CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218436Orig1s000

OTHER REVIEW(S)

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

Date:	9/19/2025
Product Name(s):	Remibrutinib
Application Type/Number(s):	NDA
Submission Number:	218436
Sponsor/Applicant:	Novartis
NEXUS Task Tracking Tool ID #:	2025-16391
Reviewer(s):	Huei-Ting Tsai, PhD Division of Epidemiology II
Master Epidemiologist:	Natasha Pratt, PhD Division of Epidemiology II
Division Leadership:	Monique Falconer, MD Division of Epidemiology II
Sub-Office Director:	David Moeny, R.PH., MPH Office of Pharmacovigilance and Epidemiology
Sentinel Program Lead:	Patricia Bright, PhD

1. BACKGROUND INFORMATION

1.1. Medical Product

Remibrutinib (NDA 218436 by Novartis) is a selective inhibitor of Bruton's Tyrosine Kinase (BTK), belonging to the drug class of BTK inhibitor. It was proposed to be orally administrated 25 mg twice daily. Remibrutinib is a small molecular drug with 507.54 g/mol weight, is highly protein-bound (95.4%), and has a half-life 1 to 2 hours.

Remibrutinib is indicated for the treatment of adult patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite treatment with H1-antihistamine therapy. CSU affects 0.5-1% of the U.S. population, predominantly women aged 20-40 years. The condition is characterized by spontaneous, recurrent urticaria with or without angioedema lasting at least 6 weeks without identifiable cause. The first line treatments for CSU are second-generation H1-antihistamines, and H1- antihistamines plus omalizumab or dupilumab are second line therapies. However, women can remain symptomatic after H1-antihistamine and omalizumab therapy. Therefore, there can be remibrutinib-exposed pregnancies should pregnant women seek third line treatment for CSU.

BTK is an intracellular cytoplasmic tyrosine kinase expressed in key immune cells, such as mast cells, basophils, B-cells, macrophages, and thrombocytes. BTK plays a crucial role in signaling through IgE and- and IgG-mediated immune responses. Remibrutinib specifically inhibits mast cell and basophil degranulation by blocking IgE- and IgG-mediated FcεR1 activation, which prevents the release of histamine and other proinflammatory mediators that cause the characteristic symptoms of itching, hives, and angioedema in CSU patients.

1.2. Describe the Safety Concern

The safety concern for remibrutinib pregnancy exposure stems from three converging factors described below.

1. Potential exposure among pregnancy: CSU most commonly affects women aged 20-40 years when women are of reproductive potential. Therefore, we anticipate pregnancy exposure to remibrutinib. However, available clinical data from clinical trials is insufficient for risk assessment on the effect of remibrutinib on major birth defects, miscarriage, or other adverse maternal or fetal outcomes because only 5 out of 9 reported pregnancies during clinical trials had an outcome available, including 1 full term normal infant with a 12-month follow up, 1 full term healthy infant, 1 spontaneous abortion reported to be due to patients' risk factors, including obesity and use of oral contraceptives, and 2 elective abortions.

2. Class effect precedent: Other approved BTK inhibitors (ibrutinib, pirtobrutinib, zanubrutinib) have demonstrated embryo-fetal toxicity in animal studies at clinically relevant doses, with findings including visceral malformations, skeletal variations, and cardiac defects. For example, for ibrutinib, increased skeletal variations (fused sternebrae) was noted in rabbits at 2.8 times the human exposure.

3. Possible penetration across placenta: Remibrutinib has a small molecular weight (507.54

g/mol), which makes it likely to cross the placenta and result in fetal exposure.

Considering the potential for remibrutinib exposure among CSU patients during pregnancy, DPMH recommends issuing a postmarketing requirement (PMR) for a pregnancy registry and database study to address the regulatory gap of insufficient clinical data of remibrutinib use in pregnancy. The recommendation was based on two rationales: 1) animal reproduction studies in other BTK inhibitors have demonstrated embryofetal toxicity at clinically relevant doses and 2) remibrutinib is systemically absorbed and will likely be transferred to the fetus.

The requested pregnancy registry study will allow prospective monitoring of pregnancy and fetal outcomes among exposed women and may provide inferential information on the relationship between remibrutinib use and maternal and fetal outcomes. The complementary database study may allow the Agency to obtain the safety information more timely, before completion of the registry study in 2038. This approach balances access to an effective CSU treatment for women of reproductive potential while systematically collecting safety data to detect and quantify any pregnancy-related risks, ultimately informing evidence-based clinical decision-making and risk communication.

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

2.2. Regulatory Goal[1]

- ☐ 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*.

[1] 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.

☐ 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: *Click here to enter text.*

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	
☐ Exposures (and Comparators)	
☒ Outcomes	Performance of code-based algorithms for identifying the composite outcome of major congenital malformations (MCMs) in claim data sources has been reported to vary by database.[2,3] The positive predictive value of algorithms for composite MCMs was reported with a range between 44%-68% in a US commercial administrative database.[3] It is unclear how well code-based algorithms for composite MCM will perform in the Sentinel system. The request of outcome adjudication through medical charts allows the study to confirm the accuracy of a safety event and equips the study for evaluating pregnancy safety of remibrutinib. However, Sentinel does not have the capacity to

[2] Ishikawa T, Oyanagi G, Obara T, Noda A, Morishita K, Takagi S, Inoue R, Kawame H, Mano N. Validity of congenital malformation diagnoses in healthcare claims from a university hospital in Japan. Pharmacoepidemiol Drug Saf. 2021 Jul;30(7):975-978. doi: 10.1002/pds.5244. Epub 2021 Apr 16. PMID: 33835610.
[3] Chomistek AK, Phiri K, Doherty MC, Calderbank JF, Chiuve SE, McIlroy BH, Snabes MC, Enger C, Seeger JD. Development and Validation of ICD-10-CM-based Algorithms for Date of Last Menstrual Period, Pregnancy Outcomes, and Infant Outcomes. Drug Saf. 2023 Feb;46(2):209-222. doi: 10.1007/s40264-022-01261-5. Epub 2023 Jan 19. Erratum in: Drug Saf. 2023 May;46(5):515. doi: 10.1007/s40264-023-01280-w. PMID: 36656445; PMCID: PMC9981491.

	conduct chart review for outcome adjudication.
☒ Covariates	Several covariates relevant to pregnancy and infant outcomes, e.g. prior pregnancy complications, prior still birth or fetal growth restriction, and lifestyle risk factors, such as smoking, substance use etc., are either unavailable or incomplete in the Sentinel system.
☐ Analytic Tools	
Overall ARIA sufficiency determination	
☒ Insufficient ☐ Sufficient	We determine the Sentinel system is insufficient because it does not have the capacity to conduct chart review for outcome adjudication. The Sentinel system also does not have information on several important covariates for confounding control. Therefore, we request a registry study, which is not limited in confounding adjustment as it will be in a database study. We also request a complementary database study with capacity of outcome adjudication to obtain pregnancy safety information in a more timely manner before the completion of the pregnancy registry study in 2038.

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

Pregnancy Exposure Registry:
Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to remibrutinib during pregnancy with an appropriate comparator population(s). Collect data outside the U.S. to reach the target sample size, if feasible. The registry will identify and record major and minor congenital malformations, pregnancy complications, spontaneous abortion, stillbirths, neonatal deaths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes should be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Pregnancy Complementary Safety Study:
Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to remibrutinib during pregnancy compared to appropriate comparator population(s).

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PATRICIA L BRIGHT
09/26/2025 11:59:09 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	September 9, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 218436
Product Name, Dosage Form, and Strength:	Rhapsido (remibrutinib) tablet, 25 mg
Applicant Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	September 4, 2025
TTT ID #:	2025-13040-1
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Novartis Pharmaceuticals Corporation submitted revised container label and carton labeling received on September 4, 2025 for Rhapsido. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Rhapsido (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

Novartis Pharmaceuticals Corporation implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Shermock S. Review of Revised Label and Labeling for Rhapsido (NDA 218436). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAY 12. TTT ID: 2025-13040.

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DAMON A BIRKEMEIER
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VALERIE S VAUGHAN
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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:	September 9, 2025
To:	Phuong Nina Ton, PharmD Senior Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Rhapsido (remibrutinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 218436
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On January 31, 2025, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 218436/ New Molecular Entity for Rhapsido (remibrutinib) tablets, for oral use. This NDA proposes an indication for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1-antihistamine 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 Pulmonology, Allergy, and Critical Care (DPACC) on February 19, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Rhapsido (remibrutinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft Rhapsido (remibrutinib) PPI received on January 31, 2025, and received by DMPP and OPDP on August 28, 2025.
- Draft Rhapsido (remibrutinib) Prescribing Information (PI) received on January 31, 2025, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 28, 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.

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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MARY E CARROLL
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MARCIA B WILLIAMS
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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: September 8, 2025

To: Nina Ton, Regulatory Project Manager
Division of Pulmonology and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for RHAPSIDO® (remibrutinib) tablets, for oral use

NDA: 218436

Background:
In response to DPACC's consult request dated February 19, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for RHAPSIDO® (remibrutinib) tablets, for oral use.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 28, 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 will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the applicant to the electronic document room, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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/s/

QUYNH-NHU D CAPASSO
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: August 27, 2025 **Date consulted:** May 27, 2025

From: Abigail Melake, Data Analyst, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Leyla Sahin, MD, Deputy Director for Safety, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Pulmonology, Allergy and Critical Care (DPACC)

Drug: Remibrutinib

NDA: 218436

Applicant: Novartis

Subject: Pregnancy and Lactation Labeling

Indication: Chronic spontaneous urticaria (CSU)

Materials Reviewed:

- DPMH consult request from DPACC, dated May 2, 2025. DARRTS Reference ID: 5597711
- Applicant's submission to NDA 218436, dated January 31, 2025.
- Applicant's proposed labeling submitted to NDA 218436, dated January 31, 2025.

- Division of Nonmalignant Hematology consult review, dated June 25, 2025. DARRTS Reference ID: 5615321

Consult Question: We request DPMH review Sections 8.2 and 8.3, specifically the advice about breastfeeding and contraception, and confirm the language follows current labeling recommendations.

INTRODUCTION AND BACKGROUND

On January 31, 2025, the applicant (Novartis) submitted a 505(b)(1) New Drug Application (NDA) for remibrutinib. The Division of Pulmonology, Allergy and Critical Care (DPACC) consulted the Division of Pediatrics and Maternal Health (DPMH) on May 27, 2025, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- The applicant submitted NDA 218436 for remibrutinib, a selective oral inhibitor of Bruton's Tyrosine Kinase (BTK), for the treatment of adult patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite treatment with H1-antihistamine treatment. BTK is a cytoplasmic tyrosine kinase and member of the TEC[1] kinase family and is expressed in selected cells of the adaptive and innate immune system, including mast cells, basophils, macrophages, B cells and thrombocytes. BTK appears to play a role for signaling through the FcεR1 for IgE and the activating FcγR for IgG, as well as the B cell antigen receptor. BTK inhibition also appears to block mast cell and basophil activation/degranulation *in vitro* and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated diseases.
- Other BTK inhibitors that have been approved by the FDA include acalabrutinib, ibrutinib, pirtobrutinib and zanubrutinib and are indicated to treat malignancies, including mantle cell lymphoma, chronic lymphocytic leukemia, Waldenström's macroglobulinemia, chronic graft versus host disease, marginal zone lymphoma, and follicular lymphoma. DPMH MHT was consulted to comment on the benzyl alcohol content of ibrutinib. Otherwise, DPMH MHT was not consulted to review these drug products.
    - The labelings for ibrutinib, pirtobrutinib and zanubrutinib contain Warnings and Precautions (W&P) for embryo-fetal toxicity based on animal data.
        - For ibrutinib, the embryo-fetal development (EFD) study findings included visceral malformations (heart and major vessels), increased resorptions and post-implantation loss in rats and skeletal variations (fused sternebrae) in rabbits at 20 times and 2.8 times, respectively, the human exposure.
        - For pirobrutinib, the EFD study findings included decreased fetal weights, malformations of the urinary tract (absent or abnormal ureters and kidneys) and variations of the reproductive tract (malpositioned ovaries and misshapen uterus) and bone (misshapen sternebrae) in rats at 3 times the human exposure.
        - For zanubrutinib, the EFD study findings included malformations of the heart (2 or 3-chambered hearts) at 5 times the human exposure. In the pre- and post-

[1] TEC stands for "tyrosine kinase expressed in hepatocellular carcinoma" and is a class of tyrosine kinases that play a role in the immune system and development of blood cells.

natal development (PPND) study, adverse ocular findings (cataract and protruding eye) occurred in rats at approximately 5 times the human dose.

- The labeling for acalabrutinib does not contain a Warnings and Precautions for embryo-fetal toxicity; however, under Use in Specific Populations, it states, "May cause fetal harm and dystocia." Dystocia (prolonged or difficult labor) was observed in rats in the PPND study at approximately 2 times the human dose. Underdeveloped renal papilla were also observed in rats at approximately 5 times the human dose.
- The labelings for all approved BTK inhibitors advise against breastfeeding due to the potential for adverse reactions such as hemorrhage, infections, cytopenias, secondary malignancies, cardiac arrhythmias, and hepatotoxicity.

Drug Characteristics[2]

Drug Class	Bruton's tyrosine kinase inhibitor
Proposed mechanism of action	(b) (4)
	Remibrutinib inhibits mast cell and basophil degranulation mediated by pathogenic IgE or IgG directed against the FcεR1 or IgE. (b) (4)
	(b) (4)
Proposed dosage form and administration	25 mg orally twice daily
Molecular weight	507.54 g/mol
Half-life	1 to 2 hours
% protein bound	95.4%
Drug-drug interactions	(b) (4)

Current State of the Labeling

There is no current labeling as this is a new drug application that has not been previously approved.

[2] Proposed remibrutinib labeling with input from the DPACC review team

REVIEW
PREGNANCY

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is a condition characterized by spontaneous and recurrent urticaria, with or without angioedema, for at least 6 weeks duration without an identifiable cause.[3] CSU is different from urticaria that occurs secondary to a known trigger or underlying disease, such as chronic inducible urticaria, hereditary angioedema, vasculitis or mastocytosis. The pathophysiology of CSU is not fully understood but thought to be primarily driven by mast cell activation and degranulation with IgE and IgG mechanisms that lead to the release of histamine and other inflammatory mediators.[4,5] These mediators cause itching, swelling and redness.

CSU is characterized by urticarial lesions that have three typical features: central swelling with surrounding erythema, pruritus and each lesion lasts for a short period of time (30 minutes to 24 hours) without residual scarring or bruising of the skin. Angioedema, when present, manifests as episodic submucosal or subcutaneous swelling, often affecting areas of the body with loose connective tissue in an asymmetric pattern. Some patients report systemic symptoms such as headache, fatigue, malaise, pain or swelling of joints, wheezing, flushing, gastrointestinal symptoms, muscle or bone pain, and palpitations.[6,7]

CSU affects 0.5% to 1% of the general U.S. population and most commonly affects women than men. Most patients that develop CSU are between the ages of 20 and 40 years, although it can affect all age groups. CSU is a self-limited disorder that lasts an average of 2 to 5 years.[8,9] However, CSU significantly impacts quality of life by affecting sleep, causing fatigue and affecting work productivity. In one survey, approximately 70% of CSU patients reported mild-to-severe anxiety and depression. In another survey, 1 out of 5 CSU patients reported missing at least one hour of work in one week.[10,11]

Disease Management and Current Treatment Options

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[3] Zuberbier, Torsten et al. "The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria." Allergy vol. 77,3 (2022): 734-766. doi:10.1111/all.15090

[4] Min TK, Saini SS. Allergy Asthma Immunol Res. 2019;11(4):470–481. doi:10.4168/aair.2019.11.4.470

[5] Maurer M, Eyerich K, Eyerich S, et al. Int Arch Allergy Immunol. 2020;181(5):321–333. doi:10.1159/000507218

[6] Doong JC, Chichester K, Oliver ET, Schwartz LB, Saini SS. Chronic Idiopathic Urticaria: Systemic Complaints and Their Relationship with Disease and Immune Measures. J Allergy Clin Immunol Pract. 2017;5(5):1314-1318. doi:10.1016/j.jaip.2016.11.037

[7] Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcepsilonRI or anti-IgE autoantibodies. J Am Acad Dermatol. 1999;40(3):443-450. doi:10.1016/s0190-9622(99)70495-0

[8] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. Allergy. 2011;66(3):317-330. doi:10.1111/j.1398-9995.2010.02496.x

[9] Stepaniuk, P, M Kan, and A Kanani, 2020, Natural history, prognostic factors and patient perceived response to treatment in chronic spontaneous urticaria, Allergy Asthma Clin Immunol, 16:63.

[10] Maurer M, Abuzakouk M, Bérard F, et al. Allergy. 2017;72(12):2005–2016. doi:10.1111/all.13209.

[11] Balp M-M, Krupsky K, Balkaran BL, et al. Oral presentation at: European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2023; June 9–11, 2023; Hamburg, Germany.

CSU may be managed by taking antihistamines; however, approximately 25% of patients remain symptomatic despite increasing doses of antihistamines.[12] For patients with CSU that is inadequately controlled with antihistamines, guidelines recommend treatment with omalizumab or dupilumab. However, up to 30% of individuals with CSU may remain symptomatic despite antihistamine and omalizumab use.

CSU and Pregnancy

The impact of pregnancy on CSU and chronic inducible urticaria was examined in an international questionnaire study of 288 pregnancies that found that just over one-half of respondents believed their urticaria improved during pregnancy. The mean duration of chronic urticaria was seven years, and 67% of patients had CSU. During pregnancy, symptoms improved in 51% of patients, worsened in 29% of patients , and there was no change in symptoms in 20% of patients. After giving birth, 44% patients noted that their disease activity remained unchanged compared with during pregnancy. Patients with more than one pregnancy reported similar changes during each pregnancy.[13]

Nonclinical Experience

In an embryo-fetal development (EFD) study in pregnant rabbits, remibrutinib was administered orally at doses of 100, 300, and 450 mg/kg/day during the period of organogenesis. Increased fetal external malformations (e.g., open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (transiently reduced food consumption and adverse clinical signs) occurred at 300 mg/kg/day (141-times the MRHD based on AUC). The fetal findings were considered unlikely to be secondary to the maternal toxicity. The dose of 450 mg/kg/day was not tolerated by the pregnant rabbits.

In an EFD study in pregnant rats, remibrutinib was administered orally at doses of 100, 300, and 1000 mg/kg/day during the period of organogenesis. Remibrutinib did not cause adverse effects to the fetus at exposures up to 126 times that at the MRHD based on AUC.

In a pre- and postnatal development (PPND) study, remibrutinib was administered orally to pregnant rats at doses of 100, 300, and 1000 mg/kg/day from gestation day 6 to lactation day (LD) 21. Remibrutinib induced adverse effects at 1000 mg/kg/day (approximately 194 times the MRHD based on body surface area [BSA]), affected maternal animals (moribundity and clinical signs of toxicity, slightly longer gestation lengths) and offspring up to LD1 (slightly higher mean number of stillborn, dead, or missing pups, and smaller mean litter size). No adverse effects at doses up to 1000 mg/kg/day were noted in the surviving offspring developing into adulthood. No effects were observed at 300 mg/kg/day (approximately 58 times the MRHD based on BSA).

The reader is referred to the Pharmacology/Toxicology (PharmTox) review by Dr. Edward Dougherty.

[12] Kaplan A, Lebwohl M, Giménez-Arnau AM, Hide M, Armstrong AW, Maurer M. Allergy. 2023;78(2):389–401. doi:10.1111/all.15603

[13] Kocatürk E, Al-Ahmad M, Krause K, et al. Effects of pregnancy on chronic urticaria: Results of the PREG-CU UCARE study. Allergy. 2021;76(10):3133-3144. doi:10.1111/all.14950

Reviewer comment: DPMH discussed the animal studies with the PharmTox team to clarify the conclusions of the animal reproduction studies submitted by the applicant because the adverse developmental effects occurred at greater than 100 times the maximum recommended human dose in both rabbits and rats. PharmTox explained that the safety margins for remibrutinib are large compared to other approved BTK inhibitors. Additionally, remibrutinib's lack of embryo-fetal toxicity findings may be due to its increased specificity compared to other BTK inhibitors. While remibrutinib inhibits BTK and BTK-related kinases, TEC and BMC, at higher concentrations, the other BTK inhibitors, which have been associated with embryo-fetal toxicity findings, inhibit other kinases including ITK[14], BMX[15], EGFR[16] and JAK3[17]. DPMH and PharmTox agreed to remove the statement in subsection 8.1 Pregnancy of the proposed labeling that recommends (b) (4)

Clinical Data[18,19]

The applicant excluded pregnant and lactating women from the remibrutinib phase 3 clinical trials. Women of childbearing potential were also excluded from the clinical trial unless they were using effective contraceptives (including oral contraceptives) during dosing and for 7 days after stopping of study treatment.. Male contraception was not required by the applicant. Women of child-bearing potential were informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agreed that to participate in the study, they must adhere to the contraception requirements.[20] The applicant also provided Pregnancy Outcomes Reporting Consent forms for female participants who took the study treatment.

The applicant reported nine pregnancies, with outcomes available in five pregnancies. Four pregnancies occurred in three ongoing studies, and five pregnancies occurred in four completed studies. As per the study protocols, treatment was discontinued when pregnancy was discovered.[21] The following pregnancy outcomes were observed:

- Full term normal infant with a normal 12-month follow-up
- Full term healthy infant
- A 33-year-old patient on oral contraceptive became pregnant six months after starting remibrutinib. She had a spontaneous abortion, but the event was not reported as related to study treatment due to the patient's risk factors including obesity and use of oral contraceptives.
- Two elective abortions during the first trimester due to "patient decision." No further information was provided.

Review of Literature

Applicant's review:

[14] ITK: Interleukin-2-inducible T-cell Kinase
[15] BMX: Bone marrow X-linked kinase
[16] EGFR: Epidermal Growth Factor Receptor
[17] JAK3: Janus Kinase 3 Inhibitors
[18] NDA 218436 SN0000, Module 5.2, Protocol, p. 42
[19] NDA 218436 SN0000, Module 2.5, Clinical Overview, p. 61
[20] NDA 218436 SN0000, Module 5.2, Protocol, p. 55
[21] NDA 218436 SN0000, Module 2.7, Summary of Clinical Safety, p. 128

The applicant did not provide a review of published literature of remibrutinib use during pregnancy.

DPMH Review:
Due to lack of access to some resources, only a limited literature review was possible. DPMH conducted a review of published human studies in PubMed and Embase using the following search terms: "Bruton's tyrosine kinase inhibitor" OR "BTK inhibitor" AND "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," "spontaneous abortion," "safety," "embryotoxic," AND "reprotoxic." No relevant publications were found.

Reviewer comment: There is no available data from published literature to inform the use of remibrutinib during pregnancy.

LACTATION
Nonclinical Experience
The applicant reported that adverse findings in rats related to reproductive and developmental toxicity were limited to effects affecting maternal animals and offspring (up to Lactation Day 1) in the pre- and postnatal developmental (PPND) study at the high dose of 1,000 mg/kg/day.[22] There were no animal lactation studies conducted with remibrutinib.

Clinical Data
There were no cases of remibrutinib exposure during lactation in the clinical drug development program.

Review of Literature
Applicant's review:
The applicant did not provide a review of published literature of remibrutinib use during lactation. The applicant noted that it is not known if remibrutinib is transferred into human milk after administration. There are no data on the effects of remibrutinib on the breastfed child or on milk production.

DPMH review:
DPMH conducted a search for published human studies in PubMed, using the search terms: "Bruton's tyrosine kinase inhibitor" OR "BTK inhibitor" AND "lactation" OR "breastfeeding." No publications were found.

Reviewer comment:
There are no clinical data or literature sources to inform remibrutinib use during lactation. The available information from LactMed for the approved BTK inhibitors is not applicable to remibrutinib. DPMH discussed the breastfeeding recommendations with the Clinical Team via email on August 7, 2025. Although it is likely that remibrutinib will transfer to human milk based on the drug's characteristics, remibrutinib does not have the same adverse event profile as other BTK inhibitors, and there are no significant adverse events that have been seen in adults that would suggest risk in the exposed breastfed infant.[23]

[22] NDA 218436, SN000, Module 2.7.4, Summary of Clinical Safety, p.128
[23] Communication with the Clinical Pharmacology Team, July 24, 2025.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The applicant reported no adverse effects were observed in rats in the combined male and female fertility and early embryonic development (FEED) study or in the embryo-fetal development (EFD) study up to the highest tested dose of 1,000 mg/kg/day, or up to 79 times (females) and 15 times (males) the maximum recommended human dose.[17]

Review of Literature

Applicant's review:

The applicant did not provide a review of published literature of remibrutinib and its effects on males or females of reproductive potential.

DPMH review:

DPMH conducted a literature search for studies in humans in PubMed, using the search terms "Bruton's tyrosine kinase inhibitor" OR "BTK inhibitor" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant information was found.

Reviewer comment:

There are no available clinical data or literature sources to inform the use of remibrutinib in males and females of reproductive potential.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available clinical data with use of remibrutinib during pregnancy from clinical trials are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. EFD studies in pregnant rabbits demonstrated fetal external malformations (open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity at 141 times the MRHD based on AUC with no findings observed in rats at 126 times the MRHD based on AUC. Based on discussions with the Pharmacology-Toxicology Team, the animal findings are not clinically relevant because the safety margins for remibrutinib are large compared to other approved BTK inhibitors. Additionally, remibrutinib's lack of embryo-fetal toxicity findings may be due to its increased specificity for BTK-related kinases (TEC and BMC) at higher concentrations compared to other BTK inhibitors, which have associated embryo-fetal toxicity findings, that inhibit other kinases including ITK, BMX, EGFR, and JAK3. DPMH does not recommend including language in Warnings and Precautions for embryo-fetal toxicity but agrees with including the nonclinical data in subsection 8.1 "Risk Summary" and "Data-Animal Data."

DPMH recommends including a statement on the U.S. background risk of major birth defects and miscarriage at the end of the "Risk Summary" in subsection 8.1, per the Pregnancy and Lactation Labeling Rule.

CSU affects females of reproductive potential, and there is the potential for remibrutinib exposure during pregnancy. DPMH recommends issuing a postmarketing requirement (PMR) for a pregnancy registry and database study for the following reasons: 1.) Although animal

reproduction studies with remibrutinib suggested malformations at high dose multiples, animal reproduction studies in other drugs in the class have demonstrated embryofetal toxicity at clinically relevant doses. 2.) Remibrutinib is systemically absorbed and will likely be transferred to the fetus.

Lactation

There are no nonclinical or clinical data on the presence of remibrutinib in animal and human milk, respectively. There are no clinical data about the effects of remibrutinib on the breastfed infant or on milk production. Based on remibrutinib's characteristics, transfer of remibrutinib into human milk is likely. However, remibrutinib does not have the same adverse event profile as other BTK inhibitors, and there are no significant adverse events that have been seen in adults taking remibrutinib that would suggest risk in the exposed breastfed infant. Therefore, DPMH recommends including the standard developmental benefit/risk statement in subsection 8.2 of labeling as follows:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

CSU affects females and reproductive potential, and there is the potential for remibrutinib use during lactation. DPMH recommends a PMR for a clinical lactation study for the following reason: based on the drug's characteristics, it is likely that remibrutinib will be present in human milk.

Females and Males of Reproductive Potential

DPMH does not recommend including subsection 8.3 in labeling because there are no concerns for embryofetal toxicity when remibrutinib is used at clinically relevant doses. Additionally, there are no concerns for infertility based on animal fertility studies.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on July 8, 2025. DPMH recommendations are below and reflect the discussions with DPAAC. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

[redacted]

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

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The Clinical Inspection Summary

Date	August 4, 2025
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Katherine Clarridge, M.D., Clinical Reviewer, DPACC Stacy Chin, M.D., Team Leader, DPACC Nina Ton Phuong, Senior Regulatory Project Manager, DPACC Division of Pulmonology, Allergy, and Critical Care (DPACC)
NDA #	218436
Applicant	Novartis Pharmaceuticals Corp.
Drug	Rhapsido (remibrutinib)
NME (Yes/No)	Yes
Proposed Indication(s)	Chronic spontaneous urticaria
Consultation Request Date	March 19, 2025
Summary Goal Date	August 28, 2025
Action Goal Date	September 30, 2025
PDUFA Date	September 30, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Anderson, Gogate, Palumbo, and Tarpay were inspected in support of NDA 218436, covering two studies: CLOU064A2301 and CLOU064A2302. Based on the results of the inspections, the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites generally appear acceptable in support of the respective indication. However, several unreported protocol deviations were identified at Dr. Gogate's site, including the inappropriate enrollment and randomization of one subject to remibrutinib who had received omalizumab 33 days before randomization, violating exclusion criteria seven which states that subjects were to be excluded if they took omalizumab within four months of randomization. Another subject was inappropriately enrolled and randomized to placebo despite being on Excedrin as needed for migraines, containing acetylsalicylic acid that exceeded the 100 mg/day limit specified in exclusion criteria 19. These unreported protocol deviations did not cause harm to any subjects and are unlikely to impact the study's efficacy or safety results.

II. BACKGROUND

According to the sponsor, Rhapsido (remibrutinib) is a selective oral Bruton's tyrosine kinase (BTK) inhibitor. The sponsor submitted this application for treatment of chronic spontaneous

urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. The Sponsor submitted two pivotal studies consisting of two replicate studies: CLOU064A2301 and CLOU064A2302. Four BIMO Review-Based clinical investigator inspections were requested. The following describes the two studies:

Protocol CLOU064A2301: "A multicenter, randomized, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety, and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines."

The study was a randomized, double-blind, placebo-controlled, multi-center study to demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU with respect to change from baseline in Weekly Urticarial Activity Score (UAS7), Weekly Itch Severity Score (ISS7), and Weekly Hives Severity Score (HSS7) at Week 12.

Sites: Subjects were randomized in 18 countries and included Argentina (9 centers), Australia (3 centers), Bulgaria (3 centers), Colombia (4 centers), Czech Republic (4 centers), France (6 centers), Hungary (3 centers), India (10 centers), Italy (4 centers), Japan (7 centers), South Korea (10 centers), Mexico (3 centers), Russia (1 center), Singapore (1 center), Spain (7 centers), Taiwan (2 centers), Turkey (9 centers), and United States (30 centers).

Subjects: A total of 470 subjects were randomized (i.e., 157 received placebo, 313 subjects received remibrutinib), and 376 subjects completed the study (i.e., 124 who received placebo, 252 subjects who received remibrutinib).

Study initiation and completion dates: November 30, 2021 (date first subject, first visit); January 19, 2024 (date last subject, last visit)

Database lock date; study unblinding date: February 23, 2024; February 27, 2024

This study included an up to a 4-week screening period, 24-week double-blind treatment period, 28-week open-label treatment period, and 4-week follow-up period. Subjects with CSU were randomized 2:1 to receive remibrutinib 25 mg twice daily or placebo. All subjects were on a stable second generation H1-antihistamine throughout the entire study.

Key inclusion criteria: Male and female subjects ≥18 years of age with CSU for ≥6 months prior to screening and inadequately controlled by second generation H1-antihistamines at the time of randomization. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Absolute change in Weekly Urticarial Activity Score (UAS7), Weekly Itch Severity Score (ISS7), and Weekly Hives Severity Score (HSS7) at Week 12

The UAS7 is a composite of ISS7 and HSS7 and assesses the severity of itch and number of hives reported by the subject over a period of seven days. Each day, subjects scored the number of hives they experience and their severity of itch twice daily in their eDiary on a scale from zero to three. The daily itch severity and number of hives scores are added together to get

a daily Urticaria Activity Score (UAS). The UAS7 is then calculated by summing the daily UAS scores over seven days. The baseline weekly score is derived by adding up the average daily scores of the seven days preceding the randomization date; Week 12 weekly score is derived by adding up the average daily scores from Day 78 to Day 84 from randomization. Higher scores reflect greater disease activity.

Protocol CLOU064A2302: "A multicenter, randomized, double-blind, placebo-controlled Phase 3 study of remibrutinib (LOU064) to investigate the efficacy, safety, and tolerability for 52 weeks in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines"

The study was a Phase 3 randomized, double-blind, placebo-controlled, multi-center study to demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU with respect to change from baseline in UAS7, ISS7, and HSS7 at Week 12.

Sites: Subjects were randomized in 18 countries including Austria (1 center), Brazil (1 center), Canada (8 centers), China (16 centers), Denmark (2 centers), Germany (18 centers), India (10 centers), Malaysia (5 centers), Poland (5 centers), Russia (5 centers), Slovakia (4 centers), South Africa (3 centers), Switzerland (3 centers), Taiwan (2 centers), Thailand (4 centers), United Kingdom (3 centers), United States (30 centers), and Vietnam (2 centers).

Subjects: A total of 455 subjects were randomized (i.e., 155 subjects received placebo, 300 subjects received remibrutinib), and 388 subjects completed the double-blind treatment Period (i.e., 129 who received placebo, 259 subjects who received remibrutinib).

Study initiation and completion dates: December 1, 2021 (date first subject, first visit); January 5, 2024 (date of last subject, last visit)

Database lock date; study unblinding date: February 14, 2024; February 16, 2024

CLOU064A2301 and CLOU064A2302 had similar study designs.

Primary efficacy endpoint: Absolute change in UAS7, ISS7, and HSS7 at Week 12

III. RESULTS (by site):

1. **Dr. John Anderson**
   504 Brookwood Blvd
   Suite 250
   Birmingham, AL, 35209-6802
   Protocol CLOU064A2301, Site 5001
   PDUFA Inspection Dates: May 12-15, 2025

For Protocol CLOU064A2301, five subjects were screened, four subjects were enrolled and randomized, and three subjects completed the study. One subject withdrew from the study.

An audit of the study records was conducted for all four randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, informed consent forms, subject records, medical histories, adverse event reports, concomitant medications, laboratory reports, investigational product storage area and shipment records, institutional review board and monitor correspondence, training records, financial disclosure statements, and electronic source records for verification of primary efficacy endpoint.

The daily values for the Hives Severity Score (HSS) and Itchy Severity Score (ISS) were verified by comparing the scores reported in the electronic source documents against the sponsor's subject data line listings during the seven days preceding the Baseline and Week 12 visits. No discrepancies were noted. There was no underreporting of adverse events.

2. **Dr. Shaila Gogate**
   125 Rampart Way
   Suite 100
   Denver, CO 80230-6429
   Protocol CLOU064A2301**,** Site 5007
   PDUFA Inspection Dates: April 15-24, 2025

For Protocol CLOU064A2301, 19 subjects were screened, 14 subjects were enrolled and randomized, and 10 subjects completed the study. Subject (b) (6), randomized to remibrutinib, was discontinued due to adverse event of exacerbation of hives. One subject was lost to follow up. Two subjects were transferred to another site.

Study records were reviewed for all 19 screened subjects. Records reviewed included, but were not limited to, protocol and amendments, regulatory files, financial disclosure, Institutional Review Board approval, delegation of study personnel, training, drug accountability, monitoring, eligibility, informed consent forms, laboratory sample collection, concomitant medications, protocol deviation reporting, adverse event reporting, and electronic source records for verification of primary efficacy endpoint.

Subject (b) (6) was inappropriately enrolled after receiving omalizumab on (b) (6) According to exclusion criteria 7, subjects were to be excluded if they took omalizumab within four months of randomization. Per the eligibility form, this subject received the first dose of remibrutinib on (b) (6). Per the progress notes and treatment record, this subject received an injection of Xolair (omalizumab) for chronic urticaria on (b) (6), at 1:00 p.m. Then, on (b) (6), it was documented in a progress note that the "Patient now enrolled in study, so no further Xolair being administered for now." Subject (b) (6) completed the study through Week 52.

Reviewer's comment: Subject (b) (6) *was ineligible for enrollment but was randomized to remibrutinib. This protocol deviation was not documented in the sponsor's subject data line listings or in the list of concomitant medications. While prior omalizumab treatment could potentially confound remibrutinib efficacy assessment, this single subject who received 300 mg*

omalizumab 33 days before study treatment is unlikely to meaningfully affect the overall efficacy results.

Subject (b) (6) was inappropriately enrolled despite being on Excedrin as needed for migraines, which contains acetylsalicylic acid exceeding the 100 mg/day limit specified in exclusion criteria 19.

Reviewer's comment: Remibrutinib is a Bruton's tyrosine kinase inhibitor and reported to have a low rate of bleeding events. Subject (b) (6) was enrolled despite being on Excedrin which contains 250 mg of acetylsalicylic acid. This medication was not reported as a concomitant medication or protocol deviation in the sponsor's data line listings. This subject was randomized to placebo with no evidence of harm.

Subjects (b) (6) did not receive required FSH screening tests as specified by protocol for all female subjects who did not have medical documentation of bilateral oophorectomy or 12 months of amenorrhea.

Reviewer's comment: Both subjects lacked the medical documentation required per protocol. Subject (b) (6) was a 48-year-old female randomized to remibrutinib who reported abstinence, and Subject (b) (6) was a 48-year-old female randomized to placebo who reported taking oral contraceptives for birth control. Despite these unreported protocol deviations, no subject harm occurred, and home pregnancy tests remained negative throughout the study for both participants.

The daily values for the Hives Severity Score (HSS) and Itchy Severity Score (ISS) were verified by comparing the scores reported in the electronic source documents against the sponsor's subject data line listings during the seven days preceding the Baseline and Week 12 visits. No discrepancies were noted. There was no underreporting of adverse events.

3. **Dr. Michael Palumbo**
   180 Fort Couch Road
   Suite 375
   Pittsburgh, PA 15241-1041
   Protocol CLOU064A2302, Site 5202
   PDUFA Inspection Dates: May 6-9, 2025

For Protocol CLOU064A2302, 13 subjects were screened, 11 subjects were enrolled and randomized, and 10 subjects completed the study. One subject withdrew from the study.

Informed consent forms were reviewed for all 13 screened subjects. Study records for primary efficacy data verification were reviewed for 11 randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, IRB approvals, sponsor correspondence, regulatory documents, delegation logs, informed consent forms, training records, financial disclosures, medical records, investigational product accountability, eligibility, adverse event reporting, protocol deviations, concomitant medications, and

electronic source records for verification of primary efficacy endpoint.

The daily values for the Hives Severity Score (HSS) and Itchy Severity Score (ISS) were verified by comparing the scores reported in the electronic source documents against the sponsor's subject data line listings during the seven days preceding the Baseline and Week 12 visits. No discrepancies were noted. There was no underreporting of adverse events.

4. **Dr. Martha Tarpay**
   4200 W Memorial Road
   Suite 206
   Oklahoma City, OK 73120
   Protocol CLOU064A2302, Site 5213
   PDUFA Inspection Dates: May 12-15, 2025

For Protocol CLOU064A2302, five subjects were screened, four subjects were enrolled and randomized, and two subjects completed the study. Subject (b) (6), randomized to remibrutinib, withdrew due to an adverse event of bruising. One subject withdrew consent from the study.

An audit of the study records was conducted for all five screened subjects. Records reviewed included, but were not limited to, protocol and amendments, IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, drug accountability records, site signature and responsibility logs, site training documentation, adverse event reporting, test article accountability, eligibility checklists, and electronic source records for verification of primary efficacy endpoint.

The daily values for the Hives Severity Score (HSS) and Itchy Severity Score (ISS) were verified by comparing the scores reported in the electronic source documents against the sponsor's subject data line listings during the seven days preceding the Baseline and Week 12 visits. No discrepancies were noted. There was no underreporting of adverse events.

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Review Division /Division Director/
Review Division /Medical Team Leader/
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NONMALIGNANT HEMATOLOGY

CONSULT REVIEW

Date: June 25, 2025
From: Saleh Ayache, M.D.
Medical Reviewer, Division of Nonmalignant Hematology
Subject: Request of input on the Applicant's proposed labeling regarding the risk of bleeding for remibrutinib

To: Phuong Nina Ton, RPM
Regulatory Health Project Manager
CDER/ORO/DROII

Through: Margaret Thompson, MD, PhD
Medical Team Leader, DNH
And
Tanya Wroblewski, M.D.
Division Director, DNH

I. Background

Novartis submitted NDA 218436 for remibrutinib, a selective oral inhibitor of Bruton's Tyrosine Kinase (BTK), for the treatment of adult patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite treatment with H1-antihistamine treatment. Remibrutinib inhibits mast cell and basophil degranulation mediated by pathogenic IgE or IgG directed against the FcεR1 or IgE. It blocks IgE- and IgG-mediated FcεRI activation of mast cells and basophils. In patients with CSU, remibrutinib prevents the release of histamine and other proinflammatory mediators that cause itch, hives, or angioedema.

The Division of Pulmonology, Allergy and Critical Care (DPACC) consulted the Division of nonmalignant Hematology (DNH) requesting the Divisions input on the appropriate safety analyses to assess the risk of bleeding and/or cytopenias and the appropriate language to convey this safety signal in the USPI for remibrutinib.

In the clinical studies with remibrutinib, the Applicant included bleeding and cytopenias as an adverse event of special interest (AESIs) based on its mechanism of action and the established safety profiles of other drugs in the class. To identify cases of the AESI of bleeding, the Applicant used a customized search strategy adding the PTs of platelet aggregation abnormal,

platelet aggregation decreased, platelet aggregation inhibition, platelet dysfunction, platelet function test abnormal and platelet toxicity to the MedDRA SMQ Hemorrhages (Broad). To identify cases of the AESI of cytopenia, the Applicant used the MedDRA SMQ Hematopoietic Cytopenias.

(b) (4)

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II. DNH Responses

Bleeding is a known adverse event associated with BTK inhibitors and important consideration in their use. The potential mechanism of bleeding is thought that BTKi interfere with platelet aggregation and adhesion by affecting collagen-mediated platelet activation and glycoprotein VI signaling. The risk of bleeding can vary depending on the specific BTK inhibitor used (higher bleeding risk of bleed with first-generation BTKis, e.g., ibrutinib, compared to second-generation, e.g., acalabrutinib, zanubrutinib), patient characteristics (e.g., higher risk with age > 65 years have), and concomitant medications (e.g., anticoagulant or antiplatelet medications).

Question 1:

Does the hemorrhage SMQ used by the Applicant with added terms platelet aggregation abnormal, platelet aggregation decreased, platelet aggregation inhibition, platelet dysfunction, platelet function test abnormal and platelet toxicity adequately capture the risk of bleeding and would DNH recommend different SMQs or additional terms? Is there a preferred approach to group and capture the preferred terms (PTs) pertaining to bleeding for labeling purposes?

The Division does not agree with the Applicant's custom medical query for hemorrhage, specification with the inclusion of the preferred terms platelet aggregation abnormal, platelet aggregation decreased, platelet aggregation inhibition, platelet dysfunction, platelet function

test abnormal, and platelet toxicity. Hemorrhagic adverse events should represent the observed of events of bleeding during the trial and not the risk of bleeding.

Although, there is an association between abnormal platelet aggregation test results and an increased risk of bleeding, this relationship is not always straightforward. Studies show a moderate relationship between an abnormal test and risk of bleeding, which can vary, depending on the type of platelet function test used, the underlying condition being investigated, severity of the aggregation abnormality, and hemostatic abnormalities.

For the purpose of remiburitinib labeling, we recommend utilization of the Standardized MedDRA Query (SMQ) or the FDA-Medical Query (FMQ) narrow for hemorrhage, incorporating the Preferred Terms that capture actual observed bleeding events, their frequency, and severity as documented during clinical trials.

Question 2

Regarding the risk of bleeding during surgical intervention, the Applicant has used language included in the labels for other BTK inhibitors. Is the proposed labeling, including the length of interruption, an appropriate recommendation for all BTK inhibitors? (Remubrutinib Tmax ~ 1 h; half-life ~ 1-2 h)

Generally, it takes 5-6 half-lives for a drug to be nearly completely eliminated from the body. Thus, the Applicants proposed 3 to 7 days, apparently based on other BTKi, is longer than would be required based on the half-life of remubrutinib. We recommend asking the Applicant for their rationale of using similar recommendations as other BTKi rather than based on the characteristics of their own drug.

Question 3

Additionally, the Applicant has pulled language from other BTK inhibitor labels to describe the potential effect of remibrutinib on antithrombotic agents as outlined in Section 7.2. Given the observed signal for remibrutinib, is this an appropriate characterization of the risk of bleeding when concomitantly administered with antithrombotic agents?

If sufficient evidence exists to characterize the safety profile of remibrutinib when co-administered with antithrombotic agents, this information should be reflected in the product labeling. However, in the absence of such data, the characterization of potentially increased bleeding risk associated with concomitant administration of remibrutinib and antithrombotic agents should be guided by the labeling of other Bruton's tyrosine kinase inhibitors (BTKis).

References:

1. Mechanism of bleeding: Levade, M., et al. (2014). Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. Blood, 124(26), 3991-3995.

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06/26/2025 04:15:58 PM

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06/27/2025 11:09:25 AM

ABPM STUDY REPORT REVIEW

NDA no., SDN, receipt date[1]	NDA 218436	SDN 001	4/28/2025
Applicant	Novartis Pharmaceuticals Corporation		
Name of drug	Remibrutinib		
Proposed indication	Treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1-antihistamine treatment		
Proposed dose	25 mg QD with or without food		
Protocol number	CLOU064A2305		
Protocol title	A multicenter, open-label Phase 3 study: ambulatory blood pressure monitoring in adult patients with chronic spontaneous urticaria inadequately controlled by H1-antihistamines treated with remibrutinib up to 12 weeks		
Document(s) reviewed (include direct links)	CLOU064A2305 CSR (NDA 218436 SN 0000)		
Clinical division	DPACC		

Abbreviations: IND/NDA/BLA, investigational new drug application/new drug application/biologic license application; SDN, supporting document number

1 EXECUTIVE SUMMARY

The Applicant conducted an ABPM study at the therapeutic dose in the intended patient population. The study design and analysis are consistent with the draft pressor guidance. The study supports concluding that 25 mg remibrutinib is not associated with clinically significant changes in blood pressure.

2 LABELING RECOMMENDATIONS

Below are proposed edits to the label submitted to SN 0001 (link).

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Effects on blood pressure

The effect of remibrutinib treatment on blood pressure was assessed in CSU patients using a 24-hour blood pressure measurement by ambulatory blood pressure monitoring (ABPM) at steady state (Week 4) compared to baseline in a multicenter, open-label (b) (4) study (A2305). The study enrolled 144 patients with CSU inadequately controlled by (b) (4) H1-Antihistamine, who were administered remibrutinib 25 mg (b) (4) (twice daily)). Remibrutinib 25 mg b.i.d was not associated with clinically significant changes in blood pressure. (b) (4)

(b) (4)

Reviewer's comments: *We recommend simplifying the description of the study findings and only describe the findings as showing no clinically significant increase in blood pressure.*

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Remibrutinib is a Bruton's tyrosine kinase inhibitor (BTKi) indicated for the treatment of chronic spontaneous urticaria (CSU). Proposed therapeutic dosing for treatment of urticaria is 25 mg BID with or without food.

3.2 ABPM STUDY OVERVIEW

The Applicant assessed the effects of remibrutinib on BP in a single arm, open-label study in adult patients with chronic spontaneous urticaria at the intended therapeutic dose (CLOU064A2305). Assessment of BP includes 24-h ABPM at baseline and at 4 weeks.

For additional information about the study see section 6.1.

4 QUESTION-BASED REPORT REVIEW

1. Are there nonclinical or previous clinical experience showing a potential for an increase in BP?

No, the Applicant did not report any increases in blood pressure in nonclinical safety pharmacology studies or in the pooled clinical databases 1 or 2.

Hypertension, however, is a known and potential toxicity of inhibition of BTK resulting from interactions between oxidative stress, endothelial dysfunctions, and alterations in signaling pathways.[1] Ibrutinib, the first approved BTKi, has a warning in the label for hypertension. Other BTKis (acalabrutinib, zanubrutinb, pirtobrutinib) do not have warnings for hypertension.

2. Is the study design and analysis plan acceptable?

Yes, the design of the study design and analysis plan are consistent with the draft pressor guidance.

3. Is the study population representative of the indicated population?

Yes, the study was performed patients with CSU that is inadequately controlled by second generation H1-antihistamines, the intended patient population.

4. Are there any significant changes in SBP, DBP, or HR?

No significant changes in SBP, DBP and HR were observed.

[1] Xu, et al. Front Pharmacol 2025 (link)

5. **What is the increase in predicted CV risk for the intended patient population based on the increase in SBP?**

No increase in SBP was observed and no assessment of predicted increase in CV risk was therefore performed.

6. **Are there any concerns with missing data in the study that impacts study interpretability?**

No, the percent of subjects that were excluded from the primary analysis population is not higher than contemporary ABPM studies. However, there were participants that without valid ABPM data, per Applicant's criteria, that were included in the primary analysis. Sensitivity analysis to exclusion of these data was conducted, which confirmed the results of the primary analysis.

7. **Are there any concerns with treatment compliance or drug exposure that impacts study interpretability?**

No, the Cmax at week 4 is not significantly different from the Cmax at week 12 in the Phase 3 study (CLOU064A2302). However, there were 10 participants without PK data available at week 4 and the investigator had concerns about compliance for 5 participants. Sensitivity analysis to exclusion of these data was consistent with the primary findings.

8. **Are there any significant differences between CS IRT's independent analysis and Applicant's analysis?**

No, the results of our analysis are consistent with the Applicant's analysis.

9. **Are there other concerns not addressed above?**

No.

5 STUDY REVIEW

5.1 DISPOSITION

The Applicant's primary analysis population was the full analysis set and only excluded participants that discontinued prior to the ABPM visit (week 4). The Applicant's ABPM population therefore included 143 participants (Table 1).

Participants with AHP treatment prior to week 4 were included in the analysis, but measurements after the initiation of the AHP were excluded and the increase was imputed based on average 24-h SBP at baseline. One participant met this criterion (b) (6) as the participant received bisoprolol to treat ventricular and atrial extra-systoles. However, this participant should not have been enrolled per protocol as bisoprolol was initiated prior to study start (exclusion criterion #10).

The primary analysis population did not consider compliance and participants without valid APBM per protocol criteria were also included. We therefore defined a sensitivity population that excluded the following participants:

1. Discontinuation prior to week 4.
2. No valid ABPM data at baseline and week 4 per protocol criteria.
3. No PK data collected at week 4.

4. Investigator determined that participant was not compliant with study drug administration based on their assessment, which considered ediary, capsule count, and patient interview.

This new population included 118 participants and most participants that were excluded were due to concerns about compliance (10 due to missing PK, 5 due to investigator assessment) and invalid ABPM (9).

Table 1: Disposition table for ABPM study

Category	Remibrutinib 25 mg b.i.d. N=144 n (%)
Patients treated	144 (100.0)
ABPM	143 (99.3)
ABPM Sensitivity Population	118 (81.9)
Excluded from ABPM population	1 (0.7)
Discontinued	1 (0.7)
Excluded from ABPM sensitivity population	26 (18.1)
No PK data on week 4	10 (6.9)
No valid ABPM	9 (6.2)
Investigator determined participant not compliant with drug administration	5 (3.5)
Prohibited AHP prior to week 4	1 (0.7)
Discontinued	1 (0.7)
Discontinued study	7 (4.9)
Unsatisfactory therapeutic effect	2 (1.4)
Adverse event	2 (1.4)
Subject decision	2 (1.4)
Lost to follow-up	1 (0.7)

Source: Reviewer's analysis

5.2 EXPOSURE

The Applicant did not systematically collect information about compliance in the ABPM study (Table 2). There were 5 participants were the investigator determined were not compliant with study drug administration.

PK measurements were collected at week 4 on the day after the completion of the ABPM recording at 45 min and 90 min post-dose (Tmax is ~60 min). The geometric mean Cmax at week 4 is similar to the geometric mean Cmax at Week 12 in the Phase 3 study and there is no accumulation with the BID dosing regimen (Table 3).

Table 2: Exposure in ABPM study, Full Analysis Set

Characteristic	Remibrutinib 25 mg b.i.d. N=144
Duration (days)	
Mean (SD)	85.0 (11.1)
Median (min, max)	86.0 (9.0, 100.0)

Source: Reviewer's analysis

Table 3: Comparison of geometric mean Cmax (CV%) between ABPM and Phase 3, Full Analysis Set

Treatment	ABPM Study (Week 4)	Phase 3 (Week 12)
25 mg BID	43.0 (91.0%)	50.3 (109.7%)

Source: Reviewer's analysis

5.3 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The study inclusion criteria and general demographics in the ABPM study are consistent with the Phase 3 study (Table 4).

Table 4: Demographics in ABPM study, Full Analysis Set

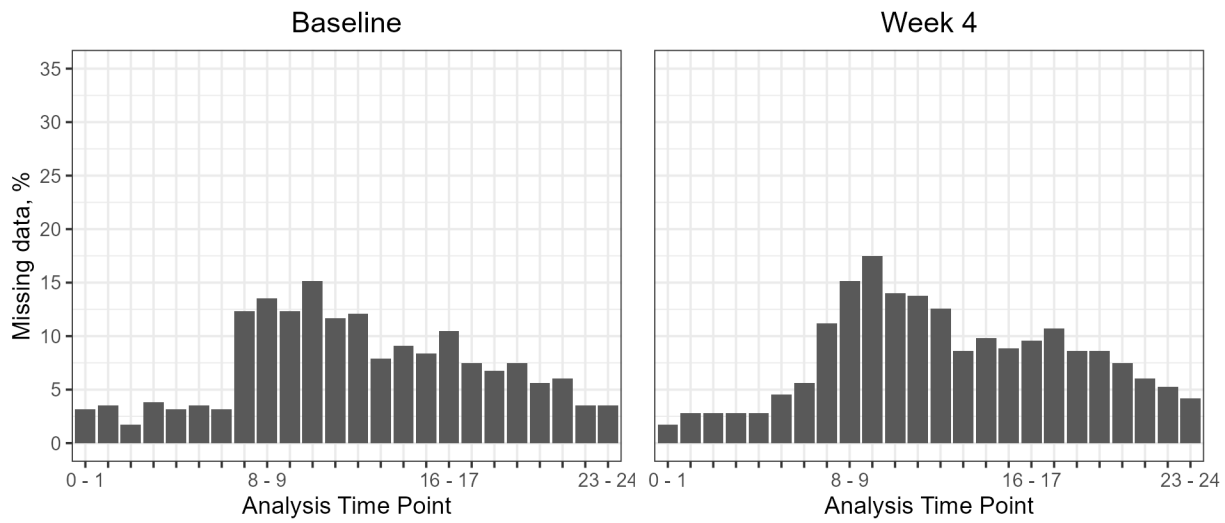
Characteristic	Remibrutinib 25 mg b.i.d. N=144
Sex, n (%)	
Male	39 (27.1)
Female	105 (72.9)
Age, years	
Mean (SD)	42.2 (14.5)
Median (min, max)	42.0 (18.0, 75.0)
Race, n (%)	
Asian	19 (13.2)
White	89 (61.8)
Not Reported	32 (22.2)
American Indian or Alaska Native	1 (0.7)
Black or African American	3 (2.1)
Ethnicity, n (%)	
Not Hispanic or Latino	94 (65.3)
Not Reported	33 (22.9)
Hispanic or Latino	17 (11.8)
Systolic BP, mm Hg	
Mean (SD)	117.1 (13.1)
Median (min, max)	116.0 (85.0, 175.0)
Diastolic BP, mm Hg	
Mean (SD)	75.0 (9.0)
Median (min, max)	74.0 (57.0, 104.0)

Source: Reviewer's analysis

5.4 MISSING DATA

The pattern of participants with missing ABPM data by hour is consistent between baseline and Week 4 and numerically higher during the day compared to the night (Figure 1). The extent of missing data in the ABPM study is consistent with contemporary ABPM studies.

Figure 1: Average hourly missing data by analysis visit relative to start of ABPM recording, ABPM Population



Source: Reviewer's analysis

5.5 PRIMARY ENDPOINT

The primary endpoint was change from baseline for time-weighted (AUC_{0-24}/24) average 24-h SBP analyzed using an ANCOVA model with baseline 24-h ambulatory SBP as covariates. Awake (7am – 10pm) and asleep (10pm – 7am) changes in SBP were analyzed similarly.

No significant increase in SBP and DBP was observed in all time-intervals (Table 5). The reviewer's primary analysis results confirmed the Applicant's primary analysis.

One participant with AHP treatment prior to week 4 were included in the analysis, but measurements after the initiation of the AHP were excluded and the increase was imputed based on average 24-h SBP at baseline. The Applicant conducted sensitivity analysis using the sensitivity population that excluded this participant. The results confirmed the Applicant's primary analysis. (CSR; Table 11-2)

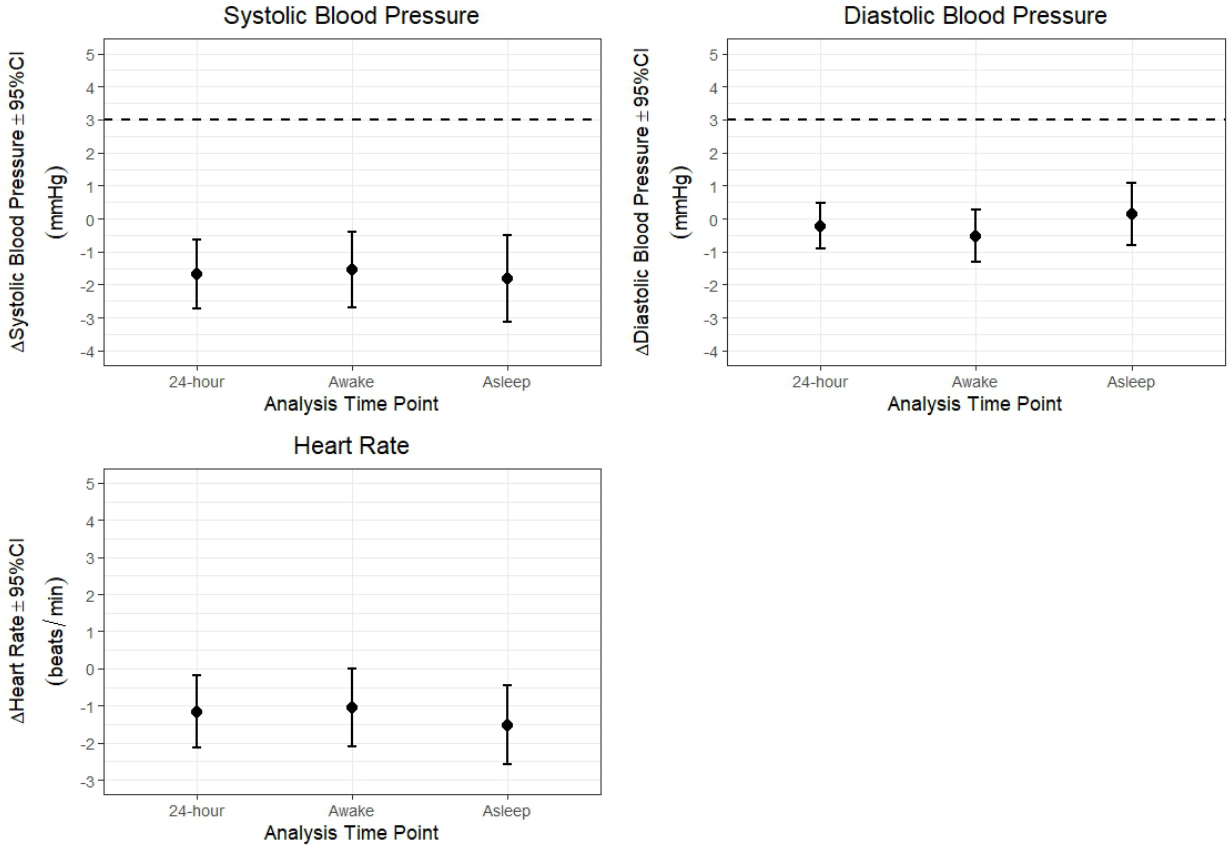
The reviewer conducted three sensitivity analyses (Table 6).

First, the reviewer used average 24-h instead of time-weighted average and similar finding were observed.

Second, the reviewer conducted a sensitivity analysis by multiple imputation on the ABPM population with imputed hourly average change from baseline in SBP. The results confirmed the reviewer's primary analysis.

Third, as described in section 5.1, the reviewer defined a different sensitivity population excluding subjects having concerns about compliance and invalid ABPM. The reviewer conducted the sensitivity analysis on the sensitivity population for time-weighted (AUC_{0-24}/24) average 24-h average change from baseline in SBP using an ANCOVA model. The estimates were slightly lower than the reviewer's primary analysis. No significant increase in SBP was observed.

Figure 2: Time-window averages (time-weighted 24-h, daytime, and nighttime) for systolic and diastolic blood pressure and (24-h, daytime, and nighttime) average for heart rate, ABPM Population



Source: Reviewer's analysis

Table 5: Time-window averages (time-weighted 24-h, daytime, and nighttime) for systolic and diastolic blood pressure and (24-h, daytime, and nighttime) average for heart rate, ABPM Population

	Remibrutinib 25 mg b.i.d.
Systolic Blood Pressure, mmHg	
Week 4	
24 Hour	-1.7 (-2.7 to -0.6)
Awake	-1.6 (-2.7 to -0.4)
Asleep	-1.8 (-3.1 to -0.5)
Diastolic Blood Pressure, mmHg	
Week 4	
24 Hour	-0.2 (-0.9 to 0.5)
Awake	-0.5 (-1.3 to 0.3)
Asleep	0.1 (-0.8 to 1.1)

	Remibrutinib 25 mg b.i.d.
Heart Rate, bpm	
Week 4	
24 Hour	-1.2 (-2.1 to -0.2)
Awake	-1.0 (-2.1 to 0.0)
Asleep	-1.5 (-2.6 to -0.5)

Source: Reviewer's analysis

Table 6: 24 h averages for systolic blood pressure, ABPM Population or ABPM Sensitivity Population

		Remibrutinib 25 mg b.i.d.
Systolic Blood Pressure, mmHg		
Week 4	n	
Arithmetic 24-h average	143	-1.7 (-2.8 to -0.7)
Multiple imputation	143	-1.6 (-2.7 to -0.4)
Sensitivity population	118	-2.5 (-3.5 to -1.4)

Source: Reviewer's analysis

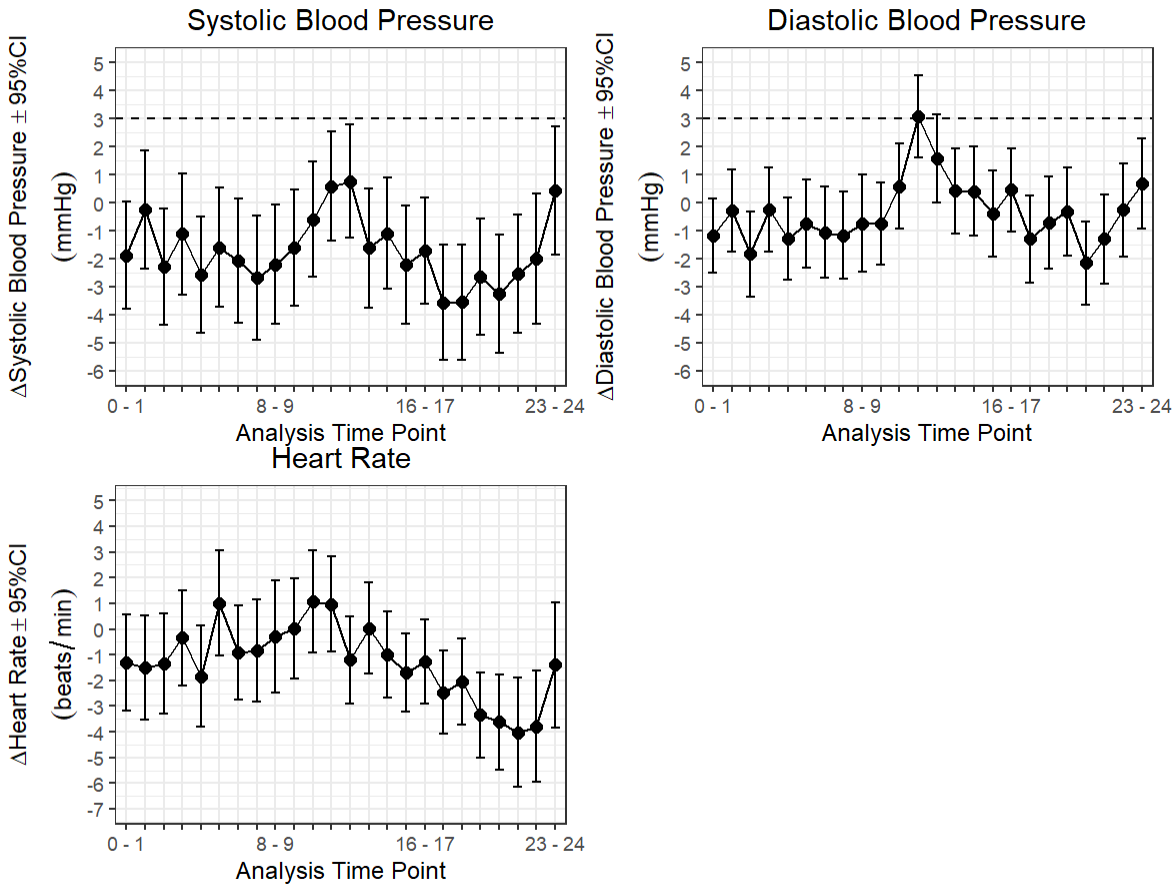
5.6 ADDITIONAL ANALYSES

5.6.1 HOURLY AVERAGE

The hourly average ABPM measurements were analyzed using an MMRM model. This analysis was performed for each parameter independently. The model included change from baseline as response variable, and baseline and hourly time point as fixed effects. The model used hourly time points as repeated component in the model. An unstructured covariance structure was applied for the MMRM.

No significant increase in SBP was observed at all time-points. No significant increase in DBP was observed except for one timepoint (Hour 11-12). (Figure 3) These findings are consistent with the primary endpoint. (section 5.5)

Figure 3: Hourly averages relative to start of the ABPM recording, ABPM Population

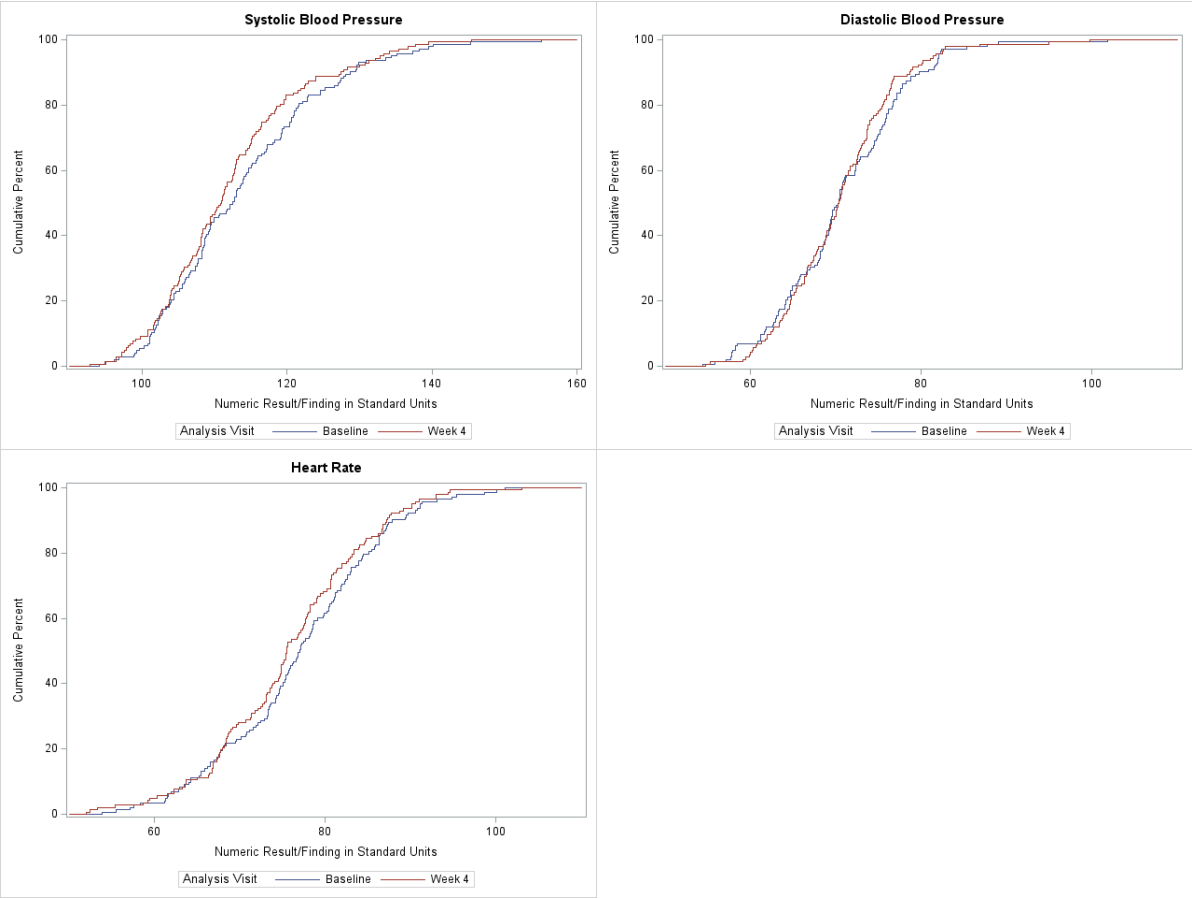


Source: Reviewer's analysis

5.6.2 DISTRIBUTION ANALYSIS

The cumulative distribution function (CDF) plot of the time-weighted 24-h average in SBP, DBP, and 24-h average HR are shown in Figure 4 for baseline and post-baseline (week 4). No significant shift was observed between baseline and post-baseline, which is consistent with the primary analysis (section 5.5).

Figure 4: Cumulative distribution for systolic and diastolic blood pressure and heart rate, ABPM Population



Source: Reviewer's analysis

5.6.3 OUTLIER ANALYSIS

The Applicant reports that one subject had SBP ≥160 mmHg or >20 mmHg change from baseline and five subjects had DBP ≥100 mmHg or >10 mmHg change from baseline. We performed outlier analysis using 24-h mean measurements instead of individual measurements, because the 24-h mean measurement is a more stable measurement. One of the subjects was excluded from the outlier analysis since that subject was exposed to a prohibited antihypertensive treatment prior to Week 4. The results showed that no observed subjects with a mean 24-h SBP of ≥160 mmHg or DBP of ≥110 mmHg.

Table 7: Outlier analysis for change from baseline in 24-h SBP, DBP and HR, ABPM Population

	Remibrutinib 25 mg b.i.d.
Systolic Blood Pressure	
Post-Baseline	142
>= 120 mm Hg	53.0 (37.3%)
>= 140 mm Hg	3.0 (2.1%)
>= 160 mm Hg	0.0 (0.0%)
Diastolic Blood Pressure	
Post-Baseline	142
>= 90 mm Hg	4.0 (2.8%)

	Remibrutinib 25 mg b.i.d.
>= 110 mm Hg	0.0 (0.0%)
>= 120 mm Hg	0.0 (0.0%)
Heart Rate	
Change from Baseline	142
>= 5 bpm	44.0 (31.0%)
>= 10 bpm	13.0 (9.2%)
>= 15 bpm	4.0 (2.8%)
>= 20 bpm	0.0 (0.0%)

Source: Reviewer's analysis

5.6.4 SAFETY

There were two participant who experienced a treatment-emergent AE related to hypertension.[2] The AEs were reported after the week 4 visit and were reported to be mild, though for one of the two participants the AE led to withdrawal. The 24-h SBP was not increased in the participant that had the drug discontinued, however, a significant increase in 24-h SBP was observed in the other participant (107 mmHg to 132 mmHg). AHP rescue medication was not initiated in this study.

Table 8: Safety analysis in ABPM study, Full Analysis Set

Adverse Event Category	Remibrutinib 25 mg b.i.d. N=144 n (%)
Any AE in group	2 (1.4)
Blood pressure increased	1 (0.7)
Hypertension	1 (0.7)
Maximum severity	
Severe	0
Moderate	0
Mild	2 (1.4)
Serious	0
Resulting in discontinuation	1 (0.7)
Relatedness	0

Source: Reviewer's analysis

5.7 CV RISK ASSESSMENT

No increase in SBP was observed and no assessment of predicted increase in CV risk was therefore performed.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cder-ond-abpm@fda.hhs.gov

[2] Based on Narrow FMQ for "Systemic Hypertension" (version 2.1)

6 APPENDIX

Removed if previously reviewed.

6.1 PROTOCOL SUMMARY

Study Design	**Key Design Features**
Protocol number	CLOU064A2305
Key objective(s)	To rule out an increase of > 3 mmHg in 24-hour average SBP at steady state (Week 4) compared to baseline, measured by ABPM.
Overall study design (e.g., randomization, blind, control)	Single-arm, open-label study.
Study population and key inclusion/exclusion criteria	Adult patients with chronic spontaneous urticaria
Study duration	16 weeks
Study Arms	
Dosing regimen	25 mg BID. Participants were allowed to continue to take their background therapy (H1-AH at local label-approved doses) with a stable regimen throughout the study.
Controls	None
Treatment duration	12 weeks
BP/Cardiac Inclusion/Exclusion Criteria	
Inclusion criteria	
Exclusion criteria	• Participants unable to tolerate 24-hour ambulatory blood pressure measurement using automatic ABPM device • Ongoing or past history of hypertension and/or SBP ≥ 140 or ≤ 90 OR DBP ≥ 90 or ≤ 60 mmHg at screening • Participants working night shifts • Participants taking/requiring medications prohibited by the protocol (including those known to interfere with blood pressure assessments in the study) • Evidence of clinically significant cardiovascular, neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders, gastrointestinal disease or immunodeficiency that, in the Investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the participant
Statistical Considerations	
Analysis population	Participants without ongoing or past history of hypertension and with 90<SBP <140mmHg, 60< DBP<90 mmHg at screening, with inadequately controlled CSU despite treatment with second generation H1-AH who have CSU duration ≥ 6 months, a UAS7 score ≥ 16, ISS7 ≥ 6 and HSS7 score ≥ 6 in the last 7 days prior to Baseline (Day 1).
Primary BP endpoint	Change from baseline in 24-hour weighted average SBP at Week 4. Weighted SBP is derived as AUC divided by the time duration.

Secondary BP endpoint	- Change from baseline in 24-hour weighted average DBP at Week 4 - Change from baseline in daytime weighted average SBP/DBP at Week 4 - Change from baseline in nighttime weighted average SBP/DBP at Week 4
Non-inferiority margin	3 mmHg
Justification for sample size	Assuming a standard deviation of 10 mmHg for change from baseline in 24-hour average SBP, a sample size of 119 participants will provide a power of 90% to exclude 3 mmHg drug effect (based on the upper limit of the two-sided 95% CI). Approximately 12% drop-out is expected at Week 4, thus 136 participants are required to be enrolled.
Re-estimation of sample size	No
Statistical methods for BP	ANCOVA with adjustment of baseline.
Planned interim analysis	A primary analysis may be conducted when all participants have completed their Week 4 visit or discontinued early. It will focus on ABPM, safety, and PK data.
Blood pressure assessments	
ABPM schedule	- Baseline (within 4 days of starting treatment) - Week 4
Frequency of ABPM measurements	Per Applicant: "*During the 24-hour-period of device use, typically 2-4 inflations per hour were done during the day and 1-2 inflations per hour during sleep.*" Review of data indicates likely: 3 measurements per hour for 7a – 10p and 2 measurements per hour for 10p – 7a.
Repeat ABPM session criteria	- 1. ≥65% successful measurements - 2. ≥22 total hours - 3. ≤5 hours missing - 4. ≤3 hours consecutive missing
ABPM device	(b) (4) blood pressure
Other BP assessments	Baseline, Week 4 (-1 day), Week 4, Week 8, Week 12, Early Treatment Discontinuation, Week 16/Follow-up.
Method for capturing awake / asleep	Clock time: - Awake: 7a – 10p - Asleep: 10p – 7a
PK Assessments	
PK assessments	Week 4: 45- and 90-min post-dose.
How will dosing be recorded?	Timing of study drug (morning dose) will be recorded in the eCRF.

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/

LARS JOHANNESEN
06/13/2025 12:15:06 PM

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06/13/2025 01:20:27 PM

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06/13/2025 01:55:16 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: June 2, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Phuong Nina Tong, RPM
DPACC

Subject: QT Consult to NDA 218436 (SDN 1)

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

This memo responds to your consult to us dated 3/19/2025 regarding the Applicant's proposed label. We reviewed the following materials:

- Summary of Clinical Pharmacology Studies (NDA 218436 / SDN 1; link);
- Previous IRT reviews for IND 131325 dated 11/16/2020 and 11/12/2021 in DARRTS;
- Proposed labeling (NDA 218436 / SDN 1; link);
- E-R report (NDA 218436 / SDN 1; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 218436 / SDN 16; link).

Consult Request from the Division: Novartis submitted an NDA for the proposed indication of treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment.

Please review the label which includes the cardiac electrophysiology information in Section 12.2.

There is no standalone QT study. We previously agreed that the risk of QT prolongation of remibrutinib is adequately characterized in studies (# CLOU064X2101 and # CLOU064X1101) and is acceptable as a substitute to the thorough QT study. Please see the QT review dated 11/12/2025 and advice dated 11/15/2021 under IND 131325.

IRT response for the Division: Below are proposed edits to the label. Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

1 BACKGROUND

1.1 Product Information

Remibrutinib is a Bruton's tyrosine kinase indicated for the treatment of chronic spontaneous urticaria. Proposed therapeutic dosing for treatment of urticaria is 25 mg BID with or without food.

The Applicant's initial CQT analysis was previously reviewed and accepted as a TQT substitute (IND 131325, IRT review dated 11/12/2021). This analysis included healthy volunteer SAD/MAD studies CLOU064X2101 and CLOU064X1101. Dosing ranged from 0.5-400 mg in SAD, 10-600 mg QD, and 100-200 mg BID. Concentration-dependent QTc prolongation was observed in this study, which appears to be hERG mediated. At a dose of 600 mg QD (Cmax = 531.5 ng/mL), the point estimate for ΔΔQTcF was 7.5 msec (90% CI: 5.0 to 10.0). However,

QTc prolongation is not expected at Cmax (198 ng/mL) of the high clinical exposure scenario (CYP3A4 inhibition).

This submission contains an updated CQT analysis. The dataset includes study Phase IIb study CLOU064A2201 (protocol) in addition to the SAD/MAD studies CLOU064X2101 and CLOU064X1101. Based on the updated CQT analysis, the predicted mean (90% CI) ΔΔQTcF at the 2-fold high clinical exposure scenario (Cmax = 534 ng/mL) was 6.35 (4.35 to 8.35) msec.

Phase IIb study CLOU064A2201

Participants were randomized in a 1:1:1: 1:1:1:1 ratio to the following dosing groups: 10 mg QD, 35 mg QD, 100 mg QD, 10 mg BID, 25 mg BID, 100 mg BID, and Placebo. Duration of treatment was 12 weeks. ECG sampling times were at screening and on weeks 0, 2, 4, 8, 12, and 16. Single ECG measurements were at screening and weeks 2, 8, and 16. A pre-dose triplicate ECG measurement was taken at week 0. Pre-dose and one-hour post-dose triplicate ECG measurements were taken at weeks 4 and 12. PK sampling times on weeks 4 and 12 were pre-dose, and 0.5-, 1-, 2-, 3-, and 4-hours post-dose.

Reviewer's comment: *C-QTc analysis based on pooled data requires homogenous data from the pooled studies to prevent bias in QTc assessment. The updated C-QTc analysis includes a Phase IIb study with a different design compared to the Phase I studies. The Applicant's report of the updated C-QTc analysis does not include heterogeneity assessment, therefore it is unclear if the data can be pooled. For this reason, the estimated ΔΔ*QTcF based on the updated model is considered unreliable. QTc prolongation risk labelling for remibrutinib will therefore rely on the previously reviewed C-QTc analysis that was based on Phase I data only.*

1.2 Clinical Pharmacology

Selected PK properties of remibrutinib include the following:

- Tmax of ~1 hour
- Primarily eliminated by CYP3A4-mediated metabolism. <1% of the dose is renally excreted as unchanged remibrutinib. No metabolites exceed 10% of total drug-related material.

In dedicated studies, geometric mean ratios for the effect of intrinsic and extrinsic factors on remibrutinib Cmax include the following:

- Coadministration with a strong CYP3A4 inhibitor (ritonavir) versus alone: 3.3.
  - Labeling recommendation: Use caution.
- Severe hepatic impairment versus normal hepatic function: 1.99.
  - Labeling recommendation: No dose adjustment.
- High-fat meal versus fasted: 0.95.
  - Labeling recommendation: Take with or without food.

Table 1: Summary of dose and exposure assessment

	Mean C_{max}

Highest therapeutic or clinical trial dosing regimen	25 mg BID	59 ng/mL
Applicant's High clinical exposure scenario	3.3-fold increase with CYP3A4 inhibition	195 ng/mL
Highest dose in QT assessment	600 mg QD	532 ng/mL
C_{max} Ratio (QT/high clinical)	532 / 195 = 2.68	

1.3 Nonclinical Cardiac Safety

Remibrutinib inhibits hERG with an IC50 of 1.4 µM, which corresponds to a hERG safety margin of 79x (MW: 507.54 g/mol; PB: 96.4%) to high clinical Cmax.

No prolongation of the QTc interval was observed in a single dose GLP invasive telemetry study in dogs at doses up to 450 mg/kg (free Cmax (200 mg/kg): 432 ng/mL or 47x high clinical Cmax). In contrast, QTc prolongation (<10%) was observed on days 2 and 3 of a 3-day study in dogs at 400 mg/kg (free Cmax: 168 ng/mL or 19x high clinical Cmax).

(b) (4)

1.4 Clinical Cardiac Safety

In the completed studies, including pivotal Phase 3 studies in CSU and Phase 2 studies in patients with CSU, Sjögrens' syndrome, asthma, and hidradenitis suppurativa which investigated remibrutinib doses up to 100 mg b.i.d. up to 52 weeks, and in the final analyses of the Phase 3 CSU studies, no notable trend was observed for the change of ECG over time; no finding in ECG recordings or AEs suggestive of pro-arrhythmic events were noted.

See Highlights of Clinical Pharmacology and Cardiac Safety for additional details.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

ELIFORD N KITABI
06/02/2025 10:42:37 AM
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06/02/2025 10:44:55 AM

Memorandum
Date: 30 May 2025
Due Date: 30 May 2025

Anne C. Miranowski -S Digitally signed by Anne C. Miranowski -S Date: 2025.05.30 11:47:17 -04'00'

From: Anne Miranowski, MD, Clinical Review Branch 1 (CRB1)/ Division of Clinical and Toxicology Review (DCTR)/ Office of Vaccines Research and Review (OVRR)/ Center for Biologics Evaluation and Research (CBER)
To: Phuong Ton
Through: Kathleen Hise, MD, Team Leader and Deputy Branch Chief (on detail), CRB1/DCTR/OVRR/CBER and Joohee Lee, MD, Branch Chief (on detail), CRB1/DCTR/OVRR/CBER

JOOHEE LEE -S Digitally signed by JOOHEE LEE -S Date: 2025.05.30 12:22:46 -04'00'

Product Information: NDA 218436 Remibrutinib (LOU064)
Inter-Center Consult#: 01066955
Subject: CBER Clinical Review of [redacted] (b) (4) Phase I Study (CLOU064F12101) entitled: "A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the modulation of immune response to four different types of vaccines by concomitant and interrupted administration of remibrutinib in healthy subjects" [redacted] (b) (4) and inclusion of recommendations on administration of live or live-attenuated vaccinations with remibrutinib in the USPI.

Executive Summary

This memorandum addresses the Division of Pulmonary, Allergy, and Critical Care (DPACC) consultation requesting CBER's advice on [redacted] (b) (4) the vaccine immune response study [redacted] (b) (4) and inclusion of the recommendation to avoid the use of live or live-attenuated vaccinations during treatment with remibrutinib in the USPI for remibrutinib.

Consult Questions

Question 1:

Does the Agency agree with the relevance of [redacted] (b) (4) the vaccine immune response study [redacted] (b) (4)?

Question 2:

Does the Agency agree with the recommendation to avoid the use of live or live-attenuated vaccinations with remibrutinib in Section 7, Drug Interactions, of the USPI?

Question 3:

Does the Agency agree with the recommendation to advise patients to avoid vaccines containing live virus during treatment with remibrutinib as discussed in Section 17, Patient Counseling Information, of the USPI?

Background

The applicant (Novartis) has submitted a new drug application (NDA) for remibrutinib for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

CSU is defined as the spontaneous occurrence of itchy wheals (hives), angioedema or both, lasting for at least 6 weeks. Wheals and angioedema in CSU involve the degranulation of mast cells, which release histamine, proteases and cytokines. These mediators induce vasodilatation, increase vascular permeability, and stimulate sensory nerve endings leading to swelling, redness and itch. CSU can be debilitating, is associated with intense itching and has a major impact on patient's quality of life, comparable to that of severe coronary artery disease.

Remibrutinib is an orally administered highly selective, potent covalent inhibitor of Bruton's tyrosine kinase (BTK), which is selectively expressed in cells of the adaptive and innate immune system including B cells, macrophages, mast cells, basophils, and thrombocytes. It modulates B cell function without depletion. As a cytoplasmic kinase, BTK has a pivotal role for the signal transmission in the Fc gamma receptors (FcγR) for immunoglobulin G (IgG), Fc epsilon receptor-1 (FcεR1) for immunoglobulin E (IgE), and B cell antigen receptor (BCR). It is likely that inhibition of BTK will result in an inhibition of autoreactive B cells, as well as inflammation mediated by allergenic IgE and autoreactive IgG. Numerous BTK inhibitors are approved for the treatment of B cell malignancies. Remibrutinib is currently under development as an oral therapy for patients with chronic spontaneous urticaria (CSU), Sjögren's syndrome (SjS), and multiple sclerosis. Mast cells and basophils play a key role in the pathophysiology of CSU, and it has been demonstrated that BTK inhibition leads to blockade of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated allergies. Thus, BTK inhibition has being investigated as a therapeutic concept for the treatment of CSU. In a Phase 2b study in patients with CSU (CLOU064A2201) investigating doses of 10, 35, 100 mg q.d. and b.i.d. for 12 weeks, remibrutinib showed a favorable safety profile and was overall well tolerated. The incidence rate of infections was comparable to that of the placebo arm. Two Phase 3 studies in participants with CSU (CLOU064A2301 and CLOU064A2302) investigating a dose of 25 mg b.i.d for 52 weeks met their primary and key secondary endpoints with a favorable safety profile as well.

The mechanism of action of BTK inhibitors, blockage of B cell receptor– and myeloid fragment crystallizable receptor–mediated signaling with resultant decreased B cell activation, antibody class-switching, expansion, and cytokine production would be expected to impact the

immunogenicity of vaccines. Indirectly, by decreasing antigen presentation to T cells, BTK inhibitors may lead to altered T-cell responses and interferon induction by vaccination. In vivo studies in a rat and mouse model demonstrated an inhibitory effect of remibrutinib on antibody responses to sheep red blood cells and KLH, respectively. Antibody-mediated humoral response to the SARS-CoV-2 whole spike and spike receptor binding domain in chronic lymphocytic leukemia (CLL) patients receiving BTK inhibitors was reduced to 40% compared to 73% in non-treated/monitored CLL patients.[1] De novo immune response to hepatitis B vaccine was nearly absent in CLL patients on BTK inhibitors and impaired in treatment-naïve patients, while the recall immune response to Shingrix (recombinant adjuvanted varicella zoster vaccine) was not significantly different between CLL patients on BTK inhibitors and treatment-naïve patients.[2]

Approximately 4,933 participants have been enrolled in 30 clinical studies, including healthy volunteers and patients with atopic dermatitis, CSU, asthma, multiple sclerosis, peanut allergy, hidradenitis suppurativa, and SjS who have received remibrutinib at single doses ranging from 0.5 mg to 600 mg and multiple daily doses up to 600 mg q.d. and 200 mg b.i.d. Vaccination with live and live-attenuated vaccines was not allowed in the completed studies. In the completed studies (recruitment and study treatment starting from March 2020), no increased rate of infections was observed, and the rate (and severity) of reported COVID-19 infections was in line with that in the general population.

Study Design

CLOU064F12101 was a double-blinded, placebo-controlled, parallel-group study to evaluate the impact of concomitant or interrupted remibrutinib treatment regimens in comparison with placebo on the response to three vaccines in healthy participants. One hundred seven (107) participants (females of non-childbearing potential and males) were randomized in a 1:1:1 ratio to one of three treatment arms: concomitant remibrutinib (25 mg b.i.d) treatment, interrupted remibrutinib treatment (25 mg b.i.d), or placebo. Participants were administered 3 different vaccines: a T cell-dependent vaccine (quadrivalent seasonal influenza (Influsplit Tetra/Fluarix Tetra, GSK)), a T cell-independent 23-valent pneumococcal polysaccharide vaccine (PPV-23, Pneumovax 23), and a T cell-dependent neoantigen (keyhole Limpet hemocyanin (KLH), Immucothel) on Day 15.

The study consisted of a 28-day screening period, a 43-day treatment period, followed by a Study Completion evaluation (Day 57) within 2 weeks after last study drug administration. A safety follow-up call was performed approximately 30 days after the last study drug administration (Day 72). The following figure describes the study design:

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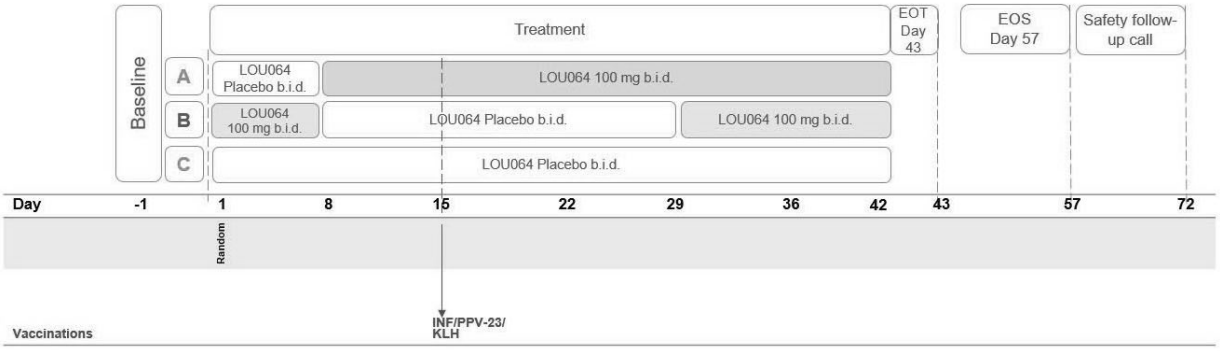
[1] Diefenbach, Catherine, et al. "Impaired humoral immunity to SARS-CoV-2 vaccination in non-Hodgkin lymphoma and CLL patients." MedRxiv (2021).

[2] Pleyer C, Ali MA, Cohen JI, et al. “Effect of Bruton tyrosine kinase inhibitor on efficacy of adjuvanted recombinant hepatitis B and zoster vaccines.” Blood; 137(2):185-9 (2021).



A: Concomitant treatment (100 mg b.i.d.); B: Interrupted treatment (100 mg b.i.d.); C: Placebo. Treatment ratio: 1 : 1 : 1.

Source: Clinical Study Report, v1.0, for Study No. CLOU064F12101

Study Objectives and Endpoints:

	Objective	Endpoint
Primary	To evaluate if immune responses following vaccinations in healthy participants with interrupted remibrutinib treatment non-inferior relative to placebo for:	Achievement of response where response is defined as:
	• T cell-dependent vaccine (Seasonal Influenza, quadrivalent vaccine)	• ≥4-fold increase of hemagglutinin antibody titers at 28 days (Day 43) after vaccination compared with baseline (i.e., seroconversion) if baseline (pre-vaccination) hemagglutinin antibody titers ≥ 1:10 • ≥1:40 hemagglutinin antibody titers at 28 days (Day 43) after vaccination if baseline (pre-vaccination) hemagglutinin antibody titers <1:10
	• T cell-independent vaccine (PPV-23)	• ≥2-fold increase of immunoglobulin G (IgG) titers 28 days (Day 43) after vaccination compared with baseline for at least 50% of serotypes (≥12 out of 23)
Secondary	To assess the immune response following vaccinations in healthy participants with concomitant remibrutinib treatment relative to placebo for:	Achievement of response where response is defined as:
	• T cell dependent vaccine (Seasonal Influenza, quadrivalent vaccine)	• ≥4-fold increase of hemagglutinin antibody titers at 28 days (Day 43) after vaccination compared with baseline (i.e., seroconversion) if baseline (pre-vaccination) hemagglutinin antibody titers ≥ 1:10 • ≥1:40 hemagglutinin antibody titers at 28 days (Day 43) after vaccination if baseline (pre-vaccination) hemagglutinin antibody titers <1:10

	• T cell independent vaccine (PPV-23)	• ≥2-fold increase of immunoglobulin G (IgG) titers 28 days (Day 43) after vaccination compared with baseline for at least 50% of serotypes (≥12 out of 23)
	To assess the effect of concomitant and interrupted remibrutinib treatment on the immune response following vaccinations in healthy participants relative to placebo over time, for a:	
	• T cell-dependent vaccine (Seasonal Influenza, quadrivalent vaccine)	• Anti-hemagglutinin antibody titers at baseline and after vaccination
	• T cell-independent vaccine (PPV-23)	• Immunoglobulin G (IgG) titers at baseline and after vaccination
	To evaluate if the immune response following T cell-dependent de novo vaccine (KLH) with interrupted remibrutinib treatment in healthy participants is non-inferior relative to placebo	• T cell dependent antibody response as measured by anti-KLH IgG and IgM titers 28 days after vaccination (Day 43)
	To assess the effect of concomitant remibrutinib treatment on the immune response following T cell-dependent de novo vaccine (KLH) in healthy participants relative to placebo over time	• T cell dependent antibody response as measured by anti-KLH IgG and IgM titers at baseline and after vaccination
	To investigate the safety and tolerability of remibrutinib administered as 100 mg b.i.d. for up to 35 days in healthy participants	• All safety assessments (including vital signs, ECGs, safety laboratory parameters, and AEs)
	To explore the safety and reactogenicity of the vaccinations administered to healthy participants receiving remibrutinib	• All safety assessments, including vital signs, ECGs, safety laboratory parameters, and AEs (solicited AEs occurring for 7 days following vaccinations / unsolicited AEs collected throughout the study)
	To assess the PK of remibrutinib at a 100 mg b.i.d. dose	• PK parameters: AUCtau,ss (Day 15 only), AUClast, Cmax,ss, Tmax,ss

Reviewer comment: *CBER/OVRR provided guidance that was included in a Type C Meeting WRO (under IND 131325) dated July 19, 2022. that evaluation of specific immunogenicity endpoints (considered to be clinically meaningful immune responses for inferring effectiveness* (b) (4) *) are needed to support* (b) (4) *this coadministration trial. KLH was not applicable because it is not a licensed vaccine.:*

a. Quadrivalent Influenza Vaccine (QIV)

Co-primary endpoints for hemagglutination inhibition (HI) antibodies to each viral strain contained in the vaccine (e.g., a total of eight coprimary endpoints for a quadrivalent vaccine): 1) geometric mean titer (GMT), and 2) seroconversion rates (defined as the percentage of subjects with either a pre-vaccination HI titer

< 1:10 and a postvaccination HI titer > 1:40 or a pre-vaccination HI titer > 1:10 and a minimum four-fold rise in post-vaccination HI antibody titer).

b. PPV-23, Pneumovax23

Opsonophagocytic antibody (OPA) assay is believed to measure functional antibodies involved in protection against pneumococcal disease, as supported by nonclinical and clinical data (Pneumovax 23 full prescribing information). The OPA antibody assay provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease.

<u>Excerpt from 2022 ICCR memo</u>: There is no established immunologic correlate of protection for pneumococcal vaccines, as the levels of IgG anti-polysaccharide binding antibodies that correlate with protection (against invasive pneumococcal disease or non-bacteremic pneumonia) have not been clearly defined (Chapter 47 – Pneumococcal polysaccharide vaccines in Vaccines, 7th Edition, Plotkin, Orenstein, and Offit, Eds., 2017; and Pneumovax®23 full prescribing information). Therefore, evaluation of serum IgG antibody titer by ELISA is not adequate to inform the effectiveness of pneumococcal or meningococcal vaccines and anti-pneumococcal antibody data generated using IgG (and IgM) antibody levels are not sufficient (b) (4) *.. The relevance of ELISA assay measurements in adults is limited by the assays' detection of both functional and nonfunctional antibodies, and lack of correlation between ELISA and OPA has been observed in certain populations (e.g., the elderly) (Adacel full prescribing information). OPA antibody titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. For PPSV23, opsonophagocytic activity (OPA) titers were measured at pre-vaccination, and at Week 12 post-vaccination. Modification of ELISA to include preabsorption with pneumococcal C-polysaccharide and serotype 22F polysaccharide (to reduce non-specific background activity due to nonfunctional antibodies) has improved correlation of ELISA with OPA assay. Based on comparison of immunogenicity and clinical disease data pooled from three placebo-controlled efficacy studies with the earlier 7-valent pneumococcal conjugate vaccine, ELISA has been used along with OPA assay to estimate effectiveness of Prevnar 13 against invasive pneumococcal disease in children, though the emerging practice is to rely on OPA assay rather than on ELISA. In summary, the ELISA assay alone has not been used to support adult efficacy claims for either pneumococcal polysaccharide vaccine or pneumococcal conjugate vaccine. The clinical studies supporting U.S. licensure of Pneumovax 23 assessed clinical disease endpoints as the primary outcome measures (Pneumovax 23 full prescribing information), while U.S. licensure of Prevnar 13 for adults was supported by comparative immunogenicity assessments with*

Pneumovax 23, using OPA assay (Prevnar 13 full prescribing information). Hence, your choice to use serum IgG levels to pneumococcal serotypes to assess the humoral immune response to Pneumovax 23 is not an appropriate immunologic endpoint to assess protection against invasive pneumococcal disease as previously outlined (b) (4) *An appropriate immunogenicity endpoint includes use of the OPA assay to determine the GMT in each treatment arm for each serotype included in the vaccine at the proposed time point.*

c. KLH, Immucothel

KLH antigen is not an FDA-licensed vaccine, and antibody responses to KLH are of uncertain clinical significance, both generally and specifically with regard to predicting whether immune responses to FDA-licensed vaccines will be protective. Use of KLH for assessing neoantigen immune response is thus considered a research test by CBER and not applicable to regulatory decision-making regarding vaccine effectiveness (b) (4) *Because the impact of concomitant KLH administration may confound interpretation of immunogenicity data from the influenza and PPV-23 vaccines, the contribution of the immunologic data for KLH antigens should be carefully considered with regard to the overall goals of the study and the implications for labeling, although the inclusion of a placebo arm may mitigate some of this risk.*

In addition to the above discussion of the acceptability of the immunogenicity assessments performed, CBER requires adequate validation of the antibody assays used by the sponsor in their study (b) (4) *of vaccine effectiveness based on data generated using those assays. Assay validation data was not provided by the sponsor for any of the included antibody assays. In the absence of such data, a rigorous assessment of the immunogenicity results generated is infeasible thereby further limiting any conclusions that can be drawn from this study.*

Study Population

Key Inclusion Criteria:

Consenting male and non-childbearing potential females 18 through 55 years of age in good health with VS and BMI within prespecified ranges.

Key Exclusion Criteria:

1. Use of other investigational drugs within 5 half-lives or 30 days prior to first dosing, whichever was longer.

2. Current evidence or past medical history of clinically significant ECG abnormalities or a family history (grandparents, parents, and siblings) of a prolonged QT interval syndrome or other abnormalities in cardiac conduction, history of additional risk factors for Torsade de Pointes (TdP) (e.g., heart failure, hypokalemia) and/or known history or current clinically significant arrhythmias. Abnormal ECG defined as PR > 220 msec, QRS complex > 120 msec, for males and females QTcF > 450 msec, or any other morphological changes, other than early repolarization, nonspecific S-T or T-wave changes.
3. History or presence of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer)
4. History or presence of any clinically significant disease of any major system organ class including (but not limited to) cardiovascular, pulmonary, metabolic, hepatic, renal, hematologic, endocrine, neurological or psychiatric diseases which had not resolved within two weeks prior to initial dosing
5. Hypersensitivity to remibrutinib or drugs from the same compound class or its excipients.
6. Any contraindication for the use of the Pneumovax 23, influenza or KLH vaccine, including any acute infection, fever or hypersensitivity reactions, or known hypersensitivity to any relevant component of the vaccines to be administered in this study (e.g., hen's egg or shellfish/KLH).
7. History of vaccination with the 2022-2023 seasonal influenza vaccine or known clinical diagnosis of influenza infection during the 2022-2023 influenza season prior to enrollment.
8. History of vaccination with pneumococcal vaccines.
9. History of previous exposure or immunization with KLH.

Reviewer comment*: The ability to extrapolate the results of this study, completed in a healthy adult population, 18-55 years of age, to the intended population of individuals with CSU is unknown. In addition, it is less certain how well the accepted immune markers discussed above to QIV and Pneumovax 23 (GMT and seroconversion rates for QIV and OPA antibody assays for Pneumovax 23) predict vaccine effectiveness in the background of immunosuppressive therapies that may affect a component of the vaccine response, such as T-cell responses or cytokine production, not measured by the selected immune marker.*

Question 1

Does the Agency agree with the relevance of (b) (4) *the vaccine immune response study* (b) (4) *?*

FDA Response to Question 1

No, we do not agree for the following reasons:

- Phase 1 Study CLOU064F12101did not utilize immunogenicity evaluations that CBER has previously accepted to inform effectiveness of the respective vaccines included in this study. For QIV, clinically meaningful immune responses used by CBER for inferring effectiveness of influenza vaccines include the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: 1) GMT and 2) seroconversion. For Pneumovax 23, CBER instructed on the use of OPA antibody assay to measure functional antibodies involved in protection against pneumococcal disease. This information was

conveyed to the sponsor prior to the start of the study in the Type C Meeting WRO dated July 19, 2022 as per the first reviewer comment above. Instead, in Study CLOU064F12101, seroconversion rates were used to assess immunogenicity for QIV and anti-pneumococcal antibody data generated using IgG antibody levels were used to assess immunogenicity for Pneumovax 23. Therefore, the results of this study do not support (b) (4) vaccine effectiveness of QIV and Pneumovax 23 in patients taking remibrutinib.

- The study was conducted in healthy adult volunteers, therefore the ability to extrapolate the study results to the intended population of individuals with CSU treated with is unknown.
- KLH antigen is not an FDA-licensed vaccine, and antibody responses to KLH are of uncertain clinical significance. Use of KLH for assessing neoantigen immune response is thus considered a research test by CBER and not applicable to regulatory decision-making regarding vaccine effectiveness.

Question 2

Does the Agency agree with the recommendation to avoid the use of live or live-attenuated vaccinations with remibrutinib in Section 7, Drug Interactions, of the USPI?

FDA Response to Question 2

We agree that the recommendation to avoid the use of live or live-attenuated vaccines would be appropriate to include in the USPI for remibrutinib. If the primary team agrees with inclusion in Section 7, it should cross-reference the primary location for the statement in Section 5 [Warnings and Precautions].

Notably, this recommendation is not included in the USPIs of previously approved BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib). The primary team may consider reaching out to the review teams for these BTK inhibitors to better understand the rationale(s) for not including a recommendation to avoid the use of live or live-attenuated vaccines with these drugs of similar mechanisms of action to remibrutinib. We consider this statement to be useful for the CSU population who may be more likely than the immunocompromised populations for which the other BTK inhibitors are indicated to be considered candidates for vaccines containing live viruses.

Question 3

Does the Agency agree with the recommendation to advise patients to avoid vaccines containing live virus during treatment with remibrutinib as discussed in Section 17, Patient Counseling Information, of the USPI?

FDA Response to Question 3

Please see response to Question 2. We agree that high-level general statements regarding the use of vaccines, such as to avoid the use of live vaccines, would be reasonable to include in Sections 5, 7 and 17.

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/

PHUONG N TON
06/02/2025 01:07:03 PM
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	May 12, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 218436
Product Name, Dosage Form, and Strength:	Rhapsido (remibrutinib) tablet, 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	January 31, 2025
TTT ID #:	2025-13040
DMEPA 1 Safety Evaluator:	Susan Shermock, PharmD, CPPS
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

1 INTRODUCTION

As part of the approval process for Rhapsido (remibrutinib) tablet, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Rhapsido 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.

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

3 CONCLUSION

The proposed Rhapsido 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 Pulmonology, Allergy, and Critical Care (DPACC) in Section 4 and for Novartis Pharmaceuticals Corporation in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

A. Prescribing Information

1. General Issues

    a. As currently presented, the proprietary name is denoted by the placeholder “TRADENAME.” We refer to our March 28, 2025, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Rhapsido, was found conditionally acceptable. We recommend replacing the placeholder “TRADENAME” with the conditionally acceptable proprietary name “Rhapsido” throughout the PI.

2. Section 16 How Supplied/Storage and Handling

    a. As currently presented in Storage, the unit of measure is missing from some of the temperature references. Unclear storage information may lead to confusion and potential risk of deteriorated drug medication errors. We recommend adding the unit of measure after each numerical degree in this section. Revise “15° - 30°C (59° - 86°F)” to “15°C to 30°C (59°F to 86°F)”.

b. The prescribing information includes a statement to [redacted] (b) (4) [redacted] (b) (4) However, the container labels and carton labeling state "Dispense and store in the original container". We confirmed with our Office of Pharmaceutical Quality colleagues that the drug product needs to be dispensed in the original container to prevent the uptake of moisture. Thus, we recommend updating Section 16 to state "Dispense and store in the original container to protect from moisture."

B. Patient Package Insert (PPI)

a. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME." We refer to our March 28, 2025, Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Rhapsido, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name "Rhapsido" throughout the PPI.

b. Revise the statement [redacted] (b) (4) [redacted] (b) (4) To "Store in the original container in order to protect from moisture."

5 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

Table 2. Identified Issues and Recommendations for Novartis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The placeholder for the lot number is missing.	Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
2.	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7> Labeling requires the expiration date to appear on the immediate container and all other packaging.

Table 2. Identified Issues and Recommendations for Novartis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The location for the human readable portion of the product identifier is missing from the label for the 60-tablet bottle sellable unit.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the container label.
Carton Labeling			
1.	We note the NDC is located on the principal display panel (PDP) of the 30-count sample carton and the top of the sample carton labeling containing two 30-count bottles (60 total tablets).	To ensure consistency between the 30 tablet and 60-count tablet sample carton labeling for the location of the assigned NDC placeholder.	Consider updating the location of the assigned NDC placeholder from the top panel of the sample carton labeling containing two 30-count bottles (60 total tablets) to the PDP to match the current design of the 30-count sample carton labeling.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Rhapsido received on January 31, 2025 from Novartis Pharmaceuticals Corporation.

Table 3. Relevant Product Information for Rhapsido	
Initial Approval Date	N/A
Active Ingredient	remibrutinib
Indication	Treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.
Dosage Form	tablet
Strength	25 mg
Route of Administration	Oral
Dose and Frequency	25 mg twice daily
How Supplied	60-count HDPE bottle (commercial pack) (commercial pack) 30-count HDPE bottle (physician pack)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in the original packaging in order to protect from moisture.
Container Closure	Child-resistant (CR) closure

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 Rhapsido labels and labeling submitted by Novartis Pharmaceuticals Corporation.

- Prescribing Information received on January 31, 2025, available from \\CDSESUB1\EVSPROD\nda218436\0000\m1\us\proposed-clean.docx
- Patient Package Insert received on January 31, 2025, available from \\CDSESUB1\EVSPROD\nda218436\0000\m1\us\proposed-clean.docx
- Container Label received on January 31, 2025
- Professional Sample Container Label received on January 31, 2025
- Professional Sample Carton Labeling 30-count received on January 31, 2025
- Professional Sample Carton Labeling 60-count received on January 31, 2025

B.2 Container Label(s) and Carton Labeling Images

(b) (4)

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

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

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/

SUSAN B SHERMOCK
05/12/2025 04:53:47 PM

DAMON A BIRKEMEIER
05/12/2025 04:58:47 PM