take it as soon as possible on the same day (b) (4) [redacted]

B. Patient Package Insert (PPI)

1. As currently presented, the proprietary name is denoted by the placeholder "*TM*". We reference our December 9, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Wayrilz, was found conditionally acceptable. We recommend replacing the placeholder "*TM*" with the conditionally acceptable proprietary name, Wayrilz.

6 RECOMMENDATIONS FOR GENZYME CORPORATION

A. General Comments (Bottle and Blister Pack Container Labels and Carton Labeling)

1. The placement of the graphic above the proprietary name competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. Placing a graphic immediately before, within, or after the proprietary name can lead to misinterpretation because graphics may look like an additional letter in the proprietary name or detract from legibility. Delete, move, and/or decrease the prominence of the graphic above the proprietary name.
2. As currently presented, the proprietary name is denoted by the placeholder "Tradename". We are unable to assess the prominence and readability of the intended presentation of the proprietary name. We reference our December 9, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Wayrilz, was found conditionally acceptable. We recommend replacing the placeholder "Tradename" with the conditionally acceptable proprietary name, Wayrilz, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
3. We note that the statement (b) (4) [redacted] on the container labels and carton labeling. This statement is unnecessary and contributes to clutter, reducing

readability of important information. We recommend removing the statement, [redacted] (b) (4) to improve readability of the container labels and carton labeling.

4. We note that the statement [redacted] (b) (4) is proposed on the container labels and carton labeling. This statement is unnecessary and contributes to clutter on the container labels and carton labeling. We recommend removing the statement, [redacted] (b) (4) on the container labels and carton labeling.
5. The manufacturer information (e.g., manufacturer name) competes in prominence with critical product information (e.g., proprietary name, established name, strength). Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel (PDP) in accordance with 21 CFR 201.15. Decrease the manufacturer information in size and prominence so it does not compete with the prominence of important product information on the PDP.
6. The statement of dosage statement includes a specific dose rather than referring to the Prescribing Information. As there are administration specific instructions due to drug interactions, we recommend referring users to the Prescribing Information for dosing and administration instructions. Therefore, we recommend revising the statement of dosage statement to "Recommended Dosage: see Prescribing Information.

B. Bottle Container Labels

1. We note a barcode at the top of the PDP. Please clarify if this is the linear barcode or another barcode.
2. The "Rx only" statement appears more prominent than other critical information (e.g., established name) on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend reducing the size of the "Rx only" statement so it does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3. We note that the carton labeling states to dispense in original package and protect from light and moisture; however, this information is missing on the bottle container label. For consistency with the carton labeling and to minimize the risk of deteriorated drug medication errors, we recommend including this information as part of the storage statement on the side panel and revising the storage statement to "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.".

C. Bottle Carton Labeling and Blister Pack Inner and Outer Carton Labeling

1. We note that the statement [redacted] (b) (4). For readability and to minimize

the risk of deteriorated drug medication errors, we recommend removing the statement, [redacted] (b) (4) and relocate all storage information on the side panel to appear as "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.".

D. Blister Pack Container Labels and Blister Pack Inner and Outer Carton Labeling

1. It is not immediately clear that the designated strength (i.e., 400 mg) is per single unit (tablet). Failure to clearly express the product strength in 400 milligrams per single unit (tablet) may lead to wrong dose errors. We recommend revising the strength statement "400 mg" to state "400 mg per tablet" to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
2. We note the placement of the strength statement on the blister pack labels and labeling is inconsistent with the placement of the strength statement on the bottle labels and labeling. For consistency with the bottle labels and labeling, we recommend relocating the strength statement directly underneath the established name and dosage form.

E. Blister Pack Container Label

1. We note the samples provided does not contain the blister pack container label submitted below. Therefore, please clarify if the label below is intended for the commercial product and the location of this label.

(b) (4) [redacted]

2. As currently presented, it is not clear that the sun represents dose #1 and the moon represents dose #2. Therefore, for clarity, we recommend labeling the sun and moon images with "Dose 1" and "Dose 2".

F. Blister Pack Outer Carton Labeling

1. The established name is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2. As currently presented for the outer carton labeling, the net quantity statement (b) (4) [redacted] may be improved for clarity. We recommend revising the net quantity statement to “Each carton contains a total of 56 tablets in two blister packs of 28 tablets each.”.

G. Blister Pack Inner Carton Labeling
   1. As currently presented for the inner carton labeling, the net quantity (b) (4) [redacted] is inconsistent with the package type term “blister pack”. For consistency, we recommend revising the net quantity to state “Each blister pack contains 28 tablets”.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Wayrilz received on August 29, 2024 from Genzyme Corporation.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Wayrilz</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>rilzabrutinib</td></tr>
<tr><td>Indication</td><td>Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) [redacted] (b) (4) [redacted] to a previous treatment.</td></tr>
<tr><td>Dosage Form</td><td>tablet</td></tr>
<tr><td>Strength</td><td>400 mg</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dose and Frequency</td><td>• Recommended dosage: 400 mg orally twice daily; swallow whole with water and with or without food.
• Advise patients not to cut, crush or chew tablets.
• Avoid in patients with moderate or severe hepatic impairment.</td></tr>
<tr><td>How Supplied</td><td>The *TM* film-coated tablets are orange, capsule-shaped, and debossed with "P" on one side and "400" on the other side.

<u>How Supplied:</u>
<table>
<tr><th>Package Size/Type</th><th>Content</th><th>NDC Number</th></tr>
<tr><td>60-count bottle</td><td>Bottle containing 60 film-coated tablets with a child-resistant closure</td><td>58468-0251-6</td></tr>
<tr><td>56-count carton</td><td>Carton containing 2 blister packs, each [redacted] (b) (4) (58468-0251-0) (b) (4) [redacted] 28 film-coated tablets (b) (4) [redacted].</td><td>58468-0251-5</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>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.</td></tr>
<tr><td>Container Closure</td><td>• The primary packaging selected for commercial distribution of the finished product is a white opaque [redacted] (b) (4) ([redacted] (b) (4) - aluminum blister package.
• The primary packaging selected for commercial distribution of finished product is white high density polyethylene (HDPE) round 100 mL bottle with child-resistant closure (CRC) and induction inner seal. [redacted] (b) (4)</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Wayrilz labels and labeling submitted by Genzyme Corporation.

- Prescribing Information received on August 29, 2024, available from \\CDSESUB1\EVSPROD\nda219685\0001\m1\us\proposedpi.pdf
- Patient Package Insert received on August 29, 2024, available from \\CDSESUB1\EVSPROD\nda219685\0001\m1\us\proposedppi.pdf
- Container labels received on August 29, 2024
- Carton labeling received on August 29, 2024

B.2 Container Labels and Carton Labeling Images

(b) (4)

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219685
Submission Number	1
Submission Date	8/29/2024
Date Consult Received	10/10/2024
Drug Name	Rilzabrutinib
Indication	Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment.
Therapeutic Dose	400 mg BID
Clinical Division	DNH
Protocol Review	Protocol (04/05/2018) Revised protocol (07/25/2018)

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 10/10/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 132668 dated 04/05/2018; 07/25/2018 in DARRTS;
- Study report PR1008-014 (NDA 219685 / SDN 001; link);
- Study protocol PR1008-014 (NDA 219685 / SDN 001; link);
- Cardiac safety report – last appendix in SAP (NDA 210695 / SDN 001; link);
- Applicant's Proposed Label (NDA 219685 / SDN 001; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA219685 / SDN 011; link).

1 SUMMARY

Rilzabrutinib was associated with concentration-dependent shortening of the QTcF interval in this thorough QT (TQT) study – see Table 1 for overall results.

The clinical study PRN1008-014 was a single center, two-part study in healthy adult participants. Part A was a randomized, open label, 3-period, complete crossover study. Part B was a randomized, blinded, single dose, placebo-controlled, double dummy, 4-period, complete crossover TQT study. The C_{max} for the supratherapeutic dose in the TQT study (400 mg rilzabrutinib and 200 mg BID of ritonavir) resulted in a C_{max} that is 0.8-fold the high clinical exposure. This difference in C_{max} is not considered significant considering the observed concentration-QTc findings. Data were analyzed using exposure-response analysis as the primary analysis, which showed concentration-dependent QTc shortening (section 4.5). The findings of the primary analysis are consistent with the by-time analysis (section 4.3).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>
• High clinical exposure: coadministration of a strong CYP3A4 inhibitor is anticipated to be 5-fold the clinical exposure (section 3.1).
• TQT study C_{max} is 589 ng/mL, which is 0.8-fold the high clinical exposure scenario.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>400 mg BID, oral tablets (highest therapeutic or clinical trial dosing regimen)</td><td>150 ng/mL</td><td>-4.4</td><td>(-5.0 to -3.8)</td></tr>
<tr><td>ΔΔQTcF</td><td>Coadministration of 400 mg rilzabrutinib with a strong CYP3A inhibitor (ritonavir) 100 mg</td><td>589 ng/mL</td><td>-9.2</td><td>(-11.0 to -7.3)</td></tr>
<tr><td>ΔΔQTcF</td><td>High clinical exposure scenario (400 mg BID + strong CYP3A4 inhibition)</td><td>750 ng/mL</td><td>-11.0</td><td>(-13.3 to -8.6)</td></tr>
</table>
</td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated nonclinical risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 Responses to Questions Posed by Applicant

Not applicable.

1.2 Comments to the Review Division

In this TQT study, rilzabrutinib was observed to shorten the QTc interval without changes in PR or QRS. This pattern of ECG changes is consistent with mexiletine, a Vaughan-Williams IB sodium channel blocker. If rilzabrutinib is a sodium channel blocker, then it could be associated with an increased proarrhythmic risk in patients with structural heart disease. Because the Applicant has not conducted experiments to elucidate the mechanism of the observed QTc shortening it is not possible to rule out that rilzabrutinib is a sodium channel blocker. If the Division wants to better understand the mechanism of the observed QTc shortening, then additional in vitro studies, such as a sodium channel assessment, could be considered.

2 RECOMMENDATIONS

Below are proposed edits to the label submitted to SDN 001 (link). Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

[redacted] (b) (4)

[redacted] (b) (4)

Reviewer's comment: *We propose to describe the observed concentration-dependent QTc shortening in section 12.2 and recommend inclusion of the predicted changes at therapeutic and high clinical concentrations. The Applicant did not include predictions for these two concentrations, and we therefore inserted our results in the proposed label.*

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant (Sanofi) is proposing rilzabrutinib (PRN1008/SAR444671), a tyrosine kinase inhibitor, for the treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response [redacted] (b) (4) to previous treatment.

The proposed therapeutic dose is 400 mg BID.

The Applicant initially proposed a two-part TQT study. The first part (Part A) was an [redacted] (b) (4) The second part (Part B) [redacted] (b) (4) We did not agree with this design and proposed a 5-way cross-over design. (DARRTS 04/05/2018)

The Applicant modified the design of both Parts A and B. Part A is now a 3-way cross-over with 400 mg, 1200 mg, and 100 mg plus 100 mg ritonavir. Part B is now a 4-way cross-over study with 400 mg, either 1200 mg or 100 mg plus ritonavir, moxifloxacin, and placebo. The sample size was also increased to 28 subjects. We agreed with the changes and proposed that the Applicant considered pre-specifying a plan to address increases in HR, should they be observed. (DARRTS 07/25/2018)

There were two additional revisions to the study protocol following our review, which did not alter the study significantly.

In the final study, the treatments were: rilzabrutinib 400 mg, rilzabrutinib 400 mg with 200 mg ritonavir (100 mg ritonavir with rilzabrutinib and 100 mg 12 hours later), placebo, or moxifloxacin 400 mg.

No significant effects of ritonavir are expected at the doses studied.[1]

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety (link).

Table 2. Summary of Dose and Exposure Assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	400 mg BID, oral tablets	150 ng/mL ($C_{max,ss}$)
Applicant's High clinical exposure scenario	5-fold increase with strong CYP3A4 inhibition	750 ng/mL
Highest dose in QT assessment	400 mg with 100 mg BID ritonavir.	589 ng/mL
C_{max} Ratio	589 / 750 ~ 0.8-fold	

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of rilzabrutinib on the hERG current in the study report (210222.TBU, link). The hERG current was assessed at near physiological temperature (35 - 37°C) using manual patch clamp assay using a step-ramp protocol every 5 seconds.

The positive control terfenadine (60 nM) inhibited hERG potassium currents by 80.1 ± 8.1 % (n=2).

Samples of the test article solutions collected from the outflow of the chamber were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of rilzabrutinib were within 15% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.

The hERG IC_{50} was 3.5 µM, which corresponds to a hERG safety margin of 124-fold (MW: 665.77 g/mol; PB: 97.5%) using the high clinical exposure scenario (Table 2).

The Applicant also evaluated the effects of rilzabrutinib on hERG in an automated patch clamp assay (130520.QSJ, link) at room temperature. Details of the voltage protocol were not provided. Precipitation was visible at the highest dose in the study 10 µM and the Applicant notes that it was detectable with TurboSol analysis. In this study, 34% inhibition was observed at 10 µM, which might be an underestimate due to drug loss. No inhibition was observed at 1 µM.

The precipitation observed at the high concentration (10 µM) in the automated QPatch experiment may be due to variations in the batch/lot numbers of the test drug, as batch

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[1] Sarapa et al. *Ritonavir 100 mg Does Not Cause QTc Prolongation in Healthy Subjects: A Possible Role as CYP3A Inhibitor in Thorough QTc Studies*. Clin Pharmacol Ther 2008;83(1):153-9

specific molecular weights of rilzabrutinib may vary from batch to batch due to the degree of hydration, which may impact the solvent volumes and solubility. In addition, hygroscopic DMSO has a significant impact on the solubility of rilzabrutinib, newly opened DMSO is recommended for making the stock solution of rilzabrutinib. It is not clear if the newly opened DMSO was used in the QPatch experiment.

The in vivo QT study (WIL-958004, link) assessed the effects of rilzabrutinib on ECG parameters following single oral doses to conscious telemetrized male dogs (n=4). The study included two phases: cardiorespiratory phase and a toxicokinetic phase. In the CR phase, doses were administered in a Latin square cross-over with approximate 3-day washout.

ECGs were collected continuously starting 1 hour prior to dosing and ending 24 h after dosing. The QT interval was corrected for heart rate using the Van de Water correction formula.

In the toxicokinetic phase, doses were administered in the same order within animal and PK was collected at serial post-dose time-points.

The free C_{max} of the highest dose in the study is 3760 ng/mL. The protein binding in dogs is 96%. The highest dose is therefore 8-times higher than the high clinical exposure (Table 2). No changes in QTc, HR, PR, or QRS were observed at the highest dose.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

Mean placebo-corrected ΔQTcF (ΔΔQTcF) was mostly negative after dosing with rilzabrutinib, with the largest (negative) ΔΔQTcF value of -10.2 ms at 2 hours post-dose on rilzabrutinib 400 mg plus ritonavir.

The primary analysis for rilzabrutinib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *Results from the reviewer's analysis are similar to the Applicant's results. Please see Section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

The results of the Applicant's analysis show that the study demonstrated assay sensitivity (lower bound at the geometric mean Cmax is >5 msec).

Reviewer's comment: *The reviewer's findings are consistent with those reported by the Applicant. Please see section 4.3.1.1 for details.*

3.2.1.1.1 QT Bias Assessment

Not performed.

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The reviewer's analysis has slightly different threshold for PR (>220 msec and 25% over baseline). The analysis also shows no significant outliers for QTc, HR, PR and QRS intervals.*

3.2.3 Exposure-Response Analysis

The Applicant used the model recommended in the white paper. Briefly, the Applicant modelled the relationship between ΔΔQTcF and rilzabrutinib concentration using the recommended linear mixed effect model with intercept, and random effects for intercept and C-QTc slope. The results of the Applicant's analysis show an absence of significant QTc prolongation. As stated in the Applicant's report, the estimated C-ΔΔQTcF slope was -0.01 ms per ng/mL (90% CI: -0.016, -0.0010), and the estimated intercept was -2.0 ms (90% CI: -3.25 to -0.82). Both the slope and the intercept were statistically significant at the 0.1 level.

Reviewer's comment: *The reviewer's model, and the Applicant's model both predicted upper bound of 90% CI of ΔΔQTc is below 10 msec at Cmax (See section 4.5).*

3.2.4 Safety Analysis

There were no serious AEs or AEs that resulted in discontinuation. None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 Evaluation of the QT/RR Correction Method

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG Assessments

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader in a blinded manner. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not performed.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. Since the unstructured covariance matrix did not converge for any of the analyses, the model also includes a compound symmetry covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The by-time ΔΔQTcF values by treatment are shown in Table 3. The minimum lower bound of ΔΔQTcF value was -12.8 msec observed at 2 hours post-dose on rilzabrutinib 400 mg plus ritonavir.

Figure 1. Mean and 90% CI of ΔΔQTcF Time-Course (Unadjusted CIs)

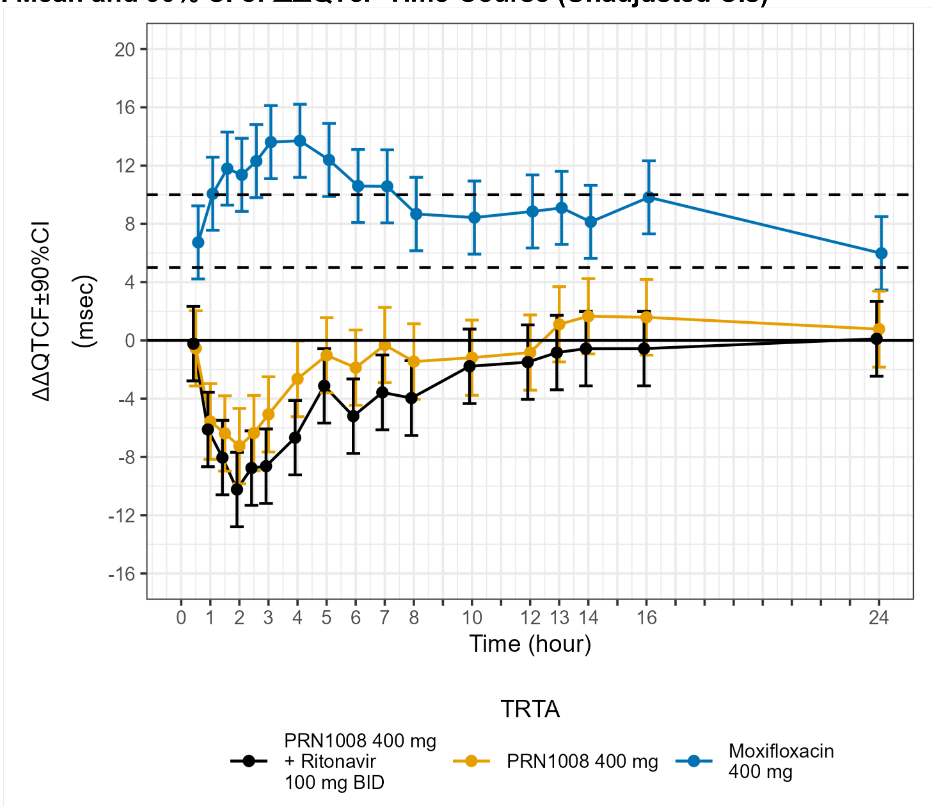


Table 3. Point Estimates and the 90% CIs for ΔΔQTcF at each timepoint.

Time (hour)	Treatment group							
	PRN1008 400 mg + Ritonavir 100 mg BID				PRN1008 400 mg			
	ΔQTCF		ΔΔQTCF		ΔQTCF		ΔΔQTCF	
	LSmean (msec)	LSmean placebo (msec)	Diff LS Mean (msec)	90.0% CI (msec)	LSmean (msec)	LSmean placebo (msec)	Diff LS Mean (msec)	90.0% CI (msec)
0.5	-3.4	-3.2	-0.2	-2.8, 2.3	-3.7	-3.2	-0.5	-3.1, 2.0
1.0	-6.7	-0.6	-6.1	-8.7, -3.6	-6.1	-0.6	-5.6	-8.2, -3.0
1.5	-9.4	-1.3	-8.0	-10.6, -5.5	-7.7	-1.3	-6.4	-9.0, -3.8

Treatment group								
Time (hour)	PRN1008 400 mg + Ritonavir 100 mg BID				PRN1008 400 mg			
	∆QTCF		∆∆QTCF		∆QTCF		∆∆QTCF	
	LSmean (msec)	LSmean placebo (msec)	Diff LS Mean (msec)	90.0% CI (msec)	LSmean (msec)	LSmean placebo (msec)	Diff LS Mean (msec)	90.0% CI (msec)
2.0	-10.8	-0.6	-10.2	-12.8, -7.7	-7.9	-0.6	-7.3	-9.8, -4.7
2.5	-10.0	-1.2	-8.8	-11.3, -6.2	-7.6	-1.2	-6.4	-8.9, -3.8
3.0	-10.1	-1.4	-8.6	-11.2, -6.1	-6.5	-1.4	-5.1	-7.7, -2.5
4.0	-8.6	-1.9	-6.7	-9.2, -4.1	-4.6	-1.9	-2.6	-5.2, -0.0
5.0	-9.7	-6.5	-3.1	-5.7, -0.6	-7.6	-6.5	-1.0	-3.6, 1.6
6.0	-14.3	-9.1	-5.2	-7.8, -2.6	-11.0	-9.1	-1.9	-4.5, 0.7
7.0	-13.8	-10.2	-3.6	-6.1, -1.0	-10.5	-10.2	-0.3	-2.9, 2.3
8.0	-12.4	-8.5	-4.0	-6.5, -1.4	-9.9	-8.5	-1.5	-4.0, 1.1
10.0	-7.6	-5.9	-1.8	-4.3, 0.8	-7.0	-5.9	-1.2	-3.8, 1.4
12.0	-7.6	-6.1	-1.5	-4.0, 1.1	-6.9	-6.1	-0.8	-3.4, 1.7
13.0	-6.4	-5.5	-0.8	-3.4, 1.7	-4.4	-5.5	1.1	-1.5, 3.7
14.0	-2.8	-2.3	-0.6	-3.1, 2.0	-0.6	-2.3	1.7	-0.9, 4.2
16.0	2.2	2.8	-0.6	-3.1, 2.0	4.3	2.8	1.6	-1.0, 4.2
24.0	-4.9	-5.0	0.1	-2.5, 2.7	-4.2	-5.0	0.8	-1.8, 3.4

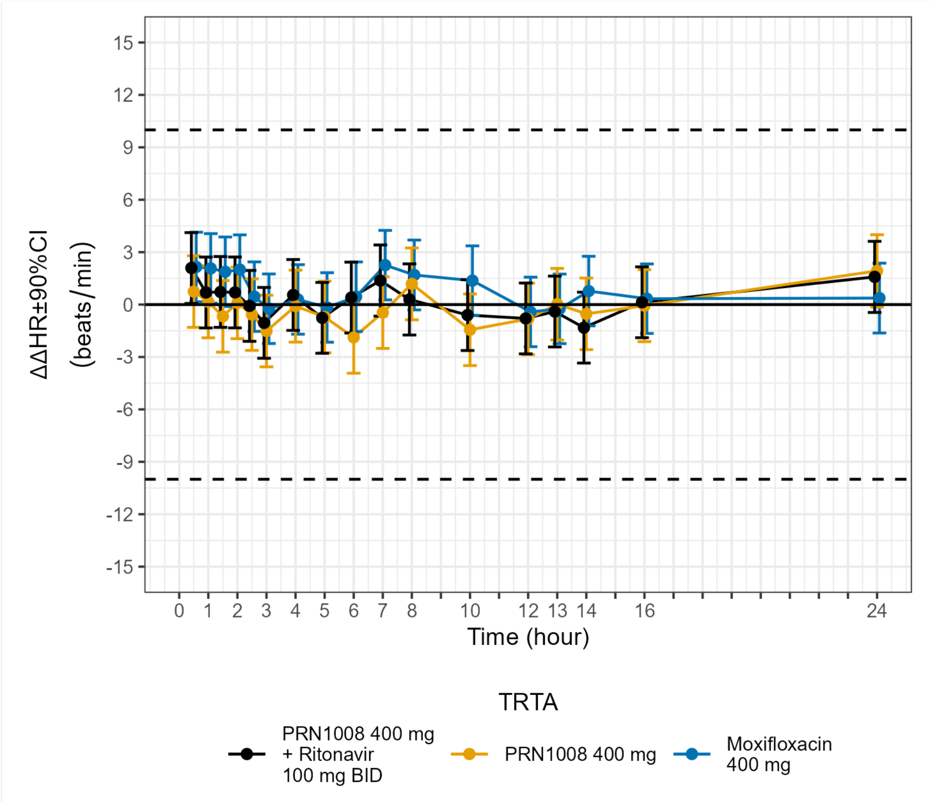
4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see section 4.5.1.1 for details.

4.3.2 HR

Figure 2 displays the time profile of ∆∆HR for different treatment groups.

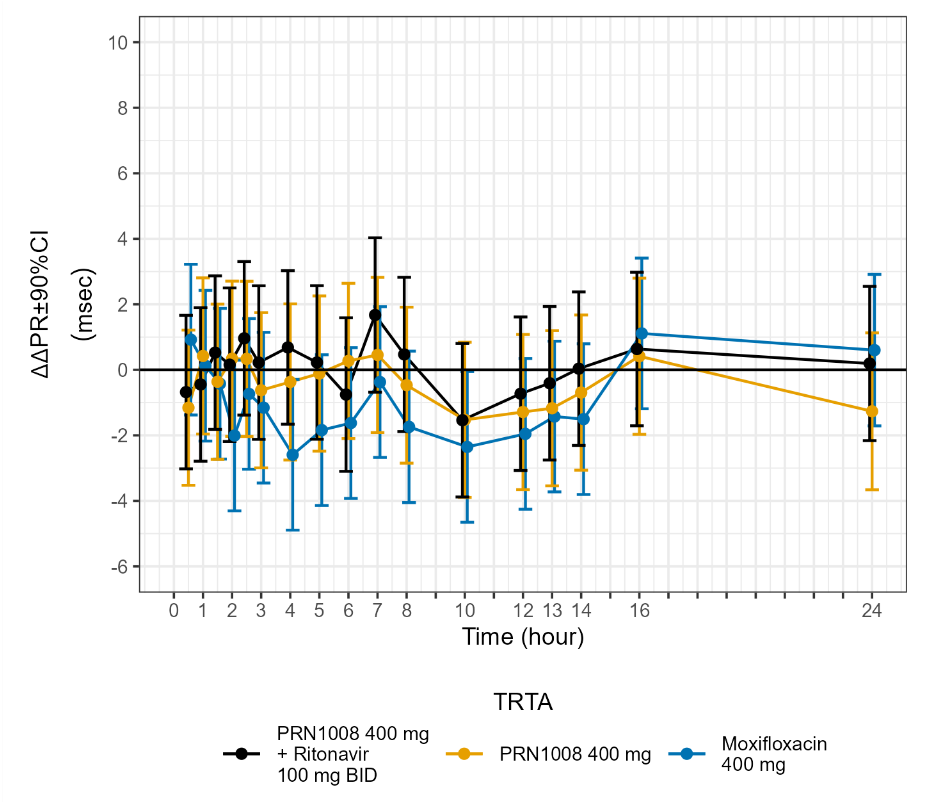
Figure 2. Mean and 90% CI of ΔΔHR Time-Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

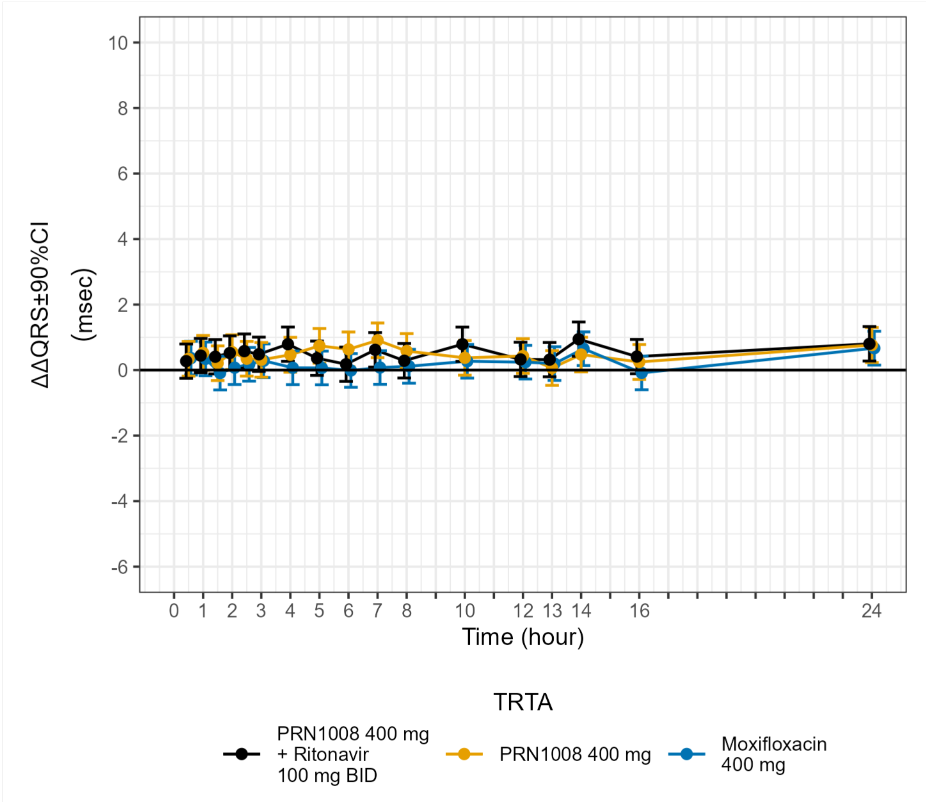
Figure 3. Mean and 90% CI of ΔΔPR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4. Mean and 90% CI of ΔΔQRS Time-Course



4.4 Categorical analysis

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects had QTcF value >480 msec. None of the subjects had ΔQTcF value >30 msec.

4.4.2 HR

None of the subjects had HR>100 beats/min.

4.4.3 PR

None of the subjects had PR value >220 msec.

4.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

4.5 Exposure-Response Analysis

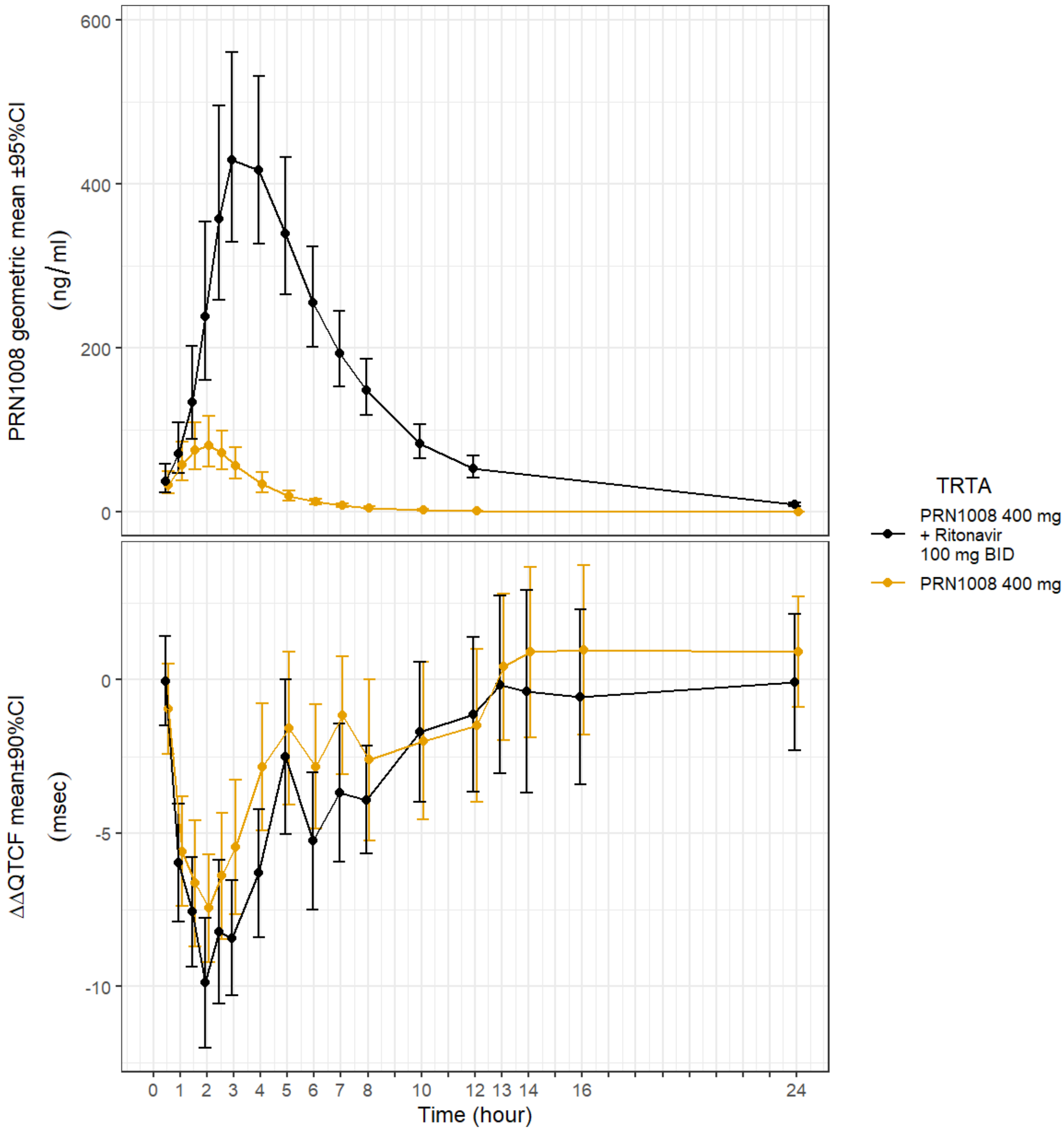
Exposure-response analysis was conducted using all subjects receiving rilzabrutinib 400 mg (n = 32) or rilzabrutinib 400 mg with ritonavir (n = 33) or placebo (n = 35) or moxifloxacin 400 mg (n = 36) who had baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with a 1-hour earlier QTc shortening relative to PRN1008 T_{max} (see Table 3). As the plot does not indicate significant difference between ΔΔQTcF at T_{max} and the mean maximum ΔΔQTcF (at 2-hours), the earlier QTc shortening is not likely to introduce significant bias in linear C-QTc relationship. Figure 6 shows the relationship between drug concentration and ΔQTcF and shows a slight deviation from linearity. The findings of the linear concentration-QTc analysis are consistent with the by-time analysis.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[2]



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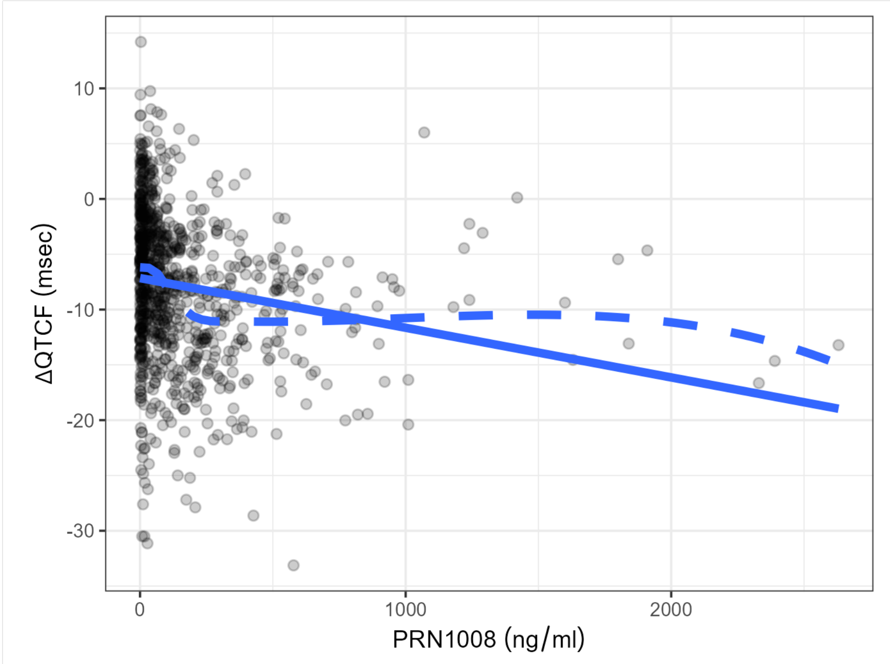
[2] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4. Findings from the C-QTc analysis indicate that rilzabrutinib is associated with QTc shortening at the recommended therapeutic dose.

Figure 7. Goodness-of-Fit Plot for QTcF

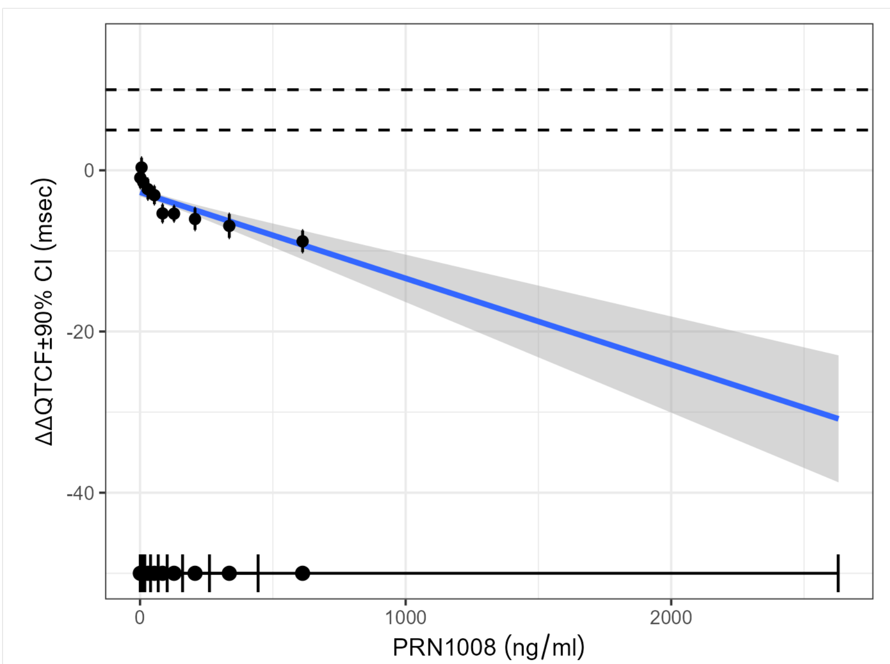


Table 4. Predictions From Concentration-QTcF Model

Actual Treatment	Rilzabrutinib (ng/ml)	ΔΔQTCF (msec)	90.0% CI (msec)
400 mg BID, oral tablets (Highest therapeutic or clinical trial dosing regimen)	150.0	-4.4	(-5.0 to -3.8)
Coadministration of 400 mg rilzabrutinib with a strong CYP3A inhibitor (ritonavir) 100 mg	589	-9.2	(-11.1 to -7.3)
High clinical exposure scenario (400 mg BID + strong CYP3A4 inhibition)	750	-11.0	(-13.3 to -8.6)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and ΔΔQTcF is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 9, and the predicted QTcF at the geometric mean C_{max} is listed in Table 5.

Figure 8. Time-Course of Moxifloxacin Concentration (Top) and QTcF (Bottom)

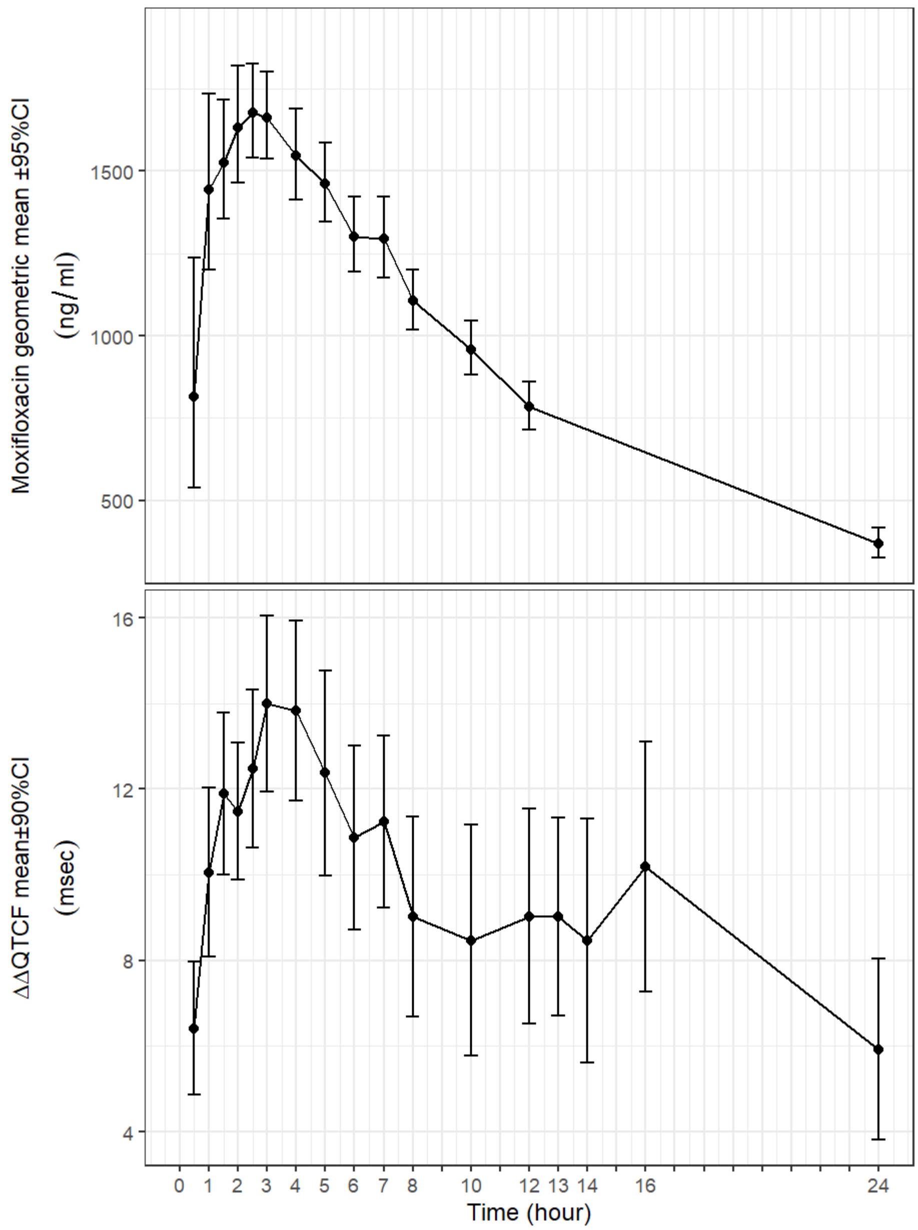


Figure 9. Goodness-of-Fit Plot of ΔΔQTcF for Moxifloxacin

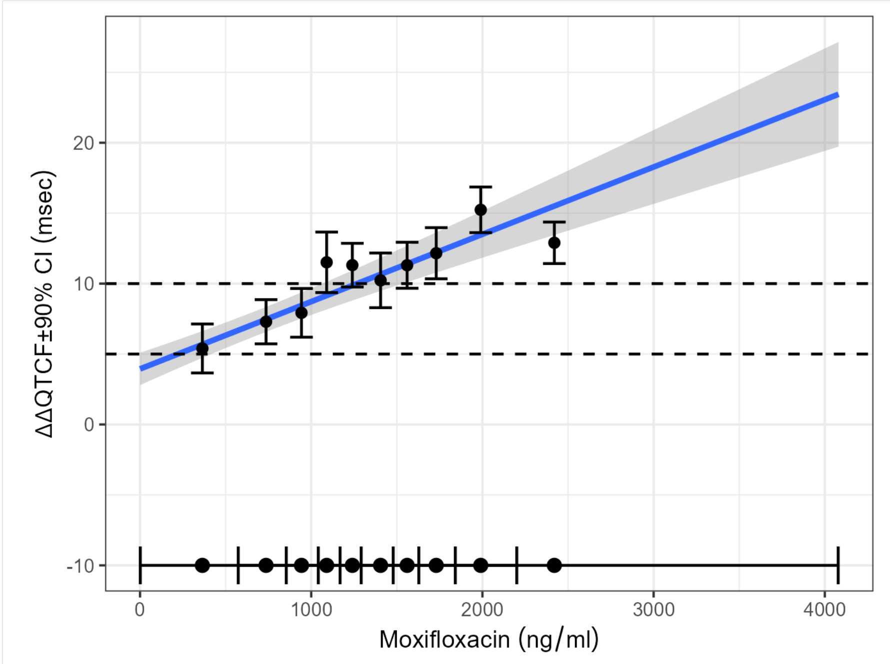


Table 5. Predictions From Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/ml)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	2,268.7	14.8	(12.9 to 16.8)

4.6 Safety assessments

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

The protocol was previously reviewed.

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/

XUTONG ZHAO
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MICHAEL Y LI
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LARS JOHANNESEN
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CHRISTINE E GARNETT
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