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RESEARCH**

APPLICATION NUMBER:

218436Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218436
Priority or standard	Priority
Submit date(s)	1/31/2025
Received date(s)	1/31/2025
PDUFA goal date	9/30/2025
Division/office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review completion date	9/30/2025
Established/proper name	Remibrutinib
(Proposed) proprietary name	RHAPSIDO
Pharmacologic class	Kinase inhibitor
Other product name(s)	LOU064
Applicant	NOVARTIS PHARMACEUTICALS CORP
Dosage form(s)/formulation(s)	Tablet, film-coated
Dosing regimen	25 mg orally BID
Applicant-proposed indication(s)/ population(s)	Treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine treatment
SNOMED CT code for proposed indication disease term(s)¹	396331005 (chronic idiopathic urticaria)
Regulatory action	Approval
Approved dosage (if applicable)	25 mg orally BID
Approved indication(s)/ population(s) (if applicable)	Treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine treatment
SNOMED CT code for approved indication disease term(s)¹	396331005 (chronic idiopathic urticaria)

¹ For internal tracking purposes only.

Abbreviations: BID, twice daily; LOU064, remibrutinib; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AAS	angioedema activity score
AAS7	weekly angioedema activity score
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
AI	acceptable intake
ALT	alanine aminotransferase
AMS	accelerator mass spectrometry
API	active pharmaceutical ingredient
ARA	acid-reducing agent
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BMX	bone marrow X-linked kinase
BP	blood pressure
BSEP	bile salt export pump
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
C _{6h}	plasma concentration measured at 6 hours postdose
C _{24h}	plasma concentration measured at 24 hours postdose
CBER	Center for Biologics Evaluation and Research
CD	cluster of differentiation
CDER	Center for Drug Evaluation and Research
CL	clearance
CL/F	apparent clearance
CL _r	renal clearance
CL _{ss} /F	apparent oral clearance at steady state
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CP	comparability protocol
CrCL	creatinine clearance
CSR	critical supersaturation ratio
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
CTCS	Computational Toxicology Consultation Service
CU	content uniformity
CV	coefficient of variation
CYP	cytochrome P450
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
ddf _m = bw	denominator degrees of freedom = betweenwithin
DLQI	dermatology quality of life index

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DMPK	drug metabolism and pharmacokinetics
EAOR	exposure-adjusted occurrence rate
EC	established condition
EC ₅₀	half-maximal effective concentration
ECG	electrocardiogram
eDiary	electronic (device) diary
EE	ethinylestradiol
E _{max}	maximum induction effect
E-R	exposure-response
FAS	full analysis set
FaSSGF	fasted state simulated gastric fluid
FaSSIF	fasted state simulated intestinal fluid
FeSSIF	fed state simulated intestinal fluid
FcεR	Fc epsilon receptor
FcεRI	Fc epsilon receptor-1
FcγR	Fc gamma receptor
FCT	film-coated tablet
FDA	Food and Drug Administration
FFM	fat-free mass
F _{gut}	fraction of oral remibrutinib that escapes gut metabolism
FM	fat mass
f _m CYP3A4	fractional contribution of CYP3A4
f _u	unbound fraction
f _{u,inc}	fraction unbound in incubation
GD	gestation day
GFJ	grapefruit juice
GLP	good laboratory practice
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HGC	hard gelatin capsule
HI	hepatic impairment
HSS	hives severity score
HSS7	weekly hives severity score
IC ₅₀	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-6	interleukin 6
IMP	investigational medicinal product
IND	investigational new drug
IndC ₅₀	substrate concentration that induce enzyme by 50%
Ind _{max}	maximal fold induction of an enzyme or gene expression
INR	international normalized ratio
IPC	in-process control
IR	Information Request

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ISR	incurred sample reanalysis
ISS	itch severity score
ISS7	weekly itch severity score
ITK	interleukin-2 inducible T-cell kinase
IV	intravenous
K_{app}	time-dependent inhibition constant
K_{deg}	degradation constant
K_I	inhibition constant (time-dependent)
K_i	inhibition constant (reversible inhibition)
K_{irr}	irreversible binding constant
$K_{I,u}$	unbound inhibition constant (time-dependent inhibition)
$K_{i,u}$	unbound inhibition constant (reversible inhibition)
K_{inact}	enzyme inactivation constant
K_{syn}	synthesis rate constant
KLH	keyhole Limpet hemocyanin
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLOQ	lower limit of quantification
LS	least squares
LSC	liquid scintillation counting
LVG	levonorgestrel
MAD	multiple-ascending dose
MAR	missing at random
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measures
MRHD	maximum recommended human dose
N	total number of subjects
n	number of subjects with given characteristic
NDA	new drug application
	(b) (4)
NIR	near-infrared
NIRS	near-infrared spectroscopy
	(b) (4)
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OC	oral contraceptive
OCMQ	OND custom medical uery
OCT	organic cation transporter
OFA	optimized-for-aging (rat)
OL	open-label
PACMP	postapproval lifecycle management protocol
PBPK	physiologically based pharmacokinetic
PCA	passive cutaneous anaphylaxis
PD	pharmacodynamic

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P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
pKa	acid dissociation constant
PMR	postmarketing requirement
PopPK	population pharmacokinetic
PPI	proton-pump inhibitor
PPV-23	polysaccharide vaccine, Pneumovax 23
PRC	precipitation rate constant
PRO	patient-reported outcome
PT	preferred term
QC	quality control
QD	once daily
QTcF	QT corrected for heart rate by Fridericia's formula
RAS	randomized analysis set
RDO	retrieved dropout
RRA	remote regulatory assessment
RTRT	real-time release testing
RTV	ritonavir
SAD	single-ascending dose
SAE	serious adverse event
SAF	safety analysis set
SDN	supporting document number
SF	scaling factor
SIL	stable-isotope-labeled
SIVA	Simcyp ® In Vitro Data Analysis
SRBC	sheep red blood cells
TDI	time-dependent inhibition
TEAE	treatment-emergent adverse event
TEC	tyrosine kinase expressed (in hepatocellular carcinoma)
THP-1	Tohoku Hospital Pediatrics-1
T _{max}	time to maximum plasma concentration
TMDD	target-mediated drug disposition
TXK	tyrosine kinase
t _{1/2}	half-life
UAS	urticaria activity score
UAS7	weekly urticaria activity score
ULN	upper limit of normal
UPDD	urticaria patient daily diary
USPI	United States Prescribing Information
V _{1/F}	apparent central volume of distribution
V _{2/F}	apparent peripheral volume of distribution
VA	variant alternative
VS	variant selected
V _{ss}	volume of distribution at steady state
V _{ss/F}	apparent volume of distribution at steady state

I. Executive Summary

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1. Overview

1.1. Summary of Regulatory Action

The Applicant, Novartis Pharmaceuticals Corporation, submitted NDA 218436 for remibrutinib (tradename: RHAPSIDO), an oral inhibitor of Bruton's tyrosine kinase (BTK), for "the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine treatment" at a proposed dosage of 25 mg orally twice daily. Because the Applicant redeemed a priority review voucher, the NDA was reviewed by a multidisciplinary review team on a priority review timeline. Each team recommends approval of remibrutinib for the proposed dosage and indication.

To support the NDA for remibrutinib, the Applicant submitted results from two adequate and well-controlled clinical investigations, CLOU064A2301 (REMIX-1) and CLOU064A2302 (REMIX-2), hereafter referred to as Trials A2301 and A2302. Trials A2301 and A2302 were replicate phase 3, randomized, double-blind, placebo-controlled trials that enrolled 925 adults to evaluate remibrutinib 25 mg orally twice daily over 52 weeks. Both trials demonstrated statistically and clinically significant improvements in patient-reported outcomes (PROs) of itch and hives.

The available safety data were adequate for review and the observed safety profile is acceptable for its intended use in antihistamine-refractory CSU patients. The most common adverse reactions were nasopharyngitis, bleeding (petechiae, contusion, ecchymosis), headache, nausea, and abdominal pain. Bleeding reactions were mild or moderate in severity, and a Warning and Precaution for bleeding risk was added to labeling.

The submitted clinical program is adequate to support the efficacy and safety of remibrutinib at the approved recommended dosage for the treatment of CSU in adult patients who remain symptomatic despite H1-antihistamine treatment. The clinical review team concludes that the improvement in itch and hives scores observed in the pivotal trials are clinically meaningful treatment benefits of remibrutinib that outweigh the potential risks and that remibrutinib will provide a novel oral treatment option in the armamentarium of CSU therapies. The NDA meets all applicable chemistry, manufacturing, and controls standards to support the purported identity, strength, quality, and purity of the remibrutinib drug product. The NDA includes appropriate preapproval nonclinical and clinical pharmacology studies. Postmarketing requirement (PMR) studies will be issued for pediatric studies to evaluate remibrutinib in children 12 to 17 years of age and 6 to 11 years of age with CSU, including a nonclinical juvenile toxicity study in rats, a pregnancy exposure registry, a pregnancy claims database retrospective cohort study, and a clinical lactation study.

The regulatory action for this application is Approval.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

To support the proposed indication for remibrutinib, the Applicant completed two replicate, adequate and well-controlled, pivotal trials, A2301 (REMIX-1) and A2302 (REMIX-2). The trials evaluated the efficacy and safety of remibrutinib in 912 adult subjects with CSU who remained inadequately controlled despite treatment with second-generation H1-antihistamines. The study design consisted of a 52-week treatment period, including a 24-week double-blind, placebo-controlled treatment phase followed by a 28-week open-label period where all subjects received remibrutinib, and concluded with a 4-week treatment-free follow-up period. A total of 925 subjects were randomized in a 2:1 ratio to remibrutinib 25 mg twice daily or placebo across both trials, with 470 subjects in Trial A2301 and 455 subjects in Trial A2302. Efficacy results were based on the 912 subjects who were treated in the 24-week blinded, controlled treatment period. The coprimary efficacy endpoints were the absolute change from baseline in weekly itch severity score (ISS7) and weekly hives severity score (HSS7) at Week 12. The ISS7 (range 0 to 21) was defined as the sum of the daily itch severity scores (range 0 to 3) recorded over a 7-day period. The HSS7 (range 0 to 21) was defined as the sum of the daily hive severity scores (range 0 to 3) recorded over a 7-day period. The key secondary endpoint was absolute change from baseline in weekly urticaria activity score (UAS7) at Week 12. The UAS7 (range 0 to 42) was a composite of the ISS7 and HSS7. Higher scores indicate greater symptom severity with a score of 0 reflecting absence of symptoms. Efficacy outcomes based on the UAS7 and its ISS7 and HSS7 components are direct, relevant measures of how patients with CSU feel and are established PRO endpoints for CSU development programs.

In Trial A2301, remibrutinib demonstrated statistically significant superiority over placebo with treatment differences of -2.63 (95% CI: -3.70 -1.56 ; $p < 0.001$) for ISS7 and -3.61 (95% CI: -4.85 , -2.36 ; $p < 0.001$) for HSS7 at Week 12. Trial A2302 showed similar results with treatment differences of -3.23 (95% CI: -4.29 , -2.16 ; $p < 0.001$) for ISS7 and -4.47 (95% CI: -5.71 , -3.23 ; $p < 0.001$) for HSS7 at Week 12. Likewise, the change from baseline in UAS7 at Week 12 in Trials A2301 and A2302 were -6.22 and -7.68 , respectively, compared to placebo and both statistically significant.

Efficacy was further supported by statistically significant and clinically meaningful results of secondary endpoints assessed by responder analyses on the UAS7, including $UAS7 \leq 6$ and $UAS7 = 0$. Compared to placebo, a higher proportion of subjects treated with remibrutinib achieved $UAS7 \leq 6$ at Week 12 (50% versus 25% in A2301; 47% versus 20% in A2302) and complete absence of itch and hives ($UAS7 = 0$) at Week 12 (31% versus 11% in A2301; 28% versus 7% in A2302). Further, the onset of statistically significant differences in the treatment effect were observed at Week 2 with 34% and 30% of subjects in the remibrutinib group achieving $UAS7 \leq 6$ compared to 3% and 6% of subjects in the placebo group in Trials A2301 and A2302, respectively.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• CSU is defined by the presence of spontaneous, recurrent urticaria (i.e., hives) for at least 6 weeks duration and without an identifiable cause. • The main clinical feature of CSU is hives with prominent pruritus; some patients experience angioedema in addition to hives. • CSU is a common condition with peak incidence in middle age (4th to 5th decade) and higher prevalence in women (2-3x more than men). • Activation of mast cells and basophils is central to the pathogenesis of CSU. • CSU is a nonprogressive, self-limited disorder in most patients, with a 1-year spontaneous remission rate of 30 to 50% and an average duration of 2 to 5 years.	CSU is a common condition, primarily affecting adults, that causes significant morbidity in patients with diminished quality of life. CSU is generally self-limited, resolving over several years, but some patients have more persistent disease.
Current treatment options	• Current guideline recommended first-line treatment options for CSU include H1-antihistamines (H1AH) at approved doses and up to 4-fold higher than approved doses. Most patients are successfully treated with H1AH. • For adults and adolescents 12 years and older who remain symptomatic despite H1AH treatment, omalizumab is recommended by national and international treatment guidelines. Dupilumab was also recently approved for CSU patients who remain symptomatic despite H1AH treatment. • Approximately 25 to 33% of patients remain symptomatic despite treatment with H1AH and omalizumab. Available data show that dupilumab is not effective in omalizumab refractory patients. Off-label therapies (e.g., cyclosporine, H2AH hydroxychloroquine, leukotriene receptor agonists) may be used to treat refractory symptoms and systemic corticosteroids may also be used periodically to gain short term control of worsening symptoms. The alternative off-label therapies have significant adverse event profiles.	Although safe and effective therapies exist for treatment of CSU, a subset of patients experience symptoms refractory to available treatment options. Additional treatment options with different mechanisms of action and routes of administration are desirable.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Substantial evidence of effectiveness of remibrutinib in CSU patients who remain symptomatic despite H1-antihistamine treatment was established in Trials A2301 and A2302, two identical, phase 3, randomized, double-blind, placebo-controlled trials. • The coprimary endpoints of change from baseline relative to placebo in ISS7 and HSS7 at Week 12 were statistically significant in both trials. Efficacy was supported by secondary endpoint results for change from baseline in UAS7 at Week 12, proportion of subjects with UAS7 ≤ 6 at Weeks 2 and 12, and proportion of subjects with a complete response, defined as UAS7 =0, at Week 12. • Exploratory subgroup analyses of subjects who had previously used omalizumab showed a similar treatment effect as in the overall population.	Remibrutinib demonstrated statistically significant and clinically meaningful effects on the primary symptoms of CSU, itch and hives. A meaningful treatment difference was observed by Week 2 and sustained through Week 24.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- The NDA safety database includes approximately 2900 subjects who were exposed to at least one dose of remibrutinib. Trials A2301 and A2302 provide the primary safety database for the proposed dosage and indication, and consists of 912 total subjects, with 868 treated with remibrutinib, of whom 772 were exposed for ≥24 weeks and 438 exposed for ≥52 weeks. - There were no deaths in the clinical development program. Nonfatal serious adverse events (SAEs) and adverse events leading to treatment discontinuation were infrequent. - The most common treatment-emergent adverse events (TEAEs) were nasopharyngitis, hemorrhage, headache, nausea, and abdominal pain. - Remibrutinib treatment was associated with an increased risk of bleeding, likely due to its pharmacologic effect on platelet function. Bleeding reactions primarily manifested as petechiae, contusion, ecchymosis, or purpura. A small number of subjects discontinued treatment due to bleeding reactions; however, all reactions were considered mild or moderate in severity. There was no correlation between increased risk of bleeding and thrombocytopenia. - Occurrence of other adverse events of special interest (AESIs) such as infections, cytopenias, and hepatotoxicity was similar between treatment groups. - A dedicated hepatic impairment (HI) study revealed 2- to 3.5-fold increases in remibrutinib systemic exposures across any degree of liver dysfunction. - Remibrutinib is susceptible to CYP3A4-mediated drug interactions. Moderate and strong CYP3A4 inhibitors increase exposure by 2- to 4-fold, while strong CYP3A4 inducers decrease exposure by ~75%. - Due to its mechanism of action, remibrutinib has the potential to impact the immune response to vaccinations. Although the Applicant conducted a vaccine immune response biomarker clinical study, the design and endpoints were inadequate to yield clinically relevant results.	The safety database is adequate to assess the safety of remibrutinib at the proposed dosage for the proposed context of use. A Warning and Precaution will be added for risk of bleeding. Because a single nominal dose and dosing regimen of remibrutinib (i.e., 25 mg BID) was evaluated in the pivotal phase 3 trials, there are limited clinical data to guide dose adjustments for patients who are expected to experience higher systemic exposures with the recommended dosage. Given the benefit/risk assessment of remibrutinib for CSU, a conservative approach will be taken in labeling to recommend avoidance of use in patients with any degree of HI and with concomitant strong or moderate CYP3A inhibitors. Given the lack of clinical outcome data, a Warning and Precaution will be added to recommend avoiding live or live-attenuated vaccines in patients receiving remibrutinib (b) (4) The potential risks of remibrutinib can be adequately addressed through labeling and pharmacovigilance. No REMS is required.

Abbreviations: BID, twice daily; CSU, chronic spontaneous urticaria; CYP, cytochrome P450; H2AH, H2 antihistamines; HSS7, weekly hives severity score; ISS7, weekly itch severity score; NDA, new drug application; REMS, risk evaluation and mitigation strategies; UAS7, weekly urticaria activity score

2.2. Conclusions Regarding Benefit-Risk

As described in Section [1.2](#), the Applicant has demonstrated substantial evidence of effectiveness for remibrutinib 25 mg twice daily (BID) for the treatment of CSU in adult patients who remain symptomatic despite H1-antihistamine treatment. The safety assessment of remibrutinib revealed no concerning safety signals that would preclude approval or require narrowing of the indicated target population or adding a limitation of use. Potential risks can be addressed through labeling and routine pharmacovigilance. Given that CSU is generally a self-limited condition with several therapeutic treatment options, the team recommends adding a Warning and Precaution to the United States Prescribing Information (USPI) for risk of bleeding and avoiding use in patients with hepatic impairment or concomitant cytochrome P450 (CYP)3A4 medication use due to increased drug exposure and risk of adverse reactions. The Pediatric Research Equity Act PMRs will be issued to conduct studies in pediatric subjects 12 to 17 years of age and subsequently 6 to 11 years of age, pending results of a repeat juvenile toxicity study in rats. As CSU disproportionately affects women of child-bearing age, PMRs will also be issued to identify unexpected serious risks of adverse maternal, fetal, and infant outcomes resulting from remibrutinib use during pregnancy and unexpected serious risks of the potential presence of remibrutinib in human breast milk resulting in effects on the breastfed infant.

In conclusion, the review team has determined that the benefit-risk assessment is favorable and supports the approval of remibrutinib 25 mg orally twice daily for the proposed indication of treatment of CSU in adult patients who remain symptomatic despite H1-antihistamine treatment. Although the development program did not enrich for a population of subjects who were refractory to all available therapies, there is a need for additional treatment options with varying mechanisms of action and alternative routes of administration.

II. Interdisciplinary Assessment

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3. Introduction

Chronic spontaneous urticaria, formerly known as chronic idiopathic urticaria, is a nonprogressive, typically self-limited, condition characterized by recurrent pruritic hives (wheals), with or without angioedema, for 6 weeks or longer without an identifiable etiology. The urticarial lesions are typified by central swelling with surrounding erythema, pruritus, and evanescent time course with individual lesions lasting up to 24 hours without residual scarring or bruising of the skin. When present, angioedema manifests as episodic submucosal or subcutaneous swelling, often affecting areas of the body with loose connective tissue in an asymmetric pattern. CSU is distinct from urticaria and/or angioedema that occurs secondary to a known trigger or underlying disease such as chronic inducible urticaria, hereditary angioedema, mastocytosis, autoimmune conditions, etc. CSU is a common condition affecting approximately 0.5 to 1% of the general population with higher prevalence in adult females and peak incidence in the 4th decade of life. CSU is a self-limited condition in most patients with a mean duration of 3 to 5 years and 2-year spontaneous remission rate of 30 to 50%; however, some patients may experience symptoms for decades.

The underlying pathophysiology of CSU involves degranulation of cutaneous mast cells and basophils leading to release of histamine and other mediators (e.g., cysteinyl leukotrienes, prostaglandins, platelet-activating factor, proinflammatory cytokines) that cause vasodilation, increased vascular permeability and pruritus, resulting in the characteristic wheals and angioedema ([Lang 2022](#)). Urticarial skin lesions have a predominantly lymphocytic infiltrate with occasional presence of eosinophils and neutrophils. Although mast cell activation is central to the underlying disease process of CSU, the precise mechanisms, especially in the absence of external triggers, remain incompletely understood.

Standard of care consists of nonsedating H1-antihistamines as first-line therapy, with dose escalation up to the four times approved doses. Although most patients will experience a partial or complete response with antihistamines alone, approximately 40 to 65% will remain sufficiently symptomatic to require escalation in therapy. Current treatment guidelines recommend omalizumab as an approved second-line therapy; however, about 30% of patients have symptoms refractory to omalizumab. Dupilumab was recently approved for patients who remain symptomatic despite H1-antihistamines; however, the clinical program failed to demonstrate a benefit in patients who are refractory to omalizumab. Cyclosporin, used off-label, remains a third-line option in nonresponders, but requires close monitoring for adverse reactions. Though there are safe and effective therapies for CSU, a sizeable subset of refractory patients exist for whom additional therapeutic options would be beneficial.

Remibrutinib (LOU064) is an oral BTK inhibitor that inhibits mast cell and basophil degranulation mediated by pathogenic immunoglobulin E (IgE) or immunoglobulin G (IgG) directed against the Fc epsilon receptor-1 (FcεRI) or IgE. It blocks IgE- and IgG-mediated FcεRI activation of mast cells and basophils and the subsequent release of histamine and other proinflammatory mediators that cause itch, hives, and angioedema.

The proposed indication is for the treatment of CSU in adult patients who remain symptomatic despite H1-antihistamine treatment at a proposed dosage of 25 mg orally twice daily. BTK inhibition represents a novel therapeutic target for CSU.

Although remibrutinib does not have breakthrough therapy designation for this indication nor meet criteria for a priority review, the Applicant submitted the NDA using the Rare Pediatric Disease Priority Review Voucher (NDA 217759); therefore, this application was granted a priority review. The following key efficacy and safety issues were identified during the review.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Evaluation of Weekly Angioedema Activity Score Efficacy Claims

3.1.2. Key Safety Review Issues

3.1.2.1. Bleeding Risk

3.1.2.2. Infection Risk

3.1.2.3. Cytopenias

3.1.2.4. Vaccine Immune Response

3.1.2.5. Use in Patients With Hepatic Impairment

3.1.2.6. Concomitant Use With CYP3A4 Modulators

3.2. Approach to the Clinical Review

The efficacy and safety review of remibrutinib for the proposed indication of CSU in adult patients who remain symptomatic despite H1-antihistamines treatment is based on the results from two identical, pivotal, phase 3 trials, REMIX-1 (CLOU064A2301; referred to as Trial A2301) and REMIX-2 (CLOU064A2302; referred to as Trial A2302). The study protocols are described in Section [6.2.2](#). A detailed clinical pharmacology review is available in Section [5.2](#).

Data from Trials A2301 and A2302 provided primary evidence evaluating the efficacy of remibrutinib versus placebo in the treatment of CSU. These data are presented in Section [6.2.2.8](#). For the evaluation of safety, data from Trials A2301 and A2302 were analyzed by the clinical data scientist using the R programming environment and the clinical reviewer using JMP

Clinical and the Analysis Toolbox (Office of Computational Science). The safety results are presented in Section [7](#).

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

Treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine treatment.

2. SEE was established with

a. Adequate and well-controlled clinical investigation(s):

- i. Two or more adequate and well-controlled clinical investigations, **OR**
- ii. One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. One adequate and well-controlled clinical investigation and confirmatory evidence ([May 1998](#); [December 2019](#); [September 2023](#))

OR

c. Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch) ([May 1998](#))

3. Complete response, if applicable

- a. SEE was established
- b. SEE was not established

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for Remibrutinib (LOU064)

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
REMIX-1 (CLOU064A2301)	Adults with CSU who remain symptomatic despite H1AH treatment	Control type: Placebo concurrent in double-blind period	Drug: Remibrutinib (LOU064)	Coprimary: - Absolute change from baseline in ISS7 at Week 12 - Absolute change from baseline in HSS7 at Week 12	Planned: 450 subjects per trial	Centers: - REMIX-1: 115 - REMIX-2: 122
REMIX-2 (CLOU064A2302) (identical designs)		Randomization: Stratified randomization	Dose: 25 mg BID	Secondary: See footnotes ¹	Actual: REMIX-1: - Remibrutinib (N=313) - Placebo (N=157) REMIX-2: - Remibrutinib (N=300) - Placebo (N=155)	Countries: 18 per trial Japan (27) China (65) AMEA (291) United States (200) LaCAN (117) RE (212)
		Randomization ratio: 2:1	Number treated: REMIX-1: - Remibrutinib (N=309) - Placebo (N=153) REMIX-2: - Remibrutinib (N=297) - Placebo (N=153)			
		Blinding: Double-blind in Period 1 and open-label in Period 2	Duration: 24-week double-blind period; 28-week open-label period			

Source: Clinical Study Report and adsl.xpt

¹ Key secondary endpoints: Achievement of UAS7 ≤6 (yes/no) at Week 12 and achievement of UAS7 =0 (yes/no) at Week 12. See Clinical Study Report for other secondary endpoints.

Abbreviations: AMEA: Asia, Middle East and Africa; BID, twice daily; CSU, chronic spontaneous urticaria; H1AH, H1-antihistamine; HSS7, weekly hives severity score; Ig, immunoglobulin; ISS7, weekly itch severity score; No., number; LaCAN: Latin America, Caribbean and Canada; RE, Regional Europe; UAS7, weekly urticaria activity score

4. Patient Experience Data

Patient experience data used to assess the efficacy of remibrutinib are summarized in [Table 4](#).

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Sections 6.2.2.5 , 6.2.2.8.3 , 6.2.2.8.4 and 15.1.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Remibrutinib is an oral, small molecule inhibitor of BTK, a member of the tyrosine kinase expressed (in hepatocellular carcinoma) (TEC) family of nonreceptor tyrosine kinases consisting of BTK, TEC, bone marrow X-linked kinase (BMX), interleukin-2 inducible T-cell kinase (ITK), and tyrosine kinase (TXK). It inhibits both unphosphorylated and phosphorylated BTK with nanomolar potency. BTK is expressed on mast cells, basophils, B-cells, macrophages, microglia, and platelets. In B-cells, BTK is an important mediator of B-cell receptor signaling involved with

B-cell survival, proliferation, migration, and differentiation of memory B-cells in antibody producing plasma cells. In mast cells and basophils, BTK is a component of FcεRI and Fc gamma receptor (FcγR) signaling. In platelets, BTK is implicated in aggregation and clot retraction.

CSU is a chronic skin disease characterized by the presence of chronic (lasting ≥6 weeks with three to four occurrences/week) hives with no identifiable cause. Patients with CSU exhibit increased numbers of dermal mast cells and circulating inflammatory markers, including interleukin 6 (IL-6). In approximately 50% of patients with CSU, IgG autoantibodies against IgE or FcεRI have been detected. In these cases, autoantibodies may activate mast cells and basophils resulting in the release of mediators such as histamine. Remibrutinib is proposed as an inhibitor of mast cell and basophil degranulation mediated by pathogenic IgE or IgG directed against the FcεRI or IgE and blocker of 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. In vivo, remibrutinib showed a response in two animal models relevant to CSU, a mouse reverse passive Arthus model and a mouse passive cutaneous anaphylaxis model. These are models of skin mast cell degranulation induced by FcγR- and Fc epsilon receptor (FcεR)-mediated hypersensitivity.

Established Pharmacologic Class Discussion

(b) (4)

(b) (4) Remibrutinib inhibits human BTK with nanomolar potency (half-maximal inhibitory concentration [IC₅₀]: 0.6 to 7.5nM) and is more selective for BTK compared to the BTK-related enzymes TEC and BMX (IC₅₀: 124 to 141nM). However, clinical pharmacokinetic data from the proposed clinical dose of 25 mg BID suggests a remibrutinib concentration of approximately 128nM, which is sufficient to potentially inhibit the BTK-related kinases TEC and BMX (refer to [Table 5](#) below). Therefore, the totality of in vitro and in vivo pharmacology data submitted support the established pharmacologic class of remibrutinib as a kinase inhibitor.

Table 5. Estimated Concentrations of Remibrutinib Based on Clinical Data

Clinical Dose¹	AUC_{0-24h}(h*ng/mL)	C_{max,ss} (ng/mL)	Concentration (uM)
25 mg BID	390	64.9	0.1278
100 mg BID	1522	219	1.4

Source: Reviewer-generated table

¹ Clinical dose data for 25 mg and 100 mg twice daily (BID) dose obtained from Study A2201 where the AUC_{0-24h} was calculated as 2*AUC_{tau}. Note that the drug product used for the study is not the to-be-marketed formulation (see Study BBT002-popPK-001).

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max,ss}, maximum plasma concentration at steady state

5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology and pharmacokinetics of remibrutinib are summarized below in [Table 6](#).

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	<i>Pharmacologic Activity</i>
Established pharmacologic class (EPC)	Kinase inhibitor
Mechanism of action	Inhibits both unphosphorylated and phosphorylated Bruton's Tyrosine Kinase (BTK). Remibrutinib inhibits mast cell and basophil degranulation mediated by pathogenic immunoglobulin E (IgE) or IgG directed against the Fc epsilon receptor-1 (FcεRI) or IgE. It blocks IgE- and IgG-mediated FcεRI activation of mast cells and basophils; therefore, prevents the release of histamine and other proinflammatory mediators that cause itch, hives, or angioedema.
Active moieties	Remibrutinib
QT prolongation	It was previously determined that the risk of QT prolongation was adequately characterized in Studies X2101 and X1101, which are acceptable substitutes for a thorough QT study. Based on two phase 1 clinical trials, at concentrations approximately nine times the mean maximal concentration provided by the recommended dosage, clinically significant QTc prolongation was not observed. Refer to the QT-IRT review in DARRTS dated June 2, 2025 (Reference ID: 5601158).

Characteristic	Drug Information						
	General Information						
Bioanalysis	Whole blood concentrations of remibrutinib were measured using LC-MS/MS assays. The bioanalytical methods were adequately validated, and the in-study performance was acceptable.						
Healthy subjects versus patients	No clinically relevant differences in remibrutinib pharmacokinetics were observed between healthy volunteers and patients with chronic spontaneous urticaria (CSU).						
Drug exposure at steady state following the therapeutic dosing regimen	Table 7. Simulated Arithmetic Mean (SD) PK Parameters for Remibrutinib in Typical Subjects With CSU at Steady State Following 25-mg BID Dose <table border="1"> <thead> <tr> <th>Parameter</th> <th>Mean (SD)</th> </tr> </thead> <tbody> <tr> <td>AUC_{tau} (hr.ng/mL)</td> <td>193 (136)</td> </tr> <tr> <td>C_{max,ss} (ng/mL)</td> <td>57 (27)</td> </tr> </tbody> </table> Source: Reviewer generated table based on the results reported in population pharmacokinetics of remibrutinib, Tables 7-10 and 7-11. Abbreviation(s): AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max,ss}, maximum plasma concentration at steady state; BID, twice daily; CSU, chronic spontaneous urticaria; PK, pharmacokinetic; SD, standard deviation	Parameter	Mean (SD)	AUC _{tau} (hr.ng/mL)	193 (136)	C _{max,ss} (ng/mL)	57 (27)
Parameter	Mean (SD)						
AUC _{tau} (hr.ng/mL)	193 (136)						
C _{max,ss} (ng/mL)	57 (27)						
Range of effective dose(s) or exposure	In the pivotal phase 3 trials (A2301 and A2302), 25 mg BID was the only dosage evaluated and demonstrated superiority to placebo on the coprimary efficacy endpoints of change from baseline to Week 12 in the weekly hives severity score (HSS7) and the weekly itch severity score (ISS7). In a phase 2 dose-ranging study (A2201), all remibrutinib dosages evaluated, ranging from 10 mg QD to 100 mg BID demonstrated improvement over placebo in the primary endpoint of change from baseline to Week 4 in the weekly urticaria activity score (UAS7). Notably, the treatment effect was comparable across all dosages remibrutinib with no apparent dose-response.						
Maximally tolerated dose or exposure	In healthy subjects, the highest dosage of remibrutinib evaluated was 600 mg QD for 12 days in Study X2101 (see Section 14.2.1.1). In subjects with CSU, the highest dosage of remibrutinib evaluated was 100 mg BID for 12 weeks in Study A2201 and 52 weeks in Study A2201E1 (see Sections 14.2.7, 17.3, and 17.4). Including the double-blind and open-label period in the pivotal trials, subjects were exposed to remibrutinib 25 mg BID up to a maximum of 61 weeks (see Section 7.5).						
Dose proportionality	In Study A2201, remibrutinib steady-state C _{max} and AUC _{tau} increases in an approximately dose-proportional manner over the dosage range of 10 mg twice daily to 100 mg twice daily (0.4 to 4 times the highest approved recommended dosage) in subjects with CSU.						

NDA 218436
RHAPSIDO (remibrutinib, LOU064)

Characteristic	Drug Information
Accumulation	Following the administration of multiple doses of 25 mg twice daily, C_{max} increases 1.6-fold and AUC_{0-4} increases 2.7-fold. The AUC_{0-4} at steady state was obtained from Study A2201 following the administration of 25 mg BID, while the initial AUC_{0-4} was calculated from Study X2101 following administration of the first dose of 25 mg. Both studies, X2101 and A2201, employed an identical hard gelatin capsule formulation and bioanalytical method. The median body weight of subjects in both studies was 77 kg. Study X2101 was conducted in a generally healthy population, whereas Study A2201 was performed on subjects with CSU. Note that there is accumulation despite the short half-life of remibrutinib. This is likely due to the distribution/disposition of remibrutinib in human body.
Time to achieve steady state	Following twice daily dosing of remibrutinib, steady state was achieved by Day 2.
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed formulation (film-coated tablet) was used in all phase 3 trials. The interim formulation used during development was compared to the to-be-marketed formulation in a comparative BA study (X2105). Study X2105 was conducted to compare remibrutinib systemic exposure between the interim hard gelatin capsule formulation used in phase 1 and 2 clinical trials and the to-be-marketed film-coated tablet formulation. Relative to the hard gelatin capsule formulation, the film-coated tablet formulation yielded 28% lower C_{max} and 20% lower AUC_{0-inf} . Refer to Section 14.2.3 for details. These differences are considered small with no clinical relevance.
Absorption	
Bioavailability	The absolute bioavailability for the to-be-marketed film-coated tablet formulation was not determined.
T_{max}	Median T_{max} is approximately 1 hour under fasted conditions.
Food effect (fed/fasted) Geometric least-squares mean and 90% CI	No clinically meaningful food effect was observed. Following the administration of remibrutinib 25 mg BID using the to-be-marketed film-coated tablet formulation to healthy subjects, a standard high-fat meal delayed T_{max} by approximately 1 hour compared to the T_{max} in the fasted state. In comparison to the fasted state, the C_{max} was slightly lower in the fed state with a geometric LSM ratio (90% CI) (fed/fasted) of 0.951 (0.763 to 1.19) and the AUC_{0-12h} was slightly higher in the fed state with a geometric LSM ratio (90% CI) (fed/fasted) of 1.33 (1.19 to 1.49) (see Section 14.2.4).
Distribution	
Volume of distribution	Based on population PK analysis, remibrutinib volume of distribution at steady state was 58 L (central compartment) and 1180 L (peripheral compartment).
Plasma protein binding	Remibrutinib plasma protein binding is 95.4%
Drug as substrate of transporters	Remibrutinib is a substrate for P-glycoprotein (P-gp), but it is not a substrate for other tested efflux or uptake transporters.

Characteristic	Drug Information
	Elimination
Mass balance results	The recovery of radioactivity following oral administration was incomplete, with only 56.2% of the administered dose being accounted for at the end of Day 8. The reason for this is unclear but the Applicant attributes this to technical issues. The majority of the recovered radioactivity was excreted in feces (31.8%) and then urine (24.4%). The recovery of intravenously administered [¹⁴C]-remibrutinib was nearly complete at the end of Day 4, with the majority of the radioactivity also recovered in feces (67% to 71.7%). About 26% to 30% of the radioactivity was recovered in the urine following IV dosing. Following oral administration, remibrutinib was the predominant species in blood, constituting 16.7% of the blood ¹⁴C-AUC_{0-24h}. The unchanged remibrutinib in excreta represented 1.86% of the administered dose and none of the metabolites accounted for ≥10% of the total. The amount of unchanged remibrutinib excreted in urine was minimal, constituting 0.65% of the oral dose, suggesting negligible renal excretion of remibrutinib. Following IV dosing, the amount of unchanged remibrutinib excreted in urine was 2.93%. In urine, none of the metabolites accounted for >10% for the total. Remibrutinib is assumed to be completely absorbed (Fa >98%) and extensively metabolized, as only 1.21% of the oral dose was excreted in feces as unchanged remibrutinib. Unchanged remibrutinib was not detected in feces following intravenous administration. In feces, none of the metabolites accounted for >10% for the total. There was no specific distribution of drug-related components into blood cells following either intravenous or oral administration of remibrutinib. The AUC_{0-inf} of total radioactivity in plasma was marginally higher than that in whole blood (14900 h*ng-eq/mL versus 12700 h*ng-eq/mL) following oral administration. The AUC_{0-inf} of total radioactivity following intravenous administration in plasma and whole blood were also comparable (16.9 versus 18.5 h*ng-eq/mL in IV Arm A and 13.2 versus 12.8 h*ng-eq/mL in IV Arm B), indicating an equal distribution of total radioactivity between plasma and red blood cells. For additional details see Section 14.2.2.
Clearance	Based on population PK analysis, the apparent oral clearance of remibrutinib is 160 L/hr.
Half-life	The elimination half-life of remibrutinib is 1 to 2 hours.
Metabolic pathway(s)	Remibrutinib is primarily metabolized by CYP3A4.
Primary excretion pathways (% dose)	Following the oral administration of 100-mg radiolabeled remibrutinib, unchanged remibrutinib in excreta represented 1.86% of the administered dose (0.65% in urine and 1.21% in feces). Following IV administration of radiolabeled remibrutinib, the amount of unchanged remibrutinib in urine was 2.93% of the dose with none detected in feces. No metabolite in urine or feces accounted for at least 10% of total exposure following oral or IV dosing.

Characteristic	Drug Information
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	No clinically meaningful effect of body weight on the pharmacokinetics of remibrutinib was observed. The impact of body weight on the pharmacokinetics of remibrutinib was assessed through the combined effects of fat-free mass (FFM) and fat mass (FM) using population PK analysis. Overall, no clinically significant differences in the pharmacokinetics of remibrutinib were observed over the body weight range of 39 to 162 kg.
Age	Population PK analyses indicated that age (18 to 80 years) does not significantly impact the pharmacokinetics of remibrutinib in subjects with CSU.
Race/Ethnicity	Based on population PK analysis, no clinically meaningful effect of race/ethnicity (59.3% non-Asian, 8.8% Mainland Chinese, 12.2% Japanese, and 19.7% other Asian) on the pharmacokinetics of remibrutinib was observed.
Renal impairment	No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Renal excretion of remibrutinib was found to account for <1% of total blood clearance. In the mass balance study, the amount of unchanged remibrutinib excreted in urine was $\leq 2.9\%$ of the dose. In addition, population PK analysis indicated that creatinine clearance, ranging from 23 to 275 mL/min, did not significantly influence the clearance of remibrutinib.
Hepatic impairment	The use of remibrutinib should be avoided in patients with mild, moderate, or severe hepatic impairment (HI) (Child-Pugh Class A, B, or C). Following the administration of remibrutinib at a dose of 25 mg twice daily, the geometric mean ratios for patients with mild, moderate, and severe HI compared to subjects with normal hepatic function were 1.85, 1.65, and 1.99, respectively, for C_{max}, and 2.33, 2.3, and 3.49, respectively, for $AUC_{last,ss}$ (see Section 14.2.5).
	<i>Drug-Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism or transporters system by remibrutinib	Coadministration of remibrutinib at 100 mg with a single dose of 0.25 mg digoxin (a P-gp substrate) increased digoxin C_{max} by 2.1-fold and AUC by 1.4-fold (see Section 14.2.6.2). Coadministration of remibrutinib at 100 mg with a single dose of 10-mg rosuvastatin (a BCRP and OATP1B substrate) increased rosuvastatin C_{max} by 1.6-fold and AUC by 1.7-fold (see Section 14.2.6.2). Remibrutinib at the recommended dose of 25 mg twice daily is not expected to have a clinically relevant effect on the pharmacokinetics of midazolam (CYP3A4 substrate), combined oral contraceptives containing ethinylestradiol and levonorgestrel (CYP3A4 substrate), tolbutamide (CYP2C9 substrate), caffeine (CYP1A2 substrate), and coproporphyrin I (endogenous OATP1B substrate) based on in vivo DDI studies conducted with high doses of remibrutinib (100 mg) and physiologically based pharmacokinetic (PBPK) simulations. Refer to Sections 14.2.6 and 14.5.3 for details.

Characteristic	Drug Information
Effect of other drugs on remibrutinib	<i>Drug-Interaction Liability (Drug as Victim)</i> Remibrutinib C_{max} increased by 3.3-fold and AUC increased by 4.3-fold following concomitant administration with ritonavir 100 mg BID for 4 days (strong CYP3A4 inhibitor) (see Section 14.2.6.1). Remibrutinib C_{max} increased by 1.24-fold and AUC increased by 1.3-fold when coadministered with grapefruit juice (see Section 14.2.6.1). Remibrutinib C_{max} is predicted to increase by approximately 1.9-fold and AUC is predicted to increase by approximately 2.3-fold following concomitant administration with erythromycin (a moderate CYP3A4 inhibitor) 500 mg four times a day for 7 days (see Section 14.5.3). Remibrutinib C_{max} decreased by 74% and AUC decreased by 77% following concomitant administration with carbamazepine (a strong CYP3A4 inducer) 300 mg twice daily for 14 days (see Section 14.2.6.2). Remibrutinib C_{max} is predicted to decrease by approximately by 60% and AUC is predicted to decrease by approximately 64% following concomitant administration with efavirenz (a moderate CYP3A4 inducer) 600 mg once daily for 14 days (see Section 14.5.3). No clinically relevant changes in remibrutinib exposure were observed among subjects with CSU who were concomitantly taking acid-reducing agents. The risks and benefits of coadministration of antithrombotic agents with remibrutinib should be considered due to the potential platelet inhibitory effect of remibrutinib as a BTK inhibitor. No PK data are available for the coadministered anticoagulants in phase 3 trials. Exposure-response analysis indicated no significant relationship between the incidence of bleeding and increasing remibrutinib concentration at steady state.

Source: Reviewer-generated summary table.

Abbreviation: AUC, area under concentration-time curve; AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{last} , area under the concentration-time curve from time 0 to last timepoint; AUC_{Iau} , area under the concentration-time curve over the dosing interval; BA, bioavailability; BCRP, breast cancer resistance protein; BID, twice daily; CI, confidence interval; C_{max} , maximum observed plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state; CYP, cytochrome P450; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; Fa, fraction absorbed; ID, identifier; IgG, immunoglobulin G; IV, intravenous; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LSM, least-squares mean; OATP, organic anion transporting polypeptide; PK, pharmacokinetic; QD, once daily; QT-IRT, QT-interdisciplinary review team; T_{max} , time to maximum plasma concentration

6. Efficacy (Evaluation of Benefit)

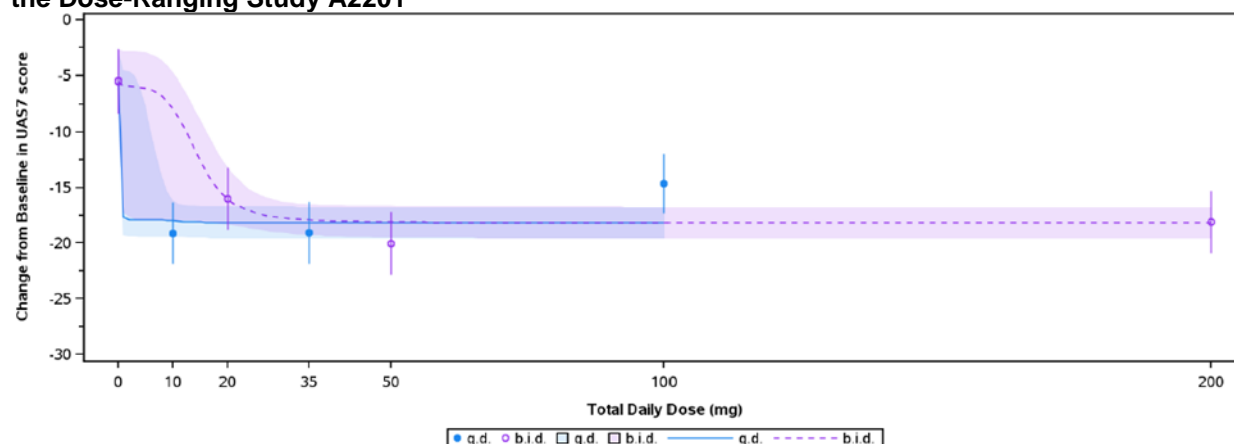
6.1. Assessment of Dose and Potential Effectiveness

Supporting Evidence for the Selected Dose

Dose-Ranging

The selection of remibrutinib 25 mg BID dosing for the pivotal phase 3 clinical Trials A2301 and A2302 was based on findings from a dose-ranging phase 2 study (A2201) (see Section 14.2.7). In Study A2201, adult subjects with CSU who remained inadequately controlled on second-generation H1-antihistamines were randomized to receive remibrutinib at various dosing regimens: 10 mg once daily (QD), 35 mg QD, 100 mg QD, 10 mg BID, 25 mg BID, 100 mg BID, or placebo. The primary endpoint in Study A2201 was the change from baseline in the UAS7 at Week 4 compared to placebo. The estimated difference in least-squares means relative to placebo were as follows: -13.66 for 10 mg QD, -13.64 for 35 mg QD, -9.21 for 100 mg QD, -10.55 for 10 mg BID, -14.58 for 25 mg BID, and -12.62 for 100 mg BID. Notably, all dose groups demonstrated an improvement over placebo in UAS7 at Week 4. The treatment effect was comparable across all dose groups evaluated in Study A2201 but was numerically highest among subjects randomized to receive the 25-mg BID dosage. This finding is further corroborated by the dose-response relationship, which demonstrated that all dosages lie on the plateau region of the response curve (Figure 1). Importantly, the observed dose-response relationship is defined based on improvement over the placebo as there is no apparent difference between any of the administered dosing regimens, irrespective of dosing frequency.

Figure 1. Dose-Response Relationship Based on Change From Baseline UAS7 Score at Week 4 in the Dose-Ranging Study A2201



Source: Study A2201 Clinical Report, Figure 11-1

The dose is displayed as total daily dose.

The dose-response curve shows the median value from 5000 bootstrap samples.

The shaded area displays the 90% prediction interval from 5000 bootstrap samples.

The dots with the error bar represent LS mean and 90% CI from the MMRM.

Abbreviations: BID, twice daily; CI, confidence interval; LS mean, least-squares mean; MMRM, mixed model for repeated measures; QD, once daily; UAS7, weekly urticaria activity score

Similar results were observed for numerous secondary endpoints, including the change from baseline to Week 12 in UAS7, the change from baseline in UAS7 over time, the proportion of subjects achieving a UAS7 score of 0 at Week 12, and the proportion of subjects achieving a UAS7 score ≤ 6 at Week 12. For all endpoints, improvement over placebo was demonstrated at all dosages of remibrutinib, with numerically greatest response observed with the 25-mg BID dosage (refer to Figure 11-2, and Tables 11-4 and 11-5, clinical study report for Study A2201).

Based on the relatively flat dose-response observed in Study A2201, the Agency recommended evaluating more than one remibrutinib dose in phase 3 trials; however, the Applicant chose to carry forward a single nominal dose and dosing regimen of remibrutinib 25 mg BID. Although 25-mg BID remibrutinib resulted in the numerically greatest response for the primary endpoint and numerous secondary endpoints, Study A2201 was not designed to evaluate for significant differences between the various remibrutinib dosing regimens. All dosages demonstrated improvement over placebo with overlap observed in the treatment effects.

Phase 3 Trials

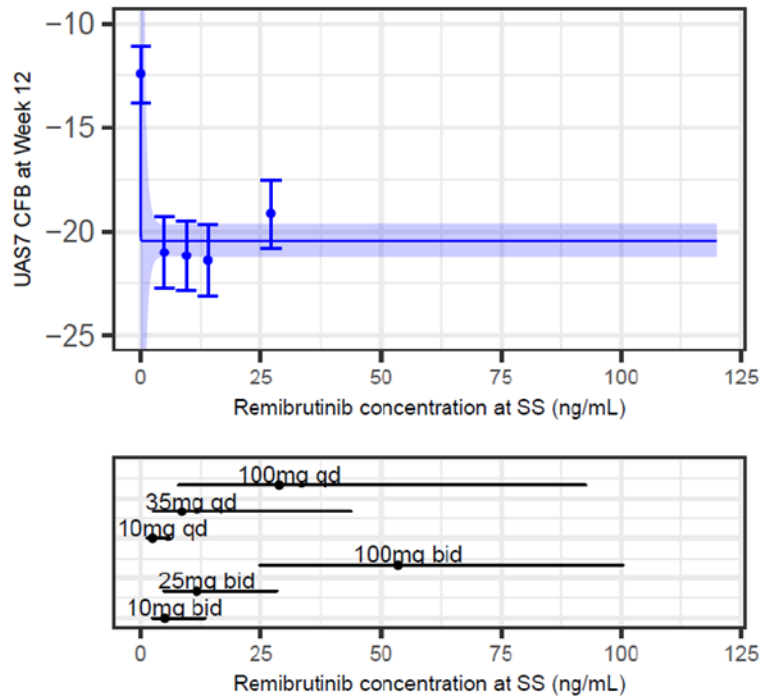
In pivotal phase 3 Trials A2301 and A2302, 25 mg BID was the only dosing regimen evaluated in adult subjects with CSU inadequately controlled by H1-antihistamines. For full details on the study designs and efficacy results from Trials A2301 and A2302, refer to Sections [6.2.1](#) and [6.2.2](#), respectively. In both trials, treatment with 25-mg BID remibrutinib yielded significant improvements over placebo in the coprimary efficacy endpoints of change from baseline to Week 12 in the HSS7 and the ISS7.

Exposure-Response Analyses

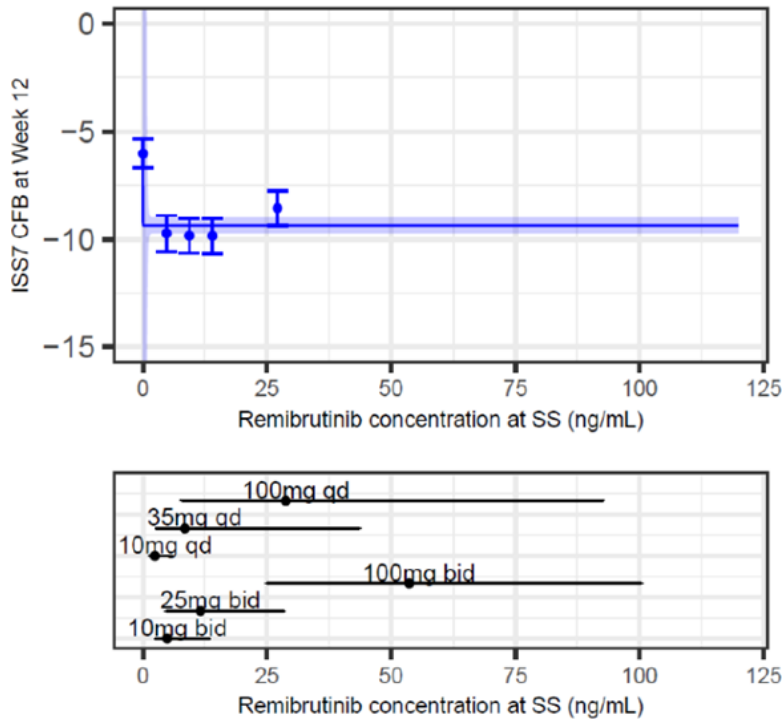
The 25-mg BID dosing regimen was also supported by exposure-response (E-R) analyses, which evaluated the correlation between the average steady-state concentration of remibrutinib and changes from baseline in ISS7, HSS7, and UAS7. Efficacy data and simulated average steady-state concentrations of remibrutinib at six dose levels (10 mg QD, 35 mg QD, 100 mg QD, 10 mg BID, 25 mg BID, 100 mg BID) plus placebo from the dose-ranging phase 2 study (A2201) and the two phase 3 trials (A2301 and A2302) were included in the E-R analyses. Analyses demonstrated a maximum induction effect (E_{max}) type of E-R relationship across all measured endpoints, with the plateau of therapeutic effect achieved at relatively low drug exposures ([Figure 2](#)). Refer to Section [14.5.2](#) for details. Results of the E-R analyses are similar to the dose-response relationship observed in Study A2201. The E-R relationship appears to be primarily driven by the difference from the placebo group as there was little difference in efficacy across quartiles of average concentrations at steady state.

Figure 2. Exposure-Response Relationship for Change From Baseline in UAS7, ISS7, and HSS7 at Week 12 vs. $C_{avg,ss}$ Based on Pooled Data Across Trials A2201, A2301, and A2302

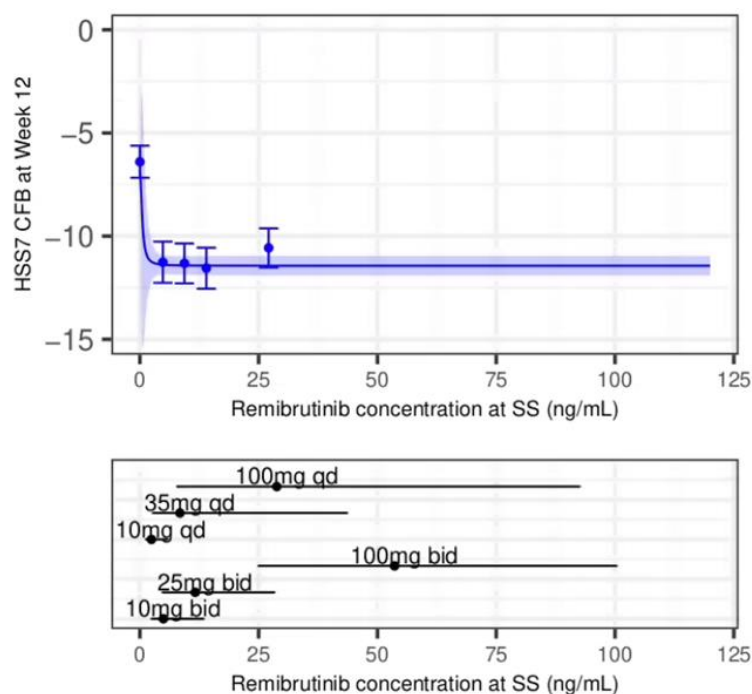
A: Change From Baseline in UAS7



B: Change From Baseline in ISS7



C: Change From Baseline in HSS7



Source: Applicant's E-R report, Figures 7-14, 7-15, and 7-16

Top panel: Blue line is the model predicted response with 95% CI (shaded area). Blue dots with error bars represent mean with 95% CI of the observed response by quartile of positive $C_{avg,ss}$ distribution, and a separate bin for placebo response (plotted at $C_{avg,ss}=0$).

Bottom panel: Summary of individual $C_{avg,ss}$ by dosing regimen: median and the 5th to 95th percentiles of distribution for each dosing regimen are represented with the dot and the horizontal bar.

Abbreviations: BID, twice daily; $C_{avg,ss}$, average concentration at steady state; CFB, change from baseline; CI, confidence interval; E-R, exposure-response; HSS7, weekly hives severity score; ISS7, weekly itch severity score; QD, once daily; SS, steady state; UAS7, weekly urticaria activity score

The E-R analyses for safety, based on data from the phase 2 study (A2201) and the two phase 3 trials (A2301 and A2302), did not identify a significant relationship between remibrutinib exposure and adverse events (AEs), serious adverse events (SAEs), or AEs of special interest (bleeding, cytopenia, and infection). Refer to Section [14.5.2](#) for details.

The available data indicate that the proposed dosage of 25 mg BID is appropriate for the treatment of adult patients with CSU who remain symptomatic despite H1-antihistamine treatment.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Efficacy Trials, A2301 and A2302

The efficacy of remibrutinib for CSU was primarily demonstrated through two large, identically designed phase 3 pivotal trials: CLOU064A2301 (A2301) and CLOU064A2302 (A2302). These were global, randomized, double-blind, placebo-controlled trials that evaluated remibrutinib 25 mg twice daily versus placebo in adult subjects with CSU inadequately controlled by H1-antihistamines. Both trials had a 52-week treatment period, consisting of a 24-week placebo-

controlled treatment period followed by a 28-week single-arm, unblinded treatment period. The primary efficacy analysis was conducted at Week 12.

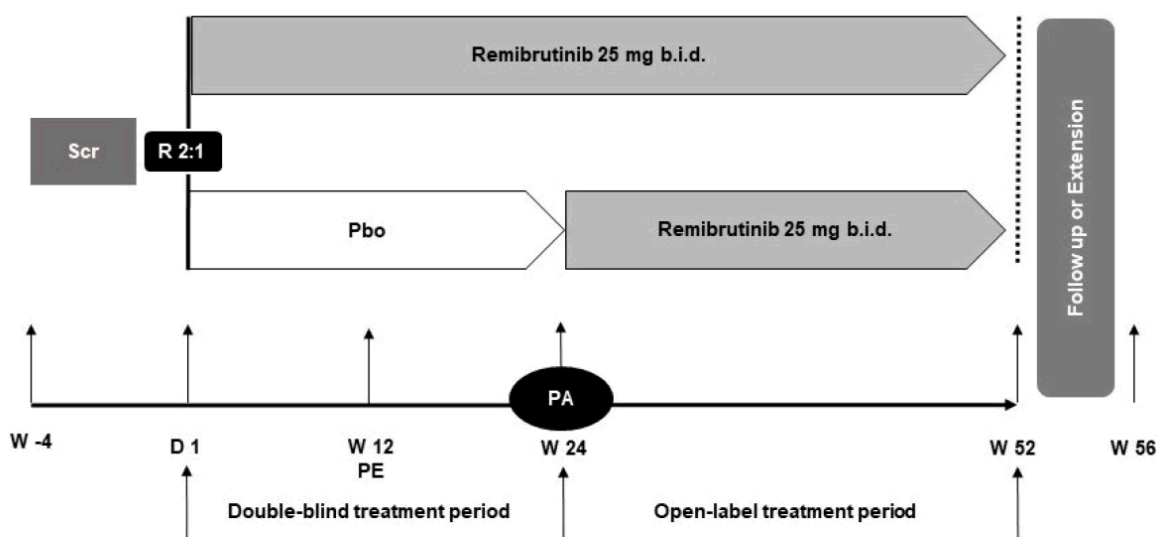
6.2.2. Trials A2301 and A2302

6.2.2.1. Design and Conduct, Trials A2301 and A2302

Given that Trials A2301 (REMIX-1) and A2302 (REMIX-2) were identical in design, the protocols are discussed in tandem. Both were multicenter, 52-week, randomized, double-blind, parallel-group, placebo-controlled phase 3 trials investigating the efficacy, safety, and tolerability of remibrutinib 25 mg twice daily in adult subjects with CSU inadequately controlled by H1-antihistamines. After obtaining informed consent, subjects entered a screening period of up to 4 weeks during which subjects underwent an evaluation to determine their eligibility. The screening visit included a physical exam, collection of demographic information, height and weight measurements, vital signs assessment, and electrocardiogram (ECG) recording. Subjects received their electronic (device) diary (eDiary) during the screening period, which was used throughout the study to complete the urticaria patient daily diary (UPDD) containing the urticaria activity score (UAS) and angioedema activity score (AAS).

Eligible subjects were randomized in a 2:1 ratio to receive either remibrutinib 25 mg or matching placebo orally twice daily for 24 weeks. Following the double-blind, placebo-controlled treatment period, all subjects received open-label remibrutinib for the remaining 28 weeks of the trial. After completing the 52-week treatment period, subjects were followed for 4 weeks off-treatment. The study schematic is shown in [Figure 3](#). The schedule of study assessments is in Section [15.1.1](#).

Figure 3. Study Design, Trials A2301 and A2302



D-1: Day 1, b.i.d.: bis in die/twice a day, mg: milligram(s), Pbo: placebo, PA: Primary Analysis, PE: Primary Endpoint, Scr: Screening, W: Week

Source: Applicant-provided CSRs, p. 40

6.2.2.2. Eligibility Criteria, Trials A2301 and A2302

Key eligibility criteria for the trials are summarized below.

Inclusion Criteria

- Male and female adult subjects ≥ 18 years of age at the time of screening.
- CSU duration for ≥ 6 months prior to screening (defined as the onset of CSU determined by the investigator based on all available supporting documentation).
- Diagnosis of CSU inadequately controlled by second-generation H1-antihistamines at the time of randomization defined as:
  - Presence of itch and hives for ≥ 6 consecutive weeks prior to screening despite use of second-generation H1-antihistamines during this time period
  - UAS7 score (range 0 to 42) ≥ 16 , ISS7 score (range 0 to 21) ≥ 6 and HSS7 score (range 0 to 21) ≥ 6 during the 7 days prior to randomization (Day 1)
- Documentation of hives within 3 months before randomization (either at screening and/or at randomization; or documented in the subjects' medical history).
- Subjects must not have had more than one missing UPDD entry (either morning or evening) in the 7 days prior to randomization during screening (Day 1).

Exclusion Criteria

- Clearly defined predominant or sole trigger of chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold, heat, solar, pressure, delayed pressure, aquagenic, cholinergic, or contact urticaria.
- Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or drug-induced urticaria.
- Any other skin disease associated with chronic itching that might influence the investigator's opinion, the trial evaluations, or results, e.g., atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis.
- Use of prohibited medications (see [Table 99](#)).
- Known history or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
- Pregnancy or lactation.

- Women of child-bearing potential,¹ defined as all women physiologically capable of becoming pregnant, unless using highly effective methods of contraception during dosing and for 7 days after stopping of study treatment. Highly effective contraception methods included:
  - Total abstinence (when in line with preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal were not acceptable methods of contraception.
  - Female sterilization (surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking investigational drug. Oophorectomy alone must have been confirmed by follow-up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female subjects in the trial, the vasectomized male partner should be the sole partner for that subject.
  - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring, or transdermal hormone contraception, or placement of an intrauterine device or intrauterine system. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form.
- Major surgery within 8 weeks prior to screening or planned surgery for the duration of the trial.
- History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive these vaccinations at any time during study drug treatment.
- Evidence of clinically significant cardiovascular (such as, but not limited to myocardial infarction, unstable ischemic heart disease, New York Heart Association Functional Classification Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to Visit 1), 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 subject, interfere with the interpretation of the trial results or otherwise preclude participation or protocol adherence of the subject.
- Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids.

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¹ Women were considered not of child-bearing potential if they were postmenopausal or had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow-up hormone level assessment was she considered not of child-bearing potential. Women were considered postmenopausal if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).

- Hematology parameters at screening:
  - Hemoglobin: <10 g/dL
  - Platelets: <100000/mm³
  - Leucocytes: <3000/mm³
  - Neutrophils: <1500/mm³
- Significant bleeding risk or coagulation disorders.
- History of gastrointestinal bleeding, e.g., in association with use of nonsteroidal anti-inflammatory drugs, that was clinically relevant (e.g., requiring hospitalization or blood transfusion).
- Requirement for antiplatelet medication, except for acetylsalicylic acid up to 100 mg/day or clopidogrel. The use of dual antiplatelet therapy (e.g., acetylsalicylic acid + clopidogrel) was prohibited.
- Requirement for anticoagulant medication (for example, warfarin or novel oral anticoagulants).
- History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels of more than 1.5x upper limit of normal (ULN) or international normalized ratio (INR) of more than 1.5 at screening.
- History of renal disease, creatinine level above 1.5x ULN, or estimated glomerular filtration rate <45 mL/min (using the Cockcroft-Gault equation) at screening.
- Evidence of an ongoing hepatitis C infection (e.g., defined by the detection of hepatitis C RNA at screening) and/or an ongoing hepatitis B infection (defined by the detection of hepatitis B virus surface antigen [HBsAg] and/or hepatitis B virus [HBV]-DNA at screening; subjects who are positive for antihepatitis B core antibodies but who are negative for antibodies against HBsAg and HBV-DNA can be included into the trial if they agree to monitoring for HBsAg and HBV-DNA reactivation).
- Known or suspected ongoing, chronic, or recurrent infectious disease including but not limited to opportunistic infections (e.g., tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis) and/or known positivity for HIV infection. HIV antigen/antibody tests will be performed to determine HIV status if required according to local regulations.
- Use of other investigational drugs within five half-lives or within 30 days (for small molecules) prior to screening or until the expected pharmacodynamic (PD) effect has returned to baseline (for biologics), whichever is longer; or longer if required by local regulations.
- Previous use of remibrutinib or other BTK inhibitors.
- History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

6.2.2.3. Study Treatments, Trials A2301 and A2302

Remibrutinib was formulated as 25-mg film-coated tablets (FCT). There was a formulation change between phase 2 and 3 trials from a hard gelatin capsule to FCT; for additional information on formulations evaluated in previous studies, see Section [14.2](#). The investigational medicinal product (IMP) was packaged and labeled according to the International Council for Harmonisation (ICH) good manufacturing process and good clinical practice guidelines. Subjects were treated with one of the following IMPs according to the assigned treatment sequence:

- Remibrutinib 25-mg FCT administered orally twice daily
- Matching placebo FCT administered orally twice daily

Each subject was instructed to take one FCT in the morning and one FCT in the evening. Compliance was assessed by the investigator and/or study personnel in the drug accountability form at each study visit.

Permitted Interruptions of Study Treatment

Study treatment interruptions were permitted under predefined circumstances to manage specific safety events. For bleeding event management, treatment interruption was required 7 days before planned surgery with clinically significant bleeding risk. Following surgical recovery, subjects could resume study treatment after a 7-day period, ensuring adequate hemostatic recovery while minimizing treatment exposure gaps. In cases of hepatitis B reactivation, defined as new appearance of detectable HBV-DNA or positive HBsAg, subjects were required to initiate antiviral treatment according to local clinical practice standards and interrupt study treatment. Study treatment resumption was permitted only after HBV-DNA and HBsAg reached undetectable levels, ensuring viral suppression before BTK inhibitor re-exposure.

Discontinuations

Treatment discontinuation occurred when study medication was permanently stopped before the protocol-specified completion date and was considered an intercurrent event handled with treatment policy strategy.

6.2.2.4. Concomitant Medications, Trials A2301 and A2302

Concomitant Treatment

All subjects were required to maintain second-generation H1-antihistamine therapy at locally approved doses as mandatory background therapy throughout the trial duration. Background H1-antihistamine therapy was required to remain unchanged until the Week 12 visit to ensure consistent baseline treatment during the primary efficacy evaluation period. Modifications to background therapy were permitted after Week 12 only when medically required, specifically in cases where adverse reactions were attributable to the background therapy as determined by the investigator's clinical judgment.

Rescue Medications

Second-generation H1-antihistamines, different from those used as background medication, were permitted as rescue therapy on an as-needed basis for subjects experiencing CSU flare-ups with

unbearable symptoms during screening, treatment, and follow-up periods. The daily dose of these rescue H1-antihistamines was limited to no more than four times the locally approved dose, following current urticaria treatment guidelines.

Oral corticosteroid use was prohibited prior to Week 12 to prevent interference with the primary endpoint assessment. After Week 12, subjects could use oral corticosteroids as rescue medication for unbearable CSU flare-ups, but usage was limited to a maximum of 3 days within any 30-day period and no more than 9 total days after Week 12. The recommended corticosteroid dose was 20 to 50 mg prednisone or equivalent per day, consistent with current urticaria treatment guidelines.

Intake of rescue medication as per protocol prior to Week 12 was considered an intercurrent event handled via treatment policy strategy for data analysis.

Prohibited Medication

Biologic therapies were not permitted due to their potential to independently improve chronic spontaneous urticaria symptoms and confound efficacy evaluations. Routine oral corticosteroids, defined as more than three doses over a 5-day period, were prohibited, although oral corticosteroids were permitted as additional rescue therapy for chronic spontaneous urticaria after Week 12. For a full list of the medications prohibited during Trials A2301 and A2302 refer to [Table 99](#) in Section [15.1.2](#).

Composite strategy was applied in the setting of intake of strongly confounding prohibited medication including:

- Biologics treatment at any time before Week 12
- Cyclosporin after Week 8 to Week 12
- Systemic corticosteroids after Week 8 to Week 12

Measurements after this event were excluded from the analysis and were replaced with the worst value of the endpoint.

6.2.2.5. Efficacy Assessments, Trials A2301 and A2302

Patient Reported Outcomes

All subjects were provided with an eDiary that contained the PROs that measured symptom severity and effect on daily activities. The PROs used for primary and secondary efficacy endpoints were captured in the eDiary that contained the UPDD and the AAS. Subjects completed eDiary assessments twice daily for the UPDD and once daily for the AAS (if prompted by presence of angioedema symptoms) from screening through Week 52 or until trial discontinuation. Other PRO questionnaires were administered during trial site visits (or in the eDiary at the scheduled time if unable to attend in person).

The UPDD assessed severity of itch and number of hives, use of rescue medication, sleep and activity interference, angioedema occurrence and management, and healthcare utilization (see

[Figure 65](#) for a copy of the full instrument). Relevant components of the instrument used for efficacy endpoints included:

- Itch severity score (ISS): Itch intensity was reported twice daily on a scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate 3 = severe). The ISS7 was calculated by summing the average daily ISS scores over 7 consecutive days (range 0 to 21).
- Hives severity score (HSS): Hives severity was reported twice daily on a scale from 0 to 3 (0 = none, 1 = 1 to 6 hives, 2 = 7 to 12 hives, 3 = greater than 12 hives) (see [Figure 65](#)). The HSS7 was calculated by summing the average daily HSS scores over 7 consecutive days (range 0 to 21). The scoring system for hives has differed across CSU development programs as some HSS instruments score hives as 1 = <20 wheals, 2 = 20 to 50 wheals, 3 = >50 wheals. The HSS in this trial utilizes a more conservative scoring system.
- UAS: The UAS is a composite of the ISS and HSS. The UAS7 is the sum of daily ISS and HSS scores over 7 consecutive days (range 0 to 42). The UAS7 is an established and accepted PRO measure used to assess disease activity in chronic urticaria and considered fit-for-purpose for the proposed context of use in CSU ([Hawro et al. 2018](#); [Zuberbier et al. 2018](#)).

The AAS, as shown in [Figure 66](#), was completed daily and consists of five items, each scored 0 to 3 points. The daily score ranges from 0 to 15, with higher scores indicating greater disease activity. The assessment began with an opening question from UPDD regarding the occurrence of angioedema. When subjects responded “no” to this initial question, the AAS score for that day was assigned a value of 0. Conversely, when subjects responded “yes,” they proceeded to complete additional questions that evaluated the duration, severity, and impact of the angioedema on both daily functioning and appearance. Each response field within the assessment received a score ranging from 0 to 3 points, with higher scores indicating greater severity. For this trial, AAS results were reported as a weekly angioedema activity score (AAS7), with possible scores ranging from a minimum of 0 to a maximum of 105. Although this tool has been described in the literature to assess disease activity in recurrent angioedema ([Weller et al. 2013](#); [Zuberbier et al. 2018](#); [Kulthanan et al. 2019](#)), it has not yet been used to support regulatory decision making (b) (4).

Other PROs captured in the trials included the dermatology life quality index (DLQI), EuroQol 5-dimension 5-level, work productivity and activity impairment, urticaria control test, patient global impression of severity, and patient global impression of change. As these PROs are not considered fit-for-purpose for the proposed context of use and/or were not proposed as multiplicity-controlled endpoints or labeling claims, they are not discussed further in this review.

Biomarkers

Additional assessments included biomarker evaluations measuring total immunoglobulin levels, peripheral blood B-cell counts and subsets, and the chronic urticaria index, an in vitro basophil histamine release assay in which a subject’s serum is mixed with donor basophils and the released histamine levels are measured through a quantitative enzyme immunoassay. A chronic urticaria index value of greater than or equal to 10 presumably indicates that the subject has either an autoimmune basis for their disease (autoantibodies for IgE, FcεRI, or anti-FcεRII) or an alternate histamine-releasing factor.

6.2.2.6. Efficacy Endpoints, Trials A2301 and A2302

Coprimary Efficacy Endpoints

For the United States (based on FDA advice during development), the Applicant designated the following as coprimary efficacy endpoints:

- Absolute change from baseline in ISS7 compared to placebo at Week 12
- Absolute change from baseline in HSS7 compared to placebo at Week 12

Secondary Endpoints

- Absolute change from baseline in UAS7 compared to placebo at Week 12.
- Proportion of subjects achieving UAS7 ≤ 6 (yes/no) at Week 12.
- Proportion of subjects achieving UAS7 =0 (yes/no) at Week 12.
- Proportion of subjects achieving UAS7 ≤ 6 (yes/no) at Week 2.
- Proportion of subjects achieving DLQI =0 to 1 (yes/no) at Week 12.
- Cumulative number of weeks that subjects achieve UAS7 ≤ 6 responses between baseline and Week 12.
- Cumulative number of weeks that subjects achieve AAS7 =0 responses between baseline and Week 12.

6.2.2.7. Statistical Analysis Plan, Trials A2301 and A2302

The statistical analysis plan for Trial A2301 is Amendment 4 dated January 25, 2024, and submitted to the FDA on February 5, 2024. The statistical analysis plan for Trial A2302 is Amendment 5 dated January 25, 2024, and was submitted to the FDA on February 5, 2024. Trial A2302 was identical to Trial A2301 in its design and analysis.

Analysis Sets

The three defined analysis sets were the full analysis set (FAS), safety analysis set (SAF), and randomized analysis set (RAS).

FAS

The FAS included all subjects to whom study treatment was assigned by randomization but excluded mis-randomized subjects. Mis-randomized subjects were defined as cases where interactive response technology contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject. The FAS was used for the coprimary efficacy endpoints and all other efficacy analyses, unless otherwise stated.

SAF

The SAF that included all subjects who received at least one dose of study treatment, regardless of randomization, and subjects were analyzed according to the study treatment received. The

actual treatment was defined as the treatment received over the trial. In case of error in dispensation, the actual treatment corresponded to the treatment which was given most often. Safety set for the entire study period includes the subjects from remibrutinib 25 mg and placebo. The data from the open-label period for subjects who transitioned to remibrutinib 25 mg were not included in the safety analysis. Safety analyses were conducted using the SAF.

RAS

The RAS consisted of all randomized subjects, regardless of whether or not they received a dose of study drug, and subjects were analyzed according to the treatment they were assigned.

Intercurrent Events

For efficacy analyses, treatment policy strategy was used to handle the intercurrent events of discontinuation of study treatment due to any reason and the intake of rescue medication, switch of background medication, intake of other prohibited medication, or subjects noncompliant to treatment prior to Week 12. The Applicant's prespecified analysis used the composite strategy with values replaced by the worst value of the endpoint to handle the intercurrent event of strongly confounding prohibiting medication (e.g., biologics treatment at any time before Week 12, cyclosporin after Week 8, systemic corticosteroids after Week 8). However, the treatment policy strategy for all intercurrent events was recommended to the Applicant during the planning and is of primary regulatory interest. The results presented in this review correspond to the Applicant's prespecified intercurrent event handling strategy and comparisons of the analyses of the two estimands are discussed where relevant.

Primary Analysis

The primary analysis used a linear mixed model for repeated measures (MMRM) with data up to Week 12 to estimate treatment differences for change from baseline in ISS7 score (respectively HSS7) at Week 12. The MMRM included treatment group, baseline ISS7 score (respectively HSS7), randomization strata variables (region, prior exposure to anti-IgE biologics), week, the interaction of treatment by week, and the interaction of baseline ISS7 score (respectively HSS7) by week as fixed effects. Repeated measures within subject were modeled using an unstructured covariance of the error terms. The treatment difference at Week 12 was estimated using the least-squares (LS) mean and 95% confidence interval, along with the corresponding p-value for treatment comparison. The review team additionally considered a comparable analysis at Week 24, with details described in Section [15.1.4.2](#).

In the case of missing data prior to Week 12, the missing data were to be handled following the missing-at-random (MAR) assumption. For the intercurrent event of strongly confounding prohibiting medication, the values for all visits after the incurrent event were replaced with the worst value of the endpoint. Treatment policy strategy was planned for the intercurrent event of discontinuation of study treatment prior to Week 12 due to any reasons. The Applicant described data after the intercurrent event of treatment discontinuation as retrieved dropout (RDO) data. If no RDO data were collected after the intercurrent event, missing data were imputed based on the following rules. For subjects in the active treatment arm, if $\geq 50\%$ of subjects had RDO data at Week 12, missing data were to be imputed using multiple imputation (MI) based on observed RDO data in the active arm. If $< 50\%$ of subjects had RDO data at Week 12, missing data were to be imputed based on observed data in the placebo arm under the jump-to-reference assumption

using MI. For subjects in the placebo arm, if $\geq 50\%$ of subjects had RDO data at Week 12, missing data were to be imputed using MI based on observed RDO placebo arm data. If $< 50\%$ of subjects had RDO data at Week 12, missing data were to be imputed using MI under the MAR assumption based on the observed placebo arm data.

Sensitivity, supplementary, and subgroups analyses were conducted to evaluate the robustness of the primary analysis and the impact of baseline disease characteristics on efficacy. For details, see Sections [15.1.4.3](#), [15.1.4.4](#), and [15.1.4.6](#).

Secondary Endpoints

A closed testing procedure was prespecified to test the coprimary and key secondary endpoints with control of family-wise type I error at the one-sided $\alpha = 0.025$. The testing is strictly hierarchical, so that null hypotheses can be tested along the predefined order at the level assigned until a null hypothesis cannot be rejected, at which point the testing stops. If the null hypotheses for the coprimary endpoints were rejected, then testing proceeded sequentially to test for the following:

- Change from baseline in UAS7 score at Week 12
- Proportion of subjects with $UAS7 \leq 6$ at Week 12
- Proportion of subjects with $UAS7 = 0$ at Week 12
- Proportion of subjects with $UAS7 \leq 6$ at Week 2
- Proportion of subjects with $DLQI = 0/1$ at Week 12
- Cumulative number of weeks achieving $UAS7 \leq 6$ response between baseline and Week 12
- Cumulative number of weeks achieving $AAS7 = 0$ response between baseline and Week 12

The analysis methods for the key secondary endpoints are as follows:

The treatment difference for change from baseline in UAS7 score at Week 12 was estimated via a linear MMRM with the same specification as for the coprimary endpoints.

The number of subjects with $UAS7 \leq 6$ at Week 12 was analyzed using a logistic regression model including treatment group, region, prior exposure to anti-IgE biologics, and baseline UAS7 score as covariates. The number of subjects with $UAS7 = 0$ at Week 12, $UAS7 \leq 6$ at Week 2, and $DLQI = 0/1$ at Week 12 were analyzed similarly. However, DLQI is not considered to be a well-defined and reliable tool to estimate clinical benefit for labeling claims due to issues surrounding content validity and the interpretability of the complex, distal concepts captured in the instrument.

The cumulative number of weeks achieving $UAS7 \leq 6$ response between baseline and Week 12 was modelled using a negative binomial regression model with log link, and covariates of treatment group, region, and prior exposure to anti-IgE biologics and the subject's time in the treatment period up to Week 12 (natural log of proportion of time in treatment period, i.e., natural log of number of weeks with the response variable in treatment period/12 weeks) as an offset variable. The cumulative number of weeks achieving $AAS7 = 0$ response between baseline and Week 12 was analyzed similarly.

6.2.2.8. Results of Analyses, Trials A2301 and A2302

This section summarizes the subject disposition, baseline demographics and clinical characteristics, and primary and key secondary efficacy results from Trial A2301 to support the efficacy of remibrutinib in subjects with CSU inadequately controlled by H1-antihistamines.

6.2.2.8.1. Subject Disposition, Trials A2301 and A2302

A total of 925 subjects were enrolled across both pivotal phase 3 trials, with 912 subjects comprising the efficacy (FAS) and safety (SAF) analysis populations. Trial A2301 enrolled 470 subjects (313 randomized to remibrutinib 25 mg BID and 157 to placebo), while Trial A2302 enrolled 455 subjects (300 randomized to remibrutinib 25 mg BID and 155 to placebo) as shown in [Table 8](#). Some subjects were enrolled and randomized in error (e.g., failed to meet eligibility criteria), and therefore included in the randomized analysis set but excluded from the FAS and SAF populations because no IMP was administered. The trials utilized identical randomized, double-blind, placebo-controlled designs with a 2:1 randomization ratio favoring the active treatment arm.

Table 8. Subject Screening and Enrollment, Trials A2301 and A2302

Screening and Enrollment	Remibrutinib 25 mg	Placebo	Transitioned to Remibrutinib 25 mg	Total
<i>Trial A2301</i>				
Screened				654
Randomized analysis set	313	157		470
Double-blind treatment period				
Full analysis set	309	153		462
Safety set	309	153		462
Entire study period				
Full analysis set	309			462
Safety set	309	153	133	462
<i>Trial A2302</i>				
Screened				612
Randomized analysis set	300	155		455
Double-blind treatment period				
Full analysis set	297	153		450
Safety set	297	153		450
Entire study period				
Full analysis set	297			450
Safety set	297	153	129	450

Source: Statistical Analyst reproduced results using Applicant-submitted dataset adsl
Transitioned to remibrutinib 25 mg includes subjects initially randomized to placebo and switched to remibrutinib. The Safety set for the entire study period includes the subjects from remibrutinib 25 mg and placebo, and the data from the open-label period for subjects who transitioned to remibrutinib 25 mg were not included in the safety analysis.

Subject disposition during the 24-week double-blind treatment periods is shown in [Table 9](#), below. The completion rates across treatment groups were acceptable and relatively balanced without an excessive number of dropouts. The most commonly cited reason for treatment discontinuation was ‘subject decision’ which was comparable between arms. Notably, unsatisfactory therapeutic effect was more frequently cited as a discontinuation reason in the

placebo group compared to the remibrutinib group, which is consistent with the efficacy of active treatment.

Table 9. Subject Disposition, Double-Blind Treatment Period, FAS, Trials A2301 and A2302

Disposition	Remibrutinib 25 mg	Placebo	Total
<i>Trial A2301</i>			
No treatment due to mis-randomization	4 (1.3)	3 (1.9)	7 (1.5)
Completed double-blind study treatment	270 (86.3)	134 (85.4)	404 (86.0)
Discontinued double-blind study treatment	39 (12.5)	20 (12.7)	59 (12.6)
Primary reason for discontinuation of double-blind treatment period			
Adverse event	11 (3.5)	3 (1.9)	14 (3.0)
Lost to follow-up	3 (1.0)	0	3 (0.6)
Subject decision	21 (6.7)	13 (8.3)	34 (7.2)
Physician decision	2 (0.6)	2 (1.3)	4 (0.9)
Unsatisfactory therapeutic effect	2 (0.6)	2 (1.3)	4 (0.9)
<i>Trial A2302</i>			
No treatment due to mis-randomization	3 (1.0)	2 (1.3)	5 (1.1)
Completed double-blind study treatment	259 (86.3)	129 (83.2)	388 (85.3)
Discontinued double-blind study treatment	38 (12.7)	24 (15.5)	62 (13.6)
Primary reason for discontinuation of double-blind treatment period			
Adverse event	5 (1.7)	6 (3.9)	11 (2.4)
Lost to follow-up	0	3 (1.9)	3 (0.7)
Subject decision	23 (7.7)	8 (5.2)	31 (6.8)
Physician decision	5 (1.7)	0	5 (1.1)
Unsatisfactory therapeutic effect	0	5 (3.2)	5 (1.1)

Source: Statistical Analyst reproduced results using Applicant-submitted dataset adsl
Abbreviation: FAS, full analysis set

6.2.2.8.2. Baseline Demographics and Clinical Characteristics, Trials A2301 and A2302

The baseline demographics of the FAS population in Trials A2301 and A2302 are shown in [Table 10](#). The study populations were representative of the intended CSU patient population who are predominantly middle-aged females, and there were no major differences between treatment groups. The racial composition reflected the global nature of the trials, with subjects predominantly White or Asian, with comparable proportions across treatment groups. Approximately 20 to 25% of trial subjects were enrolled from U.S. sites. However, international treatment guidelines for CSU exist and standard of care is similar across countries. Therefore, results obtained from sites outside the United States should be applicable to a U.S. population.

Table 10. Baseline Demographics and Clinical Characteristics, FAS Population, Trials A2301 and A2302

Demographics/Characteristics	Trial A2301			Trial A2302		
	Remibrutinib 25 mg N=309	Placebo N=153	Total N=462	Remibrutinib 25 mg N=297	Placebo N=153	Total N=450
Age group, n (%)						
≥18-<65	279 (90)	140 (92)	419 (91)	274 (92)	142 (93)	416 (92)
≥65-<85	30 (10)	13 (8)	43 (9)	23 (8)	11 (7)	34 (8)
Age (years)						
Mean (SD)	44.5 (14.3)	46.0 (13.3)	45.0 (13.9)	42.0 (14.4)	41.3 (14.6)	41.7 (14.5)
Median	44.0	47.0	45.0	41.0	40.0	41.0
Min, max	18, 79	18, 79	18, 79	18, 80	18, 81	18, 81
Sex, n (%)						
Female	208 (67)	105 (69)	313 (68)	195 (66)	99 (65)	294 (65)
Male	101 (33)	48 (31)	149 (32)	102 (34)	54 (35)	156 (35)
Race, n (%)						
White	184 (60)	86 (56)	270 (58)	157 (53)	77 (50)	234 (52)
Asian	94 (30)	45 (29)	139 (30)	129 (43)	72 (47)	201 (45)
American Indian or Alaska Native	12 (4)	14 (9)	26 (6)	0	0	0
Black or African American	12 (4)	3 (2)	15 (3)	7 (2)	3 (2)	10 (2)
More than one race	6 (2)	2 (1)	8 (2)	3 (1)	1 (1)	4 (1)
Unknown	1 (0)	2 (1)	3 (1)	1 (0)	0	1 (0)
Native Hawaiian or Pacific Islander	0 (0)	1 (1)	1 (0)	0	0	0
Ethnicity, n (%)						
Non-Hispanic or Latino	235 (76)	111 (73)	346 (75)	281 (95)	147 (96)	428 (95)
Hispanic or Latino	74 (24)	42 (27)	116 (25)	16 (5)	5 (3)	21 (5)
Geographic region, n (%)						
Asia, Middle East and Africa	99 (32)	49 (32)	148 (32)	93 (31)	50 (33)	143 (32)
United States	77 (25)	38 (25)	115 (25)	56 (19)	29 (19)	85 (19)
Europe	63 (20)	31 (20)	94 (20)	79 (27)	39 (25)	118 (26)
Latin America, Caribbean and Canada	51 (17)	27 (18)	78 (17)	26 (9)	13 (8)	39 (9)
Japan	19 (6)	8 (5)	27 (6)	43 (14)	22 (14)	65 (14)
Body mass index						
Mean (SD)	27.8 (6.4)	28.4 (6.5)	28.0 (6.4)	27.0 (6.5)	26.9 (5.9)	27.0 (6.3)
Median	26.9	27.5	27.1	25.7	25.7	25.7
Min, max	16, 58	16, 54	16, 58	15, 53	18, 51	15, 53
Missing	0	1	1	0	0	0

Demographics/Characteristics	Trial A2301			Trial A2302		
	Remibrutinib 25 mg N=309	Placebo N=153	Total N=462	Remibrutinib 25 mg N=297	Placebo N=153	Total N=450
Body mass index group, n (%)						
<25 (kg/m ²)	119 (39)	56 (37)	175 (38)	137 (46)	69 (45)	206 (46)
25-<30 (kg/m ²)	95 (31)	43 (28)	138 (30)	84 (28)	50 (33)	134 (30)
≥30 (kg/m ²)	95 (31)	53 (35)	148 (32)	76 (26)	34 (22)	110 (24)

Source: Statistical Analyst reproduced results using Applicant-submitted dataset adsl

Abbreviations: FAS, full analysis set; max, maximum; min, minimum; N, number of subjects; n, number of subjects within specific demographic/with specific characteristic; SD, standard deviation

Baseline disease characteristics of the FAS populations in Trials A2301 and A2302 are shown in [Table 11](#). The study populations reported a relatively high symptom burden at baseline as measured by baseline UAS7 scores, with no major difference between treatment groups. However, an imbalance was noted in angioedema burden, with subjects in the remibrutinib group having higher baseline angioedema activity as measured by mean AAS7 scores and fewer subjects being angioedema-free at baseline. Most subjects in the trials were naïve to prior anti-IgE therapy, indicating that the study populations did not represent subjects refractory to all available therapies.

Table 11. Baseline Disease Characteristics, FAS Population, Trials A2301 and A2302

Characteristics	Trial A2301			Trial A2302		
	Remibrutinib 25 mg N=309	Placebo N=153	Total N=462	Remibrutinib 25 mg N=297	Placebo N=153	Total N=450
Baseline UAS7 score						
Mean (SD)	30.8 (7.7)	29.8 (7.6)	30.5 (7.7)	30.3 (7.9)	29.5 (7.6)	30.1 (7.8)
Median	30.0	30.0	30.0	30.5	29.0	30.0
Min, max (range 0 to 42)	16, 42	15, 42	15, 42	6, 42	8, 42	6, 42
Baseline UAS7 category						
28 ≤ UAS7 ≤ 42	205 (66)	93 (61)	298 (65)	181 (61)	88 (58)	269 (60)
16 ≤ UAS7 < 28	104 (34)	58 (38)	162 (35)	111 (37)	64 (42)	175 (39)
6 < UAS7 < 16	0 (0)	2 (1)	2 (0)	5 (2)	1 (1)	6 (1)
Baseline ISS7 score						
Mean (SD)	14.8 (4.1)	14.4 (4.0)	14.7 (4.1)	14.4 (4.3)	13.9 (4.1)	14.2 (4.3)
Median	14.0	14.0	14.0	14.0	14.0	14.0
Min, max (range 0 to 21)	6, 21	6, 21	6, 21	0, 21	4, 21	0, 21

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Characteristics	Trial A2301			Trial A2302		
	Remibrutinib 25 mg N=309	Placebo N=153	Total N=462	Remibrutinib 25 mg N=297	Placebo N=153	Total N=450
Baseline HSS7 score						
Mean (SD)	16.0 (4.5)	15.5 (4.5)	15.8 (4.5)	16.0 (4.6)	15.7 (4.4)	15.9 (4.5)
Median	16.0	16.0	16.0	16.5	15.5	16.5
Min, max (range 0 to 21)	6, 21	6, 21	6, 21	0, 21	4, 21	0, 21
Baseline AAS7 score						
Mean (SD)	28.2 (30.9)	23.6 (28.9)	26.7 (30.3)	25.3 (30.9)	19.6 (27.6)	23.3 (29.9)
Median	14.0	11.7	12.8	10.0	4.0	8.0
Min, max (range 0 to 105)	0, 105	0, 104	0, 105	0, 105	0, 105	0, 105
Missing	0	0	0	1	0	1
Baseline AAS7 =0 response						
Yes	107 (35)	62 (41)	169 (37)	124 (42)	75 (49)	199 (44)
No	202 (65)	91 (59)	293 (63)	172 (58)	78 (51)	250 (56)
Missing	0	0	0	1	0	1
Duration of CSU (years)						
Mean (SD)	6.9 (9.3)	6.1 (7.2)	6.6 (8.7)	5.5 (7.6)	4.6 (6.2)	5.2 (7.2)
Median	3.7	3.6	3.7	3.0	2.2	2.8
Min, max	0, 63	1, 42	0, 63	0, 46	0, 39	0, 46
Duration of CSU (years) category						
≤1 year	52 (17)	25 (16)	77 (17)	63 (21)	43 (28)	106 (24)
>1 to 3 years	80 (26)	45 (29)	125 (27)	84 (28)	42 (27)	126 (28)
>3 to 5 years	57 (18)	23 (15)	80 (17)	60 (20)	26 (17)	86 (19)
>5 years	120 (39)	60 (39)	180 (39)	90 (30)	42 (27)	132 (29)
Previous exposure to anti-IgE biologics						
Yes	98 (32)	49 (32)	147 (32)	89 (30)	49 (32)	138 (31)
No	211 (68)	104 (68)	315 (68)	208 (70)	104 (68)	312 (69)
Previous experience of angioedema						
Yes	172 (56)	68 (44)	240 (52)	141 (47)	67 (44)	208 (46)
No	137 (44)	85 (56)	222 (48)	156 (53)	86 (56)	242 (54)

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Characteristics	Trial A2301			Trial A2302		
	Remibrutinib 25 mg N=309	Placebo N=153	Total N=462	Remibrutinib 25 mg N=297	Placebo N=153	Total N=450
Baseline CU-index						
Positive (≥10)	90 (29)	37 (24)	127 (27)	77 (26)	48 (31)	125 (28)
Negative (<10)	215 (70)	113 (74)	328 (71)	166 (56)	76 (50)	242 (54)
Missing	4 (1)	3 (2)	7 (2)	54 (18)	29 (19)	83 (18)
Baseline total IgE level						
Normal/High (>43 IU/mL)	225 (73)	109 (71)	334 (72)	224 (75)	107 (70)	331 (74)
Low (≤43 IU/mL)	81 (26)	43 (28)	124 (27)	71 (24)	45 (29)	116 (26)
Missing	3 (1)	1 (1)	4 (1)	2 (1)	1 (1)	3 (1)

Source: Statistical Analyst reproduced results using Applicant-submitted datasets adsl and adbl

Abbreviations: AAS7, weekly angioedema activity score; CSU, chronic spontaneous urticaria; CU-index, chronic urticaria index; FAS, full analysis set; HSS7, weekly hives severity score; ISS7, weekly itch severity score; max, maximum; min, minimum; N, number of subjects; n, number of subjects with specific characteristic; SD, standard deviation; UAS7, weekly urticaria activity score

6.2.2.8.3. Primary Efficacy Results, Trials A2301 and A2302

[Table 12](#) and [Table 13](#) summarize the results for Trials A2301 and A2302 for the coprimary efficacy endpoints of change from baseline to Week 12 in HSS7 and ISS7, respectively. After adjusting for baseline HSS7 score, geographical region, prior exposure to anti-IgE biologics, visit week, treatment by visit interaction, and baseline HSS7 score by visit interaction, the estimated LS mean changes from baseline in HSS7 scores at Week 12 were greater in magnitude in the remibrutinib groups (LS means =-10.47 [SE 0.40] and -10.47 [SE 0.39]), compared to placebo (LS means =-6.86 [SE 0.55] and -6.00 [SE 0.53]) in Trials A2301 and A2302, respectively. For HSS7, the estimated differences in LS means relative to placebo were -3.61 (95% CI: -4.85, -2.36) and -4.47 (95% CI: -5.71, -3.23) in Trials A2301 and A2302, respectively. Similarly, for ISS7, after adjusting for similar covariates, the estimated least-squares mean changes from baseline in ISS7 scores at Week 12 were greater in magnitude in the remibrutinib groups (LS mean =-9.52 [SE 0.34] and -8.95 [SE 0.34]) compared to placebo (LS mean =-6.89 [SE 0.47] and -5.72 [SE 0.45]) in Trials A2301 and A2302, respectively. The estimated differences in LS means relative to placebo were -2.63 (95% CI: -3.70, -1.56) and -3.23 (95% CI: -4.29, -2.16), respectively. The coprimary endpoints in both trials were statistically significant with p-values <0.001. Results of analyses which correspond to the estimand with treatment policy strategy for all intercurrent events were substantially similar, with p-values <0.001 and small differences in point estimates and confidence intervals (at the most in the tenths place).

Table 12. Primary Efficacy Analysis: Change From Baseline in HSS7 at Week 12 in FAS, Trials A2301 and A2302

Parameter, HSS7 (Range 0-21)	Trial A2301		Trial A2302	
	Remibrutinib 25 mg N=309	Placebo N=153	Remibrutinib 25 mg N=297	Placebo N=153
Baseline, mean (SD)	16.0 (4.5)	15.5 (4.5)	16.0 (4.6)	15.7 (4.4)
Change from baseline, LS mean (SE)	-10.47 (0.40)	-6.86 (0.55)	-10.47 (0.39)	-6.00 (0.53)
Treatment difference LS mean (95% CI)	-3.61 (-4.85, -2.36)	-	-4.47 (-5.71, -3.23)	-
p-Value	<0.001	-	<0.001	-

Source: Statistical Analyst-reproduced results using Applicant-submitted datasets adsl and admiup12

MMRM, model adjusted for treatment arm, geographical region, baseline HSS7 score, prior exposure to anti-IgE biologics, visit week, treatment by visit, and baseline score by visit.

Abbreviations: CI, confidence interval; FAS, full analysis set; HSS7, weekly hives severity score; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; SD, standard deviation; SE, standard error

Table 13. Primary Efficacy Analysis: Change From Baseline in ISS7 at Week 12 in FAS, Trials A2301 and A2302

Parameter, ISS7 (Range 0-21)	Trial A2301		Trial A2302	
	Remibrutinib 25 mg N=309	Placebo N=153	Remibrutinib 25 mg N=297	Placebo N=153
Baseline, mean (SD)	14.8 (4.1)	14.4 (4.0)	14.4 (4.3)	13.9 (4.1)
Change from baseline, LS Mean (SE)	-9.52 (0.34)	-6.89 (0.47)	-8.95 (0.34)	-5.72 (0.45)
Treatment difference LS mean (95% CI)	-2.63 (-3.70, -1.56)	-	-3.23 (-4.29, -2.16)	-
p-Value	<0.001	-	<0.001	-

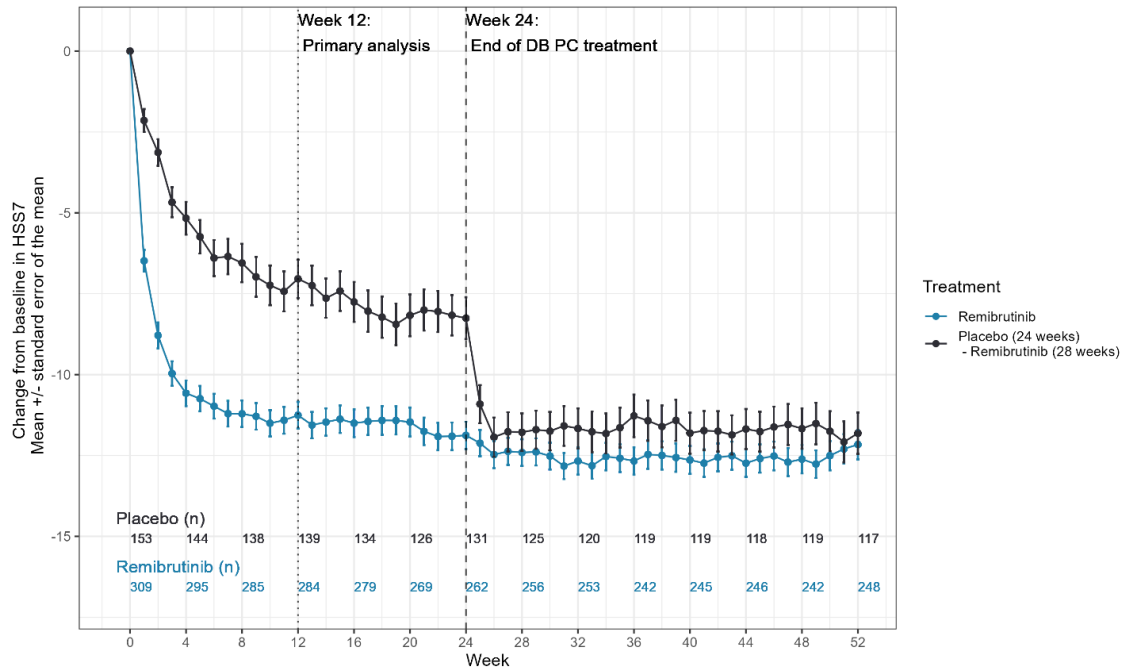
Source: Statistical Analyst-reproduced results using Applicant-submitted datasets adsl and admiup12 MMRM adjusted for treatment arm, geographical region, baseline ISS7 score, prior exposure to anti-IgE biologics, visit week, treatment by visit, and baseline score by visit.
Abbreviations: CI, confidence interval; FAS, full analysis set; ISS7, weekly itch severity score; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; SD, standard deviation; SE, standard error

In Trial A2301, one subject in the remibrutinib 25-mg group experienced the intercurrent event of intake of strongly confounding medication (see Section 6.2.2.4) prior to Week 12; results of the primary and key secondary analyses were minimally impacted by the handling of this intercurrent event with composite versus treatment policy strategy. In Trial A2302, one subject in the remibrutinib 25-mg group and one subject in the placebo group experienced the intercurrent event of intake of strongly confounding medication prior to Week 12; again, results of the primary and key secondary analyses were minimally impacted by the handling of this intercurrent event with composite versus treatment policy strategy.

Although the coprimary endpoints were evaluated at Week 12, the double-blind treatment period continued through Week 24. It is of clinical interest to consider the comparison between remibrutinib 25 mg and placebo through the end of the double-blind period for this chronic condition. The review team used an MMRM analysis to estimate treatment differences at Week 24 and results are summarized in Table 100 and Table 101 of Section 16.1.1. For change from baseline in HSS7 at Week 24, the estimated differences in LS means relative to placebo were -2.91 (95% CI: -4.16, -1.66) and -3.61 (95% CI: -4.92, -2.29) in Trials A2301 and A2302, respectively. For change from baseline in ISS7 at Week 24, the estimated differences in LS means relative to placebo were -1.81 (95% CI: -2.88, -0.73) and -3.03 (95% CI: -4.16, -1.90) in Trials A2301 and A2302, respectively. Although the effect estimates are smaller at Week 24 than Week 12, both comparisons were nominally significant.

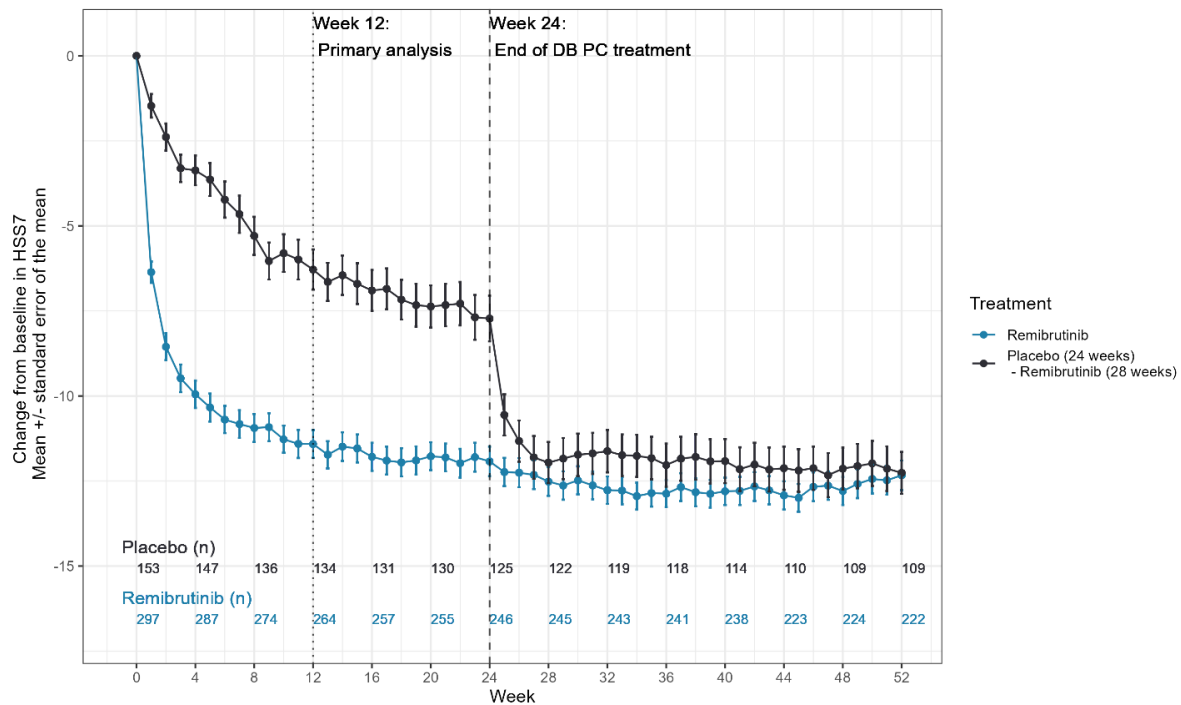
To further examine the treatment effect over time, plots of the weekly mean change from baseline with standard error bars were produced. Figure 4 and Figure 5 depict the weekly mean change from baseline in HSS7 in Trials A2301 and A2302, respectively, through Week 52. Figure 6 and Figure 7 depict the weekly mean change from baseline in ISS7 in Trials A2301 and A2302, respectively, through Week 52. Both treatment groups in both trials experienced decreases in mean changes in HSS7 and ISS7 from baseline and there is a separation between the groups during the double-blind, placebo-controlled treatment period.

Figure 4. Plot of Mean Change From Baseline in HSS7 Through Week 52 in FAS Population, Trial A2301



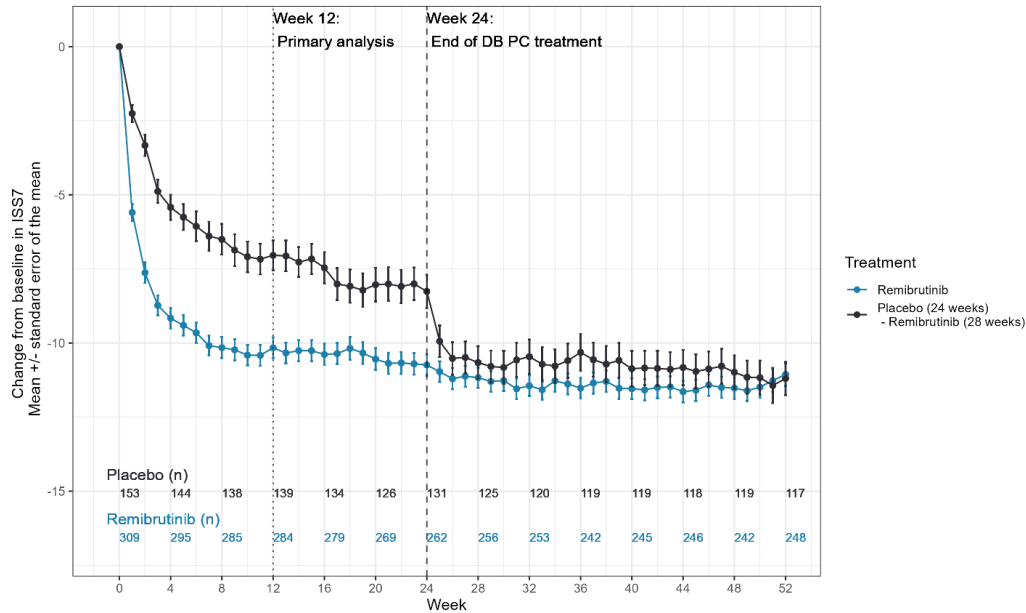
Source: Statistical Reviewer-reproduced results using Applicant-submitted dataset adqsupd
Values at every 4 weeks of the mean and standard error are displayed in [Table 102](#) of Section [16.1.2](#).
Abbreviations: DB, double-blind; FAS, full analysis set; HSS7, weekly hives severity score; PC, placebo-controlled

Figure 5. Plot of Mean Change From Baseline in HSS7 Through Week 52 in FAS Population, Trial A2302



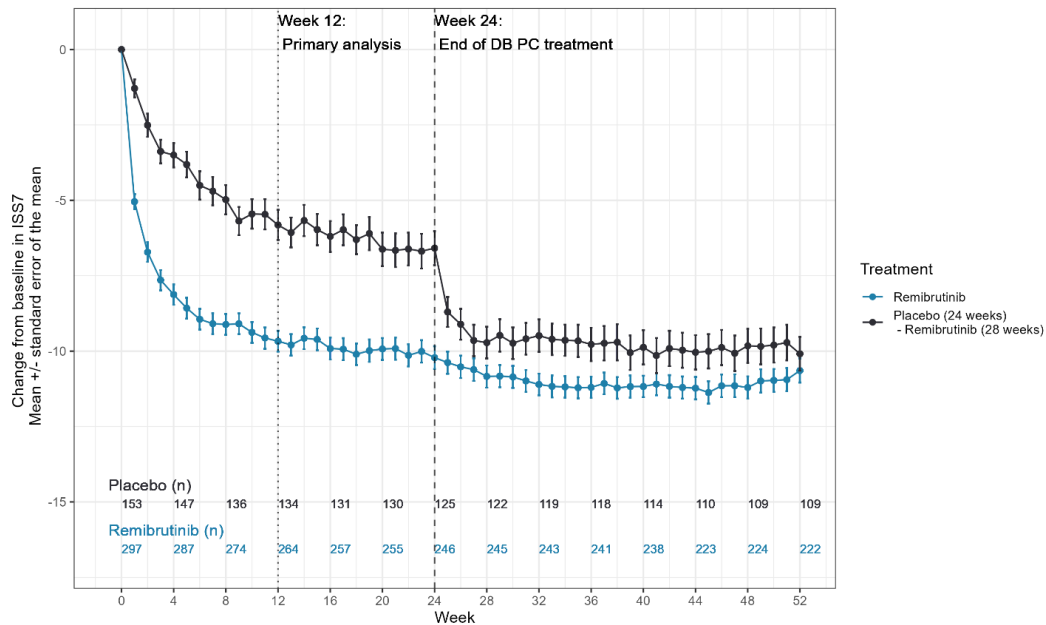
Source: Statistical Reviewer-reproduced results using Applicant-submitted dataset adqsupd
Values at every 4 weeks of the mean and standard error are displayed in [Table 103](#) of Section [16.1.2](#).
Abbreviations: DB, double-blind; FAS, full analysis set; HSS7, weekly hives severity score; PC, placebo-controlled

Figure 6. Plot of Mean Change From Baseline in ISS7 Through Week 52 in FAS Population, Trial A2301



Source: Statistical Reviewer-reproduced results using Applicant-submitted dataset adqsupd
Values at every 4 weeks of the mean and standard error are displayed in [Table 102](#) of Section 16.1.2.
Abbreviations: DB, double-blind; FAS, full analysis set; ISS7, weekly itch severity score; PC, placebo-controlled

Figure 7. Plot of Mean Change From Baseline in ISS7 Through Week 52 in FAS Population, Trial A2302



Source: Statistical Reviewer-reproduced results using Applicant-submitted dataset adqsupd
Values at every 4 weeks of the mean and standard error are displayed in [Table 103](#) of Section 16.1.2.
Abbreviations: DB, double-blind; FAS, full analysis set; ISS7, weekly itch severity score; PC, placebo-controlled

6.2.2.8.4. Key Secondary Efficacy Results, Trials A2301 and A2302

[Table 14](#) summarizes the results for the first key secondary efficacy endpoint of change from baseline to Week 12 in UAS7 for Trials A2301 and A2302. UAS7 is the sum of HSS7 and ISS7, and as such the results are closely related to the results for the coprimary endpoints. After adjusting for baseline UAS7 score, geographical region, prior exposure to anti-IgE biologics, visit week, treatment by visit interaction, and baseline UAS7 score by visit interaction, the estimated least-squares mean changes from baseline in UAS7 scores at Week 12 were greater in magnitude in the remibrutinib groups (LS mean = -20.02 (SE 0.72) and -19.41 (SE 0.70)) compared to placebo (LS mean = -13.79 (SE 0.98) and -11.73 (SE 0.95)) in Trials A2301 and A2302, respectively. In Trials A2301 and A2302, the respective estimated differences in LS means relative to placebo were -6.22 (95% CI: -8.45, -4.00) and -7.68 (95% CI: -9.91, -5.46), which were statistically significant. The analyses which correspond to the estimand with treatment policy strategy for all intercurrent events were substantially similar, with p-values <0.001 and small differences in point estimates and confidence intervals (at the most in the tenths place).

Table 14. Secondary Efficacy Analysis: Change From Baseline in UAS7 at Week 12 in FAS, Trials A2301 and A2302

Parameter	Trial A2301		Trial A2302	
	Remibrutinib	Placebo	Remibrutinib	Placebo
	25 mg N=309	N=153	25 mg N=297	N=153
Baseline, mean (SD)	30.8 (7.7)	29.8 (7.6)	30.3 (7.9)	29.5 (7.6)
Change from baseline, LS mean (SE)	-20.02 (0.72)	-13.79 (0.98)	-19.41 (0.70)	-11.73 (0.95)
Treatment difference LS mean (95% CI)	-6.22 (-8.45, -4.00)	-	-7.68 (-9.91, -5.46)	-
p-Value	<0.001	-	<0.001	-

Source: Statistical Analyst-reproduced results using Applicant-submitted datasets adsl and admiup12

MMRM adjusted for treatment arm, geographical region, baseline UAS7 score, prior exposure to anti-IgE biologics, visit week, treatment by visit, and baseline score by visit.

Abbreviations: CI, confidence interval; FAS, full analysis set; IgE, immunoglobulin E; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; SD, standard deviation; SE, standard error; UAS7, weekly urticaria activity score

[Table 15](#) summarizes the key secondary responder endpoints adjusted for geographical region, prior exposure to anti-IgE biologics, and baseline score, which were all statistically significant based on the prespecified testing procedure. For the responder endpoint of UAS7 ≤6 at Week 12, more subjects responded to remibrutinib (49.8% and 46.8%) than placebo (24.8% and 19.6%) with an estimated conditional odds ratio of 3.1 (95% CI: 2.0, 4.8) and 3.8 (95% CI: 2.4, 6.1) for Trials A2301 and A2302, respectively. For the responder endpoint of complete absence of itch and hives defined as UAS7 =0 at Week 12, more subjects responded to remibrutinib (31.1% and 27.9%) than placebo (10.5% and 6.5%) with an estimated conditional odds ratio of 3.8 (95% CI: 2.2, 6.8) and 5.8 (95% CI: 2.9, 11.6) in Trials A2301 and A2302, respectively. For these two responder analyses, the corresponding analyses for the estimand with treatment policy strategy for all intercurrent events were substantially similar, with p<0.001 and small differences in point estimates and confidence intervals (at the most in the tenths place). For the responder endpoint of UAS7 ≤6 at Week 2, more subjects responded to remibrutinib (33.7% and 30.0%) than placebo (3.3% and 5.9%) with an estimated conditional odds ratio of 15.7 (95% CI: 6.3, 39.0) and 7.9 (95% CI: 3.8, 16.7) in Trials A2301 and A2302, respectively. The intercurrent event of intake of

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strongly confounding medication did not occur for any subjects prior to Week 2, and so the handling strategy for this intercurrent event does not impact this endpoint's analysis. For the responder endpoint of DLQI =0 to 1 at Week 12, more subjects responded to remibrutinib (39.0% and 35.7%) than placebo (22.2% and 18.3%) with an estimated conditional odds ratio of 2.4 (95% CI: 1.5, 3.9) and 2.8 (95% CI: 1.7, 4.6) in Trials A2301 and A2302, respectively; however, this endpoint is not fit-for-purpose for CSU.

Table 15. Secondary Efficacy Analysis: Responder Endpoints for UAS7 in FAS, Trials A2301 and A2302

Parameter	Trial A2301				Trial A2302			
	Remibrutinib 25 mg N=309	Placebo N=153	Conditional Odds Ratio (95% CI)	p-Value	Remibrutinib 25 mg N=297	Placebo N=153	Conditional Odds Ratio (95% CI)	p-Value
UAS7 ≤6 at Week 12, n (%)	154 (49.8)	38 (24.8)	3.1 (2.0, 4.8)	<0.001	139 (46.8)	30 (19.6)	3.8 (2.4, 6.1)	<0.001
UAS7 =0 at Week 12, n (%)	96 (31.1)	16 (10.5)	3.8 (2.2, 6.8)	<0.001	83 (27.9)	10 (6.5)	5.8 (2.9, 11.6)	<0.001
UAS7 ≤6 at Week 2, n (%)	104 (33.7)	5 (3.3)	15.7 (6.3, 39.0)	<0.001	89 (30.0)	9 (5.9)	7.9 (3.8, 16.7)	<0.001

Source: Statistical Analyst-reproduced results using Applicant-submitted dataset admiup12

Response rate is the average number of subjects with response in each treatment arm in 100 imputations. Statistical model used logical regression with covariates baseline UAS7, treatment group, previous exposure to anti-IgE biologics, and region.

Abbreviations: CI, confidence interval; FAS, full analysis population; N, number of subjects; n, number of subjects within specific parameter; UAS7, weekly urticaria activity score

[Table 16](#) summarizes the results for the remaining key secondary endpoints adjusted for geographical region, prior exposure to anti-IgE biologics, and an offset for subject’s time in the treatment period up to Week 12, which were both statistically significant based on the prespecified testing procedure. The average cumulative number of weeks with UAS7 ≤6 up to Week 12 was longer for the remibrutinib group (5.2 and 4.5) compared to the placebo group (1.9 and 1.4), with an estimated rate ratio of 2.7 (95% CI: 2.0, 3.6) and 3.3 (95% CI: 2.3, 4.7) in Trials A2301 and A2302, respectively. The average cumulative number of angioedema-free weeks, defined as AAS7 =0, up to Week 12 was longer for the remibrutinib group (8.4 and 8.8) compared to the placebo group (6.7 and 6.7), with an estimated rate ratio of 1.3 (95% CI: 1.1, 1.4) and 1.3 (95% CI: 1.2, 1.5) in Trials A2301 and A2302, respectively. The analyses for these two endpoints which correspond to the estimand with treatment policy strategy for all intercurrent events were substantially similar, with p-value<0.001 and minimal differences in point estimates and confidence intervals. While the cumulative weeks endpoints show numerical advantages for remibrutinib, these findings raise several uncertainties regarding their clinical meaningfulness and practical significance for informing prescribers. These endpoints do not address whether the periods of symptom control were consecutive or intermittent; for small treatment differences, intermittent control may be less impactful to patients. The Applicant proposed to include both endpoints in Section 14 of the USPI; however, the difference of approximately 3 weeks with UAS7 ≤6 between the treatment arms is not informative beyond the other efficacy claims to be included in the label, such as the proportion of subjects achieving UAS7 ≤6 at Weeks 2 and 12 and figures of ISS7 and HSS7 over time through Week 24. For angioedema-free weeks, the difference between remibrutinib and placebo over 12 weeks represents less than two additional weeks of freedom from angioedema symptoms. While statistically significant with a rate ratio of 1.3, this translates to less than two additional angioedema-free weeks over a 3-month period. See Section [6.3.1](#) for additional discussion.

Table 16. Secondary Efficacy Analysis: Cumulative Number of Weeks Endpoints in FAS, Trials A2301 and A2302

Parameter	Trial A2301				Trial A2302			
	Remibrutinib		Rate Ratio (95% CI)	p-Value	Remibrutinib		Rate Ratio (95% CI)	p-Value
	25 mg N=309	Placebo N=153			25 mg N=297	Placebo N=153		
UAS7 $\leq$ 6 up to Week 12, LS mean (SE)	5.2 (0.4)	1.9 (0.2)	2.7 (2.0, 3.6)	<0.001	4.5 (0.5)	1.4 (0.2)	3.3 (2.3, 4.7)	<0.001
AAS7 =0 up to Week 12, LS mean (SE)	8.4 (0.3)	6.7 (0.3)	1.3 (1.1, 1.4)	<0.001	8.8 (0.3)	6.7 (0.3)	1.3 (1.2, 1.5)	<0.001

Source: Statistical Analyst-reproduced results using Applicant-submitted datasets admiup12 and admiaa12

Statistical model used negative binomial regression with log link, treatment arm, geographical region, prior exposure to anti-IgE biologics as fixed covariates. For AAS7 analysis, baseline AAS7 response is added as a fixed covariate. Natural log of (number of weeks with the response variable in treatment period/12 weeks) used as offset variable. Rate ratio >1 favors remibrutinib 25 mg.

Abbreviations: AAS7, weekly angioedema activity score; CI, confidence interval; FAS, full analysis population; LS, least squares; N, number of subjects; SE, standard error; UAS7, weekly urticaria activity score

6.2.2.8.5. Subgroup Analyses, Trials A2301 and A2302

Results of subgroup analyses by demographics and baseline disease characteristics demonstrated similar treatment effects on the primary outcome compared to results in the overall study population, all favoring remibrutinib ([Figure 69](#), [Figure 70](#), [Figure 71](#), and [Figure 72](#)). Although only a small subset of subjects had prior omalizumab exposure, an exploratory post hoc analysis showed a favorable treatment effect in this subgroup ([Figure 73](#)). See Sections [15.1.4.4](#), [15.1.4.6](#), [16.1.4](#), and [16.2.1](#) for additional details.

6.3. Key Efficacy Review Issues

6.3.1. Evaluation of Weekly Angioedema Activity Score

(b) (4)

Issue

The (b) (4) cumulative number of angioedema-free weeks (defined as AAS7 =0) from baseline to Week 12 in Trials A2301 and A2302.

Background

Angioedema is present in a substantial proportion of subjects with chronic spontaneous urticaria, affecting approximately 40 to 50% of cases, either in combination with wheals or rarely as the sole manifestation. In contrast to bradykinin mediated angioedema (e.g., hereditary angioedema), the angioedema in CSU is mast-cell mediated and typically shorter in duration (resolving within 24 to 72 hours). When present, angioedema associated with CSU generally responds to available therapies, but can be a more difficult to treat symptom in some patients. (b) (4)

(b) (4)

Assessment

The AAS is a patient-reported outcome instrument that quantifies angioedema activity over a specified period. The AAS7 refers to the sum of daily AAS scores over a 7-day period, analogous to the UAS7 used in urticaria. The AAS consists of five items, each scored daily (0 to 3 points per item, maximum 15 per day), with higher scores indicating greater disease activity. The total AAS7 is the sum of daily scores for seven consecutive days (range 0 to 105). See Section [15.1.3](#) for additional details on the content of the AAS7. Though the Division of Clinical Outcome Assessment was not formally consulted for evaluation of content validity of the AAS7, the review team generally considers the measurement tool to adequately cover relevant aspects of angioedema and that an AAS7=0 is inherently meaningful.

However, the clinical significance of the difference in average cumulative number of angioedema-free weeks (AAS7 =0) up to Week 12 between treatment groups is unclear. In the remibrutinib arm, the average number of angioedema free weeks was 8.43 compared to 6.72 weeks in the placebo arm in Trial A2301, and 8.81 weeks versus 6.68 weeks respectively in Trial

A2302. Over 24 weeks, remibrutinib subjects had more angioedema-free weeks than placebo subjects (17.43 versus 14.45 weeks in Trial A2301; 18.03 versus 13.97 weeks in Trial A2302).

Additionally, there were differences in the baseline angioedema burden between treatment groups across both pivotal studies. In Study A2301, the mean AAS7 score was 27.94 in the remibrutinib arm compared to 23.46 in the placebo arm, while in Study A2302, the remibrutinib arm had a mean AAS7 score of 25.18 versus 19.59 in the placebo arm. This imbalance in baseline favoring placebo added further uncertainty to the clinical interpretation of the results, particularly when considering the proportion of patients achieving angioedema-free status (AAS7 = 0) favored remibrutinib throughout the study by Week 24. In the remibrutinib group, 83.7% of subjects in Study A2301 were angioedema-free compared to 74.2% of subjects receiving placebo, while in Study A2302, the rates were 85.2% versus 72.1% respectively. Given the difference in baseline AAS7 scores, it cannot be discerned whether the increase in angioedema free weeks in the remibrutinib group was due to the effect of drug, regression to the mean, or baseline imbalance in angioedema symptoms.

While remibrutinib appeared to demonstrate statistically significant superiority over placebo in reducing angioedema burden in subjects with CSU, the clinical significance of cumulative-free weeks of AAS7 = 0 is unclear and the difference in baseline angioedema burden between the treatment arms limited interpretability. Additionally, the numerical difference between the treatment groups is relatively small without obvious clinical significance.

Conclusion

Cumulative-free weeks of AAS7 = 0 is of unknown clinical significance. (b) (4)

(b) (4)

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of remibrutinib supporting this NDA has been evaluated in a comprehensive program that included repeat-dose toxicity studies in rats and dogs, reproductive and developmental toxicity studies in rats and rabbits, and carcinogenicity studies in transgenic mice and in rats. In addition, pharmacokinetic and toxicokinetic studies were performed in dedicated studies in mice, rats, rabbits, and dogs and as part of the repeat-dose toxicity studies to support remibrutinib exposures and to compare pharmacokinetics and pharmacodynamics in animals and humans.

Pharmacology studies show that remibrutinib inhibits human BTK in vitro with nanomolar potency and is more selective for BTK compared to the BTK-related enzymes, TEC and BMX. In a safety pharmacology battery of studies, remibrutinib had no effects in respiratory or central nervous systems. Remibrutinib inhibited human ether-à-go-go-related gene currents in vitro (by 15.6%, 42.6%, 69.6%, and 88.9% for 0.3µM, 1µM, 3µM, and 10µM remibrutinib, respectively). However, there were no cardiovascular effects observed in dogs at single doses up to 450 mg/kg/day remibrutinib. Pharmacokinetic studies were conducted in rats, mice, and dogs

with single oral and/or intravenous dosing of remibrutinib. Single-dose studies demonstrated broad distribution of remibrutinib in all tissues, except for the brain, lens of the eye, spinal cord, and white fat. Remibrutinib had rapid absorption with a time to maximum plasma concentration (T_{max}) of 0.25 to 8 hours. Binding of remibrutinib to plasma proteins was high (>90%) across all species. Remibrutinib was shown to be primarily eliminated via metabolism and excretion through the feces. No major metabolites were identified in humans.

The most frequently observed findings in the repeat-dose toxicology studies were observed in the lymph nodes, thyroid glands, liver, pancreas, and blood. Similar findings have been observed with other BTK inhibitors for the liver, mesenteric lymph node, and pancreas along with hemorrhaging. Embryo-fetal toxicity occurred in pregnant animals administered BTK inhibitors during organogenesis.

Lymph Nodes

Decreased cellularity and germinal centers were observed in the mesenteric lymph nodes and gut-associated lymphoid tissue. In addition, sinusoidal red blood cells were observed in the mandibular and mesenteric lymph nodes in the 39-week dog study. Similar findings were also reported in the 26-week rat study. Sinusoidal red blood cells, sinusoidal dilatation, focal angiomatous hyperplasia, diffuse reticuloendothelial hypertrophy/hyperplasia, and/or pigmented macrophages were reported in the 2-year carcinogenicity study in rats.

Thyroid Gland

Follicular hypertrophy was observed in the 2-, 13-, and 26-week rat studies and in the 2-year carcinogenicity study in rats.

Liver

Minimal hepatocellular hypertrophy, multinucleated hepatocytes, pigment, mitosis, periportal vacuolation, and focal necrosis were observed accompanied by increased liver weights in the 26-week rat study.

Pancreas

Minimal islet fibrosis characterized by multilobulated, irregularly outlined islets with fibrosis/collagen/pigment was observed in the 26-week rat study and in the 2-year carcinogenicity study in rats. BTK inhibitors have been associated with rat-specific pancreatic lesions characterized by islet fibrosis, inflammation, and hemorrhage ([Erickson et al. 2017](#)).

Blood

Inhibition of collagen-induced platelet aggregation and prolonged bleeding time were observed in both rat and dog toxicology studies.

Table 17. Margins

Species	Nonclinical Dose			Clinical Dose Safety Margin
	Duration (Weeks)	NOAEL (mg/kg/day)	AUC _{0-24h} (ng*h/mL)	AUC _{0-24h} (25 mg BID) ¹
Rat ²	2	30	13000	33
	13	1000	4780	12
	26	30	5970	15
Dog ³	2	450	10400	27
	13	300	6350	16
	39	300	30000	77

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study CLOU064A2201)

² Exposures from the 2-week, 13-week, and 26-week rat studies were from Study 1470733, #1570128, and #1670372, respectively.

³ Exposures from the 2-week, 13-week, and 39-week dog studies were from Study 1470732, #1570127, and #1670373, respectively.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; h, hour; NOAEL, no-observed-adverse-effect level

Reproductive and Developmental Toxicity

Fertility was unaffected in rats and fetal malformations were not observed in pregnant rats. However, in an embryo-fetal development study in pregnant rabbits administered up to 450 mg/kg/day remibrutinib during organogenesis, increases in the external malformations such as eye opening, small jaws, and hyperflexion of forelimbs were observed at doses 141 times the maximum recommended human dose (MRHD) on an area under the concentration-time curve (AUC) basis. No increases in the incidence of malformations or variations were observed at doses that were 23 times the MRHD on an AUC basis. In a pre- and postnatal developmental toxicity study in rats, reduced litter, an increased number of stillborn pups, and an increased number of pup deaths were reported. No adverse remibrutinib-related changes were observed in maternal rats and offspring at doses that were 58 times the MRHD on a body surface area basis.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Remibrutinib is an oral kinase inhibitor, that primarily inhibits the activity of BTK, an enzyme involved in the signaling pathways of B-cells and other immune cells. These inhibitors have been evaluated in the treatment of hematologic malignancies and autoimmune diseases. A class effect directly due to BTK inhibition theoretically includes increased risk of bleeding in both the presence and absence of thrombocytopenia, suggesting an impaired platelet function as an underlying cause. Off-target effects such as atrial fibrillation, hypertension, ventricular arrhythmias, and increased risk of infection, including opportunistic infections, due to effects on both adaptive and innate immunity have been reported particularly in those receiving less selective BTK inhibitors for the treatment of hematologic malignancies and have been included in the Warnings and Precautions section of the label.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Remibrutinib is not yet approved in the United States or any foreign market for any indication; therefore, no postmarketing experience is available for remibrutinib.

7.4. FDA Approach to the Safety Review

The clinical data scientists and clinical reviewer performed independent safety analyses using R Studio 4.1.3, JMP, and Analysis Studio (Office of Computational Science) software programs. All clinical studies conducted as part of the remibrutinib development program for CSU were evaluated for safety; however, primary safety analyses were conducted in the SAF population (total number of subjects [N]=912), defined as all subjects who received at least one dose of study treatment, regardless of randomization, during the 24-week controlled treatment period in Trials A2301 and A2302. Subjects were analyzed according to the study treatment received. Given the identical study designs and similar safety findings in the individual trials, pooled controlled safety data from Trials A2301 and A2302 are presented in this review. In addition, supportive safety data from the open-label, uncontrolled treatment periods of Trials A2301 and A2302, the phase 2 dose-finding Study A2201, the phase 2 open-label extension Study A2201E1, the phase 3 open-label, single-arm study in Japanese adult subjects with CSU, Study 1301, were independently analyzed and reviewed (see Section [17](#)).

The prespecified safety analysis plan and definitions were reviewed during development under the IND and were acceptable to the clinical review team.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate to assess the safety of remibrutinib at the proposed dosage for the proposed indication. No data quality or integrity issues were identified in the submitted datasets or case report forms. Definitions of AEs and SAE were consistent with CFR 312.32. Treatment-emergent adverse events (TEAEs) were defined as AEs occurring from the first dose of study treatment through 4 weeks (28 days) after the last dose, or until the end of the study period, whichever came first. The Applicant determined AE severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading scale. Verbatim AEs were coded to standard AE terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 for Trials A2301 and A2302. The Applicant's mapping of verbatim terms to MedDRA preferred terms for the events reported in the trial was reviewed and found to be acceptable.

The primary safety database for remibrutinib at the proposed dosage of 25 mg BID consists of the 912 subjects treated in the 24-week, blinded, placebo-controlled, treatment periods in Trials A2301 and A2302. Additional support for the safety of remibrutinib, particularly for long-term use, is derived from the 28-week, uncontrolled, open-label treatment periods in Trials A2301 and A2302; a phase 2 randomized, double-blind, placebo-controlled, dose-ranging Study A2201 and its 52-week open-label extension Study A2201E1, and a 52-week, open-label study in adult Japanese subjects, Study A1301, all of which are discussed further in Sections [15](#) and [17](#).

Note, the Applicant also submitted a multicenter, open-label phase 3 trial, Study A2305, to evaluate the effect of remibrutinib 25 mg BID on blood pressure in subjects with CSU inadequately controlled by second generation H1-antihistamine using a 24-hour blood pressure measurement by ambulatory blood pressure monitoring (ABPM) at steady state (Week 4) compared to baseline. Refer to the ABPM study report review in DARRTS dated June 13, 2025 (DARRTS reference ID 5608166) and Sections [15.5](#) and [17.6](#) of this review for additional details.

The extent of remibrutinib exposure in Trials A2301 and A2302, as shown in [Table 18](#), is adequate to support the safety of a chronically administered drug. During the entire study period for the pivotal trials, which extended up to 56 weeks including a 4-week follow-up period, the remibrutinib 25-mg BID group achieved a median exposure duration of 52.0 weeks with a cumulative exposure of 672 patient-years. Subjects who transitioned from placebo to remibrutinib at Week 24 had a median exposure duration of 28.1 weeks with 134.48 patient-years of cumulative exposure.

Table 18. Duration of Exposure During the Placebo-Controlled and Open-Label Periods, SAF, Trials A2301 and A2302 (Pooled)

Parameter	DB Period		DB + OL Period
	Remibrutinib N=606	Placebo N=306	Remibrutinib N=868
Duration of treatment, weeks			
Mean (SD)	22.5 (5)	22 (6)	40 (15)
Median (Q1, Q3)	24 (24, 24)	24 (24, 24)	52 (28, 53)
Min, max	0.1, 29	0.3, 30	1, 61
Total exposure (person-years)	262	130	672
Subjects treated, by duration, n (%)			
<8 weeks	36 (6)	21 (7)	45 (5)
≥8 to <16 weeks	21 (4)	13 (4)	30 (4)
≥16 to <24 weeks	99 (16)	54 (18)	21 (3)
≥24 to <32 weeks	450 (74)	218 (71)	250 (29)
≥32 to <40 weeks	0	0	18 (2)
≥40 to <52 weeks	0	0	66 (8)
≥52 to <62 weeks	0	0	438 (51)

Source: adex.xpt and adsl.xpt; Software: R

Duration is 24 weeks for the double-blind period.

Abbreviations: DB, double-blind; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OL, open-label; Q1, first quartile; Q3, third quartile; SAF, safety analysis set; SD, standard deviation

7.6. Safety Results

7.6.1. 24-Week Controlled Treatment Period, Pool 1, Trials A2301 and A2302

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials A2301 and A2302

Based on the pooled analyses from the remibrutinib pivotal trials, the overall occurrences of TEAEs as well as SAEs and AEs leading to treatment discontinuation were similar between the treatment arms (Table 19). The majority of TEAEs were mild or moderate in severity (Table 19).

Table 19. Overview of Adverse Events, SAF, Trials A2301 and A2302 (Pooled)²

Event Category	Remibrutinib	Placebo	Risk Difference % (95% CI)
	N=606 n (%)	N=306 n (%)	
SAE	20 (3)	7 (2)	1 (-2, 3)
SAEs with fatal outcome	0	0	0 (-1, 0.6)
Life-threatening SAEs	1 (0.2)	0	0.2 (-1, 1)
SAEs requiring hospitalization	20 (3)	4 (1)	2 (-0.3, 4)
SAEs resulting in substantial disruption of normal life functions*	1 (0.2)	0	0.2 (-1, 1)
Other	3 (0.5)	4 (1)	-0.8 (-3, 0.4)
AE leading to permanent discontinuation of study drug	17 (3)	9 (3)	-0.1 (-3, 2)
AE leading to dose modification of study drug	47 (8)	27 (9)	-1 (-5, 3)
AE leading to interruption of study drug	47 (8)	27 (9)	-1 (-5, 3)
AE leading to reduction of study drug	0	0	0 (-1, 0.6)
AE leading to dose delay of study drug	0	0	0 (-1, 0.6)
Any AE	393 (65)	198 (65)	0.1 (-6, 7)
Severe and worse	18 (3)	7 (2)	0.7 (-2, 3)
Moderate	162 (27)	70 (23)	4 (-2, 10)
Mild	213 (35)	121 (40)	-4 (-11, 2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events are defined as the events which occurred during the on-treatment period from the first dose up to 28 days after the last dose if the subject was not enrolled in extension study.

Duration is 24 weeks for the double-blind period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

* Case of appendicitis that resulted in disruption of life; also flagged as life-threatening.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event; SAF, safety analysis set

² There was an inconsistency with the Applicant table for maximum severity after the code was updated to label an AE from 'Moderate' to "Severe and worse" after taking into account the "Life Threatening" flag submitted by the Applicant. These minor differences did not change the overall assessment of safety.

7.6.1.2. Deaths, Pooled Analyses, Trials A2301 and A2302

There were no deaths reported during Trials A2301 and A2302, or in the entire clinical development program.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials A2301 and A2302

The occurrence of SAEs during the 24-week placebo-controlled periods was relatively infrequent and mainly single events with no major imbalances between treatment groups. A total of 20 subjects (3.3%) in the remibrutinib 25-mg BID group experienced SAEs compared to 7 subjects (2.3%) in the placebo group. A subject-level listing of SAEs that occurred in the remibrutinib-treated arm are listed in [Table 20](#). Based on a review of case narratives, most SAEs were related to underlying medical conditions or coincidental medical events and appear unrelated to remibrutinib.

Table 20. Serious Adverse Events in Remibrutinib-Treated Subjects, SAF, Trials A2301 and A2302 (Pooled)

Trial No.	Age/Sex/Race	Day of Onset	Preferred Term	Description of SAE	AE Severity	Outcome	Relevant Medical History
A2301	29/F/Asian	50	Back pain	Hospitalized for car accident	Mild	Resolved D55 w/physiotherapy, acupuncture	N/A
A2301	34/M/White	3	COVID-19	Hospitalized for COVID-19	Mild	Resolved D10 w/supportive care	N/A
A2301	63/F/White	49	Spondylolisthesis	Hospitalized following fall	Severe	Resolved D152 w/lumbar surgery	N/A
A2301	18/M/White	103	Face injury	Hospitalized for motorbike accident while driving under influence	Moderate	Resolved D167 w/surgical treatment	N/A
A2301	51/F/White	54	Appendicitis	Hospitalized for appendectomy	Moderate	Resolved D64 w/appendectomy	N/A
		98	Mucinous adenocarcinoma of appendix	Diagnosed with low-grade in situ appendiceal mucinous neoplasm	Moderate	Resolved D141 w/abdominal surgery, chemotherapy	
A2301	54/M/White	35	Angina pectoris	Hospitalized	Mild	Resolved D64 w/cardiac medications	Hepatitis C cured, HTN, asthma
A2301	48/F/Unknown	51	Chronic spontaneous urticaria	Hospitalized	Severe	Resolved D57 w/antihistamine	Mechanical urticaria
A2301	45/F/White	71	Diabetic ketoacidosis	Hospitalized	Moderate	Resolved D73 with fluid therapy	DM, HTN
A2301	53/F/Asian	106	Gastrointestinal wall thickening	Hospitalized for abdominal pain; diagnosed with diverticulitis and transverse colonic wall thickening	Severe	Resolved D117 with antibiotics	N/A

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RHAPSIDO (remibrutinib, LOU064)

Trial No.	Age/Sex/Race	Day of Onset	Preferred Term	Description of SAE	AE Severity	Outcome	Relevant Medical History
A2301	60/F/Black	117	Hypokalaemia	Hospitalized on Day 145	Severe	Resolved D148 with potassium supplementation	DM, HTN, GERD hyperlipidemia hypothyroidism, arthritis, colostomy/reversal
A2302	50/F/Asian	32	Wound abscess	Hospitalized for incisional drainage	Moderate	Resolved D54 w/incision drainage, antibiotics	N/A
A2302	31/F/White	11	Nasal polyps	Hospitalized for worsening of nasal polyps	Moderate	D11 treated with Augmentin and prednisone	Chronic sinusitis, AERD, nasal polyps, angioedema, asthma allergic rhinitis
A2302	29/F/Asian	87	Food poisoning	Hospitalized	Moderate	Resolved D91	N/A
A2302	39/M/Asian	156	Gastrointestinal infection	Hospitalized	Moderate	Resolved D158	N/A
A2302	73/M/White	99	Spinal stenosis	Hospitalized for surgery (ventral discectomy and fusion of cervical vertebrae 5 and 6)	Severe	Resolved D104	Osteoarthritis
A2302	59/F/White	59	Haematuria	Hospitalized for bladder surgery	Moderate	Resolved D68	Hypothyroidism, angioedema, HTN, chronic urocystitis with squamous metaplasia

NDA 218436
RHAPSIDO (remibrutinib, LOU064)

Trial No.	Age/Sex/Race	Day of Onset	Preferred Term	Description of SAE	AE Severity	Outcome	Relevant Medical History
A2302	63/M/White	83	Contusion Head injury	Hospitalized following accident	Moderate Mild	Resolved D90	N/A
A2302	63/F/White	94	Angioedema	Hospitalized for angioedema	Severe	Resolved D99	Autoimmune thyroiditis, mechanical urticaria
A2302	71/M/Asian	93	Intervertebral disc degeneration	Hospitalized for surgery	Severe	Resolved D144	Back pain, osteoporosis
A2302	57/M/Asian	175	Arteriosclerosis coronary artery	Hospitalized for drug-coated balloon angioplasty	Moderate	Resolved D245	CAD, DM, HTN

Source: Clinical Reviewer-generated using OCS Analysis Studio, Listing Table Tool

Subjects—Dataset: Demographics; Filter: None.

Events—Dataset: Adverse Events; Filter: AESER = 'Y', TRTEMFL = 'Y', TRTAG1 = 'LOU064 25 mg BID', APERIOD = '1' - '1'.

Abbreviations: AE, adverse event; AERD, aspirin-exacerbated respiratory disease; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; D, day; DM, diabetes mellitus; F, female; GERD, gastroesophageal reflux disease; HTN, hypertension; ID, identifier; LOU064, remibrutinib; M, male; N/A, not available; No., number; SAE, serious adverse event; SAF, safety analysis set

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials A2301 and A2302

The analysis of AEs leading to treatment discontinuation is a useful indicator of the tolerability for chronic remibrutinib therapy for CSU. During the 24-week placebo-controlled period, overall, AEs leading to study treatment discontinuation were generally low and balanced between treatment groups. A total of 17 subjects (2.8%) in the remibrutinib 25-mg BID group discontinued treatment due to adverse events compared to 9 subjects (2.9%) in the placebo group. A subject-level listing of AEs that led to treatment discontinuation in the remibrutinib arm is shown in [Table 21](#). Bleeding-related events, though rare, including petechiae, purpura, and contusion, were more commonly reported reasons for discontinuation in the remibrutinib group than in the placebo group (3 [0.5%] versus 0). Otherwise, there was no clear pattern of organ specific toxicity requiring discontinuation noted during the review with isolated AEs distributed across multiple organ systems.

Table 21. Adverse Events Leading to Discontinuation in Remibrutinib-Treated Subjects, SAF, Trials A2301 and A2302 (Pooled)

Trial No.	Age/Sex/Race	Preferred Term	Day of Discontinuation	AE Severity	Investigator Assessment
A2301	30/F/White	Petechiae	15	Moderate	Related
A2301	63/F/White	Spondylolisthesis	49	Severe	Not related
A2301	18/M/White	Face injury	102	Moderate	Not related
A2301	59/F/White	Thrombocytopenia	86	Moderate	Related
A2301	36/F/White	COVID-19	87	Moderate	Not related
A2301	26/F/White	Skin odour abnormal	30	Moderate	Related
A2301	70/F/White	Eczema	18	Mild	Not related
A2301	35/F/Asian	Urticaria	1	Moderate	Related
A2301	62/F/White	Hepatic enzyme increased	81	Moderate	Related
A2301	45/F/White	Blood pressure increased	102	Mild	Related
A2301	51/F/White	Dermatitis allergic	40	Moderate	Related

Trial No.	Age/Sex/Race	Preferred Term	Day of Discontinuation	AE Severity	Investigator Assessment
A2302	23/M/Asian	Blood creatine phosphokinase increased	17	Moderate	Related
A2302	51/F/White	Gamma-glutamyl transferase increased	112	Moderate	Related
A2302	24/F/Asian	Purpura	69	Mild	Related
A2302	38/F/Asian	Tachycardia	41	Mild	Related

Source: Clinical Reviewer-generated Using OCS Analysis Studio, Listing Table Tool.

Subjects—Dataset: Demographics; Filter: None.

Events—Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRTAG1 = 'LOU064 25 mg BID' or 'Placebo', AEACN = 'DRUG WITHDRAWN', APERIODC = 'Double-Blinded Period'.

Columns (left to right): USUBJID ("Unique Subject Identifier"), TRTAG1 ("Actual Pooled Treatment 1"), AEDECOD ("Dictionary-Derived Term").

* This event was listed in the ADAE dataset, but not in the disposition dataset. Subject (b) (6) was a 51-year-old female with a past medical history of congestive heart failure, atopic dermatitis, dermatographism, and CSU who experienced an increase in gamma-glutamyl transferase on Study Day 112 to 152 U/L. No treatment intervention was reported. On Day 229, the subject received the last dose of study medication and on Day 260, gamma-glutamyl transferase was 76 U/L.

Abbreviations: ADAE, Adverse Event Analysis dataset; AE, adverse event; COVID-19, coronavirus disease 2019; F, female; ID, identifier; LOU064, remibrutinib; M, male; No., number; SAF, safety analysis set

7.6.1.5. Common Treatment-Emergent Adverse Events, Pooled Analyses, Trials A2301 and A2302

The overall incidence of TEAEs was similar between treatment groups, with 64.9% of remibrutinib subjects (393/606) and 64.7% of placebo subjects (198/306) experiencing at least one TEAE as shown in [Table 22](#). The severity distribution was predominantly mild-to-moderate across both groups, with severe adverse events occurring infrequently and in similar proportions (3.0% versus 2.3% for remibrutinib and placebo, respectively). Moderate adverse events were reported in 26.7% of remibrutinib subjects compared to 22.9% of placebo subjects, while mild events occurred in 35.1% and 39.5%, respectively.

The most commonly reported TEAEs that occurred more frequently in the remibrutinib group compared to placebo are shown in the tables below by individual preferred terms (PTs) and by standardized groupings of PTs using OND custom medical queries (OCMQs).

Table 22. Subjects With Common Adverse Events Occurring at ≥3% Frequency and Greater Than Placebo, SAF, Trials A2301 and A2302 (Pooled)

Preferred Term	Remibrutinib N=606 n (%)	Placebo N=306 n (%)	Risk Difference % (95% CI)
Any AE	393 (64.9)	198 (64.7)	0.1 (-6.3, 6.8)
Petechiae	23 (3.8)	1 (0.3)	3.5 (1.7, 5.4) *
Nasopharyngitis	40 (6.6)	14 (4.6)	2.0 (-1.4, 5.0)
Nausea	18 (3.0)	5 (1.6)	1.3 (-1.0, 3.3)
Upper respiratory tract infection	18 (3.0)	6 (2.0)	1.0 (-1.5, 3.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the events which occurred during the on-treatment period from the first dose up to 28 days after the last dose if the subject was not enrolled in extension study.

Duration is 24 weeks for the double-blind period.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAF, safety analysis set

To avoid splitting of related PTs, common TEAEs were also analyzed by OCMQ, as shown in [Table 23](#). There is no OCMQ for upper respiratory tract infection; however, the OCMQ for ‘viral infection’ showed no difference between treatment groups. The grouping of PTs by OCMQ provides a more accurate and complete representation of common adverse reactions (particularly for bleeding related events), and therefore will be used to inform prescribers in the USPI.

Table 23. Subjects With Adverse Events Occurring at ≥3% Frequency and Greater Than Placebo by System Organ Class and OCMQ (Narrow), SAF, Trials A2301 and A2302 (Pooled)

System Organ Class OCMQ (Narrow)	Remibrutinib N=606 n (%)	Placebo N=306 n (%)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)			
Nausea	18 (3.0)	5 (1.6)	1.3 (-1.0, 3.3)
Abdominal pain	18 (3.0)	6 (2.0)	1.0 (-1.5, 3.0)
Infections and infestations (SOC)			
Nasopharyngitis	67 (11.1)	27 (8.8)	2.2 (-2.1, 6.1)
Nervous system disorders (SOC)			
Headache	41 (6.8)	19 (6.2)	0.6 (-3.2, 3.8)
Vascular disorders (SOC)			
Hemorrhage	55 (9.1)	7 (2.3)	6.8 (3.8, 9.7)*

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the events which occurred during the on-treatment period from the first dose up to 28 days after the last dose if the subject was not enrolled in extension study.

Duration is 24 weeks for the double-blind period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; incl, including; OND, Office of New Drugs; PT, preferred term; SAF, safety analysis set; SOC, system organ class

7.6.1.6. Subgroup Analyses, Pooled Analyses, Trials A2301 and A2302

In general, the AE profile across different demographic subgroups was balanced between treatment groups as shown in [Table 106](#), Section [17.1](#). Differences in frequency of AEs between treatment arms was most prominent in the ≥75-year age group. However, the numbers of AEs were small and were consistent with normal age-related expectations. Although the majority of subjects were white or Asian making assessment of across all racial groups difficult, there were no clear trends indicating increased AE risk based on race. Likewise, the safety profile was consistent across sex, country, and ethnicity. See Section [17.1](#) for additional details.

7.6.1.7. Laboratory Findings, Pooled Analyses, Trials A2301 and A2302

Laboratory evaluation in the remibrutinib clinical development program included assessment of hematology, clinical chemistry, and urinalysis parameters collected per the schedule of assessments ([Table 98](#)). During the 24-week placebo-controlled period, the majority of newly occurring laboratory abnormalities were Grade 1 or Grade 2 based on CTCAE criteria and were generally balanced between the remibrutinib and placebo groups. Grade 3 and Grade 4

abnormalities were infrequent in both treatment groups, with no Grade 4 hematology events reported during the placebo-controlled period and rare Grade 3 events that were similarly distributed between groups. Laboratory findings related to liver function tests and cytopenias are discussed in Sections [7.6.1.7](#) and [7.7.3](#).

The analysis of immunoglobulin levels revealed small decreases in median IgG and immunoglobulin M (IgM) levels from baseline in the remibrutinib group (−0.64 g/L for IgG and −0.17 g/L for IgM) compared to placebo (−0.45 g/L for IgG and −0.05 g/L for IgM); however, the clinical relevance of these changes is uncertain as values remained within normal ranges and decreased levels were not associated with increased infection rates (see Section [7.7.2](#)) or other clinical findings.

7.6.1.8. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials A2301 and A2302

Because hepatotoxicity has been identified as a potential risk associated with other BTK inhibitors, the assessment of potential drug-induced liver injury was of particular interest in this application review. The exact mechanism of BTKi-induced liver injury is not fully understood and remains a relatively rare TEAE. Factors that may increase the risk of liver injury with BTK inhibitors include preexisting liver conditions, such as hepatic steatosis, and other medications. Additionally, certain BTK inhibitors have boxed warnings to highlight the risk of hepatotoxicity or list hepatotoxicity in the warnings and precautions section of the label.

The hepatotoxicity assessment for remibrutinib included a review of labs (liver enzymes—ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, and total bilirubin) and TEAEs with systematic evaluation using both CTCAE grading criteria and evaluation of drug-induced serious hepatotoxicity plots to identify potential Hy's Law cases.

During the placebo-controlled period, liver enzyme abnormalities were generally balanced between treatment groups and primarily consisted of asymptomatic, isolated transaminase elevations without concurrent bilirubin increases (i.e., ALT and/or AST without concurrent increase of bilirubin). ALT elevations >3x ULN occurred in 1.2% of remibrutinib subjects versus 1.3% of placebo subjects, with most elevations falling between 3x and <5x ULN as shown in [Table 24](#).

Table 24. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, SAF, Trials A2301 and A2302 (Pooled)

Laboratory Parameter	Remibrutinib N=606 n/N _w (%)	Placebo N=306 n/N _w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5x ULN)	8/599 (1.3)	5/300 (1.7)	0.3 (−2.6, 1.3)
Level 2 (>2x ULN)	1/599 (0.2)	4/300 (1.3)	−1.2 (−3.2, −0.1)*
Level 3 (>3x ULN)	0/599 (0)	1/300 (0.3)	−0.3 (−1.9, 0.3)
Alanine aminotransferase, high (U/L)			
Level 1 (>3x ULN)	7/599 (1.2)	4/300 (1.3)	−0.2 (−2.3, 1.3)
Level 2 (>5x ULN)	2/599 (0.3)	0/300 (0)	0.3 (−0.9, 1.2)
Level 3 (>10x ULN)	1/599 (0.2)	0/300 (0)	0.2 (−1.1, 0.9)

Laboratory Parameter	Remibrutinib N=606 n/N _w (%)	Placebo N=306 n/N _w (%)	Risk Difference % (95% CI)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3x ULN)	4/599 (0.7)	0/300 (0)	0.7 (-0.6, 1.7)
Level 2 (>5x ULN)	0/599 (0)	0/300 (0)	0.0 (-1.3, 0.6)
Level 3 (>10x ULN)	0/599 (0)	0/300 (0)	0.0 (-1.3, 0.6)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5x ULN)	7/599 (1.2)	1/300 (0.3)	0.8 (-0.8, 2.1)
Level 2 (>2x ULN)	0/599 (0)	0/300 (0)	0.0 (-1.3, 0.6)
Level 3 (>3x ULN)	0/599 (0)	0/300 (0)	0.0 (-1.3, 0.6)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks for the double-blind period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot." and "Cholestatic Drug-Induced Liver Injury Screening Plot.." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot.." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot.."

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; SAF, safety analysis set; ULN, upper limit of normal

Two subjects in the remibrutinib group experienced ALT elevations >5x ULN. The first case involved a 62-year-old female with peak ALT of 5.3x ULN at Week 12 in Trial A2301, occurring in the context of concurrent medications including amoxicillin/clavulanic acid and nonsteroidal anti-inflammatory drugs, with rapid normalization following treatment discontinuation. The second case was a 46-year-old female with peak ALT of 14.6x ULN at Week 12, also associated with concurrent metamizole and prior amoxicillin/clavulanic acid use, showing rapid normalization after treatment interruption and successful negative rechallenge upon treatment resumption.

In evaluation of drug-induced serious hepatotoxicity plot analyses, no potential Hy's Law cases (i.e., concurrent ALT or AST >3x ULN and total bilirubin >2x ULN) were identified in the SAF population during the 24-week controlled treatment period; likewise, there were no potential Hy's Law cases observed in the entire 52-week treatment periods of the A2301 and A2302 or in the supportive safety studies (see Section [17](#)). Based on available data, the proposed dosage of remibrutinib does not appear to pose a significant risk for drug-induced liver injury and no additional monitoring beyond routine clinical care is required.

7.6.1.9. Vital Signs, Pooled Analyses, Trials A2301 and A2302

Vital signs were captured according to the schedule of assessments ([Table 98](#)) at each study visit, approximately every 4 weeks. There was no clinically significant impact on vital signs with remibrutinib or major differences between treatment groups. In addition, the Applicant conducted a dedicated 24-hour ambulatory blood pressure monitoring study (A2305) in 144 subjects with CSU inadequately controlled by H1-antihistamines; the results showed no substantial change in blood pressure with remibrutinib treatment (25 mg BID) after 4 weeks. See Sections [15.6](#) and [17.6](#) and the Interdisciplinary Review Team consult memo dated June 13, 2025, for additional details regarding Study A2305.

7.7. Key Safety Review Issues

7.7.1. Bleeding Risk

Issue

Because of its mechanism of action, remibrutinib has the potential to cause bleeding.

Background

BTK inhibitors as a class, most notably ibrutinib, but also second-generation agents such as acalabrutinib and zanubrutinib, have been associated with an increased risk of bleeding. The bleeding risk may be due to BTK-dependent platelet dysfunction, which impairs platelet aggregation and increases susceptibility to both minor and, less commonly, major hemorrhagic events.

Assessment

The clinical review team consulted the Division of Nonmalignant Hematology to assist in the bleeding risk assessment for remibrutinib. Rather than the Applicant's custom query which included PTs for platelet function (platelet aggregation abnormal, platelet aggregation decreased, platelet aggregation inhibition, platelet dysfunction, platelet function test abnormal, and platelet toxicity), the Division of Nonmalignant Hematology recommended using the standardized MedDRA query or OCMQ for 'hemorrhage' as it only includes PTs for observed bleeding reactions. Although abnormal laboratory tests may correlate with increased bleeding risk, this relationship is not straightforward and varies depending on the specific test used, underlying conditions, severity of abnormalities, and other hemostatic factors. As such, the assessment of hemorrhagic adverse events should represent documented bleeding occurrences during trials, not laboratory markers of potential bleeding risk.

An analysis of bleeding TEAEs using the OCMQ for 'hemorrhage' is shown in [Table 25](#). In the pooled safety population, bleeding reactions occurred in 9% of subjects treated with remibrutinib compared to 2% in the placebo group during the 24-week controlled treatment period. Petechiae (4%) and contusion (2%) were the most commonly reported TEAEs. No severe bleeding reactions occurred. There were two bleeding events that were classified as serious, one occurred in relation to an accident and was considered serious due to hospitalization and the second event was hematuria that occurred in a subject with chronic urocystitis with squamous metaplasia. Neither event led to treatment discontinuation, and both resolved with further intervention. In the remibrutinib treatment arm, 0.5% experienced bleeding reactions that led to treatment discontinuation, while none of these reactions occurred in the placebo group. Exposure-adjusted occurrence rate (EAOR) for bleeding did not appear to increase over the entire 52-week study period compared to the placebo-controlled period, suggesting the risk did not increase with longer treatment duration and the first occurrence of bleeding events was highest within the first 4 to 12 weeks of treatment. Regarding dose-response relationships, the available data from higher doses is limited. In the phase 2b extension Study A2201E1, subjects received remibrutinib 100 mg BID (four times the proposed therapeutic dose), and one SAE of melena was reported, though this was attributed to concurrent bariatric surgery rather than drug effect (see Sections [17.1](#), [17.3](#), and [17.4](#) for additional details).

Table 25. Adverse Events Assessment of Hemorrhage FDA Medical Query (Narrow), SAF, Trials A2301 and A2302 (Pooled)

OCMQ (Narrow) Preferred Term	Remibrutinib N=606 n (%)	Placebo N=306 n (%)	Risk Difference % (95% CI)
Hemorrhage (OCMQ)	55 (9.1)	7 (2.3)	6.8 (3.8, 9.7)*
Conjunctival hemorrhage	2 (0.3)	0	0.3 (-0.9, 1.2)
Contusion	13 (2.1)	2 (0.7)	1.5 (-0.4, 3.1)
Ecchymosis	9 (1.5)	1 (0.3)	1.2 (-0.4, 2.5)
Epistaxis	5 (0.8)	1 (0.3)	0.5 (-1.0, 1.6)
Gingival bleeding	1 (0.2)	0	0.2 (-1.1, 0.9)
Hematoma	1 (0.2)	0	0.2 (-1.1, 0.9)
Hematuria	6 (1.0)	1 (0.3)	0.7 (-0.9, 1.9)
Hemorrhagic ovarian cyst	1 (0.2)	0	0.2 (-1.1, 0.9)
Intermenstrual bleeding	1 (0.2)	0	0.2 (-1.1, 0.9)
Menometrorrhagia	0	1 (0.3)	-0.3 (-1.8, 0.3)
Petechiae	23 (3.8)	1 (0.3)	3.5 (1.7, 5.4)*
Purpura	5 (0.8)	0	0.8 (-0.4, 1.9)
Urinary occult blood positive	1 (0.2)	0	0.2 (-1.1, 0.9)
Maximum severity			
Death	0	0	0.0 (-1.2, 0.6)
Life-threatening	0	0	0.0 (-1.2, 0.6)
Severe	0	0	0.0 (-1.2, 0.6)
Moderate	9 (1.5)	2 (0.7)	0.8 (-1.0, 2.3)
Mild	46 (7.6)	5 (1.6)	6.0 (3.2, 8.6)*
Serious	2 (0.3)	0	0.3 (-0.9, 1.2)
Deaths	0	0	0.0 (-1.2, 0.6)
Resulting in discontinuation	3 (0.5)	0	0.5 (-0.7, 1.4)
Relatedness	35 (5.8)	4 (1.3)	4.5 (2.0, 6.8)*
Number of subjects with AE resolution while on treatment ¹	39/55 (70.9)	3/7 (42.9)	28.1 (-7.2, 58.3)
Duration, days (AE start to end date)			
Mean (SD)	27.9 (28.2)	9 (2.6)	NA
Median (Q1, Q3)	18 (8, 44)	8 (7.5, 10)	NA
Min, max	1, 128	7, 12	NA
Number of subjects with AE unresolved ²	16/55 (29.1)	2/7 (28.6)	0.5 (-37.4, 25.9)
Number of subjects with AE resolution after end of treatment ³	13/55 (23.6)	2/7 (28.6)	-4.9 (-42.5, 20.1)
Duration, days (treatment end date to AE end date)			
Mean (SD)	69.7 (72.4)	38.5 (3.5)	NA
Median (Q1, Q3)	32 (19, 114)	38.5 (37.2, 39.8)	NA
Min, max	2, 231	36, 41	NA

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as the events which occurred during the on-treatment period from the first dose up to 28 days after the last dose if the subject was not enrolled in extension study.

Duration is 24 weeks for the double-blind period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Relatedness is determined by the investigator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

¹ AE end dates on or before treatment end dates

² AE occurred on or before treatment end date with missing end date (i.e., no end dates reported, assumed that AE continuing)

³ AE occurred on or before treatment end date with end dates after treatment end date

Abbreviations: AE, adverse event; CI, confidence interval; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCMQ, OND custom medical query; OND, Office of New Drugs; Q1, first quartile; Q3, third quartile; SAF, standard analysis set; SD, standard deviation

To further explore the imbalance in bleeding TEAEs, the review team assessed whether there is an exposure-response relationship for this safety signal. A comparison of bleeding TEAE rates (using the Applicant’s custom query) by quartiles of remibrutinib average concentrations at steady state ($C_{avg,ss}$) indicated no significant increase in bleeding events with increasing $C_{avg,ss}$ quartile. The 95% CIs for the proportion of subjects with bleeding overlapped between the different exposure quartiles across three distinct safety data pools: E-R Safety Pool 1a, E-R Safety Pool 1b, and E-R Safety Pool 2 (Table 26). Additionally, no significant difference was observed in remibrutinib $C_{avg,ss}$ between subjects who experienced bleeding and those who did not, across all three safety data pools (Figure 8). Furthermore, exposure-response analyses for safety indicated no significant relationship between the incidence of bleeding and increasing remibrutinib $C_{avg,ss}$ in any of the safety data pools examined (Figure 9).

Table 26. Comparison of Treatment-Emergent Bleeding AESI Rates by Remibrutinib $C_{avg,ss}$ in Phase 2 and 3 Clinical Trials

Exposure Subgroup	Placebo	Q1	Q2	Q3	Q4
E-R Safety Pool 1a					
Exposure range (ng/mL)	Placebo	[1.44-8.15]	[8.15-11.6]	[11.6-15.8]	[15.8-196]
n/N	7/306	4/152	4/152	6/150	6/152
Proportion (%)	2.29	2.63	2.63	4	3.95
(95% CI)	(0.92-4.66)	(0.72-6.60)	(0.72-6.60)	(1.48-8.50)	(1.46-8.39)
E-R Safety Pool 1b					
Exposure range (ng/mL)		[1.44-8.1]	[8.1-11.6]	[11.6-15.5]	[15.5-196]
n/N		5/217	6/217	7/217	10/217
Proportion (%)		2.30	2.76	3.23	4.61
(95% CI)		(0.75-5.29)	(1.02-5.92)	(1.31-6.53)	(2.23-8.31)
E-R Safety Pool 2					
Exposure range (ng/mL)	Placebo	[0.7-7.38]	[7.38-11.5]	[11.5-17.5]	[17.5-198]
n/N	4/348	5/219	4/218	3/218	3/218
Proportion (%)	1.15	2.28	1.83	1.38	1.38
(95% CI)	(0.31-2.92)	(0.75-5.25)	(0.28-3.97)	(0.28-3.97)	(0.28-3.97)

Source: Reviewer-generated table based on “Exposure-response analysis for efficacy and safety of remibrutinib in adult Subjects with Chronic Spontaneous Urticaria—Modeling Report” Tables 7-12, 7-13, and 7-14.

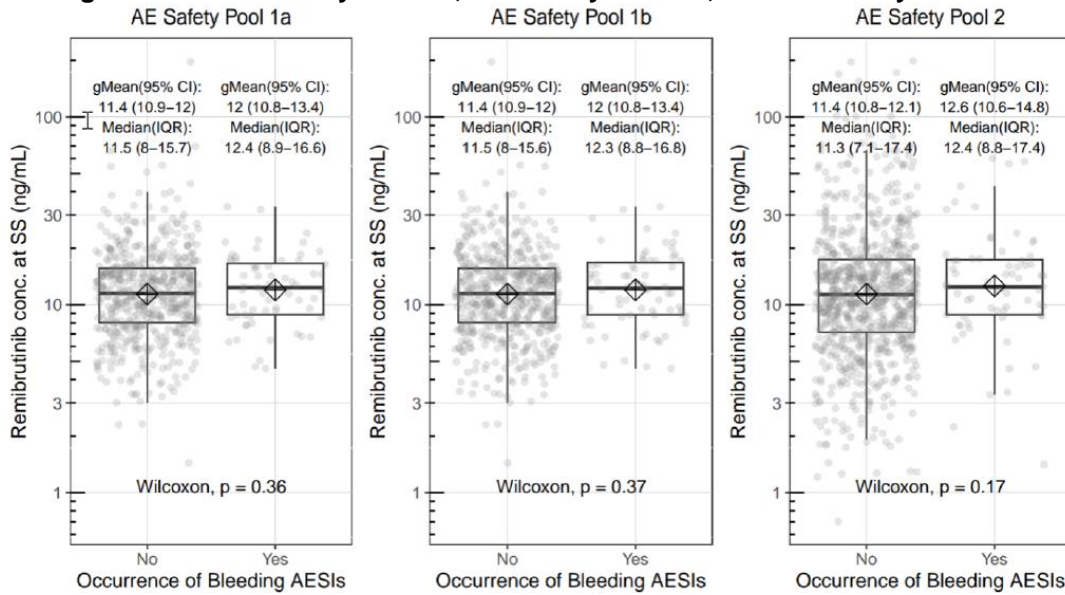
E-R Safety Pool 1a: 24-week placebo-controlled period in Trials A2301 and A2302, including all active and placebo arms, data limited to 24-week placebo-controlled period

E-R Safety Pool 1b: entire trial on-treatment period in Trials A2301 and A2302, including all data collected under remibrutinib treatment during placebo-controlled and open-label periods in Trials A2301 and A2302.

E-R Safety Pool 2: 12-week placebo-controlled period: Trials A2201, A2301 and A2302, data censored at Week 12 including all active and placebo arms (follow-up limited by the duration of double-blinded placebo-controlled period in phase 2 Study A2201).

Abbreviations: AESI, adverse event of special interest; $C_{avg,ss}$, average blood concentrations or remibrutinib at steady state; CI, confidence interval; E-R, exposure-response; N, number of subjects; n, number of subjects within specific subgroup; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4

Figure 8. Comparison of Remibrutinib $C_{avg,ss}$ Between Subjects With and Without Occurrence of Bleeding AESIs in E-R Safety Pool 1a, E-R Safety Pool 1b, and E-R Safety Pool 2



Source: Exposure-response analysis for efficacy and safety of remibrutinib in adult subjects with Chronic Spontaneous Urticaria—Modeling Report Figure 7-23.

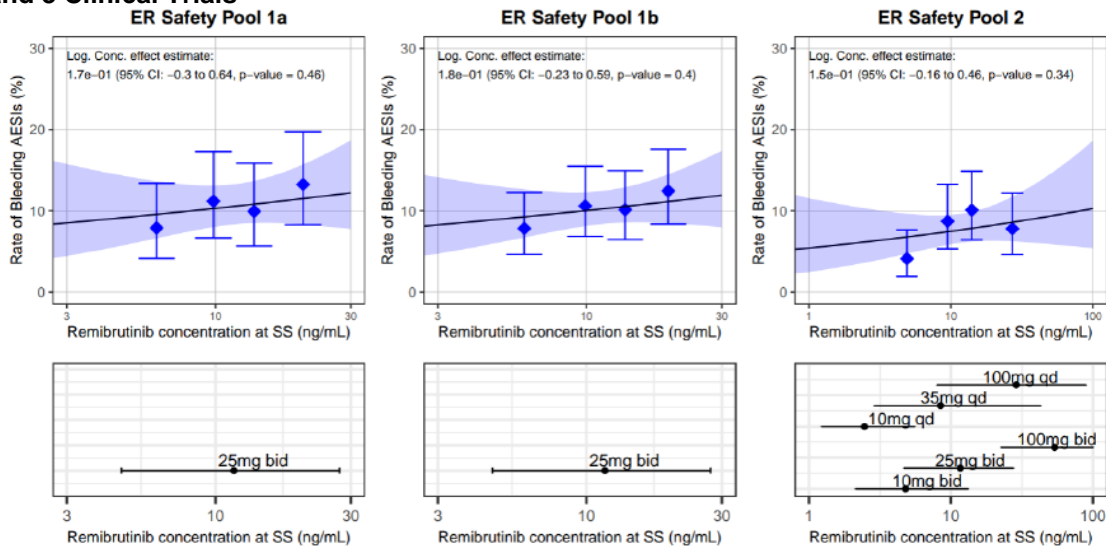
E-R Safety Pool 1a: 24-week placebo-controlled period in Trials A2301 and A2302, including all active and placebo arms, data limited to 24-week placebo-controlled period

E-R Safety Pool 1b: entire study on-treatment period in Trials A2301 and A2302, including all data collected under remibrutinib treatment during placebo-controlled and open-label periods in Trials A2301 and A2302.

E-R Safety Pool 2: 12-week placebo-controlled period: Trials A2201, A2301 and A2302, data censored at Week 12 including all active and placebo arms (follow-up limited by the duration of double-blinded placebo-controlled period in phase 2 Study A2201).

Abbreviations: AESI, adverse event of special interest; $C_{avg,ss}$, average blood concentrations or remibrutinib at steady state; CI, confidence interval; E-R, exposure-response; gMean, geometric mean; IQR, interquartile range; SS, steady state

Figure 9. Logistic Regression for the Incidence of Bleeding AESIs in E-R Safety in SS in Phase 2 and 3 Clinical Trials



Source: Exposure-response analysis for efficacy and safety of remibrutinib in adult subjects with Chronic Spontaneous Urticaria—Modeling Report Figure 7-24.

Abbreviations: AESI, adverse event of special interest; bid, twice daily; CI, confidence interval; E-R, exposure-response; qd, once daily; SS, steady state

Notably, there are limitations to the above exposure-response analyses for safety. For example, in Safety Pool 1a and Safety Pool 1b, both of which consider data from Trials A2301 and A2302, only a single remibrutinib dosage of 25 mg BID was evaluated. Although Safety Pool 2 also included data from dose-ranging Study A2201, which assessed dosages up to 100 mg BID, data are only considered for the 12-week placebo-controlled period. Thus, these analyses do not sufficiently inform the potential bleeding risk following chronic exposure to higher doses/exposures of remibrutinib.

In the proposed USPI, the Applicant recommends withholding remibrutinib for 3 to 7 days pre- and postsurgery. However, with a half-life of only 1 to 2 hours and time to maximum concentration of approximately 1 hour, the drug would be nearly completely eliminated within 5 to 10 hours (five to six half-lives). The Applicant provided justification for the interruption period in a September 4, 2025 response to a labeling information request, stating that the 3-day presurgical interruption accounts for the 48 to 72-hour platelet function recovery time following covalent BTK inhibition. The 7-day consideration for postsurgical reintroduction is primarily based on contemporary surgical literature recommendations for resuming treatment after major surgical interventions, allowing adequate time for initial wound healing and hemostatic stability.

Regarding coadministration of remibrutinib with anticoagulants, no clinical data exists because concomitant use was prohibited in the phase 3 clinical trials. Limited data were available for antiplatelet agents (aspirin up to 100 mg daily and clopidogrel up to 75 mg daily were permitted); however, the use of dual antiplatelet therapy, such as the combination of acetylsalicylic acid and clopidogrel, was prohibited.

Conclusion

Remibrutinib is associated with an increased risk of bleeding reactions, likely due to its mechanism of action and impact on platelet function; however, most events were related to bruising/petechiae/contusion rather than overt hemorrhage. Reported bleeding TEAEs were primarily mild or moderate in severity, with few requiring medical intervention or treatment discontinuation. Supportive safety data suggest that there is no increase in risk over time with extended use or higher doses; however, these data are limited. Given that CSU is a symptomatic and self-limited condition with multiple available treatment options, the review team recommends adding a Warning and Precaution to Section 5 of the USPI to inform prescribers of the potential risk of bleeding reactions and need for consideration of the benefit/risk for continued treatment if reactions occur. Given the observed safety signal for bleeding risk, withholding remibrutinib perioperatively is a reasonable recommendation and the review team accepted the Applicant's justification. The team recommends advising prescribers to consider the risks and benefits of concomitant antithrombotic use in Section 7 of the USPI given the absence of clinical data from phase 3 trials.

7.7.2. Infection Risk

Issue

Because of its mechanism of action, remibrutinib has the potential to cause immune compromise leading to increased infection.

Background

BTK is a cytoplasmic tyrosine kinase and member of the TEC kinase family, selectively expressed in cells of the adaptive and innate immune system, including B-cells, macrophages, mast cells, basophils, and thrombocytes. In addition to its role for signaling through the FcεRI for IgE and the activating FcγR for IgG, BTK plays an important role in signaling through the B-cell receptor pathway, theoretically affecting primary IgM and IgG responses. Clinical experience with other BTK inhibitors revealed an increased risk for infections.

Assessment

During the 24-week placebo-controlled periods in Trials A2301 and A2302, the overall infection rates (based on MedDRA system organ class ‘Infections and Infestations’) were comparable between the remibrutinib 25-mg BID and placebo groups, with 33% versus 34% of subjects experiencing infections, respectively. There was no difference between treatment groups in the frequency of OCMQ terms for ‘viral infection’ or ‘bacterial infection’. The exposure-adjusted incidence rates were similarly balanced at 95.6 versus 98.1 per 100 patient-years in the remibrutinib and placebo groups, respectively. The types of infections observed were consistent with those expected in the general population, predominantly consisting of respiratory tract infections including coronavirus disease 2019 (COVID-19) (10.7% versus 11.4%), nasopharyngitis (6.6% versus 4.6%), and upper respiratory tract infections (3.0% versus 2.0%) in the remibrutinib versus placebo treatment arms, respectively. Viral infections were the most frequent, while bacterial and fungal infections were reported infrequently. No opportunistic infections, as might be expected with the use of a BTK inhibitor, such as invasive aspergillosis, cryptococcosis, or *Pneumocystis jirovecii* pneumonia nor encapsulated bacterial infections were reported in the remibrutinib group.

The severity profile of infections demonstrated that most cases of infections were categorized as mild-to-moderate in nature (67 to 68% mild, 32% moderate). Serious infections were infrequent and occurred at comparable rates between treatment groups (0.8% versus 0.7%). There were two subjects in the remibrutinib treatment arm who experienced a severe infection, bronchitis and acrodermatitis, both moderate that did not lead to treatment interruption or discontinuation. Treatment modifications due to infections were minimal, with only one infection leading to study treatment discontinuation (COVID-19) and treatment interruptions occurring at similar rates between groups (8.4% versus 7.9% of events). Long-term safety data extending up to Week 52 showed no increase in infection rates with prolonged exposure. The exposure-adjusted occurrence rate decreased from 111.7 to 82.7 per 100 patient-years during the entire study period, suggesting no cumulative infection risk with extended treatment duration (see Section [17.1](#)).

From an immunological perspective, while small decreases in IgG and IgM levels were observed with remibrutinib treatment, these remained within normal ranges and showed no temporal association with infection occurrence. Similarly, no correlation was identified between cytopenia events and increased infection risk, further supporting the absence of clinically meaningful immunosuppression.

The clinical trial data demonstrate that the infection risk with remibrutinib is comparable to placebo with no evidence of opportunistic/atypical infections or increase in frequency or severity of infections attributable to the drug. There was no change to the risk of infection with long-term use up to 1 year (52 weeks).

Conclusion

Despite its mechanism of action and known BTKi class effects for increasing susceptibility to infection, remibrutinib 25 mg BID does not appear to increase infection risk in subjects with CSU.

7.7.3. Cytopenias

Issue

Because of its mechanism of action, remibrutinib has the potential to cause cytopenias.

Background

BTK inhibitors are associated with an increased risk of cytopenias due to the pharmacological effect on B-cell signaling. BTK inhibitors, particularly less selective agents, may also have off-target effects on hematopoietic progenitors. The incidence and severity of these cytopenias vary by agent and clinical context, such as concomitant use with other cytotoxic agents or chemoimmunotherapy.

Assessment

Cytopenia was captured as an AESI for remibrutinib and reported using the standardized MedDRA query ‘Haematopoietic cytopenias (broad).’ The evaluation focused on monitoring for decreases in blood cell counts, particularly neutrophils, lymphocytes, and platelets, and assessing any potential clinical consequences such as increased infection risk or bleeding events. During the 24-week placebo-controlled period in the pivotal trials, cytopenia AESIs occurred infrequently in both the remibrutinib 25-mg BID group (22, 3.6%) and the placebo group (6, 2.0%) as shown in [Table 27](#).

Table 27. Cytopenia AESIs by SMQ, SAF, Trials A2301 and A2302 (Pooled)

Cytopenia AESI	Remibrutinib N=606 n/N_w (%)	Placebo N=306 n/N_w (%)	Risk Difference % (95% CI)
Hematopoietic cytopenias (SMQ) (broad)	22 (3.6)	6 (2.0)	
Hematopoietic erythropenia (SMQ) (broad)	8 (1.3)	3 (1.0)	
Anemia	5 (0.8)	3 (1.0)	-0.2 (-2.1, 1.1)
Hemoglobin decreased	3 (0.5)	0	0.5 (-0.7, 1.4)
Hematopoietic leukopenia (SMQ) (broad)	12 (2.0)	2 (0.7)	
Leukopenia	3 (0.5)	0	0.5 (-0.7, 1.4)
Lymphopenia	0	1 (0.3)	-0.3 (-1.8, 0.3)
Monocytopenia	1 (0.2)	0	0.2 (-1.1, 0.9)
Neutropenia	7 (1.2)	1 (0.3)	0.8 (-0.7, 2.1)
Neutrophil count decreased	2 (0.3)	0	0.3 (-0.9, 1.2)
White blood cell count decreased	3 (0.5)	0	0.5 (-0.7, 1.4)

	Remibrutinib N=606 n/N_w (%)	Placebo N=306 n/N_w (%)	Risk Difference % (95% CI)
Cytopenia AESI			
Hematopoietic thrombocytopenia (SMQ) (broad)	3 (0.5)	1 (0.3)	
Thrombocytopenia	3 (0.5)	1 (0.3)	0.2 (-1.4, 1.2)

Source: Clinical Reviewer-generated using ADAE.xpt and ADSL.xpt in Analysis Studio
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects meeting criteria; N_w, number of subjects with data; SAF, safety analysis set; SMQ, standardized MedDRA query

All cytopenia AESIs were mild (75.0% versus 100.0%) or moderate (25.0% versus 0%) in severity, with no severe events reported. There were no SAEs related to cytopenia. The median time-to-event onset was 70.0 days in the remibrutinib group versus 35.0 days in the placebo group, with median event durations of 26.0 and 28.0 days, respectively. Most events resolved (90.6% versus 88.9%) while continuing the drug, and only 31.3% of events in the remibrutinib group were considered related to study treatment. No action was taken with the study treatment for most events (84.4%), with study treatment interrupted for only three events (9.4%) and discontinued for one event (3.1%) in the remibrutinib group. The difference between treatment groups was primarily driven by TEAEs for neutropenia (1.2% versus 0.3%) and neutrophil count decreased (0.3% versus 0%) in the remibrutinib and placebo groups, respectively. Grade 3 neutropenia, defined as an absolute neutrophil count of 500 to <1000/mm³, occurred in two subjects in the remibrutinib group compared to one subject in the placebo group, neither of which was associated with a clinical infection. One occurred in a 42-year-old female at Week 16 who remained on treatment. She recovered by Week 20 but then worsened to Grade 1 (absolute neutrophil count between lower limit of normal and 1500/mm³). The second occurred in a 69-year-old female at Week 8 who, after interrupting treatment for 8 days, improved to Grade 1 at Week 12.

During the placebo-controlled period, thrombocytopenia was reported in 3 patients (0.5%) in the remibrutinib treatment arm compared to 1 patient (0.3%) in the placebo group. All reported thrombocytopenia events were mild or moderate in severity, with no severe cases documented. One notable case involved a 21-year-old male patient who had a Grade 1 low platelet count at baseline and Week 2 that initially recovered to normal levels, but then developed a Grade 3 low platelet count of $39 \times 10^9/L$ at Week 24. Importantly, this patient's platelet count showed normal values when retested just 2 days later, suggesting a transient laboratory finding rather than sustained thrombocytopenia. Another case involved a 29-year-old female patient who was initially reported to have a Grade 4 platelet decrease, but this was later determined to be due to incorrect reporting of laboratory parameter units by the local laboratory, with no clinically relevant platelet decrease actually occurring. There was no temporal association between low platelet counts and bleeding AESIs in either treatment group. The infrequent low platelet counts, and increased prothrombin INR values were not temporally associated with bleeding events, and the analysis revealed no correlation between bleeding AESIs and notable decreases in platelet counts.

During the 52-week study periods, the EAOR did not increase (8.9 per 100 patient-years) compared to the placebo-controlled period (12.1 per 100 patient-years), suggesting no increase in cytopenia AESIs with longer treatment duration (see Section [17.1](#) for additional details).

In addition to cytopenia AESIs, laboratory data were also analyzed because not all lab abnormalities were captured as TEAEs by investigators. Laboratory analysis revealed minimal shifts in blood cell counts, with a downward shift in median neutrophil counts (from 4.00×10^9 cells/L at baseline to 3.75×10^9 cells/L at Week 2) and platelet counts (from 272×10^9 cells/L to 243×10^9 cells/L at Week 2) observed in the remibrutinib group. However, these levels remained stable throughout treatment and within normal ranges, returning to baseline levels upon treatment cessation. Grade 3 and Grade 4 hematology abnormalities were infrequent and generally balanced between treatment groups, with no additional events identified beyond those that were captured as AESIs. There was no association between cytopenias and clinical bleeding events or infections.

Conclusion

Cytopenia occurred infrequently in the trial with small numerical differences between treatment groups. Although remibrutinib-treated subjects were more likely to report neutropenia or thrombocytopenia, the observed imbalances do not appear clinically significant.

7.7.4. Vaccine Immune Response

Issue

Because of its mechanism of action, remibrutinib may impact the immune response to vaccinations. [REDACTED]

(b) (4)

Background

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. By decreasing antigen presentation to T-cells, BTK inhibitors may lead to altered T-cell responses and interferon induction by vaccination. To evaluate the impact of remibrutinib on vaccine response, the Applicant conducted an immunogenicity study in healthy adults. In consultation with CBER, the Agency provided feedback on the study (written responses dated July 19, 2022) outlining key concerns such as whether a 1-week interruption of remibrutinib would be sufficient for immune system recovery, the appropriateness of conducting the study in healthy volunteers rather than the intended subject population, and the selection of immunogenicity endpoints. The Agency emphasized that immunogenicity studies are inherently difficult to interpret [REDACTED], cautioning that vaccine responses cannot serve as surrogates for overall immune competence.

(b) (4)

Assessment

Study F12101 was a double-blind, 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 subjects. A total of 107 subjects were randomized in a 1:1:1 ratio to one of the three treatment arms: concomitant remibrutinib treatment, interrupted remibrutinib treatment, or placebo. Subjects were administered three 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]), on Day 15. See Section 15.6 for a detailed description of the study design.

In consultation with CBER/Office of Vaccines Research and Review, the review team concluded that the results of the vaccine immune response study were not relevant (b) (4) for various reasons. Primarily, the study failed to employ the immunogenicity evaluations that CBER had previously accepted for determining vaccine effectiveness. Specifically, it did not measure geometric mean titers and proper seroconversion rates for influenza vaccines, nor did it use the opsonophagocytic antibody assay for pneumococcal vaccines, despite CBER providing guidance on these requirements in the 2022 Type C meeting responses to the Applicant. Instead, the study used less appropriate endpoints including IgG antibody levels for pneumococcal assessment, which are insufficient (b) (4).

The inclusion of KLH as a study component further limited the study's regulatory relevance. CBER noted that KLH is not an FDA-licensed vaccine and that antibody responses to KLH lack established clinical significance for predicting responses to licensed vaccines. Finally, the study was conducted in healthy volunteers rather than the intended CSU patient population, limiting extrapolation of results.

Regarding avoidance of live or live-attenuated vaccines, with input from CBER, the review team agreed that such recommendations would be appropriate for inclusion in Sections 5 (Warnings and Precautions) and 17 (Patient Counseling Information) of the USPI. Although not routinely included in labeling for other BTKi, recommendations to avoid live/live-attenuated vaccines have similarly been included in labeling for other immunomodulators (in the absence of clinical data), and patients with CSU are more likely to be candidates for live virus vaccines compared to the immunocompromised oncology populations typically treated with approved BTK inhibitors. For more details, refer to the CBER consult memo (Inter-Center Consult No.: 01066955) dated June 2, 2025, in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) (Reference ID 5601342).

Conclusion

(b) (4)
Given the lack of clinical data on the effects of live or live-attenuated vaccines in subjects receiving remibrutinib, the review team concurs with adding a Warning and Precaution to avoid use of live and live-attenuated vaccines.

7.7.5. Use in Subjects With Hepatic Impairment

Issue

(b) (4) patients with hepatic impairment (HI).

Background

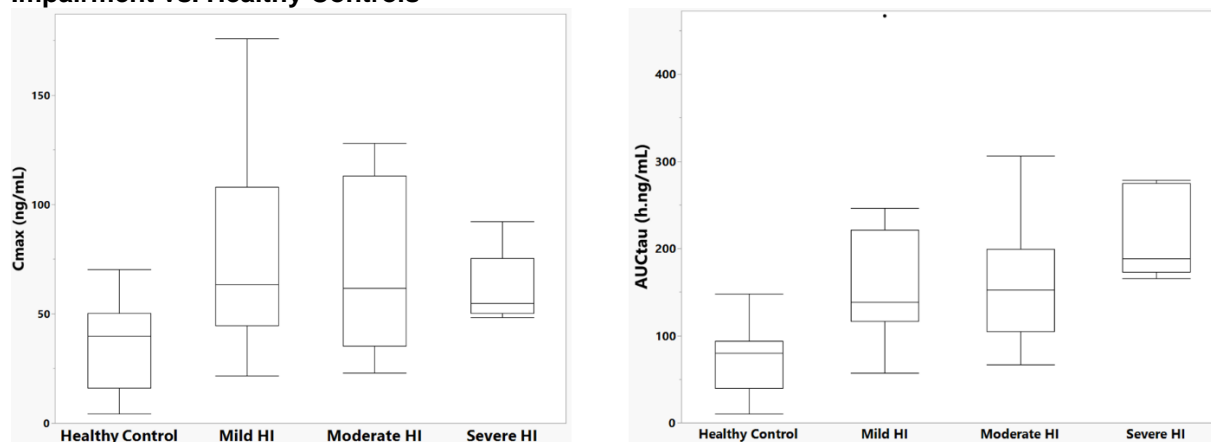
Unlike drugs that can be dose-adjusted to accommodate patient-specific factors or drug interactions, the therapeutic window and safety profile of remibrutinib do not permit dose reductions or increases to compensate for altered drug exposure as only a single dose of remibrutinib (i.e., 25 mg BID) was evaluated in the pivotal phase 3 trials A2301 and A2302. As

a result, there are limited clinical data to guide dose adjustments for patients with HI who experience 2- to 3.5-fold increases in drug exposure across all degrees of liver dysfunction (mild, moderate, and severe).

Assessment

The Applicant conducted a dedicated HI study, Study A2101, in which the pharmacokinetics of remibrutinib following administration of 25 mg BID was evaluated in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) HI compared to subjects with normal hepatic function matched for gender, age, and body weight. Following the administration of 25-mg BID remibrutinib, the geometric mean ratios for subjects with mild, moderate, and severe HI compared to subjects with normal hepatic function were 1.85, 1.65, and 1.99 for maximum plasma concentration (C_{max}), respectively, and 2.33, 2.3, and 3.49 for $AUC_{last,ss}$, respectively (Figure 10, Figure 35). For additional details, refer to Section 14.2.5.

Figure 10. Box Plots of C_{max} and AUC_{tau} in Subjects With Mild, Moderate, and Severe Hepatic Impairment vs. Healthy Controls



Source: Reviewer's Analysis based on ADPP.xpt dataset for Study A2101

Abbreviations: AUC_{tau} , area under the concentration-time curve over the dosing interval; C_{max} , maximum plasma concentration; HI, hepatic impairment

(b) (4)

(b) (4)

However, safety data from healthy subjects is not considered appropriate to reflect the safety in subjects with CSU. In addition, the safety data in subjects with CSU derived from Studies A2201 and A2201E1 are limited by the small number of subjects exposed for a short duration in the controlled Study A2201 and the inherent limitations of uncontrolled, unblinded data in Study A2201E1. Thus, exposure-response analyses for safety are not adequate to determine that chronic exposure to higher doses/exposures of remibrutinib is safe.

Furthermore, CSU is not a life-threatening disease, and other approved therapies are available for the treatment of CSU, including in patients with HI. Given the potential risks associated with remibrutinib (e.g., bleeding events) and the lack of robust safety data with remibrutinib exposures 2.3- to 3.5-fold greater than that of the recommended dosage, the benefit-risk of exposing CSU patients with HI to higher exposures of remibrutinib is not favorable.

Conclusion

Given the limitations in assessing safety following administration of higher doses of remibrutinib, the use of remibrutinib in subjects with any degree of HI (mild, moderate, or severe) should be avoided. Consideration of the condition and benefit/risk assessment led to conservative dose-adjustment recommendations, favoring contraindications rather than dose modifications when adequate safety data were unavailable to support exposure changes.

7.7.6. Concomitant Use With CYP3A4 Modulators

Issue

(b) (4) concomitant use of strong or moderate CYP3A4 inhibitors.

Background

Unlike drugs that can be dose-adjusted to accommodate patient-specific factors or drug interactions, the therapeutic window and safety profile of remibrutinib do not permit dose reductions or increases to compensate for altered drug exposure as only a single dose of remibrutinib (i.e., 25 mg BID) was evaluated in the pivotal phase 3 Trials A2301 and A2302. The drug's susceptibility to CYP3A4-mediated interactions creates scenarios where dose adjustments would theoretically be beneficial but are not available as management strategies because there are limited clinical data to guide dose adjustments.

Strong CYP3A4 inhibitors increase remibrutinib exposure by 3- to 4-fold, while strong inducers decrease exposure by 74% to 78%, yet there are no established dose-reduction or increase protocols to maintain therapeutic levels during these interactions.

Assessment

Strong CYP3A4 Inhibition

Study X2103 evaluated the impact of multiple oral doses of ritonavir 100 mg, a strong CYP3A4/P-glycoprotein (P-gp) inhibitor, or grapefruit juice, an intestinal CYP3A4 inhibitor, on the pharmacokinetics of remibrutinib following administration of 20-mg remibrutinib capsules once daily in healthy subjects (see Section [14.2.6.1](#)). Initially, remibrutinib 50 mg once daily was administered before evaluating the drug-drug interactions (DDIs) with ritonavir and grapefruit juice in order to achieve near-complete BTK receptor occupancy and steady-state conditions, thereby minimizing the influence of target-mediated drug disposition (TMDD) on remibrutinib PK measurements. Given the short apparent half-life of remibrutinib, it is not expected that administration of higher doses (i.e., 50 mg) will influence the pharmacokinetics following administration of the 20-mg dose used to evaluate the impact of CYP3A4 inhibition. The coadministration of ritonavir with remibrutinib 20 mg resulted in a 3.32-, 4.5-, and 4.31-fold increase in C_{max} , AUC_{last} and AUC_{0-inf} of remibrutinib, respectively (see Section [14.2.6.1](#)).

The coadministration of grapefruit juice with remibrutinib 20 mg resulted in a 1.24-, 1.33- and 1.28-fold increase in C_{max} , AUC_{last} and AUC_{0-inf} of remibrutinib, respectively, indicating a minimal intestinal first pass-effect on remibrutinib.

Physiologically based pharmacokinetic (PBPK) simulations predict a 2.67- and 3.65-fold increase in $C_{max,ss}$ and AUC_{tau} , respectively, of remibrutinib 25 mg BID following the oral administration of ritonavir (100 mg BID for 7 days) in healthy subjects. Additional PBPK simulations with other strong CYP3A4 inhibitors predict a 2.47- and 3.21-fold increase in $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 mg BID following the oral administration of itraconazole (200 mg QD for 7 days), and a 2.53- and 3.38-fold increase in $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 mg BID following the oral administration of ketoconazole (200 mg BID for 7 days) in healthy subjects (see Section [14.5.3](#)).

Moderate CYP3A4 Inhibition

PBPK simulations predict a 1.9- and 2.27-fold increase in $C_{max,ss}$ and AUC_{tau} , respectively, of remibrutinib 25 mg BID following the oral administration of erythromycin (500 mg QD for 7 days) in healthy subjects. Fluconazole, a moderate CYP3A4 inhibitor, administered at 200 mg QD for 7 days was predicted to increase the $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 mg BID by 1.67- and 1.89-fold, respectively (see Section [14.5.3](#)).

Weak CYP3A4 Inhibition

PBPK simulations predict a 1.04-fold increase in both $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 mg BID following the oral administration of fluvoxamine (50 mg QD for 7 days) in healthy subjects.

CYP3A4 Inducers

Study A02103 investigated the impact of carbamazepine (a strong CYP3A4 inducer) at a dosage of 300 mg BID on the exposure to remibrutinib 100 mg BID. Carbamazepine significantly decreased the $C_{max,ss}$, AUC_{tau} , and $AUC_{last,ss}$ of remibrutinib 100 mg by 74%, 77%, and 78%, respectively. Refer to Section [14.2.6.2](#) for additional details.

PBPK simulations predict a 64% and 74% reduction in the C_{max} and AUC_{tau} , respectively, of remibrutinib 25 BID when coadministered with carbamazepine compared to administration of remibrutinib alone. In addition, rifampicin (a strong CYP3A4 inducer) administered at 600 mg QD was predicted to decrease the $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 mg BID by 88% and 91%, respectively, compared to administration of remibrutinib alone (see Section [14.5.3](#)). Efavirenz (a moderate CYP3A4 inducer) administered at 600 mg QD for 7 days was predicted to decrease the $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 BID by 60% and 64%, respectively (see Section [14.5.3](#)). Dexamethasone (a weak CYP3A4 inducer) administered at 8 mg BID for 7 days was predicted to decrease the $C_{max,ss}$ and AUC_{tau} of remibrutinib 25 BID by 33% and 38%, respectively (see Section [14.5.3](#)).

Overall, the data indicate that strong or moderate CYP3A4 inhibitors significantly increase the exposure to remibrutinib 25 mg BID.

(b) (4)
(b) (4)

(b) (4) the benefit-risk of exposing patients with CSU to higher exposures of remibrutinib following coadministration with strong or moderate CYP3A4 inhibitors is not favorable.

Conclusion

The use of remibrutinib with strong or moderate CYP3A4 inhibitors should be avoided, and the USPI will be revised accordingly. Given the large decreases in remibrutinib exposure and the potential for loss of efficacy, coadministration of remibrutinib with moderate or strong CYP3A4 inducers should be avoided.

8. Therapeutic Individualization

The dose-adjustment recommendations for remibrutinib are based on a dataset encompassing population pharmacokinetic analyses, dedicated special population studies, and drug-interaction trials across diverse patient populations. Population pharmacokinetic modeling was conducted using data from 1152 subjects across multiple clinical trials, providing the foundation for evaluating intrinsic factors including age (18 to 80 years), sex (63.5% females, 36.5% males), body weight (39 to 162 kg), and race/ethnicity distributions. For renal impairment evaluation, the dataset comprised 904 subjects (78.5%) with normal renal function (creatinine clearance ≥ 90 mL/min), 222 subjects (19.3%) with mild impairment (60 to 90 mL/min), 25 subjects (2.2%) with mild-to-moderate impairment (45 to 60 mL/min), and one subject with severe impairment (15 to 30 mL/min), supplemented by mass balance Study X2104 data showing minimal renal elimination of unchanged drug (0.65% of oral dose).

Hepatic impairment assessment relied on dedicated Study A2101, which evaluated remibrutinib 25 mg BID in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment compared to matched healthy controls. Drug-interaction data were derived from multiple clinical studies, including Study X2103 evaluating ritonavir (strong CYP3A4 inhibitor) and grapefruit juice effects, Study A02103 assessing carbamazepine (strong CYP3A4 inducer) impact, and Study X2102 examining effects on CYP3A4, CYP2C9, and CYP1A2 substrates using probe drugs midazolam, tolbutamide, and caffeine. Additional interaction studies evaluated P-gp and breast cancer resistance protein (BCRP) substrate effects using digoxin and rosuvastatin as probe drugs. Food-effect data came from Study A02104, while acid-reducing agent interactions were assessed through pooled analysis of concomitant medication use in Trials A2201, A2301, and A2302.

The safety database supporting dose-adjustment decisions included exposure-response analyses from three safety pools: E-R Safety Pool 1a (24-week placebo-controlled data from Trials A2301 and A2302), E-R Safety Pool 1b (entire treatment period from Trials A2301 and A2302), and E-R Safety Pool 2 (12-week data from Trials A2201, A2301, and A2302). However, the adequacy of safety data for higher exposures was limited, with the review team noting insufficient data from healthy subjects receiving up to 600 mg once daily and limited controlled data from subjects with CSU receiving 100 mg BID in Studies A2201 and A2201E1. Thus, exposure-response analyses for safety are not appropriate to inform on safety following chronic exposure to higher doses/exposures of remibrutinib. PBPK modeling supplemented clinical data to predict interactions with various CYP3A4 modulators not directly studied, providing additional support for drug-interaction recommendations.

8.1. Intrinsic Factors

8.1.1. Age

No dosage adjustment is required based on age.

Population pharmacokinetic (popPK) analyses indicated that age (range 18 to 80 years) does not significantly impact the pharmacokinetics of remibrutinib in subjects with CSU.

8.1.2. Body Weight

No dosage adjustment is required based on body weight.

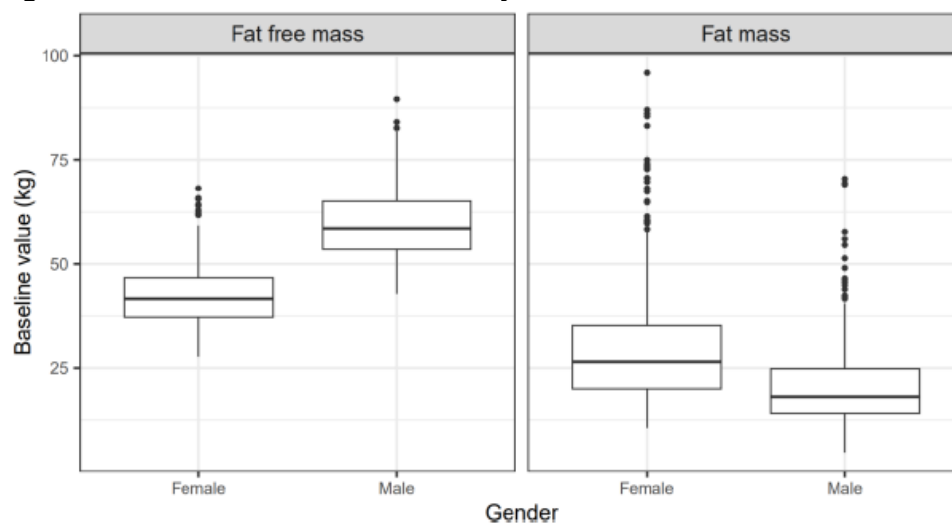
PopPK modeling demonstrated a strong positive correlation between fat-free mass (FFM) and fat mass (FM) with body weight. The final population PK model indicated that FFM and FM were significant covariates affecting remibrutinib clearance, while only FM was a significant covariate affecting volume of distribution. An increase in FM is expected to elevate the exposure to remibrutinib, which is moderately lipophilic. Given that body weight is composed of both FFM and FM, the impact of body weight on the pharmacokinetics of remibrutinib was assessed through the combined effects of FFM and FM. This analysis estimates a 20% increase in area under the AUC for subjects with CSU with a total body weight of 49 kg (5th percentile of the overall dataset) and a 20% decrease in AUC for subjects with CSU with a total body weight of 109 kg (95th percentile of the overall dataset) relative to a typical patient with body weight of 70 kg. Overall, the impact of body weight (range 39 to 162 kg) on remibrutinib exposure is not considered clinically relevant.

8.1.3. Sex

No dosage adjustment is required based on sex.

The population PK results indicated a disparity in the distributions of FFM and FM between males and females, primarily due to the lower FFM and higher FM in females compared to males ([Figure 11](#)). After accounting for body weight, there was no notable effect of sex (63.5% females and 36.5% males) on the pharmacokinetics of remibrutinib in subjects with CSU.

Figure 11. Distribution of FFM and FM by Sex



Source: Population pharmacokinetics of remibrutinib to support labeled dosage in adult subjects with chronic spontaneous urticaria, Figure 7-5

Abbreviations: FFM, fat-free mass; FM, fat mass

8.1.4. Race/Ethnicity

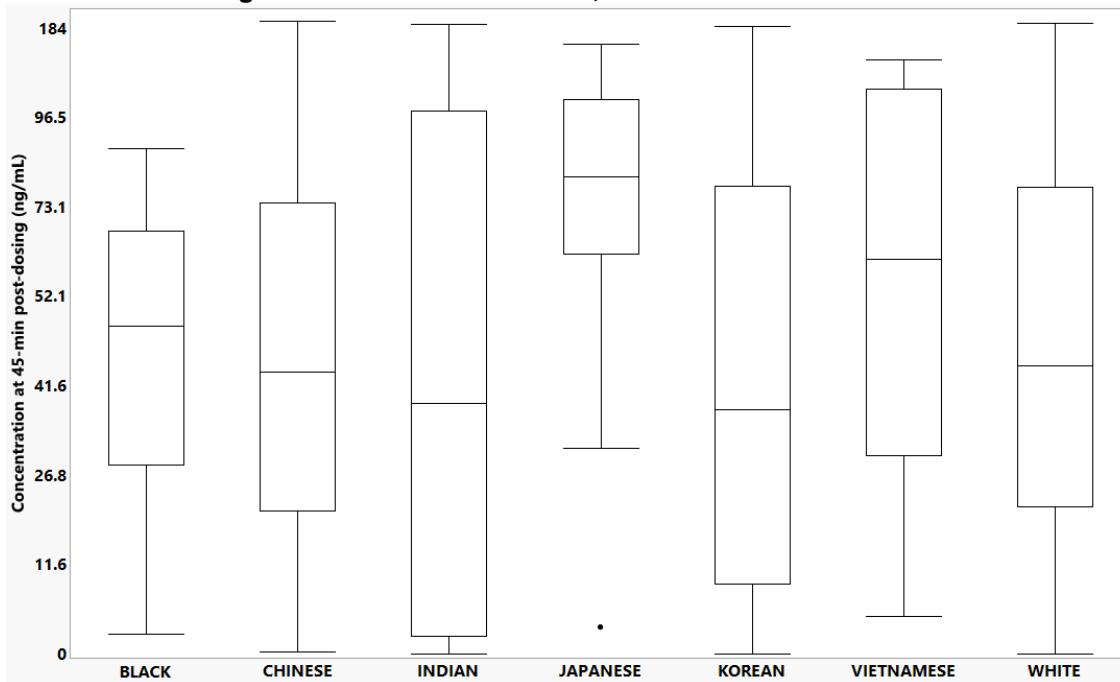
No dosage adjustment is required based on race/ethnicity.

The observed exposure to remibrutinib by race measured 45 minutes following the administration of remibrutinib at 25 mg BID at Week 12 in phase 3 Trials A2301 and A2302 combined is provided in [Figure 12](#). The postdose concentration of remibrutinib is comparable between the White (54.2%, N=265), Black (2.8%, N=14), Chinese (12.6%, N=62), and Asian non-Chinese (i.e., Indian (13.3%, N=65), Vietnamese (1.6%, N=8), and Korean (4%, N=20)) populations. Although there was a higher median concentration observed in the Japanese population (3.8%, N=19), it is within the range of variability of PK observations in the other populations. In addition, the proportion of the observed dataset that fell within the Japanese population was relatively small as compared to other race/ethnicity groups. Thus, the finding of greater median exposure among Japanese subjects should be interpreted with caution.

The overall dataset for popPK analysis was comprised of 59.3% (N=683) non-Asian (i.e., White, Black, and Others) subjects, 8.8% (N=101) Mainland Chinese subjects, 12.2% (N=141) Japanese subjects, and 19.7% (N=227) other Asian (i.e., East Asian, no Mainland Chinese, Japanese; and Asian, no East Asian) subjects. In popPK analysis, the race/ethnicity groups of Mainland Chinese, Japanese, and Other Asian were identified as significant covariates affecting the clearance of remibrutinib. All race/ethnicity groups were determined to have lower clearance relative to the reference population of non-Asian. Consequently, popPK simulations indicate that remibrutinib AUC increases by 21% in Mainland Chinese subjects, 20% in Japanese subjects, and 30% in Other Asian subjects compared to non-Asian subjects, all at the same body weight of 70 kg ([Figure 13](#)).

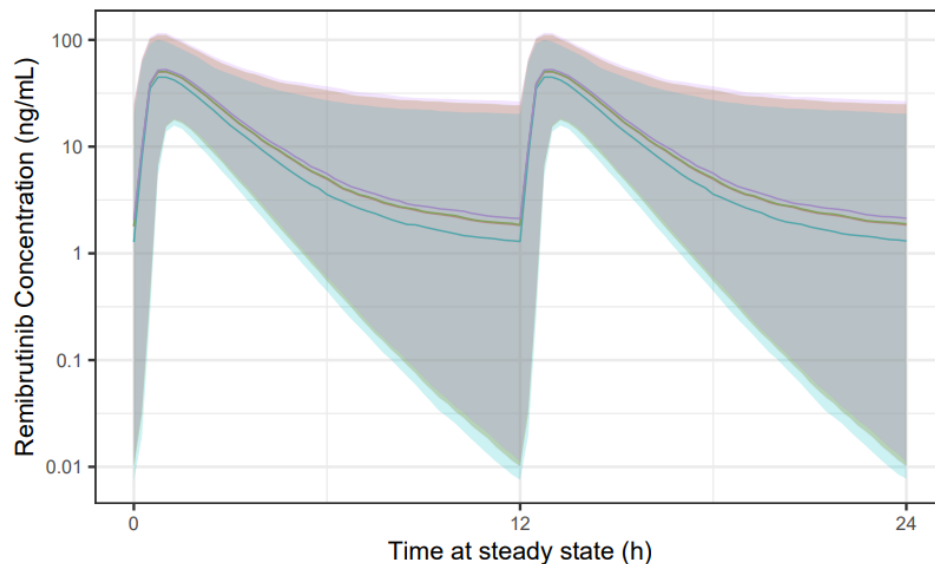
Overall, these differences in exposure are not considered to be clinically relevant.

Figure 12. Observed Remibrutinib Concentration at 45 Minutes Following the Administration of Remibrutinib 25 mg BID at Week 12 in Phase 3, Trials A2301 and A2302



Source: Reviewer's analysis based on PC.xpt and ADSL.xpt datasets for Trials A2301 and A2302
Asian population includes, 62 Chinese, 65 Indian, 19 Japanese, 20 Korean, and 8 Vietnamese subjects. The White population includes 265 subjects and the Black population includes 14 subjects.
Abbreviation: BID, twice daily

Figure 13. Simulated Profiles Assessing Ethnic Differences in Final PopPK Model for Subjects With Median Body Weight of 70 kg



Source: Population pharmacokinetics of remibrutinib to support labeled dosage in adult subjects with chronic spontaneous urticaria, Figure 7-18
Curve is median exposure. Shaded area =90% prediction Interval. Red represents Japanese subjects; green represents Mainland Chinese subjects; blue represents non-Asian subjects; purple represents Other Asian subjects.
Abbreviations: h, hour; popPK, population pharmacokinetic

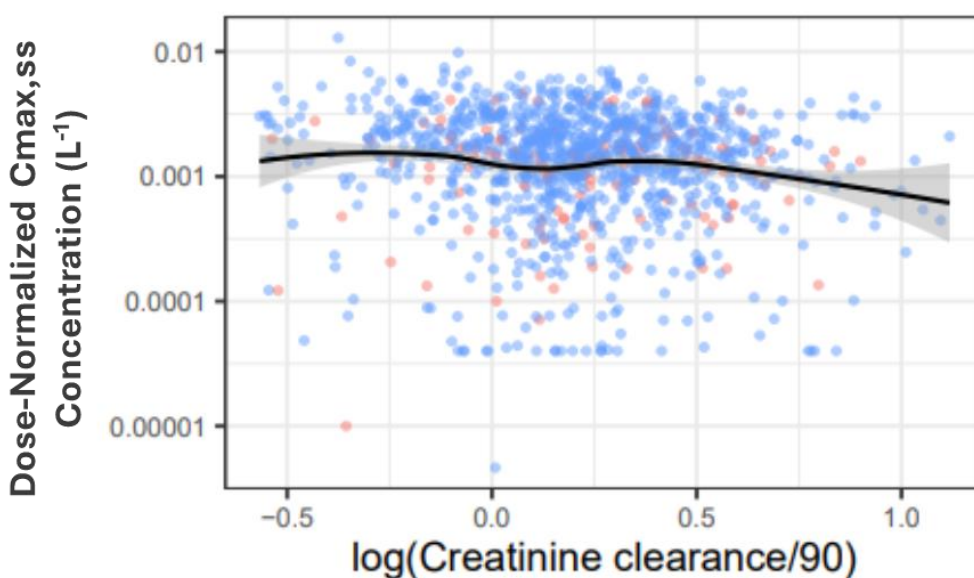
8.1.5. Renal Impairment

No dosage adjustment is required for subjects with renal impairment.

The renal clearance of remibrutinib was determined in mass balance Study X2104 in which healthy subjects received oral or intravenous (IV) doses of radiolabeled remibrutinib. Both oral and IV administration were evaluated as there was incomplete recovery of radioactivity in the oral arm due to technical issues. For additional details, refer to Section 14.2.2. Following oral administration, about 24% of the dose was recovered in the urine. The amount of unchanged remibrutinib excreted in urine was minimal, accounting for 0.65% of the oral dose, while the most abundant metabolite excreted in urine accounted for about 3.5% of the oral dose. Following IV dosing, about 26 to 30% of the dose was recovered in the urine. The percentage of unchanged remibrutinib excreted in urine was 2.93%. These findings suggest that renal excretion is a minor elimination pathway for remibrutinib. As additional supportive evidence in Study X2101 the renal clearance of remibrutinib following administration of multiple doses of 100 or 200 mg BID was found to constitute <1% of the total blood clearance (refer to Section 14.2.1.1).

PopPK analysis did not identify creatinine clearance (CrCL; range 23 to 275 mL/min) as a significant covariate affecting the clearance of remibrutinib (Figure 14). The data represent 904 subjects (78.5%) with normal renal function (CrCL $\geq$ 90 mL/min), 222 subjects (19.3%) subjects with mild renal impairment (CrCL 60 to 90 mL/min); 25 subjects (2.2%) with mild-to-moderate renal impairment (CrCL 45 to 60 mL/min); and 1 subject (0.1%) with severe renal impairment (CrCL 15 to 30 mL/min). Based on the pharmacokinetic data from Studies X2104 and X2101, as well as the popPK analysis, a dedicated renal impairment study was not considered necessary. Therefore, no dose adjustment is required for CSU subjects with renal impairment.

Figure 14. Remibrutinib Dose-Normalized Observed $C_{max,ss}$ Concentrations vs. Creatinine Clearance in Pooled Data, Log Scale



Source: Population pharmacokinetics of remibrutinib to support labeled dosage in adult subjects with chronic spontaneous urticaria, Figure 7-7

$C_{max,ss}$ refers to the averaged concentration at time after dose between 0.75 hour and 1.25 hours. Blue dots represent BID regimen and red dots represent QD regimen. The black solid curve is smooth line, and shared grey area is the 95% confidence interval. Abbreviations: BID, twice daily; $C_{max,ss}$, maximum plasma concentration at steady state; QD, once daily

8.1.6. Hepatic Impairment

The use of remibrutinib should be avoided in subjects with mild, moderate, or severe hepatic impairment. Refer to key safety review issue in Section [7.7.5](#) for details.

8.2. Extrinsic Factors

8.2.1. Food Effect

Remibrutinib can be administered with or without food.

The effect of food on exposure to remibrutinib was assessed in healthy subjects in Study A02104 following administration of 25 mg BID in the intended to-be-marketed FCT formulation. For additional details, refer to Section [14.2.4](#). Notably, the food effect was evaluated at steady state. However, the goal of food-effect evaluation is to assess the food effect on drug absorption. The about 2-fold accumulation of remibrutinib systemic exposure at steady state is not contributed by drug absorption. Therefore, the food effect on remibrutinib at steady state can be extrapolated to single dose, given the short half-life of remibrutinib (1 to 2 hours).

When remibrutinib FCTs at a dosage of 25 mg BID were coadministered with a high-fat, high-calorie meal (1000 calories, 50% fat), the pharmacokinetic parameters were not significantly altered (see Section [14.2.4](#)). Specifically, the AUC_{0-12h} increased by approximately 33%, while C_{max} decreased by roughly 5%. Additionally, the T_{max} was delayed by 1 hour. These differences in exposure are not considered to be clinically meaningful. Therefore, remibrutinib may be administered with or without food.

8.2.2. Effect of Remibrutinib on Other Drugs

The potential inhibition or induction of CYP enzymes and transporters by remibrutinib was investigated through in vitro and in vivo DDI studies. Notably, in in vivo studies, the effects of remibrutinib on the pharmacokinetics of substrates for CYP3A4, CYP2C9, CYP1A2, P-gp, BCRP, and organic anion transporting polypeptide (OATP)1B1 were studied at a higher dosage (i.e., 100 mg BID) than the recommended 25-mg BID dosage. PBPK simulations were conducted to estimate the clinical DDI risk of remibrutinib at the recommended dosage of 25 mg BID. The review team concluded that the findings from the studies conducted at the higher dosage of remibrutinib are applicable to the recommended 25-mg BID dosage.

Based on in vitro studies and static drug-interaction potential assessments, remibrutinib is not expected to significantly affect the pharmacokinetics of concomitant drugs that are substrates of CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) or transporters (bile salt export pump [BSEP], OATP1B1, OATP1B3, organic cation transporter [OCT]1, OCT2, organic anion transporter [OAT]1, OAT3, multidrug and toxin extrusion protein [MATE]1, MATE2-K, and sodium taurocholate cotransporting polypeptide), with the exception of P-gp and BCRP ([Table 28](#)).

CYP3A4 Substrates

In vitro studies have demonstrated that remibrutinib acts as a reversible inhibitor (unbound inhibition constant [reversible inhibition] $[K_{i,u}] = 14.1 \mu\text{M}$), time-dependent inhibitor (unbound inhibition constant [time-dependent inhibition] $[K_{i,u}] = 6.9 \mu\text{M}$) and inducer ($E_{\text{max}} = 28.1$ and half-maximal effective concentration $[EC_{50}] = 5.08 \mu\text{M}$) of CYP3A4. Consequently, the net effect of remibrutinib on CYP3A4 function may exhibit time-dependent characteristics. The observed reversible inhibition effect is likely more pronounced at the initiation of treatment, while the induction effect may be most evident at steady state, following administration of multiple doses of remibrutinib.

Although there is low potential for remibrutinib to have a clinically relevant impact on the pharmacokinetics of CYP3A substrates based on static DDI assessment ([Table 28](#)), the potential of remibrutinib to inhibit or induce CYP3A4 enzymes was evaluated following administration of multiple oral doses of remibrutinib 100-mg capsules in healthy female subjects using midazolam (administered on Day 3 and Day 11, following the initiation of remibrutinib dosing) as the probe substrate for CYP3A4 (Study X2102, see Section [14.2.6.3](#)). When midazolam was coadministered with multiple doses of remibrutinib 100 mg on Day 3, the plasma concentrations of midazolam were not clinically meaningfully affected, with 36% increase in C_{max} and 45% increase in AUC. Similar results were observed on Day 11, with less than 27% increase in midazolam C_{max} and 43% increase in midazolam AUC. Based on the observed effects of remibrutinib administered at four times the recommended dosage on midazolam exposure on Days 3 and 11, it can be inferred that remibrutinib has a low potential to inhibit or induce CYP3A4 substrates at the recommended remibrutinib dosage of 25 mg BID.

PBPK simulations did not predict a clinically relevant DDI effect on the exposure to the sensitive CYP3A substrate midazolam following coadministration with remibrutinib at the recommended dosage of 25 mg BID on Days 3 and 11. PBPK simulations estimate an 18% increase in midazolam C_{max} and 20% increase in midazolam AUC on Day 3; and a 22% increase in C_{max} and 25% increase in AUC on Day 11 (see Section [14.5.2](#)).

To further assess the potential of remibrutinib to affect the pharmacokinetics of CYP3A4 substrates, Study X2102 also evaluated the DDI potential between multiple oral doses of remibrutinib 100-mg capsules and combined oral contraceptives (OCs), containing ethinylestradiol (EE) and levonorgestrel (LVG), administered on Day 15 following the initiation of remibrutinib dosing. Multiple doses of remibrutinib 100 mg BID did not significantly impact the exposure to EE and LVG, with 28% increase in the C_{max} and 18% increase in the AUC of EE and 36% increase in the C_{max} and 39% increase in the AUC of LVG (see Section [14.2.6.3](#)). PBPK simulations did not predict a clinically relevant DDI effect on EE pharmacokinetics following coadministration with remibrutinib 25 mg BID (7% increase in C_{max} and 8% increase in AUC) (see Section [14.5.3](#)).

Taken together, remibrutinib has low potential to inhibit or induce CYP3A in vivo. Sensitive CYP3A substrates or combined OCs containing EE and LVG may be coadministered with remibrutinib. No clinically relevant impact on the efficacy of oral contraceptives is expected following coadministration with remibrutinib.

CYP2C9 Substrates

In vitro studies have demonstrated that remibrutinib acts as a reversible inhibitor ($K_{i,u}=7.7\mu\text{M}$) and inducer ($E_{\text{max}}=3.02$ and $EC_{50}=5.1\mu\text{M}$) of CYP2C9. However, based on static DDI assessments, remibrutinib is not expected to have a clinically relevant impact on the pharmacokinetics of CYP2C9 substrates in vivo ([Table 28](#)). Despite this, the potential for multiple oral doses of remibrutinib 100 mg BID to inhibit or induce CYP2C9 was evaluated in healthy female subjects using tolbutamide as the probe substrate (Study X2102, see Section [14.2.6.3](#)). Tolbutamide was administered on Day 3 and Day 11 following the initiation of remibrutinib treatment. Results demonstrated a 27% increase in tolbutamide plasma concentration measured at 24 hours postdose (C24h) on Day 3 and a 30% increase in tolbutamide C24h on Day 11 following coadministration with remibrutinib 100 mg BID. The Applicant selected tolbutamide C24h as a metric for CYP2C9 activity due to its purported strong correlation with tolbutamide clearance ([Jetter et al. 2004](#)). However, based on the findings from [Jetter et al. \(2004\)](#), tolbutamide C24h may overestimate the magnitude of drug interaction between remibrutinib and tolbutamide compared to that determined using C_{max} and AUC. As multiple oral doses of remibrutinib 100 mg yielded an approximate 30% increase in tolbutamide C24h, a lower magnitude may have been observed based on C_{max} and AUC. Hence, remibrutinib 100 mg is unlikely to have clinically relevant impact on the exposure to CYP2C9 substrates.

The outcomes of a static DDI model, which indicated no significant clinical interaction risk with CYP2C9 substrates, and the absence of a complete pharmacokinetic profile for tolbutamide, obviate the necessity for PBPK simulations for the impact of remibrutinib 25 mg BID on CYP2C9 substrates.

CYP1A2 Substrates

In vitro studies have demonstrated that remibrutinib acts as a reversible inhibitor ($K_{i,u}=35.3\mu\text{M}$) and inducer ($E_{\text{max}}=5.47$, $EC_{50}=4.55\mu\text{M}$) of CYP1A2. However, based on static DDI assessments, remibrutinib is not expected to have a clinically relevant impact on the pharmacokinetics of CYP1A2 substrates in vivo. The potential for multiple oral doses of remibrutinib 100 mg BID to inhibit or induce CYP1A2 was evaluated in healthy female subjects using caffeine as a probe substrate (Study X2102, see Section [14.2.6.3](#)). Caffeine was administered on Day 3 and Day 11 following the initiation of remibrutinib treatment. The administration of multiple doses of remibrutinib 100 mg BID did not affect caffeine plasma concentration measured at 6 hours postdose (C6h). In addition, there was little change in the paraxanthine to caffeine ratio at 6 hours, with reductions of 3% and 12% on Day 3 and Day 11, respectively.

The outcomes of a static DDI model, which indicated no significant clinical interaction risk with CYP1A2 substrates, and the absence of a complete pharmacokinetic profile for caffeine, obviate the necessity for PBPK simulations to assess the impact of remibrutinib 25 mg BID.

P-gp Substrates

In vitro, remibrutinib inhibited intestinal P-gp (inhibition constant [reversible inhibition] $[K_i]=0.382\mu\text{M}$) and static DDI assessments predict a potential impact of remibrutinib on P-gp substrates with R-value =517. The impact of remibrutinib on the pharmacokinetics of digoxin, a P-gp substrate, was investigated in healthy subjects in Study A02103 (see Section [14.2.6.2](#)). In healthy subjects, the C_{max} and AUC_{last} of digoxin increased by 108% and 45%, respectively,

following coadministration with remibrutinib 100 mg BID (see Section [14.2.6.2](#)). PBPK simulations predicted (b) (4) in the C_{max} and AUC, respectively, of digoxin when coadministered with multiple oral doses of remibrutinib 100 mg BID. The PBPK simulations tend to mis-predict the observed magnitude of the interaction between remibrutinib 100 mg BID and digoxin (see Section [14.5.3](#)). Therefore, due to the inherent limitations of model predictions and confidence in the predicted results, the clinical findings from Study A02103, conducted with the 100-mg BID dosage of remibrutinib, should be applicable to subjects receiving the lower dosage of 25 mg BID. The magnitude of effect at a remibrutinib dosage of 25 mg BID is expected to be lower than that at 100 mg BID. However, the difference in effect is unclear without the conduct of a dedicated clinical study.

It is therefore recommended to monitor more frequently for adverse reactions when remibrutinib is administered with P-gp substrates that have a narrow therapeutic index (i.e., drugs for which minimal concentration changes can lead to clinically significant differences in efficacy or safety).

BCRP/OATP1B1 Substrates

In vitro, remibrutinib inhibited intestinal BCRP ($K_i=0.467\mu\text{M}$) and static DDI assessments predicted a potential impact of remibrutinib on BCRP substrates with R-value =423. Although remibrutinib inhibited OATP1B1 ($K_{i,u}=2.36\mu\text{M}$) and OATP1B3 ($K_{i,u}=7.55\mu\text{M}$) in vitro, static DDI assessment predicted no drug-interaction potential between remibrutinib and OATP1B1/3 substrates (e.g., rosuvastatin). The impact of remibrutinib on the pharmacokinetics of rosuvastatin, a BCRP and OATP1B substrate, was investigated in healthy subjects in Study A02103. In Study A02103, the C_{max} and AUC_{last} of rosuvastatin increased by 56% and 65%, respectively, following coadministration with remibrutinib 100 mg BID. To distinguish between inhibition of BCRP and OATP1B, changes in coproporphyrin I exposure were also assessed. As there was no change in the plasma exposure to coproporphyrin I, it is expected that inhibition of OATP1B by remibrutinib is negligible (see Section [14.2.6.2](#)). Given that in vitro data predict a low risk of inhibition of OATP1B1 and OATP1B3 at clinically relevant concentrations, the increase in rosuvastatin plasma exposure can be attributed to an inhibitory effect of remibrutinib on BCRP.

PBPK simulations tended to mis-predict the observed magnitude of the interaction between remibrutinib 100 mg BID and rosuvastatin (see Section [14.5.3](#)). Therefore, due to the inherent limitations of model predictions and confidence in the predicted results, the clinical findings from Study A02103, conducted with the 100 mg BID dosage of remibrutinib, should be applicable to subjects receiving the lower dosage of 25 mg BID. The magnitude of effect at a remibrutinib dosage of 25 mg BID is expected to be lower than that at 100 mg BID. However, the difference in effect is unclear without conduct of a dedicated clinical study.

It is therefore recommended to monitor more frequently for adverse reactions when remibrutinib is administered with BCRP substrates that have a narrow therapeutic index (i.e., drugs for which minimal concentration changes can lead to clinically significant differences in efficacy or safety).

Table 28. Static Net Effect DDI Risk Assessment for Remibrutinib 25 mg BID at Steady State as a Perpetrator of DDIs Mediated Via Enzymes and Transporters

Protein	Parameter ¹	Total	Unbound	AUCR (only inhibition) ³⁻⁵	AUCR (only induction) ³⁻⁵	Net effect AUCR ³⁻⁵
Enzymes in liver and other organs including intestine for CYP3A - assessment based on [DMPK R1500083], [DMPK R1600703], [DMPK R1900718]						
CYP1A2	IC50/2 (μM)	40.0	35.3			
	EC50 (μM)	4.55	4.55	1.00	0.97	0.97
	E _{max} ²	5.47	-			
CYP2B6	K _i (μM)	25.6	23.7			
	EC50 (μM)	5.47		1.00	0.98	0.98
	E _{max} ²	5.45	-			
CYP2C8	K _i (μM)	5.20	5.00	1.00	NA	1.00
	K _i (μM)	8.30	7.70	1.00	0.99	0.99
CYP2C9	EC50 (μM)	5.10				
	E _{max} ²	3.02	-			
CYP2C19	K _i (μM)	9.70	7.70	1.00	NA	1.00
CYP2D6	IC50/2 (μM)	38.8	34.3	1.00	NA	1.00
	K _i (μM)	15.2	14.1			
	EC50 (μM)	5.08		1.94 ⁸	0.167 ⁸	0.833 ⁸
CYP3A ⁸	E _{max} ²	28.1	-			
	K _i (μM)	8.80	6.90			
	kinact (min ⁻¹)	0.0102	-			
Protein	Parameter	Total	Unbound	-	-	R value ⁶⁾
Transporters at the liver inlet (portal vein) - assessment based on [DMPK R2000485]						
OCT1	K _i (μM) ⁷⁾	-	1.09			1.03
OATP1B1	K _i (μM) ⁷⁾	-	2.36			1.01
OATP1B3	K _i (μM) ⁷⁾	-	7.55			1.00
Hepatic efflux transporters - assessment based on [DMPK R2301196], [DMPK R1700782]						
P-gp	K _i (μM) ⁷⁾	-	0.382			1.02
BCRP	K _i (μM) ⁷⁾	-	0.467			1.01
BSEP	K _i (μM)	-	7.80			1.00
Renal transporters - assessment based on (DMPK R2000485)						
OAT1	K _i (μM) ⁷⁾	-	9.87			1.00
OAT3	K _i (μM) ⁷⁾	-	1.09			1.01
OCT2	K _i (μM) ⁷⁾	-	9.41			1.00
MATE1	K _i (μM) ⁷⁾	-	1.70			1.00
Transporters in the intestine - assessment based on (DMPK R2301196)						
P-gp	K _i (μM) ⁷⁾	-	0.382			517
BCRP	K _i (μM) ⁷⁾	-	0.467			423

Source: Summary of Clinical Pharmacology, Module 2.7.2, Tables 6-4 and 6-5

¹ Additional process tested but not affected: reversible inhibition of CYP2A6 and CYP2E1 (tested up to 100μM remibrutinib, respectively), time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 (tested up to 100μM remibrutinib, respectively), inhibition of MRP2 (tested up to 100μM remibrutinib, inhibition of MATE2-K (tested up to 7.40μM remibrutinib, inhibition of Ntcp (tested up to 58.7 remibrutinib).

² mRNA increase relative to baseline.

³ Calculations based on unbound remibrutinib concentrations C_{max,ss,u}=0.00595μM (calculated multiplying C_{max,ss}=0.128μM by f_{u,p}=0.0465) and unbound inhibition/induction constants for enzymes. The C_{max,ss} of 0.128μM was obtained from dose-range Study A2201 following the administration of remibrutinib 25 mg BID for 12 weeks.

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⁴ Hepatic net effect calculated as $AUCR = 1 / ((1/A_h \times 1/B_h \times 1/C_h) \times f_{m,sys} + (1-f_{m,sys}))$, where $f_{m,sys}$ is equal to 0.9 (midazolam, CYP3A), 0.8 (theophylline, CYP1A2), 0.64 (efavirenz, CYP2B6), 0.58 (repaglinide, CYP2C8), 0.91 (warfarin, CYP2C9), 0.87 (omeprazole, CYP2C19), 0.9 (desipramine, CYP2D6) or 1 (worst-case assumption for all other CYP's). For net effect calculations unbound total maximal hepatic inlet plasma concentration ($[I] = f_{u,p} \times (C_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/RB)$) and unbound inhibition constants were used. A_h and B_h are equal to 1 in the absence of any inhibition effect. A_h is reversible inhibition of hepatic CYP enzymes, $A_h = 1 / (1 + [I]/K_i)$; B_h is time-dependent inhibition of hepatic CYP enzymes, $B_h = k_{deg,h} / [k_{deg,h} + ([I] \times k_{inact}) / (I_h + K_i)]$; C_h is induction of hepatic CYP enzymes, $C_h = 1 + d \times E_{max} \times [I] / (I_h + EC_{50})$.

⁵ Intestinal net effect calculated as $AUCR = 1 / ((1/A_g \times 1/B_g \times 1/C_g) \times (1-F_g) + F_g)$, where F_g is equal to 0.51 (midazolam, CYP3A). For net effect calculations $[I]_g = F_a \times k_a \times Dose / Q_{en}$ and unbound inhibition/induction constants were used. A_g is reversible inhibition of gut CYP enzymes, $A_g = 1 / (1 + [I]_g / K_i)$; B_g is time-dependent inhibition of gut CYP enzymes, $B_g = k_{deg,g} / [k_{deg,g} + ([I]_g \times k_{inact}) / (I_g + K_i)]$; C_g is induction of gut CYP enzymes, $C_g = 1 + d \times E_{max} \times [I]_g / (I_g + EC_{50})$. $F_{u,p}$ is the unbound fraction in plasma, a value of 0.0465 was used. F_a is the fraction absorbed after oral administration, a value of 1 was used. F_g is the fraction available after intestinal metabolism, a value of 1 was used. k_a is the first order absorption rate constant in vivo, a value of 0.0145 min⁻¹ was used based on popPK modeling. Q_{en} is the blood flow through enterocytes, a value of 0.3 L/min was used. Q_h is the hepatic blood flow, a value of 1.45 L/min was used. RB is the blood-to-plasma concentration ratio, a value of 0.813 was used. d is a scaling factor determined in a calibrated hepatocyte batch based on positive control inducers. If not determined, it is assumed to be 1.

⁶ R-value for reversible inhibition calculated as $R = 1 + C_{max,ss,u} / K_i$.

⁷ IC_{50} values converted to K_i ($K_i = IC_{50} / (1 + [S] / K_m)$).

⁸ Combined effect of hepatic and intestinal DDI using the net effect approach

Abbreviations: AUCR, ratio of area under the concentration-time profile; BCRP, breast cancer resistance protein; BID, twice daily; BSEP, bile salt export pump; $C_{max,ss}$, maximum plasma concentration at steady state; CYP, cytochrome P450; DDI, drug-drug interaction; DMPK, drug metabolism and pharmacokinetics; EC_{50} , half maximal effective concentration; E_{max} , maximum effect; IC_{50} , half-maximal inhibitory concentration; K_i , inhibition constant; MATE, multidrug and toxin compound extrusion; MRP2, multidrug resistance-associated protein 2; NA, not applicable; NTCP, sodium taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, p-glycoprotein; popPK, population pharmacokinetic

Antithrombotic Agents

The risks and benefits of coadministration of antithrombotic agents with remibrutinib should be considered due to BTK inhibitor drug class effect which inhibits the platelet activation. Refer to safety review issue in Section [7.7.1](#).

8.2.3. Effect of Other Drugs on Remibrutinib

In vitro data indicate that metabolism of remibrutinib is predominantly driven by CYP3A4 with a minor contribution from CYP2C19. In vitro studies also determined that remibrutinib is a substrate for P-gp, but not for other efflux and uptake transporters. For additional details, refer to Section [14.1](#).

The effect of other drugs on remibrutinib as an object was evaluated in two clinical DDI studies, X2103 and A02103. In Study X2103, the impact of ritonavir (CYP3A4/P-gp inhibitor) and grapefruit juice (intestinal CYP3A4 inhibitor) were evaluated. In Study A02103, the impact of carbamazepine (CYP3A4 inducer) was assessed. For additional details, refer to Section [14.2.6.1](#) and Section [14.2.6.2](#). PBPK modeling and simulation was also used to predict the impact of moderate and strong CYP3A4 inhibitors and inducers on the pharmacokinetics of remibrutinib 25 mg BID.

CYP3A Induction or Inhibition

Use of remibrutinib with moderate or strong CYP3A4 inducers and inhibitors should be avoided. Refer to safety review issue in Section [7.7.6](#).

P-gp Inhibition

In vitro studies suggest that remibrutinib exhibits high passive permeability at concentrations of 50µM and above, while at lower concentrations (e.g., 0.5µM), its permeability is reduced due to

an apically directed P-gp-mediated efflux process. When remibrutinib is administered at 25 mg, the intestinal local concentration of remibrutinib is expected to be approximately 197 μ M, suggesting a high passive permeability at the recommended dose of 25 mg twice daily.

Based on clinical human absorption, distribution, metabolism, and excretion (ADME) data, unchanged remibrutinib was not detected in feces following intravenous administration. Following oral administration, the amount of unchanged remibrutinib in feces was 1.21% of the oral dose. Therefore, DDI effects mediated via P-gp inhibition are not expected.

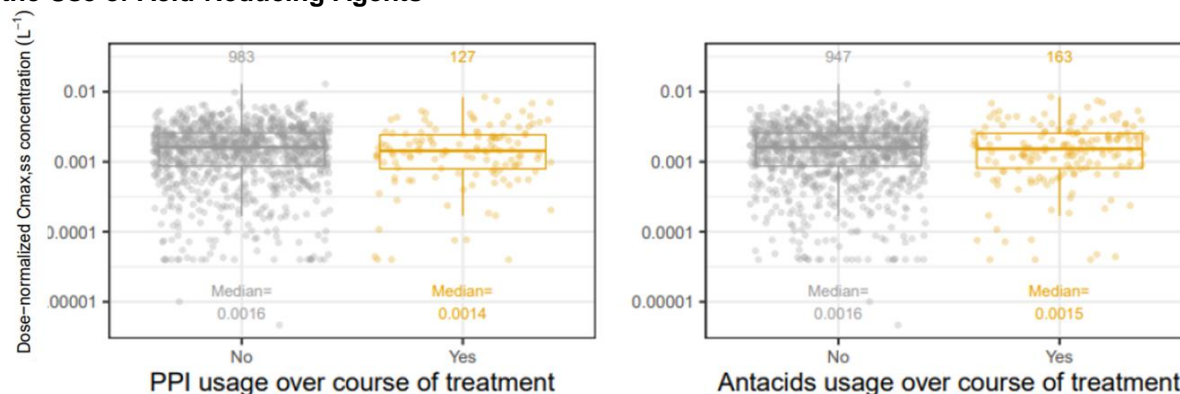
Acid-Reducing Agents

No clinically relevant changes in remibrutinib exposure are expected when remibrutinib is coadministered with acid-reducing agents (ARAs).

Remibrutinib is a weak base with pH-dependent solubility and, thus, remibrutinib absorption may be reduced at higher pH (e.g., coadministration of ARAs). The proportion of subjects who coadministered remibrutinib with proton-pump inhibitor (PPIs) (e.g., omeprazole, esomeprazole) in Trials A2201, A2301, and A2302 were 11% (N=24), 13% (N=53), and 12% (N=45), respectively. In addition, 27 (12%), 75 (19%), and 51 (14%) subjects coadministered remibrutinib with antacids in Trials A2201, A2301, and A2302, respectively.

Based on dose-normalized observed $C_{max,ss}$ of remibrutinib, there was no difference in exposure to remibrutinib between subjects who coadministered remibrutinib with ARAs and subjects who did not coadminister ARAs ([Figure 15](#)). Refer to Section [14.5.1](#) for details.

Figure 15. Plot of Remibrutinib Dose-Normalized Observed $C_{max,ss}$ Concentrations (Log Scale) vs. the Use of Acid-Reducing Agents



Source: Population pharmacokinetics of remibrutinib to support labeled dosage in adult subjects with chronic spontaneous urticaria, Figure 7-8

Most common PPIs used as comedications in Trials A2201, A2301, and A2302 include omeprazole, lansoprazole, esomeprazole, pantoprazole, ilaprazole, dexlansoprazole, rabeprazole.

Most common antacids used as comedications in Trials A2201, A2301, and A2302 include calcium carbonate, magnesium oxide/sodium alginate/sodium bicarbonate, aluminum hydroxide/magnesium carbonate, aluminum hydroxide/magnesium hydroxide/simethicone, aluminum hydroxide, and magnesium oxide.

The total number of subjects with concomitant PPI usage in Trials A2201, A1301, A2301, and A2302 is 128. The total number of subjects with concomitant antacid usage in Trials A2201, A1301, A2301, and A2302 is 168. Numbers shown above each box in the plots represent the number of subjects who had average value of dose-normalized observed $C_{max,ss}$ in the corresponding group and therefore do not align with the total number of subjects for did or did not coadminister PPIs or antacids with remibrutinib.

Study A1301 is an open-label phase 3 study of safety, tolerability, and efficacy of remibrutinib in Japanese subjects with CSU. Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady state; CSU, chronic spontaneous urticaria; PPI, proton-pump inhibitor

8.3. Plans for Pediatric Drug Development

The Applicant has an agreed upon pediatric study plan that includes deferred pediatric studies in patients 12 to <18 years of age and 6 to <12 years of age and a partial waiver of studies in children under 6 years of age because studies would be highly impracticable in this age group. Although CSU development programs may evaluate adolescents in the phase 3 trials in adults, the Agency advised the Applicant to defer pediatric studies until the benefit/risk in adults was better characterized given the novelty of the mechanistic target for this indication, the symptomatic and self-limited nature of the condition, and the potential risks associated with BTKi.

Modeling and Simulation Activity Part 1 will use adult data to select appropriate doses for adolescents, while Part 2 will incorporate data from both adult and adolescent studies to determine optimal dosing for children aged 6 to 11 years. (b) (4)

For adolescents aged 12 to less than 18 years, the plan includes Study CLOU064F12301, a double-blind, placebo-controlled, nonconfirmatory study designed to evaluate pharmacokinetics, efficacy, and safety of remibrutinib. This study will enroll at least 75 adolescent subjects with CSU who have inadequate response to H1-antihistamines, with coprimary endpoints of absolute change from baseline in ISS7 and HSS7 at Week 12. The study includes a 24-week treatment period followed by a 4-week follow-up period and was ongoing at the time of the original NDA review.

For children aged 6 to less than 12 years, Study CLOU064F12302 is planned as an open-label, uncontrolled trial focusing primarily on pharmacokinetics (b) (4)

(b) (4) Given ocular and neurobehavioral findings in the completed juvenile toxicity study in rats, an additional PREA PMR will be issued for a repeat juvenile toxicity study in older rats that approximate children 6 years of age. The results of the juvenile rat study will need to be submitted and reviewed prior to initiation of clinical study CLOU064F12302.

Age-appropriate formulation development is planned, (b) (4)
(b) (4) with final selection based on stability, dose flexibility, and palatability criteria.

The Pediatric Research Equity Act PMRs to be issued at the time of approval action are discussed in Section [24](#).

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section [13](#).

Table 29. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
Pregnancy	• In pregnant rabbits administered remibrutinib during organogenesis, remibrutinib did not cause adverse effects to the fetus at exposures up to 23 times the MRHD.^{1,2} Increased fetal external malformations (open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (transiently reduced food consumption and adverse clinical signs) occurred at 141 times the MRHD. • In pregnant rats administered remibrutinib during organogenesis, remibrutinib did not cause adverse effects to the fetus at exposures up to 126 times the MRHD.³ • In a pre- and postnatal development study in rats, remibrutinib did not cause adverse effects for maternal animals or offspring at exposures up to 58 times the MRHD in males and females, respectively.⁴
8.3 Females and Males of Reproductive Potential	• In a fertility study in male and female rats, remibrutinib had no effect on fertility and reproductive indices up to 15 times and 63 times the MRHD in males and females, respectively.⁵ • Remibrutinib can cause teratogenicity and maternal toxicity when administered orally to rabbits during organogenesis (see Section 8.1).
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	• Remibrutinib did not show evidence of carcinogenic potential in a 6-month rasH2 mouse study at oral doses up to 1500 mg/kg/day⁶ and a 2-year rat carcinogenicity study at oral doses up to 8x and 98x the MRHD based on AUC for males and females, respectively.⁷ • Remibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay and was not clastogenic in an in vitro micronucleus assay in human peripheral lymphocytes or in an in vivo blood reticulocyte micronucleus assay in rats. • Fertility data are described in Section 8.3 above.

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study A2201).

² Exposures obtained from Study 1670382.

³ Exposures obtained from Study 1670380.

⁴ TK data were not assessed in the PPND Study 2070356. Since TK data were variable in other rat studies, the safety margin was based on a mg/m² conversion and comparison to the clinical dose of 25 mg BID.

⁵ Exposures obtained from Study 1770589.

⁶ Exposures obtained from Study 1870307.

⁷ Exposures obtained from Study 1870308.

Abbreviation: AUC, area under the concentration-time curve; BID, twice daily; MRHD, maximum recommended human dose; PPND, pre- and postnatal development; TK toxicokinetic

Table 30. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg/day)	AUC (ng*h/mL)	Exposure Margins¹ (Multiples)
FEED rat, male and female	1000	5840 (males) ² 24700 (females)	15 63
EFD, rat	1000	49200 (females) ³	126
EFD, rabbit	100	8990 (females) ⁴	23
PPND, rat	300	5970 (males) ⁵ 30900 (females)	15 79

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study A2201).

² Exposures obtained from Study 1770589.

³ Exposures obtained from Study 1670380.

⁴ Exposures obtained from Study 1670382.

⁵ TK data were not assessed in the PPND Study 2070356. Since TK data were variable in other rat studies, the safety margin was based on a mg/m² conversion and comparison to the clinical dose of 25 mg BID.

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; EFD, embryo-fetal development; FEED, fertility and early embryonic development; h, hours; NOAEL, no-observed-adverse-effect level; PPND, pre- and postnatal development; TK, toxicokinetic

Pregnancy, Lactation, and Reproductive Potential Assessment

The review team consulted the Division of Pediatrics and Maternal Health (DPMH) to evaluate the proposed pregnancy and lactation labeling. For more details, refer to the DPMH consult memo dated August 28, 2025, in DARRTS (Reference ID 5649755).

The phase 3 trials excluded pregnant and lactating women from enrollment; however, nine pregnancies occurred across ongoing and completed studies, with treatment discontinued upon discovery. Five of the nine pregnancies had a known outcome: two full-term healthy infants, one spontaneous abortion in a 33-year-old subject with risk factors (obesity and oral contraceptive use) that was not attributed to study treatment, and two elective abortions due to subject decision with no additional information provided.

The results of DPMH's literature search using terms related to BTK inhibitors and pregnancy outcomes revealed limited data to inform remibrutinib use during pregnancy. Based on the literature review and animal data, DPMH concluded that available clinical pregnancy data are insufficient to identify drug-associated risks. DPMH did not recommend including language in Warnings and Precautions for embryo-fetal toxicity, but they recommended including the nonclinical data in Subsection 8.1 "Risk Summary" and "Data-Animal Data." Additional recommendations were to include 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.

For lactation considerations, the DPMH found no nonclinical or clinical data on remibrutinib's presence in animal or human milk, nor any data on its effects on breastfed infants or milk production. Despite the likelihood of remibrutinib transfer into human milk based on the drug's characteristics, DPMH determined that remibrutinib does not share the same severe adverse event profile as other BTK inhibitors and recommended including standard developmental benefit-risk language in labeling Subsection 8.2.

DPMH did not recommend including labeling Subsection 8.3 because there are no concerns for embryo-fetal toxicity when remibrutinib is used at clinically relevant doses and no fertility concerns based on animal fertility studies.

Because animal reproduction studies with remibrutinib suggested malformations at high dose multiples, animal reproduction studies in other drugs in the class have demonstrated embryo-fetal toxicity at clinically relevant doses and remibrutinib is systemically absorbed and likely to be transferred to the fetus, DPMH recommended issuing PMRs for a pregnancy registry and database study. Additionally, there is the potential for remibrutinib use during lactation, for which DPMH recommended a PMR for a clinical lactation study (see Section 24).

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed NDA 218436 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such the Office of Pharmaceutical Quality recommends **Approval** of this NDA from a quality perspective.

Drug Substance

Remibrutinib drug substance is manufactured using

(b) (4)

(b) (4)

and these are controlled to their respective specifications. The in-process controls utilized are appropriate for the commercial scale manufacturing process. In addition, the drug-substance characterization, its specification, and container closure system, are adequate. The developed and optimized manufacturing process for the drug substance has been validated with three batches at a (b) (4) kg batch scale.

The controls on the impurities in the remibrutinib drug substance are adequate, including for potential genotoxic impurities, (b) (4) impurities, and (b) (4) (b) (4). Based on the stability data presented thus far, a retest period of (b) (4) months is granted for the remibrutinib drug substance when stored (b) (4) in the proposed container closure system (b) (4).

Drug Product

Remibrutinib tablets (25 mg) are manufactured from compendial grade excipients, and a nonfunctional film coating is applied that is made from compendial grade excipients. The maximum daily dose is 50 mg, and the drug product is packaged in bottles that contain a desiccant to control moisture content. During the drug product manufacturing process, the drug

(b) (4)

(b) (4)

(b) (4) This was not

discovered until late in the development, and two of the three registration stability batches were found to have levels of (b) (4) which exceeded the current drug-product specification

acceptance criterion of not more than (b) (4). As a result, (b) (4) was optimized to produce drug product with sufficiently low levels of the (b) (4) impurity. The Applicant then manufactured three supportive stability batches in July 2024, with (b) (4) (b) (4) above, at, and below proven acceptable ranges. Nine months of 25°C/60% relative humidity stability data are available for the three supportive batches.

In addition, residual levels of (b) (4) (b) (4) that is limited to a concentration of not more than (b) (4) in the drug substance when (b) (4). As a result of the control levels for these two genotoxic impurities, the methods used for their quantitation in the drug product are key to the drug product control strategy.

The available stability data collected at multiple time points and with storage under different temperatures, support that the (b) (4) genotoxic impurity in the drug product does not increase over time. For the (b) (4) genotoxic impurity, the data are more limited, as testing did not commence until 18 months into the registration stability study, and there are 9 months of stability data available thus far for the supportive batches, manufactured in July 2024 after the discovery of the presence of (b) (4). There is a gradual increase in (b) (4) over time in the drug product.

Based on the totality of the stability data submitted to this point, considering that the Applicant will continue to collect data for the registration stability and supportive stability batches, and considering that they commit to withdraw batches from the market that have out-of-specification results or to discuss these results with the Agency, the currently proposed 24-month shelf-life is granted.

Manufacturing/Facilities



(b) (4) RRA assessment outcome is approval. Refer to

(b) (4) In addition, the Office of Quality Surveillance assessed the firm's product quality system during the RRA evaluation, and it was found to be adequate to implement established conditions.

Biopharmaceutics

The Applicant is seeking approval for the proposed drug product remibrutinib film-coated tablets, 25 mg, via the 505(b)(1) pathway. It is an immediate-release dosage form for oral administration. The clinical development of remibrutinib for CSU has been conducted under IND 131325. Remibrutinib is a new molecular entity, and it is the free form of a weak base showing high permeability and low solubility at physiological pH (Biopharmaceutics Classification System Class 2). The Applicant developed 25-mg, 50-mg, and 100-mg strengths but this NDA only includes the 25-mg strength. All strengths have formulation proportionality.

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The Applicant requested to approve RHAPSIDO as the proprietary name for the proposed drug product on May 15, 2023, under IND 1313251 and it was conditionally approved by the Agency on October 31, 2023. There is no dissolution method listed in FDA dissolution methods database or United States Pharmacopeia monograph. The Applicant developed an in-house method (Apparatus 1/basket with 900 mL of 0.1 N-hydrochloric acid, at 100 rpm, 37±0.5°C) and provided dissolution method development data and discriminating ability data.

The proposed dissolution acceptance criterion is Q^{(b) (4)}% in 20 minutes. Based on the dissolution data provided in quality control (QC) media, all exhibit batches comply with the proposed acceptance criterion. The proposed dissolution method and acceptance criterion are acceptable from biopharmaceutics perspective.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Human Subject Protections

The Applicant states that all studies were conducted in full compliance with the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice.

Clinical Site Inspections

Two clinical trial sites from each pivotal trial (A2301 and A2302) were selected for inspection. All four trial sites are in the United States. Several unreported protocol deviations were identified at one site (Site 5007, Dr. Gogate); however, none of the deviations caused harm or were expected to impact the trial's efficacy or safety results. Based on the results of the inspections, the Office of Scientific Investigations concluded that Trials A2301 and A2302 were conducted adequately, and the trial data submitted, including the primary efficacy endpoint data, appear acceptable in support of the respective indication. Please refer to the Clinical Inspection Summary from the Office of Scientific Investigations, dated August 4, 2025.

Financial Disclosures

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators* ([February 2013](#)), and by 21 CFR 54.4 (see Section [25](#)). The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoints are based on validated measurements that are not vulnerable to investigator bias. In conclusion, the likelihood

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that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

This application was not taken to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Additional Analyses and Information

12. Summary of Regulatory History

Table 31. Regulatory History

Date	Summary
February 2, 2017	IND 131325 was deemed safe to proceed
September 23, 2019	Special Protocol Assessment (SPA) agreement for a 2-year oral carcinogenicity study in rats
December 2, 2019	SPA agreement for a 26-week carcinogenicity study in 001178-T (hemizygous) rasH2 mice
December 3, 2020	End-of-phase 2 meeting. FDA provided feedback and recommendations for the following: • The nonclinical program seemed adequate to support the phase 3 clinical trials. • The need to conduct a clinical study to evaluate remibrutinib pharmacokinetics in subjects with renal impairment would depend on the results of the mass balance study. • Expected a DDI clinical study between remibrutinib and a CYP3A4 inducer. • Recommendations for CYP3A4 inducer alternatives such as carbamazepine for use in DDI studies due to shortage of rifampin. • Agreed that human metabolites data collected to date were adequate to support the initiation of phase 3 clinical trials. • Agreement with a 24-week double-blind, placebo-controlled treatment period in both phase 3 trials. • Continued to recommend using ISS7 and HSS7 as coprimary endpoints while the Applicant requested to maintain UAS7 as the primary endpoint. • Advised the Applicant to evaluate both the 10-mg and 25-mg BID doses in the phase 3 trials.
December 21, 2021	Type C meeting written responses, key points: • Agreed that the proposed clinical pharmacology program was reasonable at the current stage of development. • Agreement that dedicated renal impairment study was not required.
July 19, 2022	Type C meeting written responses, key points: • Disagreed with the proposed phase 1 study design for evaluating the impact of remibrutinib on vaccinations. • Provided feedback on the overall study design, eligibility criteria, vaccine selection, sample size, primary endpoints, and immunogenicity assessments.
March 24, 2023	Type C meeting written responses, key points: • Provided feedback on the integrated summary of efficacy (ISE) and pooled efficacy data. • Agreement on the content and proposed pooling strategy for safety data. • Found the Applicant's selected definitions for identifying AESIs reasonable and recommended including safety analyses for known or potential toxicities of BTK inhibitors as a class.

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Date	Summary
August 8, 2023	Type C meeting written responses, key points: - Requested the Applicant to submit additional information and justifications for the proposal to apply an acceptable intake limit for the (b) (4). - Agreed with the use of photon correlation spectroscopy to analyze dispersed samples of the drug product to confirm the consistency of the drug substance particle size distribution.
October 27, 2023	Pre-NDA meeting preliminary comments (meeting cancelled by Applicant), key points: - Agreement on the proposed content of the nonclinical and clinical pharmacology package to support an NDA. - Recommendation of including complete data from the 52-week pivotal trials at the time the NDA submission. - Agreed with the proposed content of the 120-Day Safety Update Report.
January 22, 2024	Type D meeting written responses (CMC), key points: - Recommendation of a daily intake of (b) (4) ng/day for (b) (4) (Potency Category 2 of the Carcinogenic Potency Categorization Approach). - Recommended a daily intake of (b) (4) ng/day for (b) (4) (Potency Category 1). - Agreed with the proposal not to routinely control (b) (4) and not to establish a sum limit for (b) (4) but disagreed with the plan for (b) (4) impurity. - Advised that a daily intake of overall exposures of (b) (4) impurities to be no more than (b) (4) ng/day.
February 20, 2024	Type D meeting written responses, key points: - Provided feedback for protocol CLOU064F12301, a phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy, pharmacokinetics, and safety of remibrutinib 25 mg twice daily in adolescents aged 12 to <18 years of age with chronic spontaneous urticaria (CSU) inadequately controlled by second generation H1AH. - Recommendation of increasing the sample size to provide an adequate pediatric safety database to inform the benefit-risk assessment for remibrutinib.
May 15, 2024	The Applicant submitted a Notification of Intent to submit an application with a Rare Pediatric Disease Priority Review Voucher.
June 24, 2024	Type D meeting preliminary comments (meeting cancelled by Applicant), key points: Recommendation of an acceptable daily intake limit of no more than (b) (4) ng/day for the (b) (4) impurities in remibrutinib products
January 31, 2025	- Novartis submitted NDA 218436 for the proposed indication of for the treatment of CSU in adult patients who remain symptomatic despite H1-antihistamine treatment. - Remibrutinib, an NME and reviewed under the Program, received a priority review with the PDUFA goal date of September 30, 2025.

Source: Correspondences in DARRTS under IND 131325 and NDA 218436
Abbreviations: AESI, adverse event of special interest; BID, twice daily; BTK, Bruton's tyrosine kinase; CMC, chemistry, manufacturing, and controls; CSU, chronic spontaneous urticaria; CYP, cytochrome P450; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; DDI, drug-drug interaction; H1AH, H1-antihistamine; HSS7, weekly hives severity score; IND, investigational new drug; ISS7, weekly itch severity score; NDA, new drug application; NME, new molecular entity; PDUFA, Prescription Drug User Fee Act; UAS7, weekly urticaria activity score

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The Applicant has conducted a comprehensive program of pharmacology, PK, and toxicology studies to support clinical development and the NDA submission of remibrutinib (referred to during development as LOU064). All pivotal toxicity studies have been submitted and reviewed previously under IND 131325. The impurities as well as some pharmacology studies have been reviewed herein under NDA 218436. The key findings from the nonclinical studies are cited and summarized in this review to support the approval of NDA 218436.

Pharmacological studies demonstrated that remibrutinib inhibited both unphosphorylated and phosphorylated BTK with a >200-fold selectivity for BTK over BTK related enzymes TEC and BMX based on IC₅₀ evaluation in enzymatic kinase assays. In cell-based assays, the inhibition of BTK was associated with reduced lymphocyte activation, inhibition of FcγR and FcεR, and reduced secretion of IL-6. Studies also demonstrated remibrutinib inhibition of collagen-induced platelet aggregation. In vivo, remibrutinib showed a response in two models of skin mast cell degranulation induced by FcγR and FcεR mediated hypersensitivity, a mouse reverse passive Arthus model, and a mouse passive cutaneous anaphylaxis model. These models are relevant for CSU.

The Applicant has conducted subchronic and chronic toxicology studies with remibrutinib in both rats and dogs. Target organs of toxicity were identified as the lymph nodes (underdeveloped germinal centers, sinusoidal red blood cells), thyroid gland (follicular hypertrophy), liver (hepatocellular hypertrophy, multinucleated hepatocytes, pigment), pancreas (islet fibrosis, pigment), and blood (prolongation of bleeding, inhibition of platelet aggregation). The nonclinical findings were not considered clinically dose-limiting. The nonclinical general toxicology studies provided sufficient support for the clinical development program.

In animal reproduction studies, remibrutinib was nonteratogenic and did not affect fertility in rats. Pregnant rats dosed with remibrutinib during the period of organogenesis did not show fetal malformations at doses up to 1000 mg/kg/day (approximately 126x the MRHD). In pregnant rabbits, remibrutinib treatment resulted in signs of maternal toxicity (clinical signs of toxicity, weight loss, and decreased food consumption) and adverse developmental outcomes (open/opaque eyes, small jaws, hyperflexion of forelimbs) at doses ≥300 mg/kg/day (approximately 141x the MRHD). In a pre- and postnatal development study in rats, potentially remibrutinib-related findings were observed at the highest dose of 1000 mg/kg/day dose (approximately 194x the MRHD). Toxicity in two maternal rats resulted in early euthanasia of these animals with one animal exhibiting reduced food consumption, reduced body weight, and poor clinical signs followed by delivery of five stillborn pups and five small, cold, weak pups that were terminated on Postnatal Day 0 to 1. In the second animal, poor clinical signs were observed along with total litter loss. Overall, the 1000 mg/kg/day dose group exhibited a reduced litter size (-11.8% compared to controls), an increase in the number of stillborn pups (15 versus 1 in the control and 300 mg/kg/day dose groups), and an increase in the number of pup deaths. No adverse remibrutinib-related changes were observed in maternal rats and offspring at doses of ≤300 mg/kg/day (approximately 58x the MRHD).

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Remibrutinib was not mutagenic in in vitro or in vivo assays. A 2-year oral study in Wistar rats and a 6-month oral study in Tg.rasH2 mice were conducted to assess the carcinogenic potential of remibrutinib. No evidence of tumorigenicity was observed in male and female Tg.rasH2 mice at doses up to 1500 mg/kg/day or in rats at exposures approximately 8x and 98x the MRHD in males and female rats, respectively.

To conclude, a complete and adequate nonclinical program was submitted, and NDA 218436 is recommended for approval from the nonclinical perspective.

Pharmacology

Remibrutinib is a small molecule inhibitor of BTK that inhibits human BTK with nanomolar potency (IC₅₀: 0.6 to 7.5nM) and was generally more selective for BTK compared to the BTK-related enzymes TEC and BMX (IC₅₀: 124 to 141nM).

In vivo, optimized-for-aging (OFA)-1 and Wistar rats were used to assess BTK target occupancy in the spleen and blood following changes to dose, exposure, and time. Following doses up to 10-mg/kg remibrutinib, these studies demonstrated high occupancy in the spleen and blood, and corresponding blood levels ranging from 2 to 71nM. Blood levels of remibrutinib were maximal by 0.5 hours postdose while BTK occupancy exhibited different kinetics in the blood and spleen with an estimated BTK half-life of 87 hours in the rat blood and 5 to 8 hours in the spleen.

In a mouse reverse passive Arthus model of a local type III hypersensitivity reaction, oral doses up to 100 mg/kg of remibrutinib were administered prior to induction of the Arthus response. In this model, remibrutinib pretreatment resulted in reduced skin swelling. In a BALB/c mouse passive cutaneous anaphylaxis (PCA) model, oral remibrutinib administration at doses up to 100 mg/kg inhibited PCA at all doses while a minimal effect was observed at high-dose IgE sensitization. These results suggest that remibrutinib was effective following low-dose IgE sensitization in this model of anaphylaxis-driven skin edema relevant to urticaria.

In a model of B-cell response to sheep red blood cells (SRBC) in OFA rats, remibrutinib was administered at daily doses up to 3 mg/kg for 3 days following immunization with SRBC. Following dosing, remibrutinib dose dependently decreased the number of SRBC-specific IgM secreting B-cells by 66 to 96%. This model showed correlation between remibrutinib pharmacokinetics, tissue BTK (spleen and blood) occupancy, and a PD effect.

Safety Pharmacology

A complete battery of safety pharmacology studies has been conducted with remibrutinib. The remibrutinib IC₅₀ at human ether-à-go-go-related gene channels expressed in HEK293 cells was calculated to be 1.4µM. The effects of remibrutinib on central nervous system function and the respiratory system were examined using a functional observation battery in a single-dose oral gavage study in Wistar rats. There were no effects on autonomic, neurologic, behavioral observations or for respiratory rate, tidal volume, minute volume, or peak inspiratory or expiratory flow observed at up to 1000 mg/kg. The effects of remibrutinib on cardiovascular system function were examined in a single-dose oral gavage telemetry study in Beagle dogs. No effects on body temperatures, heart rates, arterial pressures, or ECG parameters (including PQ, RR, QRS, QT, and QTv) were observed at doses up to 450 mg/kg.

Absorption, Distribution, Metabolism, Excretion

In rats, remibrutinib was rapidly absorbed, with a bioavailability of 7 to 29% after oral administration. A single oral dose of remibrutinib resulted in broad distribution in all tissues except for the brain, lens of the eye, spinal cord, and white fat, with a T_{max} of 0.5 to 8 hours. Similar distribution was noted in both sexes. Specific retention of total radiolabeled components in the pigmented uveal tract/retina was observed. The highest exposures (based on AUC_{last}) were observed for the kidney medulla, small intestine mucosa, skin, cecum mucosa, kidney cortex, liver, and uveal tract/retina. Following IV or oral administration in rats, remibrutinib appeared to be eliminated via metabolism with <4% of the parent compound detected in excreta and a pattern of metabolites that was qualitatively and quantitatively similar.

In dogs, a single oral dose of remibrutinib resulted in moderate absorption (41.9%) with a bioavailability of 13.5% and a median T_{max} of 2 hours. Remibrutinib was distributed into tissues (volume of distribution at steady state [V_{ss}] = 1.26 L/kg) and exhibited high clearance ([CL] = 187 L/h/kg). Excretion occurred mainly in the feces, with excretion by urine representing a minor fraction.

Remibrutinib was associated with rapid metabolism in the mouse, rat, dog, and human, with 31 metabolites identified across all species. The major metabolic pathways consisted of N-demethylation, followed by glutathione or cysteine adducts and hydrogenation leading to M11 and M17 formation observed in the mouse, rat, and human, or O-dealkylation leading to M22 observed in all species, and glucuronidation leading to M7 observed in all species. Two metabolites formed by C-hydroxylation (M25) and C-hydroxylation and N-hydroxylation (M27) were only detected in in vitro human hepatocyte incubation with only M25 also observed in vivo at levels of 1.12% of the exposure based on AUC_{0-24h} . There were no major human metabolites identified.

Very low levels of degradation were observed for remibrutinib following incubation in blood or plasma from the rat, dog, or human for up to 2 hours with preferential distribution to the plasma in all tested species and blood distribution appearing to be concentration independent. Remibrutinib highly bound to plasma proteins with no concentration dependence: 89.8%, 92.8%, and 95.4% in the rat, dog, and human, respectively. Formation of covalent drug-protein adducts was observed in human liver microsomes and human hepatocytes. Coincubation with glutathione in human liver microsomes resulted in a 55% decrease in covalent drug-protein adducts, suggesting that glutathione-mediated activation of remibrutinib contributes to the formation of these adducts. Formation of covalent drug-protein adducts was time-dependent in human, dog, and rat blood and plasma, with adduct formation higher in plasma than blood, and with adduct formation in rat and dog plasma higher than that observed in human plasma. Remibrutinib covalently bound plasma proteins without metabolic activation at high levels. Using recombinant enzymes or selective enzymatic inhibitors (ketoconazole and azamulin), CYP3A4 was determined to be the major human liver enzyme implicated in oxidative metabolism of remibrutinib in the liver with potential contributions for CYP1A1 and CYP2C19.

General Toxicology

As listed in the table below, general toxicity studies with remibrutinib were conducted in rats for up to 26 weeks and in dogs for up to 39 weeks. The pivotal studies have been reviewed previously under IND 131325 and are listed below.

Table 32. General Toxicity Studies

Species	General Toxicology Study		GLP	Report Number	Review Reference ID
	Duration (Weeks)	Doses (mg/kg; Oral Gavage)			
Rat	2	0, 30, 100, 300, 1000	Y	1470733; 42325 TSR	5594816
	13	0, 10, 100, 1000	Y	1570128; 43328 TCR	4417327
	26	0, 30, 300, 1000	Y	1670372; 45306 TCR	4496430
Dog	2	0, 50, 200, 450	Y	1470732; 42326 TSR	5594816
	13	0, 10, 50, 300	Y	1570127; 43329 TCC	4417627
	39	0, 10, 50, 300	Y	1670373-01; 45307 TCC	5569163

Source: Reviewer-generated table
Abbreviation: ID, identifier; GLP, good laboratory practice; Y, yes

Repeat-Dose Toxicology Studies in Rats

A 2-Week Rat Study (1470733; 42325 TSR)

In a 2-week oral repeat-dose toxicity study in Wistar rats (10/sex/group), animals were administered doses of 0 (vehicle), 30, 100, 300, and 1000 mg/kg/day of remibrutinib. Recovery groups (5/sex for the control and 1000 mg/kg/day dose groups) were included to assess reversibility of the findings. Mortality was observed in one female administered 100 mg/kg/day of remibrutinib which was considered potentially related to test article induced prolongation of bleeding during a tail-tip bleeding test. Target tissues were identified as the blood, lymph nodes (decreased paracortex in mesenteric, sinusoidal red blood cells), spleen (decreased periarteriolar lymphoid sheaths and decreases in marginal zone), thyroid (minimal follicular hypertrophy), and liver (increased mitosis, periportal vacuolation, focal necrosis, and inflammatory cell foci). Mild, reversible increases in WBC, lymphocytes (including B-cells and T-cells) were observed in both sexes administered ≥ 100 mg/kg/day of remibrutinib. Administration of remibrutinib was also associated with inhibition of collagen-induced platelet aggregation and prolonged bleeding time observed in both sexes at all doses. Due to changes in hemostasis at ≥ 30 mg/kg/day, the Applicant did not establish any no-observed-adverse-effect level (NOAEL) in this study; however, given the hemostatic effects are related to the pharmacology of remibrutinib and are monitorable, a NOAEL was considered to be 30 mg/kg/day with an associated Day 14 AUC_{0-24h} of 13000 ng*h/mL in males and 31900 ng*h/mL in females.

A 13-Week Rat Study (1570128; 43328 TCR)

In a 13-week good laboratory practice (GLP) toxicity study, Wistar rats (10/sex/group) were dosed by oral gavage with 0 (vehicle), 10, 100, and 1000 mg/kg/day remibrutinib. No recovery groups were included in the study. Following administration of remibrutinib, rats exhibited mild immune suppression manifested by decreased circulating B-cells (6 to 32%) in all doses in both sexes and microscopic changes in lymphoid tissues, including decreased cellularity in the mandibular and mesenteric lymph nodes coupled with increased frequency of sinusoidal red blood cells and decreased periarteriolar lymphoid sheaths and reduction in marginal zones in the spleen. These effects were attributed to the pharmacology of the test article and are monitorable in the clinical setting. In addition to the immunosuppression-related findings, the rats dosed with ≥ 100 mg/kg/day of remibrutinib exhibited changes in the thyroid (follicular hypertrophy) and liver (hepatocellular hypertrophy). No NOAEL was established by the Applicant in this study; however, given the hemostatic effects are related to the pharmacology of remibrutinib and are

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monitorable, a NOAEL was considered to be 1000 mg/kg/day with an associated Day 89 AUC_{0-24h} of 4780 ng*h/mL in males and 52800 ng*h/mL in females.

A 26-Week Rat Study (1670372; 45306 TCR)

In a 26-week GLP toxicity study, Wistar rats (20/sex/group) were dosed by oral gavage with 0, 30, 300, and 1000 mg/kg/day remibrutinib. The 300 and/or 1000 mg/kg/day groups showed dose-related increases in liver weights and microscopic changes in the liver, lymph nodes, pancreas, and thyroid glands, with females showing more pronounced effects than males. The following findings were noted in the females: the liver showed minimal hepatocellular hypertrophy, multinucleated hepatocytes, and pigment generally in the 1000 mg/kg/day dose group. The percent of rats with hepatocellular hypertrophy was 10% (2/20) and 65% (13/20) in the 300 and 1000 mg/kg/day dose groups, respectively, accompanied by increases in absolute mean liver weights (by 18% and 51%, respectively). The lymph nodes (both mandibular and mesenteric lymph nodes) showed less developed germinal centers and sinusoidal red blood cells. The pancreas showed minimal islet fibrosis and pigment, which have been reported to be rat-specific effects of BTK inhibitors. The thyroid glands showed follicular hypertrophy. The NOAEL was 30 mg/kg/day with an associated Day 176 AUC_{0-24h} of 5970 ng*h/mL in males and 30900 ng*h/mL in females.

Repeat-Dose Toxicology Studies in Dogs

A 2-Week Dog Study (1470732; 42326 TSC)

In a 2-week GLP oral repeat-dose toxicity study in beagle dogs, animals (3/sex/group) were administered doses of 0 (vehicle), 50, 200, and 450 mg/kg/day of remibrutinib. No recovery groups were included in the study. Target tissues were identified as the blood and lymph nodes, with alterations in hemostasis including prolongation of bleeding time and inhibition of ADP- and collagen-induced platelet aggregation. Microscopic findings considered potentially related to the test article were limited to sinusoidal red blood cells observed in both the mandibular and mesenteric lymph nodes in both sexes in all dose groups that correlated with macroscopic observations of red discoloration. Exposures of remibrutinib increased in a generally dose-proportional manner from 50 to 200 mg/kg/day with no obvious increase in exposure levels from 200 to 450 mg/kg/day suggesting saturation of the test article. High variability was observed; however, exposures were higher in females than males (by 1.9- to 5.4-fold). The NOAEL was considered the highest dose of 450 mg/kg/day, though higher exposures were noted at 200 mg/kg/day, resulting in a mean AUC_{0-24h} of 10400 ng*h/mL in males and a mean AUC_{0-24h} of 56300 ng*h/mL in females on Day 13.

A 13-Week Dog Study (1570127; 43329 TCC)

In a 13-week GLP oral repeat-dose toxicity study in beagle dogs, animals (3/sex/group) were administered doses of 0 (vehicle), 10, 50, and 300 mg/kg/day remibrutinib. No recovery groups were included in the study. Following administration of remibrutinib, dogs exhibited mild immune suppression manifested by decreased circulating B-cells (42 to 80%) in all doses in both sexes and microscopic changes in lymphoid tissues in all doses in both sexes, including increased frequencies of sinusoidal red blood cells in the mandibular and mesenteric lymph nodes and decreased germinal center development in the gut-associated lymphoid tissue. These effects were attributed to the pharmacology of the test article and are monitorable in the clinical

setting. Exposures increased in a less than dose-proportional manner with slightly (<2-fold) increased exposures noted in females at ≥ 50 mg/kg/day. The NOAEL was considered the highest dose of 300 mg/kg/day with an associated mean AUC_{0-24h} of 6350 and 9310 ng*h/mL in males and females, respectively, on Days 87 to 89.

A 39-Week Dog Study (1670373; 45307 TCC)

In a 39-week GLP oral repeat-dose toxicity study in beagle dogs, animals (4/sex/group) were administered doses of 0 (vehicle), 10, 50, and 300 mg/kg/day remibrutinib. No recovery groups were included in the study. Microscopic findings were observed in the mesenteric lymph node (decreased cellularity and decreases in germinal center development) and gut-associated lymphoid tissue (decreases in germinal center development). Red discoloration was observed in the cecum, duodenum, ileum, iliac lymph nodes, and mesenteric lymph nodes in several animals from remibrutinib-treated dose groups and a red mass observed in the gastric lymph node in a single male from the 300-mg/kg/day dose group. In the mandibular and mesenteric lymph nodes, this observation correlated with microscopic findings of minimal to moderate sinusoidal red blood cells in both sexes and at all doses (including controls) with increasing severity generally associating with dose. Increased fibrinogen was observed in some animals at ≥ 50 mg/kg/day. In the liver, there was increased incidence and severity of pigment in remibrutinib-treated groups compared to controls with increased intensity of positive Schmorl's stain (indicates the presence of melanin, argentaffin, chromaffin, bile, and formalin pigment) in the 300-mg/kg/day dose group compared to controls, suggestive of lipofuscin, which is considered nonadverse. The NOAEL was considered to be 300 mg/kg/day with an associated combined male and female C_{max} and AUC_{0-24h} of 4735 ng/mL and 43550 ng*h/mL, respectively.

Toxicokinetics and Exposure Margins

Adequate exposure margins between the nonclinical general toxicology studies and proposed human doses of remibrutinib were obtained throughout the clinical development program.

Table 33. Summary of Remibrutinib Exposures in Repeat-Dose Toxicity Studies

Species	Nonclinical Dose			Clinical Dose Safety Margin	
	Duration (Weeks)	NOAEL (mg/kg/day)	AUC_{0-24h} (ng*h/mL)	AUC_{0-24h} (25 mg BID) ¹	
Rat	2	30	13000 ²	33	
	13	1000	4780	12	
	26	30	5970	15	
Dog	2	450	10400 ³	27	
	13	300	6350	16	
	39	300	30000	77	

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study A2201).

² Rat exposures were from Studies #1470733, 1570128, and 1670372.

³ Dog exposures were from Studies #147032, 1570127, and 1670373.

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; h, hour(s); NOAEL, no-observed-adverse-effect level

Genetic Toxicology

Remibrutinib was considered negative for genotoxicity in an Ames test, an in vitro micronucleus assay in peripheral human lymphocytes, and an in vivo micronucleus assay in rats.

Carcinogenicity

Mouse Carcinogenicity Study (1870307; 8411537)

A 26-week oral carcinogenicity study of remibrutinib in Tg.rasH2 mice showed no evidence of carcinogenicity in mice (25/sex/dose) dosed by oral gavage with 0 (water), 0 (vehicle), 150, 500, and 1500-mg/kg/day remibrutinib once daily. The Agency concurred with the dose selection for the study on December 2, 2019. Remibrutinib had no effects on survival rates. The remibrutinib treatment groups did not exhibit increases in the incidence of tumor findings. Non-neoplastic findings included decreases in germinal center cellularity in the spleen and mesenteric lymph nodes and findings of hepatocyte cytoplasmic eosinophilic inclusions, karyocytomegaly, and/or multinucleated hepatocytes in the liver. A positive control group (N-methyl-N-nitrosourea; 75 mg/kg/day) showed expected increases in tumor incidences in the hemolymphoreticular tissue, stomach, and skin. Remibrutinib was negative for carcinogenicity under these study conditions.

Rat Carcinogenicity Study (1870308; 8425081)

A 104-week oral carcinogenicity study of remibrutinib in Wistar rats (50/sex/dose) showed no evidence of carcinogenicity at oral doses of 0 (water), 0 (vehicle), 30, 100, and 300 mg/kg/day remibrutinib once daily. The Agency concurred with the dose selection for the study on September 23, 2019. Remibrutinib had no effects on survival rates. No remibrutinib-related neoplastic changes were noted up to the highest tested dose of 300 mg/kg/day. Non-neoplastic microscopic findings included findings in the lymphoid tissues (sinusoidal red blood cells, sinusoidal dilatation, focal angiomatous hyperplasia, diffuse reticuloendothelial hypertrophy/hyperplasia, and/or pigmented macrophages), thyroid (follicular cell hyperplasia), and pancreas (islet fibrosis). Remibrutinib was negative for carcinogenicity under these study conditions.

Table 34. Summary of Remibrutinib Exposures in Rat Carcinogenicity Study

Species	Study	Nonclinical Dose		Clinical Dose Safety Margin
		NOAEL (mg/kg/day)	AUC _{0-24h} (ng*h/mL)	AUC (25 mg BID) ¹
Rat	Carcinogenicity	300	2990 (males) ²	8
			38200 (females)	98

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study A2201).

² Rat exposures were from Study 1870308.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; BID, twice daily; h, hour(s); NOAEL, no-observed-adverse-effect level

Reproductive Toxicology

Remibrutinib did not affect fertility and was nonteratogenic in rats. In rabbits, remibrutinib treatment resulted in maternal toxicity and adverse developmental outcomes at doses ≥ 300 mg/kg/day. In the rat pre- and postnatal development study, remibrutinib treatment resulted in increased number of stillborn pups, dead pups, and a smaller litter size at 1000 mg/kg/day.

Fertility Study (1770589)

In a fertility study, male and female rats (Wistar, 24/sex/dose) were dosed by oral gavage with 0, 100, 300, or 1000 mg/kg/day remibrutinib. Males were dosed for 9 weeks starting from 28 days

prior to mating and through mating. Females were dosed for 14 days prior to mating, through mating, and until Gestation Day (GD) 6. Females were sacrificed on GD 13 for uterine content examinations. No treatment-related findings were observed in any of the fertility parameters evaluated. Therefore, the NOAEL was 1000 mg/kg/day.

Embryo-Fetal Development Studies (1670380; 1670382)

In an embryo-fetal developmental study (1670380), pregnant Wistar rats (22/dose) were dosed by oral gavage with 0, 100, 300, or 1000 mg/kg/day remibrutinib during GDs 6 to 17, sacrificed on GD 21, and examined for fetal malformations and variations. No treatment-related effects were observed in any of the key parameters. The NOAEL was 1000 mg/kg/day, corresponding to a C_{max} of 4370 ng/mL and AUC_{0-24h} of 49200 ng*h/mL.

In another embryo-fetal developmental study (1670382), pregnant rabbits (New Zealand White, 20/dose) were dosed by oral gavage with 0, 100, 300, or 450 mg/kg/day remibrutinib during GDs 7 to 20, sacrificed on GD 29, and examined for fetal malformations and variations. Mortality (euthanasia) occurred at ≥ 300 mg/kg/day. One doe administered 300 mg/kg/day and the entire group of does administered 450 mg/kg/day were terminated during the period of GD 14 to 22 due to severe toxicities including abortion, clinical signs, weight loss, and decreases in feed consumption. The clinical signs included subdued/decreased activity, cold to touch, irregular respiration, decreased fecal output, pale pinnae, partially closed eyes, and red liquid material. The 450-mg/kg/day dose group was excluded from the analysis of fetal malformations and variations due to severe maternal toxicity. The 300-mg/kg/day dose group showed slight but statistically nonsignificant increases in a few external malformations such as eye opening, small jaws, and hyperflexion of forelimbs. No increases in the incidence of malformations or variations were observed in the 100-mg/kg/day dose group. The NOAEL was 100 mg/kg/day, corresponding to a C_{max} of 2360 ng/mL and AUC_{0-24h} of 8990 ng*h/mL.

Pre- and Postnatal Development Study (2070356)

In a pre- and postnatal development study, pregnant rats received daily oral doses of remibrutinib at 0 (vehicle), 100, 300, and 1000 mg/kg/day from GD 6 to Lactation Day 21. Potentially remibrutinib-related findings were observed for the 1000-mg/kg/day dose group. Toxicity in two maternal rats resulted in early euthanasia of these animals, with one animal exhibiting reduced food consumption, reduced body weight, and poor clinical signs followed by delivery of five stillborn pups and five small, cold, weak pups that were terminated on Postnatal Days 0 to 1. In the second animal, poor clinical signs were observed along with total litter loss. Overall, the 1000-mg/kg/day dose group exhibited a reduced litter size (-11.8% compared to controls), an increase in the number of stillborn pups (15 versus 1 in the control and 300-mg/kg/day dose groups), and an increase in the number of pup deaths. No adverse remibrutinib-related changes were observed in maternal rats and offspring at doses of ≤ 300 mg/kg/day. Therefore, the NOAEL was identified at 300 mg/kg/day.

Table 35. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg/day)	AUC (ng*h/mL)	Exposure Margins ¹ (Multiples)
FEED rat, male and female	1000	5840 (males) ² 24700 (females)	15 63
EFD, rat	1000	49200 (females) ³	126
EFD, rabbit	100	8990 (females) ⁴	23
PPND, rat	300	5	58

Source: Reviewer-generated table

¹ Clinical exposure of remibrutinib in healthy subjects at a twice daily dose of 25 mg was 390 ng*h/mL (Study A2201).

² Exposures obtained from Study 1770589.

³ Exposures obtained from Study 1670380.

⁴ Exposures obtained from Study 1670382.

⁵ TK data were not assessed in the PPND Study 2070356. Since TK data were variable in other rat studies, the safety margin was based on a mg/m² conversion and comparison to the clinical dose of 25 mg BID.

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; EFD, embryo-fetal development; FEED, fertility, and early embryonic development; h, hours; NOAEL, no-observed-adverse-effect level; PPND, pre- and postnatal development; TK, toxicokinetic

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Pharmacology

In Vitro Binding and Cellular Activity Study (RD-2014-00811)

Pharmacology studies submitted by the Applicant evaluated the effect of remibrutinib in vitro and in vivo. In these studies, remibrutinib generally demonstrated inhibition of both unphosphorylated and phosphorylated BTK with IC₅₀s that were >200-fold lower than those observed for the related enzymes TEC and BMX (0.6 to 7.5nM versus 124 to 141nM), with no demonstrated inhibition of ITK or TXK. In the same study using a kinase panel, remibrutinib demonstrated inhibition of BTK with an IC₅₀ of 1.1nM and PI4Kb with an IC₅₀ of 3.1μM with no apparent inhibition of other protein and lipid kinases. In an in vitro off-target screening panel, remibrutinib exhibited minimal off-target effects with inhibition of NaV1.5, human BSEP, and the rat transporter VMAT-2 observed with IC₅₀s >3μM.

In Ramos B-cell cultures, remibrutinib inhibited human phosphorylated BTK (pY551), cluster of differentiation (CD69 and CD86, and IL-6 secretion. In a human monocytic cell line, Tohoku Hospital Pediatrics-1 (THP-1) cells, remibrutinib inhibited FcγR signaling, while less potent inhibition was observed in polymorphonuclear leukocytes. This finding is consistent with the relative BTK expression levels in these cell types. Remibrutinib exhibited only minimal effects on proliferation of THP-1 cells (IC₅₀ of 35μM), and in murine Ba/F3 cells including IL-13-independent subclones (IC₅₀ >11μM; except for Ba/F3 transformed by BMX [IC₅₀ of 5.5μM]), and mouse bone marrow cells (IC₅₀ of 1.97μM). Remibrutinib inhibited the mouse and human mixed lymphocyte reaction with IC₅₀s of <4.6 and 3nM, respectively. The epidermal growth factor receptor signaling did show evidence of inhibition (IC₅₀ >60μM) after prolonged in vitro incubation (5 hours).

Table 36. Inhibition of BTK and BTK-Related Enzymes

Enzyme	IC ₅₀ (nM)
BTK unphosphorylated (Novartis, n = 5) ¹	1.3
BTK phosphorylated (Novartis, n = 2) ¹	7.5
BTK (b) (4), n = 1) ²	0.6
TEC (b) (4), n = 1) ²	124
BMX (b) (4), n = 1) ²	141
ITK (b) (4), n = 1) ²	> 10'000
TXK (b) (4), n = 1) ²	> 10'000

Source: Study RD-2014-00811; Excerpt from Applicant's submission

Abbreviations: BMX, bone marrow X-linked kinase; BTK, Bruton's tyrosine kinase; IC₅₀, half-maximal inhibitory concentration; ITK, interleukin-2 inducible T-cell kinase; n, number of subjects; TEC, tyrosine kinase expressed (in hepatocellular carcinoma); TXK, tyrosine kinase

Remibrutinib also inhibited collagen-induced platelet aggregation at low but not high collagen concentrations, suggesting that BTK inhibition blocks collagen-induced platelet aggregation at low agonist concentrations.

In an evaluation of tissue staining for human BTK using commercial antibodies, moderate to strong signals for BTK were generally observed in B-lymphocytes in the lymph node, spleen, tonsil, and thymic medulla with occasional staining of mast cells and plasma cells. Nonlymphoid tissues included epithelium (breast, renal tubules, respiratory, spleen), hepatocytes, and endometrial glands.

In Vivo PD Effects (BTK Target Occupancy; RD-2014-00816)

In vivo, OFA-1 and Wistar rats were used to assess BTK target occupancy in the spleen and blood using different doses, exposures, and times. Following doses of 1-, 3-, and 10-mg/kg remibrutinib, these studies demonstrated 75 to 99% occupancy in the spleen and 13 to 96% occupancy in the blood, with corresponding blood levels ranging from 2 to 71nM. Blood levels of remibrutinib were maximal by 0.5 hours postdose while BTK occupancy exhibited different kinetics in the blood and spleen with an estimated BTK half-life ($t_{1/2}$) of 87 hours in the rat blood and 5 to 8 hours in the spleen. BTK occupancy in the spleen was not affected by the route of administration (subcutaneous or by mouth).

In Vivo Models Relevant to CSU

In a mouse reverse passive Arthus model of a local type III hypersensitivity reaction (Study RD-2014-00813) using oral doses of 3, 10, 30, and 100 mg/kg of remibrutinib administered prior to induction of the Arthus response, remibrutinib pretreatment resulted in dose-dependent increases in exposure that increased in a less than dose-proportional manner for 3 to 10 mg/kg but in a greater than dose-proportional manner from 10 to 100 mg/kg. Dose-dependent increases in BTK occupancy in the spleen were also evident. Reduced skin swelling in the mouse reverse passive Arthus model was observed with 30- and 100-mg/kg remibrutinib. Inhibition of swelling compared to vehicle was observed when remibrutinib was administered 2 to 16 hours prior to induction of the Arthus response with a maximal response observed at 2 hours and returning to vehicle control levels at 45 hours.

In a BALB/c mouse PCA model (Study RD-2014-00912) where mast cells are activated via the FcεR by IgE and hapten-specific IgE, remibrutinib was administered at doses of 0 (vehicle), 3,

10, 30, and 100 mg/kg (by mouth) at two time points (4 hours after sensitization and 2 hours prior to hapten challenge). Following low dose IgE sensitization, remibrutinib administration inhibited PCA at all doses while a minimal effect was observed at high dose IgE sensitization for the high dose of 100-mg/kg remibrutinib. However, comparable blood concentrations of remibrutinib that were dose-proportional and comparable ~100% BTK occupancy in the spleen were observed with either approach. These results suggest that remibrutinib was effective following low-dose IgE sensitization in this model of anaphylaxis-driven skin edema relevant to urticaria.

In Vivo Correlation of Remibrutinib Pharmacokinetics, Tissue BTK Occupancy, and Mechanistic Pharmacodynamics

A model of B-cell response to SRBC in OFA rats (Study RD-2014-00858) was used to assess the correlation of remibrutinib pharmacokinetics, tissue BTK occupancy, and mechanistic PD efficacy. Remibrutinib was administered at daily doses of 0.3, 1, and 3 mg/kg for 3 days following immunization with SRBC. Following dosing, remibrutinib concentrations in the blood increased in a dose-proportional manner and were highest at 0.5 hours postdose with <10% remaining at 5 hours postdose. Dose dependent increases in BTK occupancy in the spleen were evident with increasing doses (31 to 71.6%). Remibrutinib dose-dependently decreased the number of SRBC-specific IgM secreting B-cells by 66 to 96%.

Impurities

The Applicant identified three remibrutinib drug product impurities of potential concern, including two degradants, (b) (4) and (b) (4), and (b) (4). Using in silico evaluation, potential mutagenic signals were observed for (b) (4) and (b) (4) but were not observed for (b) (4).

(b) (4)

Impurity (b) (4) is a degradation product and an identified (b) (4) remibrutinib. In a 26-week repeat-dose toxicology study in rats that received 1000 mg/kg/day of remibrutinib (Study 1670372/45306 TCR), rats were exposed to (b) (4) mg/kg of (b) (4) assuming (b) (4) across tested dose levels. The maximum human daily doses currently in development for remibrutinib is 200 mg (3.34 mg/kg). Using a specification of (b) (4)% (proposed by the Applicant) would result in a maximum human exposure of (b) (4) mg/kg (~(b) (4)-fold less than the rat exposure on a mg/m² basis). Following the International Classification for Health Accounts Q3B (R2) guideline *Impurities in New Drug Products* ([June 2006](#)), (b) (4) are generally considered qualified. Therefore, the specification of (b) (4)% is considered acceptable.

(b) (4)

(b) (4) was identified as a drug-substance degradation product (b) (4) during manufacturing. The Applicant assigned an acceptable limit of (b) (4) ppm (1.5 µg) for (b) (4) based on the threshold of toxicological concern. Following the ICH M7 (R2) guideline *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* ([April 2023](#)), a maximum daily dose of 1.5 µg/person/day would be

associated with negligible risk for a mutagenic impurity present in pharmaceuticals for long-term treatment. Therefore, the proposed specification for this impurity is considered adequate.

(b) (4)
(b) (4) is a (b) (4) in the remibrutinib drug substance (b) (4) (b) (4) that was observed during drug product manufacturing. The Applicant proposes a (b) (4) (b) (4) (b) (4) is mutagenic per ICH M7 and a Muta™ Mouse study with a (b) (4) acceptable intake (AI) of (b) (4) ng/day. The Applicant proposes an acceptable intake for (b) (4) of (b) (4) ng/day based on a structural comparison with (b) (4) Per the ICH guidance (b) (4) (b) (4) are predicted to have carcinogenic potency no higher than (b) (4)

(b) (4)
(b) (4) An intake of (b) (4) of (b) (4)/day is considered acceptable.

Conclusion

The Applicant’s proposed strategy for control of impurities is acceptable from a nonclinical perspective.

14. Clinical Pharmacology

14.1. In Vitro Studies

Clinical pharmacology-related in vitro studies are summarized in [Table 37](#).

The unbound maximum blood concentration at steady state ($C_{\max,ss,u}$) for remibrutinib at the recommended dosage of 25 mg BID is 0.00595 μ M.

Table 37. Summary of In Vitro Studies

Report/Objectives	Summary Findings and Key Conclusions
<i>Absorption and Transporters</i>	
DMPK R1500096: Evaluating the permeability and the effect of efflux-transporters (MDR1, BCRP, and MRP2) on permeability of remibrutinib	In Caco-2 cell monolayers, P_{app} efflux ratios for [³ H]-digoxin (1 μ M), [³ H]-propranolol (5 μ M), and [¹⁴ C]-mannitol (5 μ M) were 25.24, 1.77, 0.45, respectively. The P_{app} ratios for remibrutinib at 0.5 μ M and 100 μ M were 17.5 and 1.3, respectively, suggesting saturation of an apically directed transporter-mediated efflux process at higher concentrations of remibrutinib. At a lower remibrutinib concentration (0.5 μ M), LY335979 (MDR1 [P-gp] inhibitor) significantly decreased P_{app} to 0.8. No significant changes in remibrutinib permeability were observed in the presence of BCRP and MRP2 inhibitors. <i>These findings suggest that remibrutinib exhibits high passive permeability at higher concentrations, while at lower concentrations, its permeability is reduced due to an apically directed P-gp-mediated efflux process (apparent K_m of 13.8μM). The contributions of BCRP and MRP2 to this efflux process appear to be negligible</i>
DMPK R1500097: Transport study of [³ H]-remibrutinib using cryopreserved human hepatocytes to evaluate the hepatic uptake of remibrutinib by OATP1B1, OATP1B3, OCT1, and OAT2 and the potential impact of lysosomal trapping	Human hepatocyte uptake of remibrutinib (0.38 μ M) occurs mostly by a passive permeation without modulation by a solute-carrier system. The measured (nonsaturable, passive) membrane permeability for remibrutinib was 47.3 μ L/min/ mg protein and the maximum transporter-mediated membrane permeability for remibrutinib was 0 μ L/min/10 ⁶ cells. Inhibitors of OATP1B1, OATP1B3, OAT family, OCT family, NTCP, and lysosomal trapping did not impact the permeation of remibrutinib into hepatocytes.
<i>Distribution</i>	
DMPK R2300145: Evaluating the binding of [¹⁴ C]-remibrutinib in vitro	The protein binding of [¹⁴ C]-remibrutinib in human plasma at concentrations of 5, 50, 500, and 5000 ng/mL were 98, 95.3, 95.1, and 95.2%, respectively.
DMPK R1400850: Evaluating the in vitro plasma protein binding of [³ H]-remibrutinib and [³ H]-LTG751 for human.	Remibrutinib contains a reactive acrylamide moiety by design. LTG751 is an analog of remibrutinib where the reactive acrylamide has been inactivated (double bond saturated). The plasma protein binding of [¹⁴ C]-remibrutinib at concentrations of 10, 100, 1000 and 10000 ng/mL was 94.4, 95.2, 95.5, and 96%, respectively.

Report/Objectives	Summary Findings and Key Conclusions
	The mean in vitro human blood/plasma distribution of [³H]-remibrutinib and [³H]-LTG751 for human were 0.813 (over a concentration range of 100 to 10,000 ng/mL) and 0.858 (over a concentration range of 10 to 1000 ng/mL), respectively. At a concentration of 10 ng/mL, the blood/plasma distribution for remibrutinib was 0.955.
<i>Metabolism</i> DMPK R1500124: Evaluation of [³H]-remibrutinib oxidative metabolite profile in human liver microsomes (HLM), human hepatocytes, liver cytosol, and S9 fractions and using recombinant human enzymes	CYP3A4 inhibitors ketoconazole and azamulin inhibited the metabolism of remibrutinib up to 96% and 100% in HLM with an IC₅₀ value of 0.04µmol/L and 0.005µmol/L, respectively. The fraction metabolized (f_m) by CYP3A4 was estimated to be 0.95. CYP3A4 mainly formed metabolites M24 (dihydrodiol), M22 (O-dealkylation; LTP763), and M28 (demethylation). Metabolite M28 was also formed by CYP2C8 (6.3%), CYP2B6 (2.9%), CYP2C9 (1.4%) and CYP3A5 (1.8%). CYP1A1 and CYP2C19 formed a single metabolite (M15; C-hydroxylation) with an abundance >30%. [³H]-remibrutinib at 1µmol/L incubated with HLM at 1 mg/mL was extensively metabolized (83%), where M24 (19%), M28 (14%), LTP763 (8%), M23 (7%), M29 (7%) and M30 (6%) were the most abundant metabolites. These metabolites were the predominant oxidative metabolites formed by liver S9 fraction as well. Liver cytosolic enzymes were not found to have a major impact on the metabolic clearance of remibrutinib. [³H]-remibrutinib at 10µmol/L incubated in human cryopreserved hepatocytes was metabolized (50%) to M31 (11%), M24 (8.8%), M15 (6.1%), M29 (4%) and LTP763 (3%). The M28 metabolite (the major metabolite in HLM) was no longer detectable in hepatocytes after 3 hours. <i>CYP3A4 is the predominant enzyme in the hepatic oxidative metabolism of remibrutinib with minor contribution from CYP1A1 and CYP2C19.</i>

Report/Objectives   Summary Findings and Key Conclusions

Table 38. Metabolites of [³H]-Remibrutinib as Detected in Recombinant CYP450 Preparations

Peak#	RT [min]	[M-H]-	Hepatocytes	HLM	3A4	1A1	2C19	3A5	2B6	2C8	2C9
P27	1.7		o								
P28	1.9		o								
P1	4.1			o							
P2	4.2			o							
M2 (LSX574)	4.6	344.15	o	o							
P4	4.8			o							
P5	5.5			o	o						
P10.5	6.2	538.2	o	o	o	+					
P7	6.4			o	o						
P8	6.7		o	o	o						
P9	6.9		o	o	o						
M15	7.4	522.2	+	+	o	++	++				
P29	7.7		o								
M23	8.4	526.2	o	+	+						
P30	8.6		o								
M24	9.0	540.2	+	++	++					o	
M22 (LTP763)	9.3	395.1	o	+	++						
P14	9.8			o	o						
P15	10.1		o	o	o						
P16	10.2			o	o						
P17	10.6			o							
M28	10.8	492.2		++	++			o	o	+	o
P31	10.9		o								
P36	11.2				o						
M31	11.5	492.2	++	+	+					o	
P20	11.8			o	o						
M30	12.1	437.1	o	+	+						
LOU064	12.6	506.2	++	++	++	++	++	++	++	++	++
P23	13.1		o	o	o						
P24	13.2			o							
P23.8 *	14.0	508.2	o	+	+						
M29	14.7	522.2	+	+	+				o	o	

Source: Report DMPK R1500124, Table 6-2

* Tentative metabolite assignment

o: between 0 and 3% of all +; between 3 to 10% of all ++; above 10% (in bold) of all

Abbreviations: CYP, cytochrome P450; DMPK, drug metabolism and pharmacokinetics; HLM, human liver microsomes; LOU064, remibrutinib, RT, retention time.

DMPK R1600559: Identifying the human enzymes responsible for the oxidative metabolism of remibrutinib in human liver microsomes and by recombinant enzymes.

Recombinant microsomes expressing CYP3A4 or CYP1A1 showed the highest metabolic activities of [³H]-remibrutinib at a concentration of 3µM. Metabolic activities were 29.43% (12.24% M28 metabolite) with CYP3A4, and 23.08% (21.92% M15 metabolite) with CYP1A1. The metabolic activity of CYP2C19 was 2.19%. Low metabolic activity was observed with other recombinant microsomes expressing other CYP and flavin-containing monooxygenase (FMO) enzymes. The metabolic activity of HLM with [³H]-remibrutinib 3µM was 11.06%.

After accounting for the relative abundance in human liver microsomes, CYP3A4/5 is the major enzyme involved in the hepatic oxidative metabolism of [³H]-remibrutinib.

Report/Objectives	Summary Findings and Key Conclusions
<i>In Vitro Drug-Drug Interaction Studies</i>	
DMPK R1500083: Inhibitory effects of remibrutinib on CYP activities in human liver microsomes and measurement of microsomal protein binding (fumic)	In pooled human liver microsomes, the IC_{50,u} (corrected for microsomal protein binding) for the reversible inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 was 70.6, >88.3, 35.5, 9.9, 10.9, 14, 68.5, >78.9, and 27.5/26.1 (midazolam/testosterone) μM, respectively. The K_{i,u} (corrected for microsomal protein binding) for inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 was 23.7, 5, 7.7, 7.7, and 14.1 μM, respectively.
	The fraction unbound to microsomal proteins after incubation with remibrutinib (1 and 20 μM) range between 1.004 to 0.743 with protein concentrations increasing from 0.0039 mg/mL to 1 mg/mL.
	<i>Remibrutinib was an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.</i>
DMPK R1400510; DMPK R1900718: Examination of time-dependent inhibition of CYP2C9, CYP1A2, CYP2D6, CYP3A4/5, CYP2B6, CYP2C8, and CYP2C19 in HLM	In human liver microsomes, time-dependent inhibition of CYP3A4/5 by remibrutinib was observed in the presence of NADPH (K_i=8.8 μM, K_{i,u}=6.9 μM, K_{inact}=0.0102 min⁻¹). No time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 by remibrutinib was observed at concentrations up to 100 μM.
	<i>Remibrutinib is a time-dependent inhibitor of CYP3A4/5.</i>
DMPK R1300944: Evaluating the induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 (activities and mRNA) by remibrutinib	In primary human hepatocytes, remibrutinib at 10, 20, 30 and 50 μM increased CYP2B6 mRNA expression by 2.2-, 3.2-, 4-, and 6.9-fold, respectively, and enzyme activity by 2.8-, 3.78-, 3.61-, and 5.53-fold, respectively. The EC₅₀ value for half-maximal induction was 25 μM for CYP2B6. Remibrutinib at 1, 5, 10, 20, 30 and 50 μM did not increase CYP2C9 mRNA expression by >2-fold, but increased the enzyme activity by 2.4-, 2.87-, 2.2-, 2.65-, 5.25-, and 3.43-fold, respectively.
	Remibrutinib at 5, 10, 20, 30 and 50 μM increased CYP3A4 mRNA expression by 3.4-, 9.7-, 27.7-, 45.6-, 104.6-fold, respectively, and enzyme activity by 1.06-, 1.42-, 1.78-, 2.14-, 2.05-fold, respectively. The EC₅₀ was 33 μM for CYP3A4.
	The mRNA expression and activity of CYP1A2 were not >2-fold across the studied remibrutinib concentration range (up to 50 μM).
	<i>Based on the in vitro data using cryopreserved human hepatocytes from a single donor, remibrutinib may induce CYP2B6, CYP2C9 and CYP3A. remibrutinib is not expected to induce CYP1A2.</i>
DMPK R1600703: Evaluating the induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 (activities and mRNA) by remibrutinib	The potential for remibrutinib at concentrations up to 10 μM to induce CYP enzymes was determined in primary human hepatocytes derived from three individual donors. Note that incubation of remibrutinib with hepatocytes for 24 hours showed a time-dependent decrease of remibrutinib concentrations, likely due to metabolism. Thus, induction effects may be underestimated.

Report/Objectives	Summary Findings and Key Conclusions
	CYP1A2: Remibrutinib ($\geq 2.5\mu\text{M}$) showed dose-dependent induction (>2-fold) of CYP1A2 gene expression in all three donors. The average EC_{50} and E_{max} for fold-induction were $4.55\mu\text{M}$ and 5.47, respectively. More than 2-fold increase in enzyme activity in Donor 1 was observed at remibrutinib $10\mu\text{M}$. Donor 2 showed no increase in enzyme activity. Dose-dependent induction was observed in Donor 3, with >2-fold induction observed at concentrations $\geq 0.63\mu\text{M}$ with maximum induction of 8.33-fold observed at remibrutinib $5\mu\text{M}$. CYP2B6: Remibrutinib ($\geq 5\mu\text{M}$) showed dose-dependent induction (>2-fold) of CYP2B6 gene expression in all three donors. The average EC_{50} and E_{max} for fold-induction were $5.47\mu\text{M}$ and 5.45, respectively. Donor 3 showed 2.17-fold (15.9% of the maximal response in the positive control) increase in enzyme activity at remibrutinib $10\mu\text{M}$. No induction of enzyme activity was observed for Donors 1 and 2. CYP2C9: Remibrutinib ($>10\mu\text{M}$) showed dose-dependent induction (>2-fold) of CYP2C9 gene expression in all three donors. The average EC_{50} and E_{max} for fold-induction were $5.1\mu\text{M}$ and 3.02, respectively. Donor 3 showed 3.08-fold (84% of the maximal response of positive control), 2.12-fold (45.2% of the maximal response of positive control), and 3.13-fold (86% of the maximal response of positive control) increase in enzyme activity at remibrutinib 2.5, 5 and $10\mu\text{M}$, respectively. No induction of activity was observed for Donors 1 and 2. CYP3A4: Remibrutinib ($>0.31\mu\text{M}$) showed dose-dependent induction (>2-fold) of CYP3A4 gene expression in all three donors. The average EC_{50} and E_{max} for fold-induction were $5.08\mu\text{M}$ and 28.08, respectively. Donor 3 showed 1.98-fold (21.9% of the maximal response in the positive control) increase in enzyme activity at remibrutinib $10\mu\text{M}$. No induction of enzyme activity was observed for Donors 1 and 2. <i>Remibrutinib at concentrations up to $10\mu\text{M}$ induced CYP1A2, CYP2B6, CYP2C9, and CYP3A4 gene expression. Induction of catalytic activity for CYP1A2, CYP2B6, CYP2C9 was only observed in one donor.</i>
DMPK R2301196: Evaluation of the inhibitory potential of remibrutinib on the human BCRP and MDR1	The inhibition potential of remibrutinib on BCRP and MDR1 (P-gp) was determined using vesicular transport assays with inside-out membrane vesicles prepared from HEK293 cells overexpressing BCRP or MDR1. Remibrutinib showed significant loss due to nonspecific binding with an average of 31.1% in transport buffer. Nominal concentrations were therefore corrected by a factor of 0.689 at all concentrations. Remibrutinib inhibited BCRP-mediated (E3S) accumulation by 100% at concentrations $\geq 17.2\mu\text{M}$. The calculated IC_{50} was $0.533\mu\text{M}$, the calculated K_i value was $0.467\mu\text{M}$.

Report/Objectives	Summary Findings and Key Conclusions
	Remibrutinib inhibited MDR1-mediated (N-methyl-quinidine) accumulation by about 91% at the highest tested concentration of 34.5µM. The calculated IC₅₀ was 0.513µM, the calculated K_i value was 0.382µM. <i>Remibrutinib has the potential to inhibit BCRP and MDR1 efflux transporters</i>
DMPK R1500199: Evaluation of the inhibitory potential of remibrutinib on the human BCRP and P-gp and the inhibition of BCRP by LTG751	The potential for remibrutinib to inhibit BCRP and P-gp, and potential for LTG751 to inhibit BCRP were evaluated in recombinant MDCKII and LLC-PK1 cell overexpressing BCRP and P-gp, respectively. Note that nominal concentrations were corrected for nonspecific binding to glass and plastic (up to 37.4%). Remibrutinib inhibited P-gp with IC₅₀=29.4µM, K_i =29.4µM, and a maximal inhibition of 101.7% (relative to positive control) and inhibited BCRP with an IC₅₀=4.3µM and a maximal inhibition of 118.3% (relative to positive control). LTG751, an analog of remibrutinib in which the reactive acrylamide moiety has been inactivated via saturation of the double bond, inhibited BCRP with an IC₅₀=3µM and a maximal inhibition of 106.6%. <i>Remibrutinib has the potential to inhibit BCRP and P-gp efflux transporters. Based on inhibition of BCRP by LTG751, BCRP inhibition by remibrutinib is not likely related to the irreversible-binding potential of remibrutinib</i>
DMPK R1500200: Inhibitory effects of remibrutinib and LTG751 on OATP1B1/1B3 transporters	The potential for remibrutinib and LTG751 to inhibit OATP1B1/3 was determined in HEK293 cells overexpressing OATP1B1/3. The maximum inhibition of OATP1B1 and OATP1B3 relative to positive control at the highest remibrutinib concentration (66.6µM, measured) was 99.9% and 100.7%, respectively. The maximum inhibition relative to positive control of OATP1B1 and OATP1B3 at the highest LTG751 concentration (100µM, nominal) was 99.4% and 115.4%, respectively. The IC₅₀ values of OATP1B1 and OATP1B3 inhibition were 2.9µM and 9µM (for remibrutinib) and 5.2 and 8.4µM (for LTG751), respectively. The K_i values of OATP1B1 and OATP1B3 inhibition were 2.8µM and 8.8µM (for remibrutinib) and 5.1 and 8.3µM (for LTG751), respectively. <i>Remibrutinib and LTG751 have the potential to inhibit hepatic OATP1B1 and OATP1B3 uptake transporters. Based on LTG751 inhibition of OATP1B1 and OATP1B3, inhibition by remibrutinib is not likely related to the irreversible-binding potential of remibrutinib.</i>
DMPK R1500824: Evaluating the inhibitory effects of remibrutinib on OAT1 and OAT3 transporters	The potential for remibrutinib to inhibit OAT1 and OAT3 was determined in HEK293 cells overexpressing OAT1 and OAT3. The IC₅₀ and K_i values of OAT1 inhibition were 39.4µM and 38.6µM, respectively. The IC₅₀ and K_i values of OAT3 inhibition were 14.1µM and 10.6µM, respectively. The maximum inhibition of OAT1 and OAT3 relative to positive control at the highest remibrutinib concentration (66.6µM, measured) was 71.2% and 85.3%, respectively. <i>Remibrutinib has the potential to inhibit renal OAT1 and OAT3 uptake transporters.</i>

Report/Objectives	Summary Findings and Key Conclusions
DMPK R1700782: Evaluating the inhibitory potential of remibrutinib on BSEP, MRP2, MATE1, MATE2-K, OCT1 and OCT2	The potential for remibrutinib to inhibit BSEP and MRP2 were determined in vesicular transport inhibition assays with inside-out membrane vesicles prepared from HEK293 cells overexpressing BSEP or MRP2. The potential for remibrutinib to inhibit MATE1, MATE2-K, OCT1, and OCT2 were determined in uptake transporter inhibition assays using HEK293 cells stably expressing the respective uptake transporter. Relative to control, the maximum inhibition at the highest remibrutinib concentrations was 97%, 29%, 88%, 56%, 97%, and 51% for BSEP, MRP2, MATE1, MATE2-K, OCT1, and OCT2, respectively. The highest nominal remibrutinib concentrations tested in inhibition assays for BSEP, MRP2, MATE1, MATE2-K, OCT1, and OCT2 were 50, 100, 75, 75, 75, and 75µM, respectively. The IC₅₀ for transport inhibition was 8.69, 14.4, 68.8, 7.21, and 68.92µM for BSEP, MATE1, MATE2-K, OCT1, and OCT2, respectively. The K_i for transport inhibition was 7.8, 13.6, 68.3, 7.19, and 68.7µM for BSEP, MATE1, MATE2-K, OCT, and OCT2, respectively. The IC₅₀ and K_i for MRP2 inhibition were not determined. <i>Remibrutinib is an inhibitor of BSEP, OCT1, OCT2, MATE1 and MATE2-K</i>
DMPK R2000485: Evaluating the inhibitory potential of remibrutinib on MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 transporters	The potential for remibrutinib to inhibit MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 were determined in uptake transporter inhibition assays using HEK293 (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2) or MDCKII (MATE1, MATE2-K) cells stably expressing the respective uptake transporter. Nonspecific binding of remibrutinib was 67.4% in HBSS pH7.4 media (correction factor 0.326 was used for nominal concentrations used for OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 assays) and 70% in KH pH 8 media (correction factor of 0.296 was used for nominal concentrations used for MATE1 and MATE2-K assays). Relative to control, the inhibition at the highest remibrutinib measured concentrations (7.4µM for MATE1 and MATE2-K and 8.15µM for the other tested transporters) was 70%, 32%, 41%, 90%, 83%, 44%, 88%, and 44% for MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2, respectively. The IC₅₀ values for transporter inhibition were 1.71, 1.12, 2.62, and 1.1µM, and K_i was 1.7, 1.09, 2.36, 1.09µM for MATE1, OAT3, OATP1B1 and OCT1, respectively. The IC₅₀ for OAT1, OATP1B3 and OCT2 was estimated to be 9.97, 7.81, and 9.41µM and K_i was estimated to be 9.87, 7.55, and 9.41µM. Values were estimated because the maximum inhibition at the highest remibrutinib tested concentration was <50%. The IC₅₀ and K_i for MATE2-K inhibition were not determined. <i>Remibrutinib has the potential to inhibit MATE1, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2.</i>

Report/Objectives	Summary Findings and Key Conclusions
DMPK R2200876: Investigating the inhibition potential of remibrutinib, on NTCP transporter.	The potential for remibrutinib to inhibit NTCP was determined in uptake inhibition assays using HEK293 cells expressing NTCP. The remibrutinib nominal concentrations were corrected by specific factors based on nonspecific binding assays. Remibrutinib at concentrations up to 58.7µM inhibited NTCP by 33%. The IC ₅₀ and K _i are >58.7µM. <i>Remibrutinib inhibited NTCP by less than 50% at the highest test concentrations.</i>

Source: Reviewer-generated table based on in vitro studies

Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CYP, cytochrome P450 enzymes; DMPK, drug metabolism and pharmacokinetics; E3S, estrone-3-sulfate; EC₅₀, half-maximal effective concentration; E_{max}, maximal induction relative to maximal induction by the positive control; f_m, fraction metabolized; f_u, fraction of unbound test substance in microsomal incubations; GG, human γ-globulins; HEK, human embryonic kidney cells; HLM, human liver microsomes; IC₅₀, inhibitor concentration producing 50% inhibition of enzyme activity; IC_{50,u}, unbound concentration of inhibitor producing 50% inhibition of probe substrate metabolism; K_i, inhibition constant (reversible inhibition); K_{i,u}, unbound inhibition constant (reversible inhibition); K_i, inhibition constant (time-dependent inhibition); K_{i,u}, unbound inhibition constant (time-dependent inhibition); K_{inact}, maximal rate of enzyme inactivation (time-dependent inhibition); K_m, Michaelis-Menten constant (substrate concentration producing half maximal velocity); LLC-PK1, porcine kidney cell line; LTG751, an analog of remibrutinib where the reactive acrylamide has been inactivated (double bond saturated); MATE, multidrug and toxin extrusion protein; MDCKII, Madin-Darby Canine Kidney type II; mRNA, messenger ribonucleic acid; MRP2, multidrug resistance-associated protein 2; MDR1, multidrug-resistant protein 1; MRP3,4, multidrug resistance associated protein 3,4; NADPH, nicotinamide adenine dinucleotide phosphate; NTCP, sodium taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P_{app}, apparent permeability; P-gp, P-glycoprotein

14.2. In Vivo Studies

Clinical studies supporting clinical pharmacology information of remibrutinib are summarized in [Table 39](#).

In some studies, remibrutinib is also referred to by the code name LOU064.

Table 39. Summary of Clinical Pharmacology Program

Study	Objectives	Design	Drug Product and Formulation	Dose Regimen
<i>Phase 1</i> X2101	Safety, tolerability, pharmacokinetics, and pharmacodynamics of Parts 1 (SAD), 2 (MAD, QD regimen), 3 (food effect), 4 (MAD, BID regimen), 5 (formulation effect), 6 (MAD, BID regimen in subjects with AD)	<u>Part 1, 2, and 4</u> were randomized, double-blind, placebo-controlled. <u>Part 3</u> was a single-dose open-label crossover food-effect study. <u>Part 5</u> was a double-blind, single-dose, relative bioavailability study. <u>Part 6</u> was a double-blind, randomized, placebo-controlled	Remibrutinib 0.5-, 5-, and 50-mg hard gelatin capsule (HGC)	<u>Part 1</u> : 0.5, 1.5, 5, 15, 30, 60, 100, 200, 400, and 600 mg <u>Part 2</u> : 10, 25, 50, 100, 400, and 600 mg QD for 12 days <u>Part 3</u> : 60 mg single dose <u>Part 4</u> : 100 mg and 200 mg BID for 12 days <u>Part 5</u> : 50 mg single dose (b) (4) or (b) (4) or (b) (4) formulation)

Study	Objectives	Design	Drug Product and Formulation	Dose Regimen
		4-week multiple-dose study		<u>Part 6:</u> 100 mg BID for 4 weeks
X1101	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single- and multiple-ascending doses in Japanese healthy subjects	Randomized, subject-blinded, placebo-controlled study in Japanese healthy subjects	Remibrutinib 5- and 50-mg HGC	SAD: 5, 30, 100, 200, and 400 mg MAD: 100 mg BID for 5 days
X2104	Human mass balance ADME study to determine the disposition of remibrutinib	Open-label in adult healthy subjects	<u>Oral nonradiolabeled remibrutinib HGC:</u> 50 mg <u>Oral Solution:</u> 100 mg free base per 20 mL; 0.074 MBq (2 µCi) <u>IV bolus:</u> 100 µg free base per 2 mL; 0.074 MBq (2 µCi)	<u>Oral arm:</u> nonradiolabeled remibrutinib HGC 100 mg BID from Day 1 to Day 5. On the morning of Day 2, dose was replaced with 100 mg [¹⁴C]-remibrutinib as an oral solution. <u>IV Arm A:</u> nonradiolabeled remibrutinib HGC 100 mg BID from Day 1 to Day 5 + single IV dose of 100 µg [¹⁴C]-remibrutinib 1 hour after the oral morning dose on Day 2. <u>IV Arm B:</u> nonradiolabeled remibrutinib HGC 100 mg BID from Day 1 to Day 9 + a single IV dose of 100 µg [¹⁴C]-remibrutinib 1 hour after the oral morning dose on Day 6.
X2105	Evaluating the relative BA of film-coated tablet (FCT) with two different particle sizes and HGC	Randomized, open-label, three-period study in adult healthy subjects	• Remibrutinib 50-mg HGC • Remibrutinib 50-mg FCT (VS) • Remibrutinib 50-mg FCT (VA)	HGC: 100-mg single dose FCT (VS): 100-mg single dose FCT (VA): 100-mg single dose

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Study	Objectives	Design	Drug Product and Formulation	Dose Regimen
A02104	Food effect after multiple doses of remibrutinib	Randomized, open-label, two-cohort, two-period, two-sequence, crossover study in Chinese adult healthy male subjects	Remibrutinib 25- and 100-mg FCT	Remibrutinib 25 mg BID and 100 mg BID
A2101	Hepatic impairment study	Open-label in subjects with mild, moderate, and severe hepatic impairment	Remibrutinib 25-mg FCT	Remibrutinib 25 mg BID on Days 1 and 2, and a morning oral dose of remibrutinib 25 mg on Day 3
X2103	Absolute bioavailability study and DDI study to evaluate the impact of ritonavir and grapefruit juice (CYP3A4 inhibitors) on the pharmacokinetics of remibrutinib	Open-label, single sequence, three-period, crossover study in healthy adult subjects	• Remibrutinib 50-mg and 20-mg HGC • SIL-remibrutinib vials containing 100 µg powder for solution for injection • Ritonavir 100-mg capsule • Grapefruit juice (240 mL) contained only real sugar	<u>Period 1:</u> remibrutinib 50 mg on Days 1 to 3; and SIL-remibrutinib 100 µg IV QD on Day 3 <u>Period 2:</u> remibrutinib 50 mg and 240 mL grapefruit juice on Day 4; remibrutinib 20 mg QD and 240 mL grapefruit juice on Day 5 <u>Period 3:</u> remibrutinib 50 mg and ritonavir 100 mg on Day 6; remibrutinib 20 mg, SIL-remibrutinib 100 µg IV QD, and ritonavir 100 mg BID on Day 7; and ritonavir 100 mg BID on Day 8
A02103	DDI study to evaluate the impact of carbamazepine (CYP3A4 inducer) on the pharmacokinetics of remibrutinib and the impact of remibrutinib on the exposure to digoxin (P-gp substrate),	Open-label, single sequence, two-period, crossover study in healthy adult subjects	• Remibrutinib 50-mg HGC • Carbamazepine 100, 200, and 300 mg extended-release capsule • Digoxin 0.25-mg tablet • Rosuvastatin 10-mg tablet	<u>Part 1:</u> remibrutinib 100 mg BID on Days 1, 2, 23, and 24; and single morning dose on Days 3 and 25. Carbamazepine 100 mg BID on Days 4 to 6; 200 mg BID on Days 7 to 9;

Study	Objectives	Design	Drug Product and Formulation	Dose Regimen
	rosuvastatin (BCRP, OATP1B1/3 substrate), and coproporphyrin I (OATP1B substrate)			300 mg BID Days 10 to 24 and single morning dose on Day 25 <u>Part 2:</u> Single dose of digoxin 0.25 mg and rosuvastatin 10 on Days 1 and 14. Remibrutinib 100 mg BID on Days 11 to 24 (on Day 24 morning dose only)
X2102	DDI study to evaluate the impact of remibrutinib on a combined oral contraceptive (COC) (containing ethinylestradiol [EE] and levonorgestrel [LVG]), midazolam (CYP3A substrate), caffeine (CYP1A substrate), and tolbutamide (CYP2C9 substrate).	Open-label, three-period, single sequence, crossover study in healthy female subjects	• Probe cocktail containing 2-mg midazolam, 200-mg caffeine, and 500-mg tolbutamide • COC (EE 30 µg and LVG 150 µg) • Remibrutinib 100-mg FCT	<u>Period 1 (Day 1):</u> single dose of probe cocktail containing 2-mg midazolam, 200-mg caffeine, and 500-mg tolbutamide. <u>Period 2 (Day 9):</u> single oral dose of the COC (EE 30 µg and LVG 150 µg) <u>Period 3 (Day 16 to 33):</u> remibrutinib 100 mg BID for 18 days. On Day 18 and Day 26, subjects received a single dose of probe cocktail (2-mg midazolam, 200-mg caffeine and 500-mg tolbutamide) at about 30 minutes postremibrutinib morning dose. On Day 30, subjects received a single oral dose of the COC (EE 30 µg and LVG 150 µg) at about 30 minutes postremibrutinib morning dose.

Study	Objectives	Design	Drug Product and Formulation	Dose Regimen
A2201	Dose-finding study	Randomized, double-blind, placebo-controlled study in adult chronic spontaneous urticaria subjects inadequately controlled by H1-antihistamines	Remibrutinib 10-, 25-, and 50-mg HGC	Remibrutinib 10 mg QD, 35 mg QD, 100 mg QD, 10 mg BID, 25 mg BID, 100 mg BID or placebo for 12 weeks.
A2301/A2302	Phase 3 efficacy and safety studies	Randomized, double-blind, placebo-controlled, efficacy, safety, and tolerability study for 52 weeks in adult chronic spontaneous urticaria subjects inadequately controlled by H1-antihistamines.	Remibrutinib 25-mg FCT	Remibrutinib 25 mg BID for 52 weeks.

Source: Reviewer-generated table based on the complete reports of the listed studies

Abbreviations: AD, atopic dermatitis; ADME, absorption, distribution, metabolism, and excretion; BA, bioavailability; BCRP, breast cancer resistance protein; BID, twice daily; CYP3A4, cytochrome P450 3A4; DDI, drug-drug interaction; IV, intravenous; MAD, multiple-ascending dose; OATP1B, organic anion transporting polypeptide 1B; P-gp, P-glycoprotein; QD, once daily; SAD, single-ascending dose; SIL, stable-isotope-labeled; VA, variant alternative; VS, variant selected

14.2.1. Single-Dose, Multiple-Dose, and Food-Effect Studies in Healthy Subjects

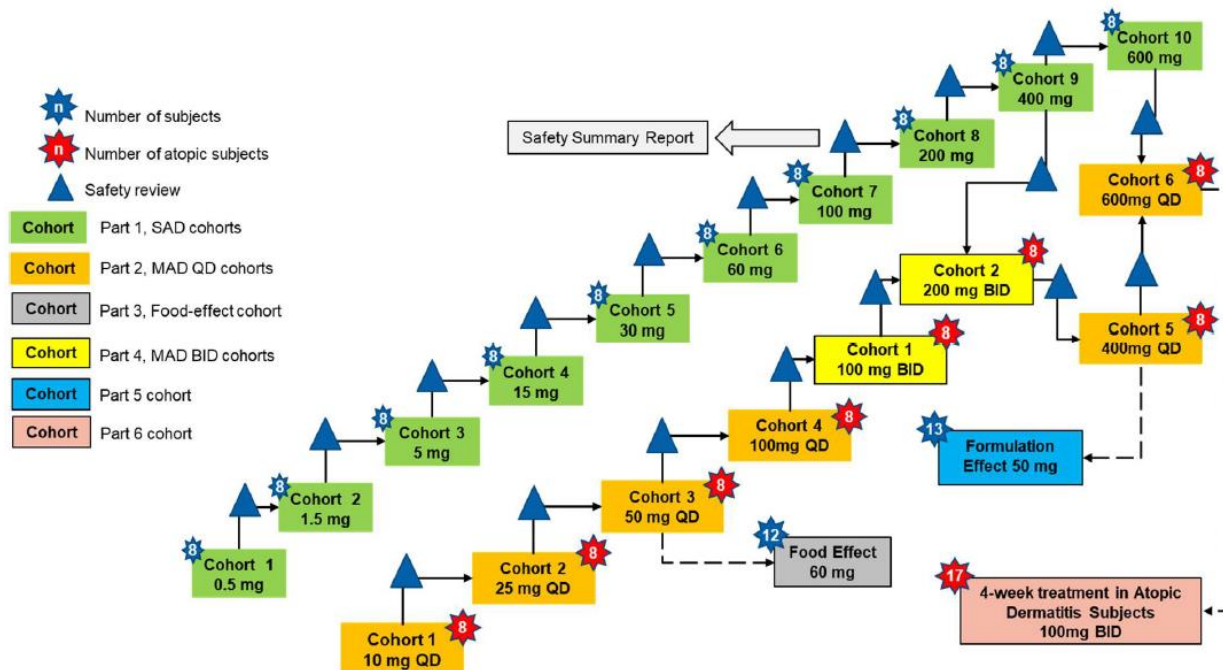
14.2.1.1. Study X2101

Study X2101 was a six-part, first-in-human study of remibrutinib using the hard gelatin capsule (HGC) drug product. The overall design of this study is illustrated in [Figure 16](#).

- Part 1 was randomized (6:2, remibrutinib:placebo), double-blind, placebo-controlled to evaluate the pharmacokinetics and pharmacodynamics of single doses of remibrutinib in healthy subjects. Doses of 0.5, 1.5, 5, 15, 30, 60, 100, 200, 400, and 600 mg were evaluated. Blood samples for PK assessment were collected at predose and up to 168 hours postdose.
- Parts 2 and 4 were randomized (6:2, remibrutinib:placebo), double-blind, placebo-controlled to evaluate the pharmacokinetics and pharmacodynamics of multiple doses of remibrutinib in healthy subjects with asymptomatic atopic diathesis. Part 2 was multiple-ascending dose (MAD) given as 13 doses over 12 days and Part 4 was MAD given as 25 doses over 12 days. Dosages in Part 2 were 10, 25, 50, 100, 400, and 600 mg QD. Dosages in Part 4 were 100 and 200 mg BID. Blood PK sampling timepoints for Parts 2 and 4 were at predose (Day 1, 2, 3, 5, 7, and 12) and up to 24 hours after first dose and up to 168 hours after the last dose on Day 12.

- Part 3 was a single-dose, open-label, crossover, food-effect study with 18 days washout period between two single 60-mg doses of remibrutinib in healthy subjects. On Day 1, following an overnight fast of at least 10 hours, subjects were given a high-calorie, high-fat meal (i.e., breakfast consisting of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz [100 g] of hash brown potatoes, 8 fl. oz [about 240 mL] of whole milk). Subjects were instructed to consume the breakfast within 30 minutes and to administer remibrutinib within 5 minutes after completion of the meal. Blood samples for PK assessment were collected at predose and up to 96 hours postdose.
- Part 5 was a double-blind, single-dose, two-sequence, relative bioavailability study to compare the pharmacokinetics and pharmacodynamics of remibrutinib after administration of a single oral dose of 50 mg of the capsule drug product containing either (b) (4) or (b) (4) drug substance in healthy subjects. Blood samples for PK assessment were collected at predose and up to 48 hours postdose. The relative bioavailability of the (b) (4) drug substance compared to the (b) (4) drug substance is not relevant for the current review. Therefore, Part 5 will not be discussed in this review.
- Part 6 was a double-blind, randomized, placebo-controlled, 4-week multiple-dose study of remibrutinib 100 mg BID in subjects with atopic dermatitis. As atopic dermatitis is not a proposed indication for remibrutinib, Part 6 will not be discussed in this review.

Figure 16. Study Design, Part 1 to 6, Study X2101



Source: Interim and Full Clinical Study X2101 Reports, Figure 9-1

The Test drug products used in Study X2101 include the following batches: remibrutinib 50 mg (Batch # 1010008635 and 1010015369 for Part 1 to 5; Batch # 2033160 for Part 6), remibrutinib 5 mg (Batch # 1010008926) and remibrutinib 0.5 mg (Batch # 1010008923).

Abbreviations: BID, twice daily; MAD, multiple-ascending dose; QD, once daily; SAD, single-ascending dose

Pharmacokinetic Results

Part 1: Single-Ascending Dose

Following single-dose administration, remibrutinib exhibited rapid absorption with median T_{max} values ranging from 0.5 to 1.25 hours across all dose levels. At lower doses (<100 mg), the blood concentrations declined below the lower limit of quantification (LLOQ) of 1 ng/mL before entering the terminal phase (Figure 17). At the lowest doses of 0.5, 1.5, and 5 mg, $t_{1/2}$ could not be estimated. The mean $t_{1/2}$ ranged from 0.5 to 3.2 hours across the dose levels of 15 to 200 mg. At higher doses, a longer half-life was observed. Specifically, at 600 mg of remibrutinib, the terminal $t_{1/2}$ extended to 14.1 hours (Table 40). Both the C_{max} and the AUC increased nonproportionally with escalating doses throughout the range from 0.5 mg to 600 mg. For instance, a 20-fold increase in dose from 30 mg to 600 mg resulted in only a 7.6-fold increase in C_{max} and a 15-fold increase in AUC_{last} . Full dose-linearity is not anticipated due to time-dependent clearance, attributed to formation of a covalent bond between remibrutinib and BTK. Based on a linear regression analysis of log-transformed parameters, over the dose range of 30 to 200-mg single dose, the increase in C_{max} was less than dose-proportional (slope 90% CI: 0.68 [0.52, 0.85]), the increase in AUC_{last} and AUC_{0-inf} was approximately dose-proportional and less than dose-proportional, respectively (slope 90% CI: 0.94 [0.78, 1.11] for AUC_{last} and 0.90: [0.75, 1.05] for AUC_{0-inf} ; data derived from Table 11-2, Interim clinical study report for Study X2101). The apparent volume of distribution increases with higher doses of remibrutinib, which may be due to saturable covalent binding of remibrutinib to BTK.

Table 40. Summary of Remibrutinib PK Parameters Values in Part 1-SAD, Study X2101

PK parameter (unit)	0.5 mg N=6	1.5 mg N=6	5 mg N=6	15 mg N=6	30 mg N=6
C_{max} (ng/mL)	0 ± 0 (NA) 0 (0-0) [6]	1.26 ± 1.12 (89.0) 1.33 (0-2.80) [6]	5.86 ± 3.37 (57.5) 5.99 (1.19-9.92) [6]	24.8 ± 14.6 (59.1) 26.6 (6.39-39.6) [6]	64.8 ± 34.3 (52.9) 55.1 (19.9-112) [6]
T_{max} (h)		0.500 (0.500-0.500) [4]	0.525 (0.500-1.02) [6]	0.500 (0.483-1.02) [6]	0.500 (0.483-3.00) [6]
AUC_{last} (h*ng/mL)	0 ± 0 (NA) 0 (0-0) [6]	0.315 ± 0.280 (89.0) 0.333 (0-0.700) [6]	2.77 ± 1.89 (68.5) 2.28 (0.882-5.87) [6]	25.1 ± 25.7 (102.0) 17.5 (4.01-74.7) [6]	75.1 ± 45.9 (61.1) 71.4 (31.0-153) [6]
AUC_{inf} (h*ng/mL)				41.3 ± 30.8 (74.7) 29.3 (18.2-76.3) [3]	77.5 ± 45.9 (59.3) 75.0 (32.1-154) [6]
$T_{1/2}$ (h)				0.557 (0.367-0.915) [3]	0.908 (0.415-1.40) [6]
V_z/F (L)				397 ± 229 (57.5) 271 (260-661) [3]	617 ± 276 (44.8) 606 (234-1070) [6]
CL/F (L/h)				511 ± 313 (61.3) 513 (197-823) [3]	523 ± 303 (57.9) 423 (195-934) [6]
MRT (h)		0.500 ± 0 (0.0) 0.500 (0.500-0.500) [4]	0.618 ± 0.0935 (15.1) 0.636 (0.500-0.738) [6]	0.981 ± 0.460 (46.9) 0.827 (0.598-1.88) [6]	1.46 ± 0.825 (56.6) 1.27 (0.691-3.07) [6]
PK parameter (unit)	60 mg N=6	100 mg N=6	200 mg N=6	400 mg N=6	600 mg N=6
C_{max} (ng/mL)	138 ± 65.3 (47.2) 150 (22.8-215) [6]	141 ± 85.7 (60.6) 133 (44.7-298) [6]	245 ± 147 (60.1) 201 (97.1-449) [6]	432 ± 334 (77.3) 331 (193-1070) [6]	511 ± 225 (44.2) 500 (240-763) [6]
T_{max} (h)	1.01 (1.00-1.50) [6]	1.03 (1.00-1.50) [6]	1.25 (0.983-3.00) [6]	1.24 (0.950-2.00) [6]	1.02 (1.00-1.52) [6]
AUC_{last} (h*ng/mL)	206 ± 118 (57.1) 229 (26.0-355) [6]	269 ± 124 (46.1) 254 (115-491) [6]	624 ± 302 (48.4) 471 (401-1100) [6]	1060 ± 937 (88.4) 739 (438-2910) [6]	1160 ± 356 (30.8) 1250 (724-1610) [6]
AUC_{inf} (h*ng/mL)	245 ± 87.6 (35.8) 245 (120-358) [5]	333 ± 143 (42.8) 285 (221-494) [3]	693 ± 330 (47.6) 544 (407-1100) [5]	1080 ± 935 (86.4) 769 (443-2930) [6]	1180 ± 403 (34.3) 1250 (754-1700) [5]
$T_{1/2}$ (h)	1.03 (0.891-1.28) [5]	0.905 (0.722-1.33) [3]	3.22 (1.34-28.4) [5]	11.4 (2.47-17.1) [6]	14.1 (12.3-34.4) [5]
V_z/F (L)	430 ± 183 (42.6) 356 (303-743) [5]	469 ± 204 (43.5) 471 (264-672) [3]	3710 ± 3620 (97.6) 2280 (433-8260) [5]	8260 ± 6300 (76.2) 6490 (2070-18500) [6]	14800 ± 6310 (42.7) 14100 (8760-24100) [5]
CL/F (L/h)	280 ± 130 (46.2) 245 (167-501) [5]	335 ± 126 (37.5) 351 (203-452) [3]	343 ± 147 (42.7) 368 (181-492) [5]	543 ± 279 (51.3) 544 (136-902) [6]	564 ± 200 (35.5) 479 (353-796) [5]
MRT (h)	1.76 ± 0.295 (16.8) 1.72 (1.47-2.30) [6]	2.84 ± 0.974 (34.3) 2.87 (1.79-3.91) [6]	3.62 ± 1.42 (39.2) 3.61 (1.80-5.84) [6]	3.76 ± 0.828 (22.0) 4.04 (2.17-4.40) [6]	5.60 ± 1.39 (23.9) 6.14 (3.89-7.09) [6]

Source: Interim Clinical Study X2101 Reports, Table 11-1

Statistics are presented as Mean ± SD (CV%) and Median (Min-Max) [n]

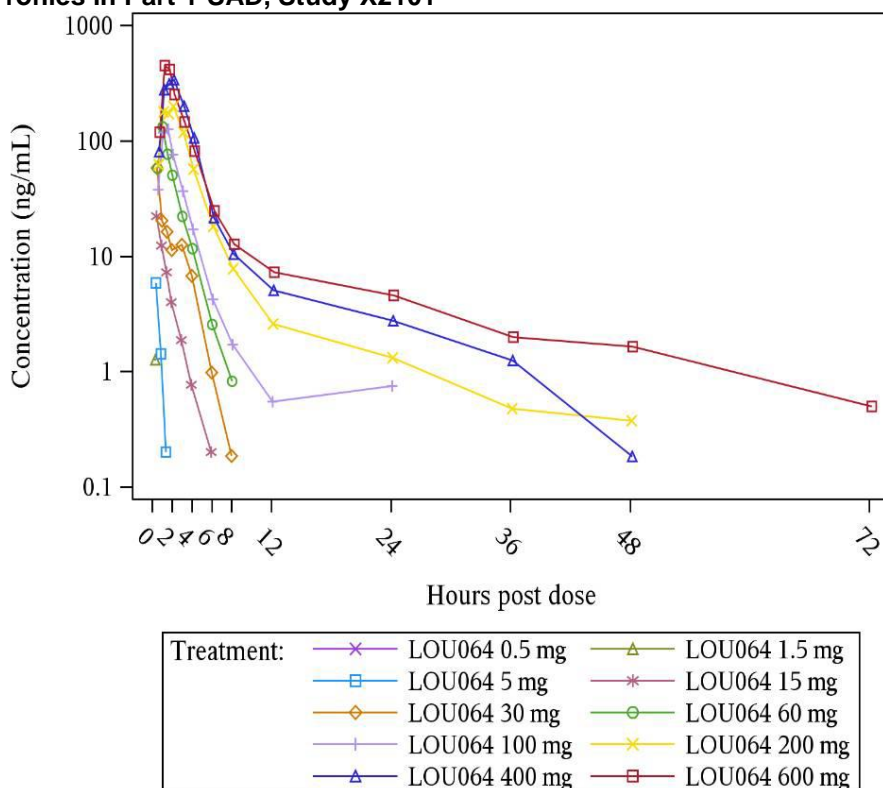
CV% = Coefficient of variation (%) = SD/Mean*100

For T_{max} and $t_{1/2}$, only Median (Min-Max) [n] are presented.

Concentrations below the LLOQ (1 ng/mL) were reported as "zero." The linear trapezoidal rule was used for AUC calculation.

Abbreviations: AUC_{inf} , area under the concentration-time curve from time zero to infinity; AUC_{last} , area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F , apparent clearance; C_{max} , maximum plasma concentration; CV, coefficient of variation; h, hour; max, maximum; min, minimum; MRT, mean residence time; N, number of subjects; PK, pharmacokinetic; SAD, single-ascending dose; SD, standard deviation; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; V_z/F , apparent volume of distribution during terminal phase after oral administration

Figure 17. Semilogarithmic Plots of the Arithmetic Mean Remibrutinib Blood Concentration-Time Profiles in Part 1-SAD, Study X2101



Source: Interim Clinical Study X2101 Reports, Figure 11.1
Remibrutinib is referred to as LOU064.
Abbreviation: SAD, single-ascending dose

Part 2: MAD

The summary statistics of the remibrutinib PK parameter values for Part 2 are presented in [Table 41](#). Analogous to Part 1, the terminal elimination phase following the final dose was discernible only at higher doses (i.e., exceeding 100 mg) ([Figure 18](#)). Accumulation was observed with an increase observed in both C_{max} and AUC from Day 1 to Day 12. This may be attributed to the covalent binding of remibrutinib to BTK. However, the contribution of target-mediated clearance to the overall clearance of remibrutinib is more pronounced at lower doses. At doses of 400 mg and 600 mg, accumulation becomes negligible. For instance, the exposure difference, as measured by AUC_{0-24h} , was 4.86-fold between Day 1 ($AUC_{0-24h}=4.94$ ng*h/mL) and Day 12 ($AUC_{0-24h}=24$ ng*h/mL) at a dosage of 10 mg QD. The accumulation ratio diminishes to 1.14-fold at 600 mg (Day 1 AUC_{0-24h} of 1080 ng*h/mL and Day 12 AUC_{0-24h} of 1230 ng*h/mL), likely due to saturation of target binding. Consequently, remibrutinib exhibits both time and dose-dependent clearance.

Similar to Part 1, C_{max} and AUC increased in a nonproportional manner with escalating doses across the entire range from 10 mg to 600 mg. Based on linear regression analysis with log-transformed parameters, over the dose range of 10 to 100 mg, the increase in C_{max} , AUC_{last} , and AUC_{0-24h} was less than dose-proportional with slope (90% CI) values of 0.64 (0.55, 0.74), 0.81 (0.69, 0.93), and 0.80 (0.68, 0.91), respectively.

Based on predose blood concentrations of remibrutinib measured on Day 2, 3, 5, 7, 9, and 12, steady-state concentration of remibrutinib was achieved by Day 2.

Table 41. Summary of Remibrutinib PK Parameters Values in Part 2-MAD QD Regimen, Study X2101

Day 1						
PK parameter (unit)	10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
C_{max} (ng/mL)	8.40 ± 2.02 (24.1) 8.03 (6.36-11.4) [6]	40.9 ± 21.6 (52.9) 37.3 (14.1-80.4) [6]	76.5 ± 22.0 (28.8) 70.1 (47.3-107) [6]	187 ± 85.0 (45.4) 189 (75.6-285) [6]	518 ± 89.1 (17.2) 513 (383-622) [6]	550 ± 87.6 (15.9) 545 (461-691) [6]
T_{max} (h)	0.517 (0.500-1.00) [6]	0.875 (0.283-1.50) [6]	0.500 (0.483-2.00) [6]	0.742 (0.500-1.95) [6]	0.750 (0.500-1.50) [6]	0.750 (0.500-3.00) [6]
AUC_{last} (h*ng/mL)	4.17 ± 1.38 (33.0) 4.40 (1.79-5.62) [6]	43.9 ± 24.6 (56.2) 45.5 (15.3-78.5) [6]	113 ± 34.2 (30.3) 103 (81.9-154) [6]	311 ± 89.1 (28.6) 333 (168-416) [6]	973 ± 379 (39.0) 826 (694-1720) [6]	1080 ± 377 (35.1) 931 (699-1700) [6]
AUC_{0-24} (h*ng/mL)	4.94 ± 1.35 (27.2) 4.94 (3.99-5.89) [2]	44.9 ± 25.2 (56.0) 46.6 (15.6-79.7) [6]	116 ± 32.9 (28.4) 107 (84.0-155) [6]	315 ± 91.5 (29.0) 338 (168-419) [6]	977 ± 378 (38.7) 826 (702-1720) [6]	1080 ± 377 (35.0) 932 (700-1700) [6]
MRT (h)	0.761 ± 0.151 (19.8) 0.768 (0.548-0.958) [6]	1.18 ± 0.490 (41.6) 1.17 (0.480-1.87) [6]	2.53 ± 1.17 (46.4) 2.44 (1.17-4.65) [6]	2.79 ± 1.28 (45.7) 2.16 (1.65-4.62) [6]	3.02 ± 1.11 (36.8) 2.94 (1.64-4.98) [6]	3.14 ± 0.580 (18.5) 3.22 (2.31-3.98) [6]
Amount recovered (mg)	0.0110 ± 0.0105 (95.8) 0.00738 (0-0.0289) [6]	0.0539 ± 0.0412 (76.4) 0.0393 (0.0177-0.132) [6]	0.122 ± 0.0270 (22.2) 0.112 (0.0945-0.165) [5]	0.335 ± 0.161 (48.0) 0.310 (0.161-0.593) [6]	0.903 ± 0.486 (53.8) 0.734 (0.335-1.51) [6]	1.27 ± 0.881 (69.3) 1.08 (0.277-2.73) [6]
Percent recovered (%)	0.110 ± 0.105 (95.8) 0.0738 (0-0.289) [6]	0.216 ± 0.165 (76.4) 0.157 (0.0709-0.528) [6]	0.244 ± 0.0540 (22.2) 0.224 (0.189-0.329) [5]	0.335 ± 0.161 (48.0) 0.310 (0.161-0.593) [6]	0.226 ± 0.121 (53.8) 0.184 (0.0837-0.378) [6]	0.212 ± 0.147 (69.3) 0.179 (0.0461-0.456) [6]

Day 12						
PK parameter (unit)	10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
C_{max} (ng/mL)	18.2 ± 5.90 (32.4) 17.2 (11.8-26.4) [6]	85.9 ± 31.5 (36.6) 76.4 (43.9-126) [6]	102 ± 22.0 (21.6) 100 (73.3-131) [6]	233 ± 84.1 (36.1) 205 (167-396) [6]	551 ± 263 (47.7) 476 (260-928) [6]	563 ± 229 (40.6) 475 (377-985) [6]
T_{max} (h)	0.625 (0.500-1.00) [6]	0.750 (0.500-1.00) [6]	1.00 (0.533-1.50) [6]	0.867 (0.733-1.50) [6]	0.758 (0.700-1.50) [6]	0.883 (0.500-3.00) [6]
AUC_{last} (h*ng/mL)	22.9 ± 3.50 (15.3) 22.4 (18.3-28.2) [6]	114 ± 59.7 (52.3) 98.2 (30.1-190) [6]	207 ± 80.4 (38.9) 179 (126-323) [6]	488 ± 172 (35.3) 444 (336-776) [6]	1300 ± 602 (46.3) 1180 (650-2310) [6]	1240 ± 341 (27.5) 1070 (953-1740) [6]
AUC_{inf} (h*ng/mL)	24.7 ± 3.65 (14.8) 24.3 (19.6-29.9) [6]	117 ± 60.4 (51.5) 102 (31.7-194) [6]	209 ± 80.0 (38.2) 181 (127-325) [6]	577 ± 207 (35.9) 595 (361-774) [3]	1330 ± 608 (45.8) 1210 (665-2330) [6]	1260 ± 338 (26.8) 1090 (994-1760) [6]
AUC_{0-24} (h*ng/mL)	24.0 ± 3.60 (15.0) 23.6 (18.9-29.3) [6]	117 ± 60.9 (52.2) 101 (30.9-194) [6]	209 ± 80.2 (38.4) 181 (127-325) [6]	485 ± 179 (36.9) 429 (336-774) [6]	1280 ± 577 (45.3) 1140 (677-2270) [6]	1230 ± 356 (29.0) 1060 (908-1740) [6]
$T_{1/2}$ (h)	0.961 (0.667-1.21) [6]	1.15 (0.680-1.33) [6]	1.15 (0.813-1.55) [6]	1.41 (1.41-11.9) [3]	8.51 (1.22-22.3) [6]	8.29 (4.69-17.3) [6]
V_{ss}/F (L)	554 ± 80.4 (16.3) 562 (407-657) [6]	407 ± 208 (51.1) 334 (247-793) [6]	431 ± 172 (40.0) 346 (313-751) [6]	1910 ± 2780 (145.9) 338 (264-5120) [3]	4400 ± 3340 (75.8) 3440 (624-8820) [6]	7130 ± 5120 (71.9) 7070 (2340-16500) [6]
CL_{ss}/F (L/h)	425 ± 64.8 (15.3) 423 (341-529) [6]	307 ± 253 (82.5) 248 (129-809) [6]	268 ± 92.8 (34.6) 276 (154-395) [6]	198 ± 88.7 (44.8) 166 (129-298) [3]	366 ± 150 (41.0) 351 (177-591) [6]	521 ± 131 (25.1) 569 (345-661) [6]
$T_{1/2,acc}$	1.00 (1.00-1.00) [6]	1.00 (1.00-1.00) [6]	1.00 (1.00-1.00) [6]	1.01 (1.00-1.73) [6]	1.18 (1.00-1.90) [6]	1.16 (1.03-1.62) [6]
Amount recovered (mg)	0.0663 ± 0.0309 (46.5)	0.114 ± 0.0706 (62.0) 0.126 (0.0326-0.217) [6]	0.233 ± 0.0880 (37.7) 0.185 (0.165-0.378) [5]	0.648 ± 0.330 (50.9) 0.561 (0.305-1.12) [6]	1.25 ± 0.647 (51.7) 1.12 (0.547-2.37) [6]	1.54 ± 0.915 (59.3) 1.43 (0.528-3.03) [6]
Amount recovered (%)	0.663 ± 0.309 (46.5) 0.630 (0.346-1.09) [6]	0.456 ± 0.283 (62.0) 0.502 (0.130-0.868) [6]	0.467 ± 0.176 (37.7) 0.370 (0.331-0.757) [6]	0.648 ± 0.330 (50.9) 0.561 (0.305-1.12) [6]	0.313 ± 0.162 (51.7) 0.280 (0.137-0.593) [6]	0.257 ± 0.153 (59.3) 0.238 (0.0880-0.506) [6]
Renal clearance (mL/min)	45.3 ± 18.0 (39.8) 41.6 (24.4-70.3) [6]	16.8 ± 6.81 (40.5) 18.9 (5.43-24.3) [6]	20.4 ± 2.40 (11.7) 20.5 (17.1-23.4) [5]	21.6 ± 5.41 (25.1) 21.1 (14.6-30.9) [6]	16.9 ± 7.13 (42.3) 14.5 (11.5-30.7) [6]	20.0 ± 8.25 (41.2) 18.1 (8.98-30.3) [6]

Source: Interim Clinical Study X2101 Reports, Table 11-3
 Statistics are presented as Mean ± SD (CV%) and Median (Min-Max) [n]
 CV% = Coefficient of variation (%) = SD/Mean*100
 For T_{max} and $t_{1/2}$, only Median (Min-Max) [n] are presented
 Urine samples were collected at predose and 24-hour collection interval after the first dose and 72-hour collection interval after the last dose.
 Concentrations below the LLOQ (1 ng/mL) were reported as "zero." The linear trapezoidal rule was used for AUC calculation.
 Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 hours; AUC_{inf} , area under the concentration-time curve from time zero to infinity; AUC_{last} , area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL_{ss}/F , apparent oral clearance at steady state; C_{max} , maximum plasma concentration; CV, coefficient of variation; h, hour; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; max, maximum; min, minimum; MRT, mean residence time; N, number of subjects; PK, pharmacokinetic; qd, once daily; SD, standard deviation; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; V_{ss}/F , apparent volume of distribution at steady state

Part 4

The summary statistics of the remibrutinib pharmacokinetic parameter values for Part 4, encompassing doses of 100 mg and 200 mg administered BID, are presented in [Table 42](#). A less-than-dose-proportional increase in both C_{max} and AUC was observed when comparing the 100-mg BID and 200-mg BID doses. From Day 1 to Day 12, the accumulation ratios for C_{max} were 1.7 and 1.5 at the 100-mg and 200-mg BID dosages, respectively. The accumulation ratios for AUC_{0-12h} were 1.5 and 1.9 for 100 mg and 200 mg, respectively. Notably, at a dose of 100 mg, a similar accumulation ratio of 1.5 was observed for AUC_{tau} (0 to 24 for QD, 0 to 12 for BID) irrespective of whether remibrutinib was administered QD or BID. The data support that

accumulation of remibrutinib exposure is due to target binding and the contribution of target-mediated clearance to overall clearance.

The renal clearance of remibrutinib constitutes approximately <1% of the total blood clearance, with specific values of 0.22% and 0.18% (calculated as the ratio of renal clearance to steady-state apparent clearance) noted at the 100-mg BID and 200-mg BID dosages on Day 12, respectively.

Table 42. Summary of Remibrutinib PK Parameters Values in Part 2-MAD BID Regimen, Study X2101

Day 1		
PK parameter (unit)	100 mg bid N=6	200 mg bid N=6
C _{max} (ng/mL)	180 ± 83.4 (46.3)	236 ± 134 (56.8)
	187 (54.8-267) [6]	255 (62.9-371) [6]
T _{max} (h)	1.50 (0.467-2.97) [6]	0.875 (0.500-1.52) [6]
AUC _{last} (h*ng/mL)	334 ± 146 (43.8)	464 ± 211 (45.5)
	343 (77.4-511) [6]	502 (187-696) [6]
AUC ₀₋₁₂ (h*ng/mL)	337 ± 147 (43.6)	464 ± 211 (45.4)
	345 (79.8-517) [6]	503 (187-696) [6]
Amount recovered (mg)	0.233 ± 0.0989 (42.5)	0.483 ± 0.463 (96.0)
	0.207 (0.166-0.430) [6]	0.310 (0.0519-1.34) [6]
Amount recovered (%)	0.233 ± 0.0989 (42.5)	0.241 ± 0.232 (96.0)
	0.207 (0.166-0.430) [6]	0.155 (0.0259-0.669) [6]
Renal clearance (mL/min)	7.86 ± 7.12 (90.6)	8.86 ± 5.25 (59.2)
	5.34 (3.29-22.2) [6]	9.93 (0.666-16.0) [6]
Day 12		
PK parameter (unit)	100 mg bid N=6	200 mg bid N=6
C _{max} (ng/mL)	306 ± 202 (66.2)	347 ± 112 (32.3)
	268 (109-600) [6]	332 (231-500) [6]
T _{max} (h)	0.775 (0.500-2.00) [6]	0.992 (0.517-2.50) [6]
AUC _{last} (h*ng/mL)	518 ± 334 (64.4)	963 ± 439 (45.6)
	441 (214-1130) [6]	889 (398-1710) [6]
AUC _{inf} (h*ng/mL)	570 ± 368 (64.6)	989 ± 442 (44.7)
	563 (219-1160) [5]	929 (412-1730) [6]
AUC ₀₋₁₂ (h*ng/mL)	496 ± 306 (61.7)	890 ± 416 (46.7)
	430 (214-1040) [6]	810 (398-1660) [6]
T _{1/2} (h)	2.84 (2.15-18.9) [5]	12.4 (2.26-26.3) [6]
V _{ss} /F (L)	2040 ± 1610 (79.0)	4590 ± 3520 (76.8)
	1920 (531-4460) [5]	4740 (866-9140) [6]
CL _{ss} /F (L/h)	255 ± 153 (60.1)	267 ± 126 (47.4)
	180 (96.4-467) [5]	247 (121-502) [6]
Amount recovered (mg)	0.398 ± 0.208 (52.3)	0.788 ± 0.434 (55.0)
	0.350 (0.147-0.676) [6]	0.753 (0.179-1.52) [6]
Amount recovered (%)	0.398 ± 0.208 (52.3)	0.394 ± 0.217 (55.0)
	0.350 (0.147-0.676) [6]	0.377 (0.0895-0.760) [6]
Renal clearance (mL/min)	9.36 ± 7.54 (80.6)	7.97 ± 3.73 (46.9)
	7.75 (1.18-23.6) [6]	8.15 (1.63-13.3) [6]

Source: Interim Clinical Study X2101 Reports, Table 11-4

Statistics are presented as Mean ± SD (CV%) and Median (Min-Max) [n]

CV% = Coefficient of variation (%) = SD/Mean*100

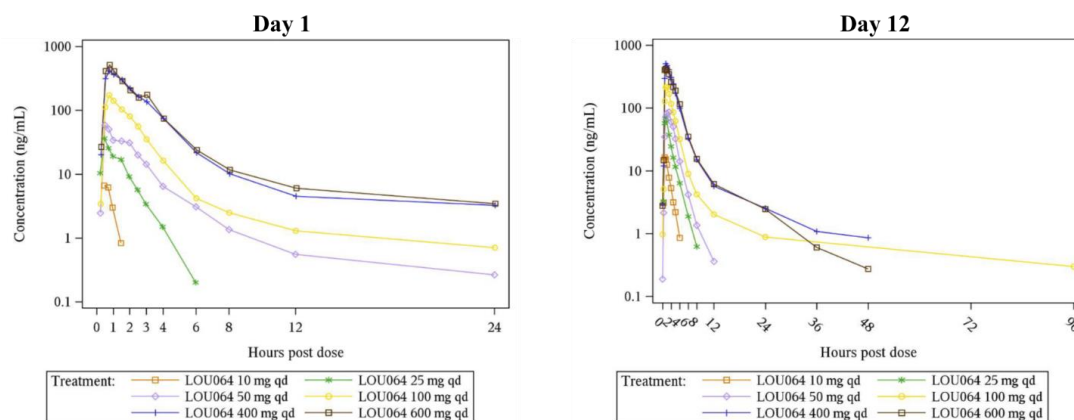
For T_{max} and t_{1/2}, only Median (Min-Max) [n] are presented

Urine samples were collected at predose and 24-hour collection interval after the first dose and 72-hour collection interval after the last dose.

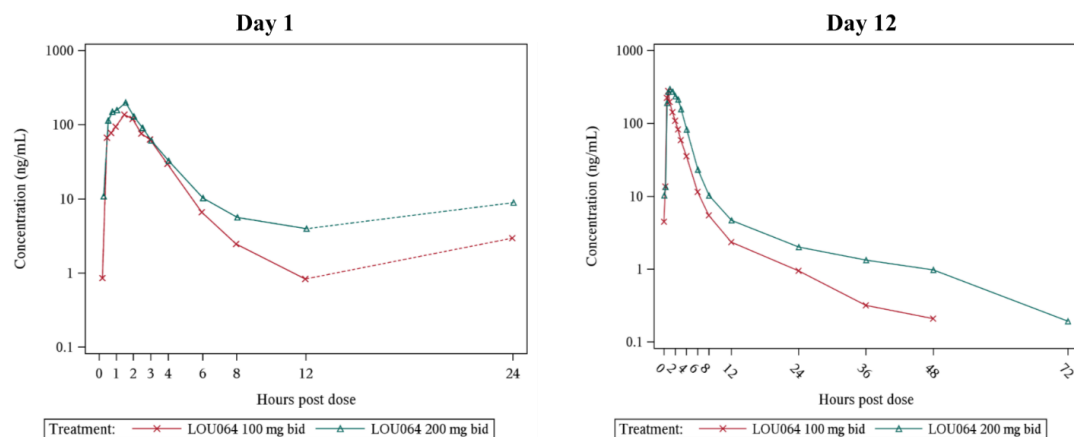
Concentrations below the LLOQ (1 ng/mL) were reported as "zero." The linear trapezoidal rule was used for AUC calculation.

Abbreviations: : AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; BID, twice daily; CL_{ss}/F, apparent oral clearance at steady state; C_{max}, maximum plasma concentration; CV, coefficient of variation; h, hour; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; MRT, mean residence time; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_{ss}/F, apparent volume of distribution at steady state

Figure 18. Semilogarithmic Plots of the Arithmetic Mean Remibrutinib Blood Concentration-Time Profiles in Part 2-MAD QD and Part 4-MAD BID Regimens, Study X2101
Part 2



Part 4



Source: Interim Clinical Study X2101 Reports, Figure 11.2 and 11.3
Remibrutinib is referred to as LOU064.
Abbreviations: BID, twice daily; MAD, multiple-ascending dose; QD, once daily

Part 3: Food Effect

The blood concentration-time profiles for the treatment arms involving remibrutinib at a dose of 60 mg, under both fasted and fed conditions, are illustrated in [Figure 19](#). The administration of a high-fat breakfast resulted in a 2-hour delay in the absorption of remibrutinib, with the T_{max} increasing from 0.767 hours under fasted conditions to 2.78 hours under fed conditions. Additionally, the AUC_{last} was augmented by 30%, while C_{max} was reduced by 20%. The statistical analysis of the food effect on the pharmacokinetics of remibrutinib is detailed in [Table 43](#).

Table 43. Statistical Analysis of Food Effect on Remibrutinib PK Parameters in Part 3, Food Effect, Study X2101

Compound: LOU064, Analyte: LOU064, Matrix: Blood						
Parameter	Profile Day	Treatment	n*	Adjusted geo-mean	Geo-mean ratio (fed vs fasted)	90% CI for geo-mean ratio
AUC _{last} (h*ng/mL)	1	LOU064 60 mg (fed)	12	224	1.30	(1.14, 1.47)
		LOU064 60 mg (fasted)	12	173		
C _{max} (ng/mL)	1	LOU064 60 mg (fed)	12	80.9	0.801	(0.638, 1.01)
		LOU064 60 mg (fasted)	12	101		

Source: Interim Clinical Study X2101 Reports, Table 11-8

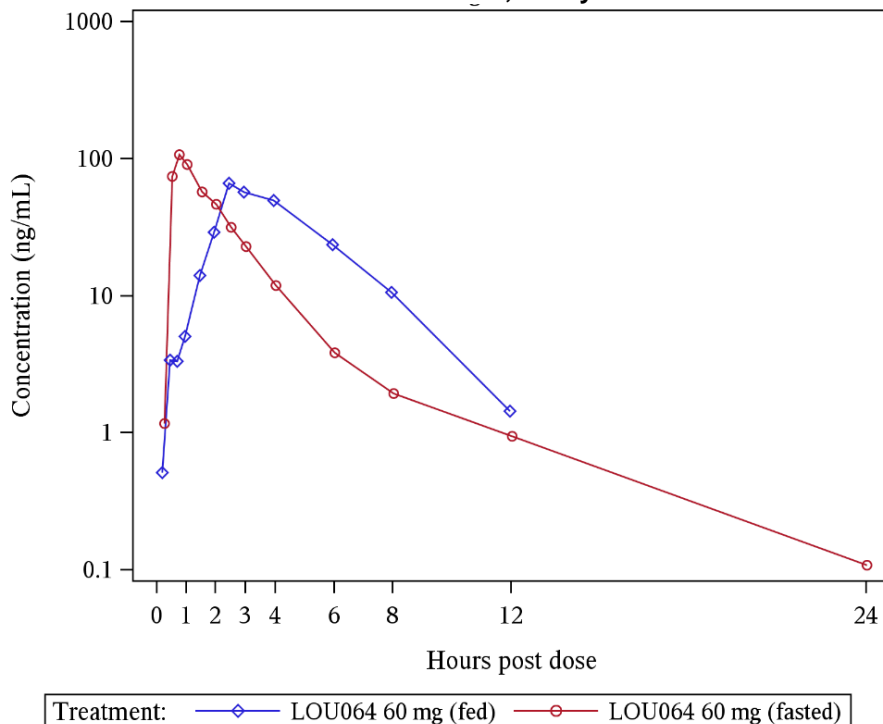
n* = number of subjects with nonmissing values

Adjusted geometric means, ratio and 90% CI are from an ANOVA model of the log-transformed data containing fixed effects for sequence, treatment, period and subject nested within sequence.

Only subjects with evaluable data for both periods (fed and fasted) are included.

Abbreviations: ANOVA, analysis of variance; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CI, confidence interval; C_{max}, maximum plasma concentration; geo-mean, geometric mean; n, number of subjects; PK, pharmacokinetic

Figure 19. Semilogarithmic Plots of the Arithmetic Mean Remibrutinib Blood Concentration-Time Profiles in Fasted and Fed State in Part 3, Study X2101



Source: Interim Clinical Study X2101 Reports, Figure 11-5
Remibrutinib is referred to as LOU064.

Pharmacodynamic Results

BTK Occupancy in Peripheral Blood

Part 1: Single-Ascending Dose Regimen

BTK occupancy exceeding 95% was observed at a dose level of 30 mg and above following a single-dose administration of remibrutinib. This level of occupancy was sustained before beginning to decline 48 hours postadministration ([Figure 20](#)).

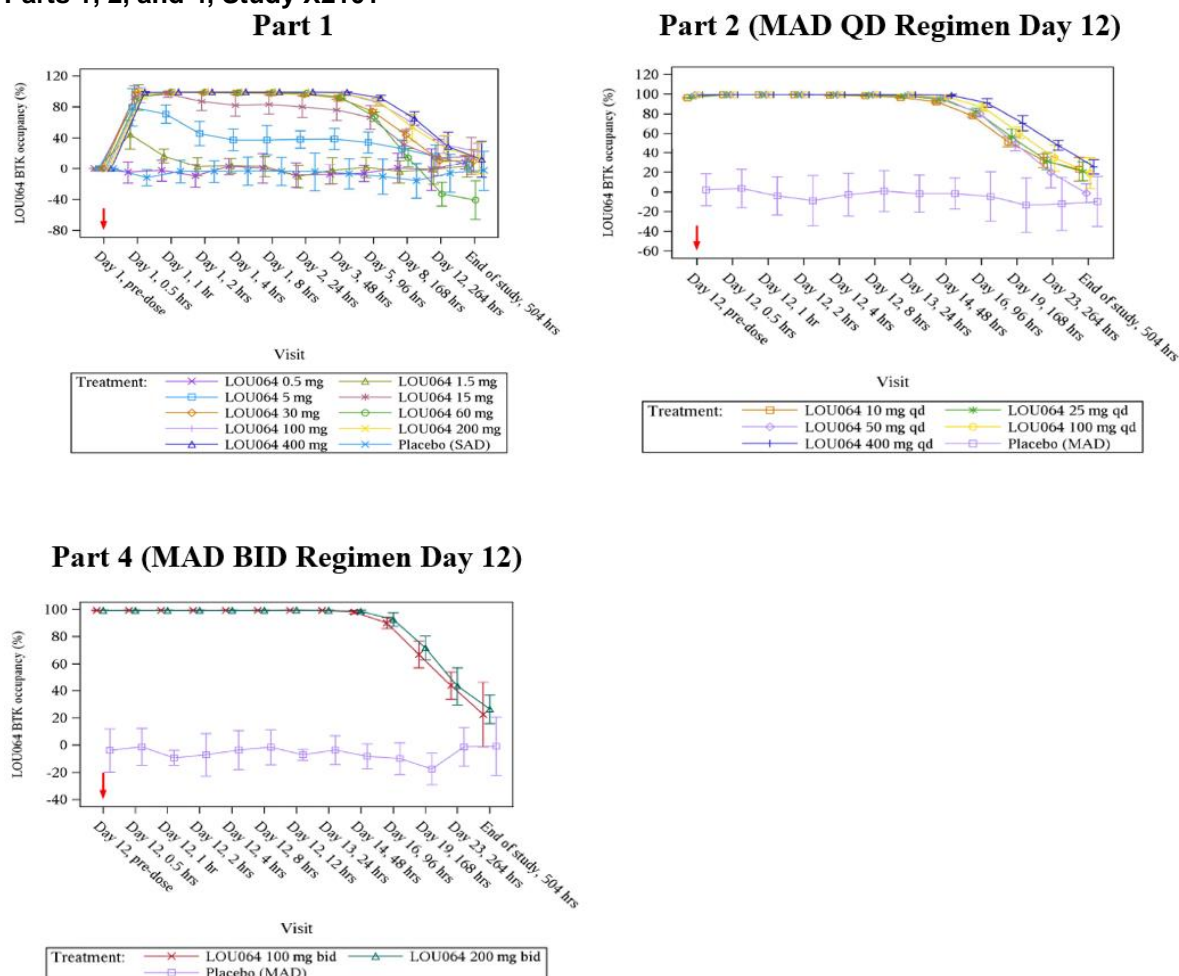
Part 2: Multiple-Dose QD Regimen

In the multiple-dose QD regimens, the BTK occupancy on Day 1 was comparable to that observed in the single-ascending dose (SAD) regimen. By Day 12, BTK occupancy exceeded 95% across all tested dose levels, ranging from 10 mg to 400 mg. This occupancy began to decline 48 hours after the final dose on Day 12 ([Figure 20](#)).

Part 4: Multiple-Dose BID Regimen

In Part 4 of the study, near-complete BTK occupancy was achieved at both the 100-mg and 200-mg doses in the multiple-dose BID regimens. This occupancy persisted until 48 hours after the last dose on Day 12 ([Figure 20](#)).

Figure 20. Arithmetic Mean (SD) Percent BTK Occupancy by Remibrutinib in Peripheral Blood in Parts 1, 2, and 4, Study X2101



Source: Interim Clinical Study X2101 Reports, Figure 11-7, 11-8, 11-9, and 11-10
 Blood sampling timepoints: Part 1: at predose and up to 504 hours postdose; Part 2 and 4: at predose (Day 1, 7, and 12) and up to 24 hours after first dose and up to 504 hours after the last dose on Day 12.
 Free BTK levels (not bound to remibrutinib) were measured in whole blood by ELISA. For Free BTK, the anticipated LLOQ was 1.45 ng/mL. Concentrations for free BTK below the LLOQ was reported in listings as '<1.45 ng/mL' and imputed in summary statistics as 0.725 ng/mL (i.e., imputed as LLOQ/2).
 Abbreviations: BTK, Bruton's tyrosine kinase; ELISA, enzyme-linked immunosorbent assay; hrs, hours; LLOQ, lower limit of quantification; MAD, multiple-ascending dose; QD, once daily; SAD, single-ascending dose; SD, standard deviation

Ex Vivo Activation of CD203c and CD63

Ex vivo inhibition of basophil activation was assessed by measuring the surface expression of cell-surface markers CD203c and CD63.

Part 1

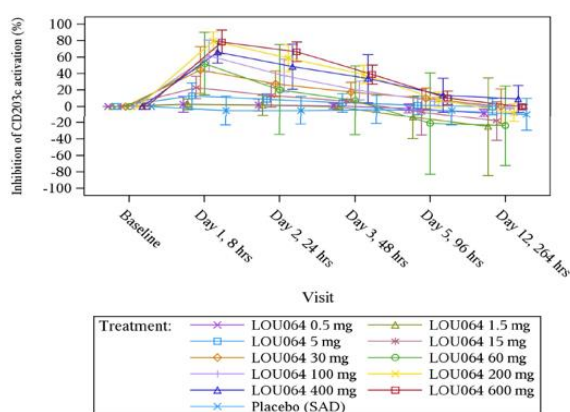
The inhibition of CD203c activation exceeded 50% at a dose of 60 mg and above. The peak inhibition of stimulated basophils (79.3% inhibition) was observed 8 hours following administration of 200 mg on Day 1 (Figure 21). A more pronounced and sustained inhibition of CD63 activation was evident at doses ≥ 60 mg. At doses of 100 mg and higher, the inhibition of CD63 activation was maintained at or above 88% for up to 48 hours post-treatment (Figure 21).

Parts 2 and 4

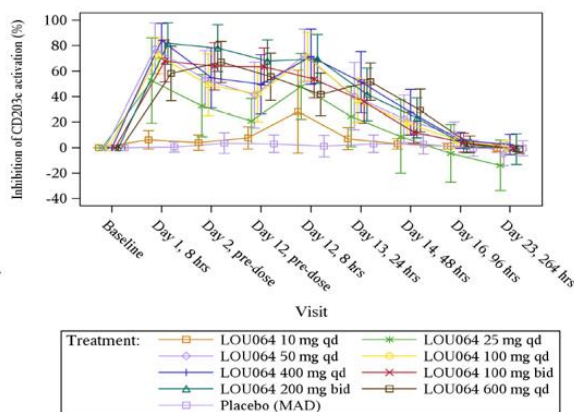
On Day 1, the highest percentage inhibition of CD203c activation was observed 8 hours postdose in the cohorts receiving 400 mg QD and 200 mg BID, with inhibition rates of 84% and 81.76%, respectively. The maximum inhibition of CD203c activation at trough was 63% for the 100-mg BID cohort on Day 12 and 67% for the 200-mg BID cohort on Day 12 (Figure 21). A more pronounced inhibition of CD63 activation was evident at doses ≥ 50 mg QD, achieving at least 95% inhibition 24 hours after the initiation of treatment (Figure 21). The lowest trough inhibition of CD63 activation was 80% following treatment with 10 mg QD on Day 12.

Figure 21. Arithmetic Mean (SD) Percent Inhibition of Basophil Activation by Remibrutinib in Peripheral Blood in Parts 1, 2, and 4, Study X2101

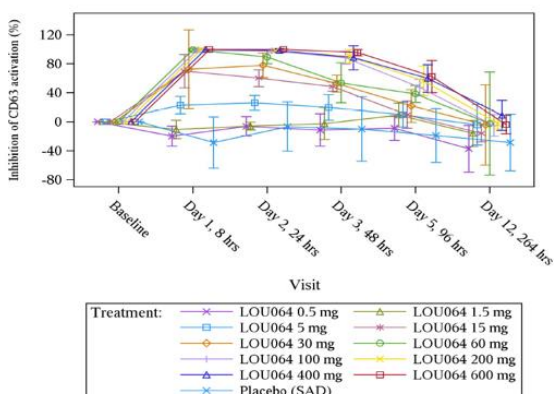
Part 1 (CD203c)



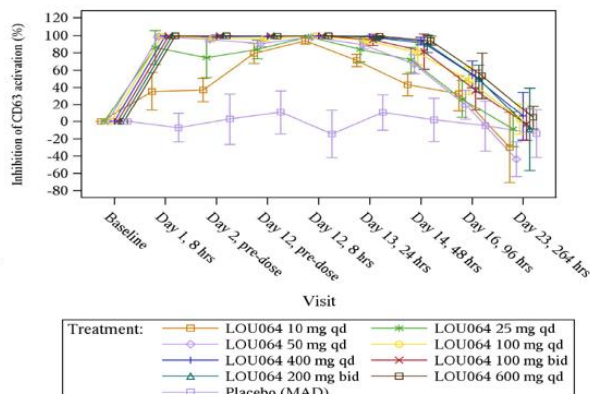
Part 2 and 4 (CD203c)



Part 1 (CD63)



Part 2 and 4 (CD63)



Source: Interim Clinical Study X2101 Reports, Figure 11-11, 11-12, 11-13.

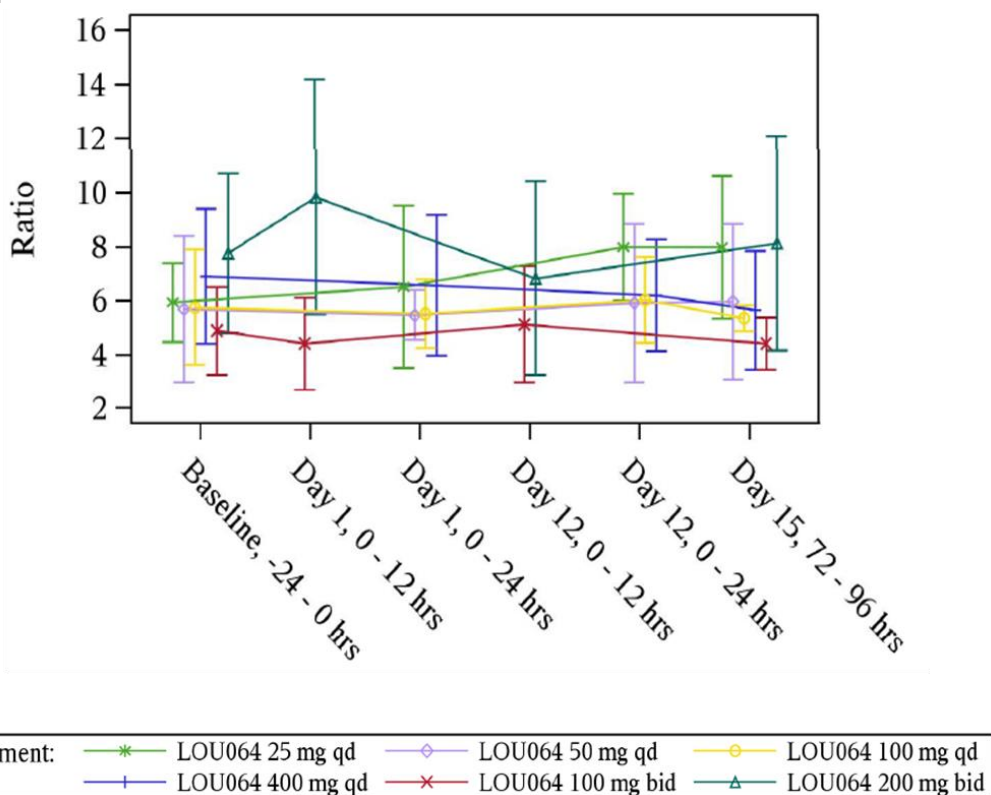
Blood sampling timepoints: Part 1: at predose and 8, 24, 48, 96, and 264 hours postdose; Part 2 and 4: at predose and 12 and 24 hours after the first dose and 8, 24, 48, 96, and 264 hours after the last dose.

Abbreviation: hrs, hours; SAD, single-ascending dose; SD, standard deviation

6β OH-Cortisol/Cortisol Ratio

The concentration ratios of 6β OH-cortisol to cortisol were measured in urine to probe for modulation of intrinsic CYP3A4 activity. There was no dose-dependent or time-dependent increase in the ratio, suggesting that remibrutinib may not modulate CYP3A4 activity (Figure 22).

Figure 22. Arithmetic Mean (SD) 6βOH-Cortisol/Cortisol Ratio-Time Profiles in Parts 2 and 4, Study X2101



Source: Interim Clinical Study X2101 Reports, Figure 11-16

Abbreviations: bid, twice daily; hrs, hours; LOU064, remibrutinib; qd, once daily; SD, standard deviation

14.2.1.2. Study X1101

Study X1101 was a randomized, placebo-controlled study designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of remibrutinib using SAD and MAD regimens in healthy Japanese male subjects. The study was divided into Part A and Part B. Part A comprised five cohorts, each receiving a single dose of remibrutinib at 5 mg, 30 mg, 100 mg, 200 mg, or 400 mg. Part B consisted of a single cohort that was administered remibrutinib at 100 mg BID for 5 days. Remibrutinib was administered as 5-mg and 50-mg HGCs.

Pharmacokinetic Results

Part A: SAD

Remibrutinib exhibited rapid absorption, with T_{max} occurring between 0.5 and 1.5 hours across all doses (Figure 23 and Table 44). Based on a linear regression analysis of log-transformed parameters, across the dose range of 30 to 400 mg, C_{max} increased in an approximately dose-proportional manner (slope 90% CI: 0.99 [0.80, 1.18]) and AUC_{last} increased in a greater than dose-proportional manner (slope 90% CI: 1.16 [1.00, 1.32]). The terminal $t_{1/2}$ ranged from 0.841 to 24.3 hours, with longer $t_{1/2}$ observed at higher doses. The apparent terminal elimination phase was not fully established until 12 hours postdose and was only measurable at doses exceeding 100 mg. Urine samples indicated that the amount of remibrutinib excreted in urine over 72 hours

following a single 100-mg dose was 0.345 mg, with a renal clearance (CL_r) of 1.12 L/h (0.28% of total apparent clearance).

Table 44. Summary of Remibrutinib PK Parameters Values in Part A-SAD Regimen, Study X1101

PK parameter (unit)	Profile day	LOU064 5 mg N=6	LOU064 30 mg N=6	LOU064 100 mg N=6	LOU064 200 mg N=6	LOU064 400 mg N=6
T _{max} (hr) #	1	0.750 (0.500-2.00) [6]	1.00 (0.500-1.50) [6]	1.25 (0.500-2.00) [6]	0.500 (0.500-1.50) [6]	1.50 (0.500-4.00) [6]
C _{max} (ng/mL)	1	12.2 ± 6.51 (53.4) [6]	60.8 ± 24.4 (40.2) [6]	209 ± 133 (63.8) [6]	404 ± 173 (42.8) [6]	798 ± 424 (53.2) [6]
AUC _{last} (hr*ng/mL)	1	7.87 ± 1.54 (19.5) [6]	95.2 ± 38.5 (40.4) [6]	320 ± 128 (40.0) [6]	705 ± 273 (38.8) [6]	2000 ± 923 (46.1) [6]
AUC _{inf} (hr*ng/mL)	1	-	97.3 ± 39.0 (40.0) [6]	327 ± 173 (52.9) [4]	682 ± 254 (37.2) [3]	1720 ± 586 (34.0) [2]
T _{1/2} (hr)	1	-	0.841 ± 0.308 (36.6) [6]	3.34 ± 4.01 (120.3) [4]	2.59 ± 0.706 (27.2) [3]	24.3 ± 6.49 (26.7) [2]
CL/F (L/hr)	1	-	363 ± 170 (46.9) [6]	395 ± 240 (60.8) [4]	321 ± 113 (35.3) [3]	246 ± 83.9 (34.0) [2]
V _z /F (L)	1	-	411 ± 144 (35.0) [6]	1340 ± 926 (69.2) [4]	1230 ± 688 (56.0) [3]	9040 ± 5250 (58.1) [2]

Source: Study X1101 Clinical Report, Table 11-1

Statistics are Mean ± SD (CV%) [n, number of subjects with available observations]

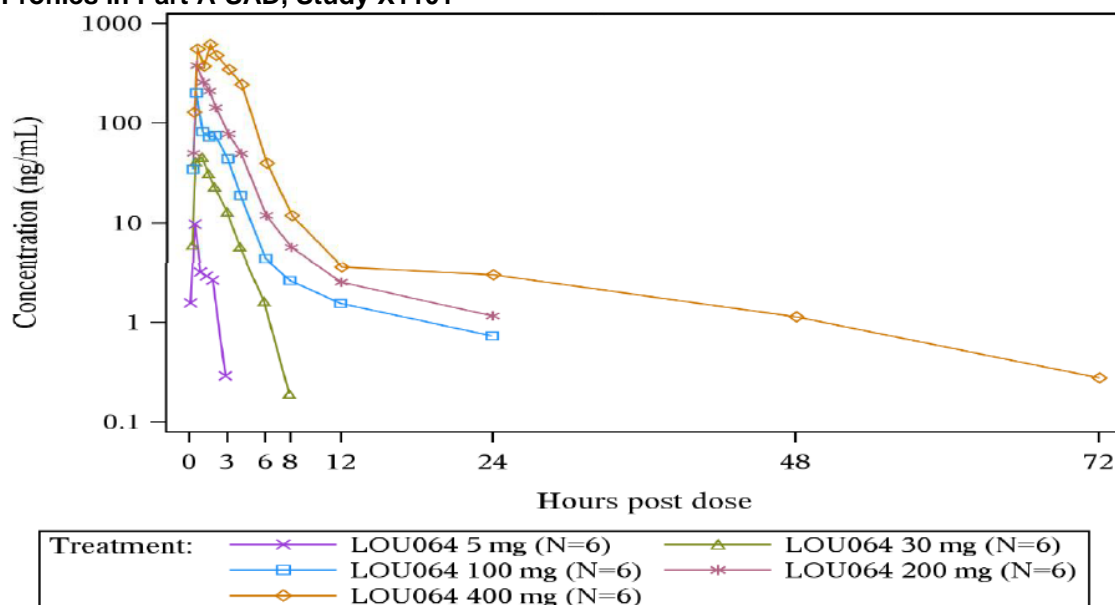
CV% = Coefficient of variation (%) = sd/mean * 100

For T_{max}, statistics are Median (Min-Max) [n, number of subjects with available observations]

Concentrations below LLOQ were treated as zero in summary statistics and for PK parameter calculations. A geometric mean was not reported if the dataset includes zero values.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; LLOQ, lower limit of quantification; LOU064, remibrutinib; N, number of subjects; PK, pharmacokinetic; SAD, single-ascending dose; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution during terminal phase after oral administration

Figure 23. Semilogarithmic Plots of the Arithmetic Mean Remibrutinib Blood Concentration-Time Profiles in Part A-SAD, Study X1101



Source: Study X1101 Clinical Report, Figure 11-1

Remibrutinib is referred to as LOU064.

Abbreviations: N, number of subjects; SAD, single-ascending dose

Part B: MAD

Following administration of remibrutinib 100 mg BID for 5 days, accumulation in C_{max} and AUC_{0-12h} was observed with accumulation ratios of 1.25 and 1.24, respectively (Table 45 and Figure 24). Steady state was achieved by Day 2. Urine samples indicated that the amount excreted in urine over 12 hours (A_{e0-12h}) and CL_r were 0.356 mg and 0.989 L/hr on Day 1, and 0.512 mg and 1.12 L/hr on Day 5, respectively.

Table 45. Summary of Remibrutinib PK Parameters Values in Part B-MAD Regimen, Study X1101

PK parameter (unit)	LOU064 100 mg BID	
	Day 1	Day 5
T _{max} (hr) #	1.00 (0.500-3.00) [6]	0.750 (0.500-3.00) [6]
C _{max} (ng/mL)	199 ± 105 (52.7) [6]	227 ± 71.6 (31.5) [6]
AUC _{0-12h} (hr*ng/mL)	392 ± 151 (38.4) [6]	479 ± 174 (36.3) [6]
AUC _{last} (hr*ng/mL)		488 ± 179 (36.7) [6]
AUC _{inf} (hr*ng/mL)		458 ± 176 (38.4) [5]
T _{1/2} (hr)		2.10 ± 0.876 (41.7) [5]
CL/F (L/hr)	299 ± 146 (48.8) [6]	256 ± 166 (64.9) [6]
Racc, AUC _{0-12h}		1.24 ± 0.291 (23.5) [6]
Racc, C _{max}		1.25 ± 0.401 (32.0) [6]

Source: Study X1101 Clinical Report, Table 11-4

Statistics are Mean ± SD (CV%) [n, number of subjects with available observations]

CV% = Coefficient of variation (%) = sd/mean * 100

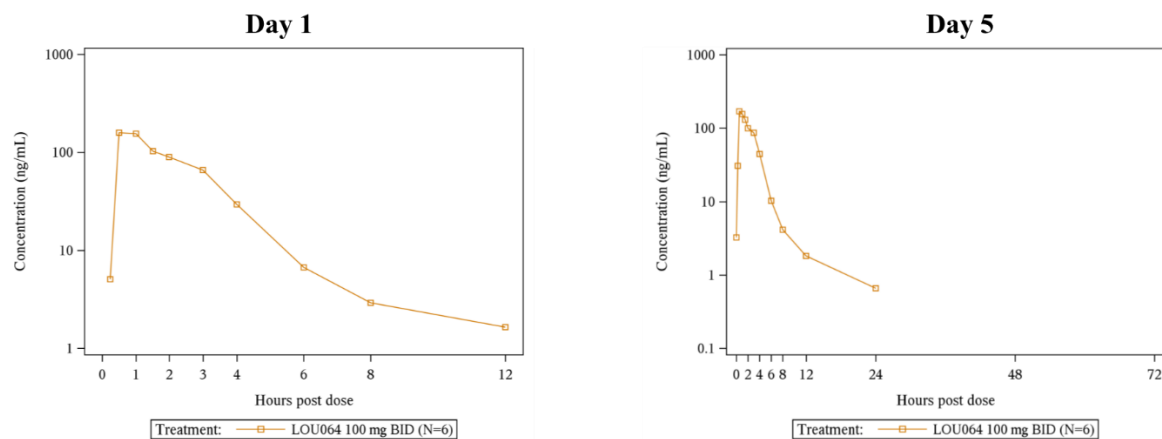
For T_{max}, Statistics are Median (Min-Max) [n, number of subjects with available observations]

CL/F = Dose / AUC_{0-12h}

Concentrations below LLOQ were treated as zero in summary statistics and for PK parameter calculations. A geometric mean was not reported if the dataset includes zero values.

Abbreviations: AUC_{0-12h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; BID, twice daily; CL/F, apparent clearance; C_{max}, maximum plasma concentration; LOU064, remibrutinib; MAD, multiple-ascending dose; PK, pharmacokinetic; Racc, Accumulation ratio; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Figure 24. Semilogarithmic Plots of the Arithmetic Mean Remibrutinib Blood Concentration-Time Profiles in Part B-MAD, Study X1101



Source: Study X1101 Clinical Report, Figure 11-3

Remibrutinib is referred to as LOU064.

Abbreviations: BID, twice daily; MAD, multiple-ascending dose; N, number of subjects

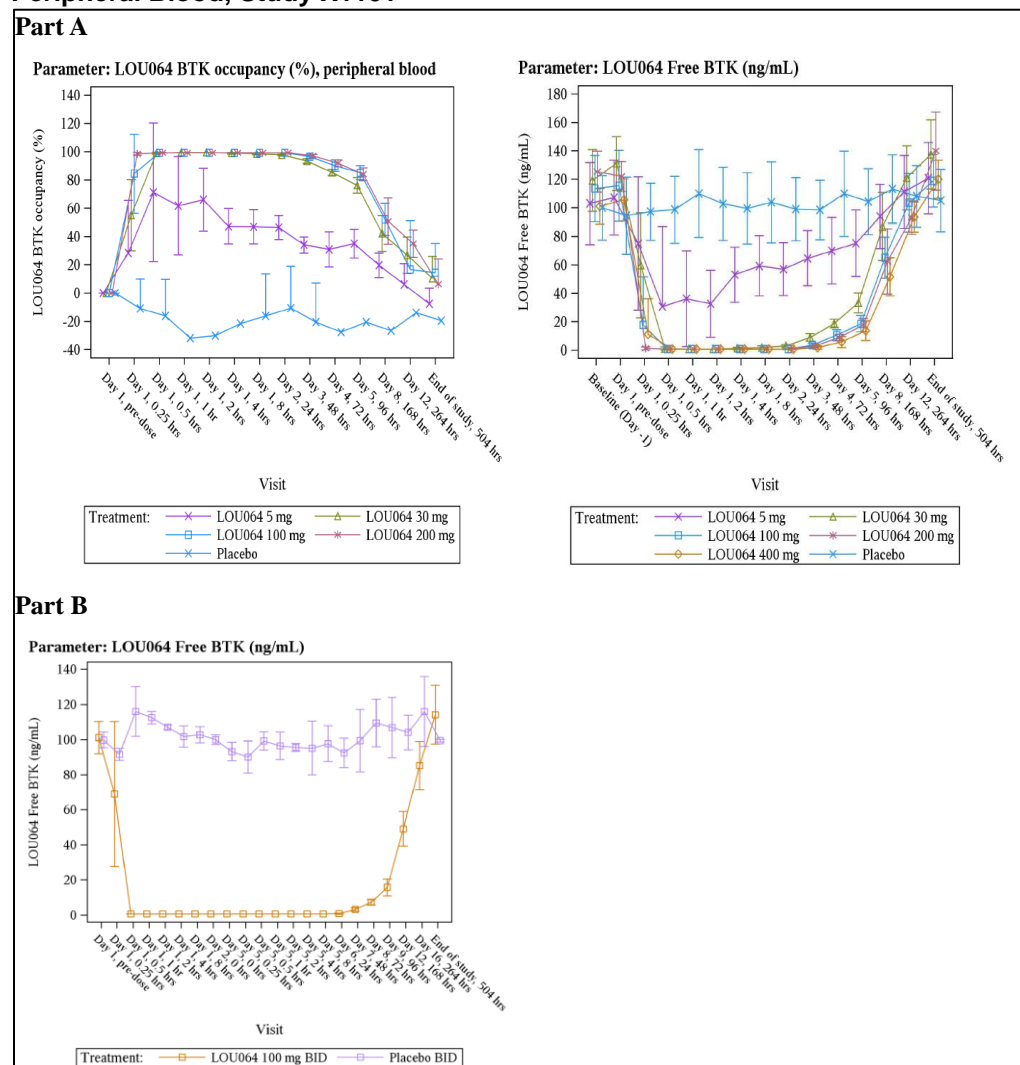
Pharmacodynamic Results

BTK Occupancy in Peripheral Blood

BTK occupancy exceeding 90% was observed at a dose level of 30 mg and above following a single dose, and this occupancy was maintained for up to 48 hours postdose (Figure 25). Due to technical difficulties, total BTK levels were not analyzed for some subjects in the 200-mg group and for all subjects in the 400-mg group.

In Part B of the study, free BTK levels were utilized as a surrogate measure for BTK occupancy (Figure 25). Following administration of 100 mg BID, free BTK levels were ablated for up to 48 hours after administration of the last dose.

Figure 25. Arithmetic Mean (SD) Percent of BTK Occupancy by LOU064 and Free BTK in Peripheral Blood, Study X1101

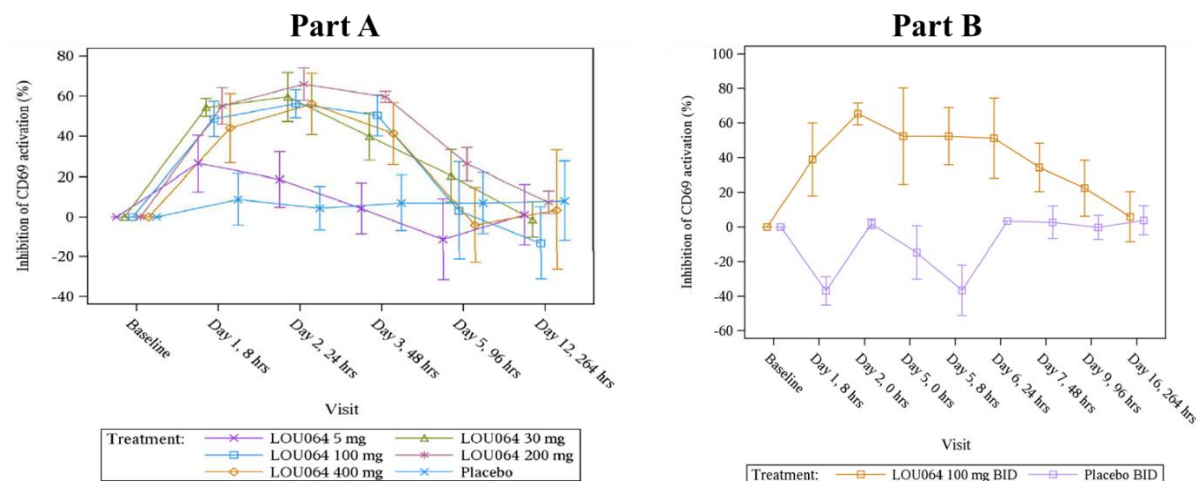


Source: Study X1101 Clinical Report, Figure 11-5 and 11-6
Abbreviations: BID, twice daily; BTK, Bruton's tyrosine kinase; hr(s), hour(s); LOU064, remibrutinib; SD, standard deviation

Inhibition of B-Cell Activation

The inhibitory effect of remibrutinib on activation of CD69, a marker found on the surface of B-cells was assessed. In Part A, remibrutinib demonstrated an inhibitory effect of $\geq 56\%$ at a dose of 30 mg, with the maximum inhibition reaching about 66% at a dose of 200 mg at 24 hours postdose. In Part B, the peak inhibitory effect of remibrutinib (i.e., 65%) was observed on Day 1 and was sustained for 24 hours following the final dose administered on Day 5 (Figure 26).

Figure 26. Arithmetic Mean (SD) Percent Inhibition of CD69 Activation, Study X1101



Source: Study X1101 Clinical Report, Figure 11-7 and 11-8
Abbreviation: BID, twice daily; LOU064, remibrutinib; SD, standard deviation

14.2.2. [¹⁴C]-Labelled Absorption, Metabolism, and Excretion Study, Study X2104

Study X2104 was a single-center, open-label study conducted in seven healthy subjects to evaluate the ADME of remibrutinib under fasted conditions. The study comprised three distinct arms: an oral arm and two IV arms (A and B). As recovery of total radioactivity from the first four subjects in the oral arm was deemed incomplete (~60%), an assessment of exhaled air was introduced for the fifth subject in the oral arm. As recovery of radioactivity did not improve after accounting for exhaled air, an additional cohort of two subjects was enrolled in which radiolabeled remibrutinib was administered IV to ensure receipt of the complete dose.

- **Oral arm (N=5):** On Day 1, subjects received 100 mg of nonradiolabeled remibrutinib BID as the HGC drug product. On the morning of Day 2, subjects were administered a single oral dose of an oral solution containing 100 mg of nonradiolabeled remibrutinib and 0.074 MBq (2 μ Ci) of [¹⁴C]-remibrutinib. To maintain steady-state conditions, the administration of nonradiolabeled remibrutinib 100-mg BID capsules was resumed in the evening of Day 2 and continued until the evening of Day 5.
- **IV Arm A (N=1):** On Day 1, the subject received nonradiolabeled 100 mg of remibrutinib HGC BID. On the morning of Day 2, 1 hour after the oral morning dose of 100 mg of nonradiolabeled remibrutinib, the subject received a single IV microdose of 100 μ g and 0.074 MBq (2 μ Ci) of [¹⁴C]-remibrutinib. To maintain steady-state conditions, the administration of nonradiolabeled remibrutinib 100-mg BID capsules was resumed in the evening of Day 2 and continued until the evening of Day 5.
- **IV Arm B (N=1):** One subject received nonradiolabeled remibrutinib HGC at a dose of 100 mg BID for 5 consecutive days. On the morning of Day 6, 1 hour after the oral morning dose of 100 mg of nonradiolabeled remibrutinib, the subject received a single IV microdose of 100 μ g and 0.074 MBq (2 μ Ci) of [¹⁴C]-remibrutinib. To maintain steady-state conditions, the administration of nonradiolabeled remibrutinib 100-mg BID capsules was resumed in the evening of Day 6 and continued until the evening of Day 9.

Schedule of PK Sampling Timepoints

Oral Arm

- Blood PK samples: Collected at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours postradiolabeled dose.
- Urine collection: Conducted at predose and on Days 1, 2, 3 to 5, 6 to 11, 15 to 16, 19 to 20, 23 to 24, and 27 to 28.
- Feces collection: Conducted at predose and on Days 2, 3 to 5, 6 to 11, 15 to 16, 19 to 20, 23 to 24, and 27 to 28.
- Exhaled air collection: Conducted on Days 2 and 3 to 5.

IV Arm A

- Blood PK samples: Collected at predose and at 5 min, 10 min, 15 min, and 20 min, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours post-IV dose.
- Urine and fecal collection: Conducted at predose and on Days 2, 3 to 5, 6 to 19, 23 to 24, 27 to 28, 31 to 32, and 35 to 36. Notably, collections were not performed on Days 12, 14, 16, and 18.
- Exhaled air collection: Conducted on Days 2 and 3 to 5.

IV Arm B

- Blood PK samples: Collected at predose and at 5 min, 10 min, 15 min, and 20 min, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours post-IV dose.
- Urine collection: Conducted at predose and on Days 6, 7 to 9, 10 to 23, 27 to 28, 31 to 32, 35 to 36, and 39 to 40. Notably, collections were not performed on Days 16, 18, 20, and 22.
- Fecal collection: Conducted at predose and on Days 5, 6, 7 to 9, 10 to 23, 27 to 28, 31 to 32, 35 to 36, and 39 to 40.
- Exhaled air collection: Conducted on Days 6 and 7.

Pharmacokinetic parameters for total radioactivity in plasma and whole blood were derived from the concentration-time data for total radioactivity. Urinary, fecal, and exhaled air recovery, as well as total recovery, were calculated. Concentrations below the LLOQ were reported as “zero,” and missing data points were explicitly labeled as such.

PK Mass Balance Results

Oral Arm

The cumulative excretions of total radioactivity in urine, feces, and total recovery are presented in [Figure 27](#) and [Table 46](#). The recovery of total radioactivity was incomplete, amounting to only 56.2% of the administered dose. The reasons for incomplete recovery of radioactivity are unclear. Of the excreted radioactivity, 31.8% was recovered in feces, with 24.9% recovered in the feces within the first 72 hours. In urine, 24.4% of the total radioactivity was recovered, with 20.7% recovered in urine within the first 24 hours. The percentage of unchanged remibrutinib

recovered in urine was 4.1% of the dose, suggesting that a significant portion of the total radioactivity recovered in urine consists of metabolites. Exhaled air was evaluated in one subject. No radioactivity was detected in exhaled air.

The Applicant attributed the incomplete recovery of radioactivity to technical issues, supported by the following observations:

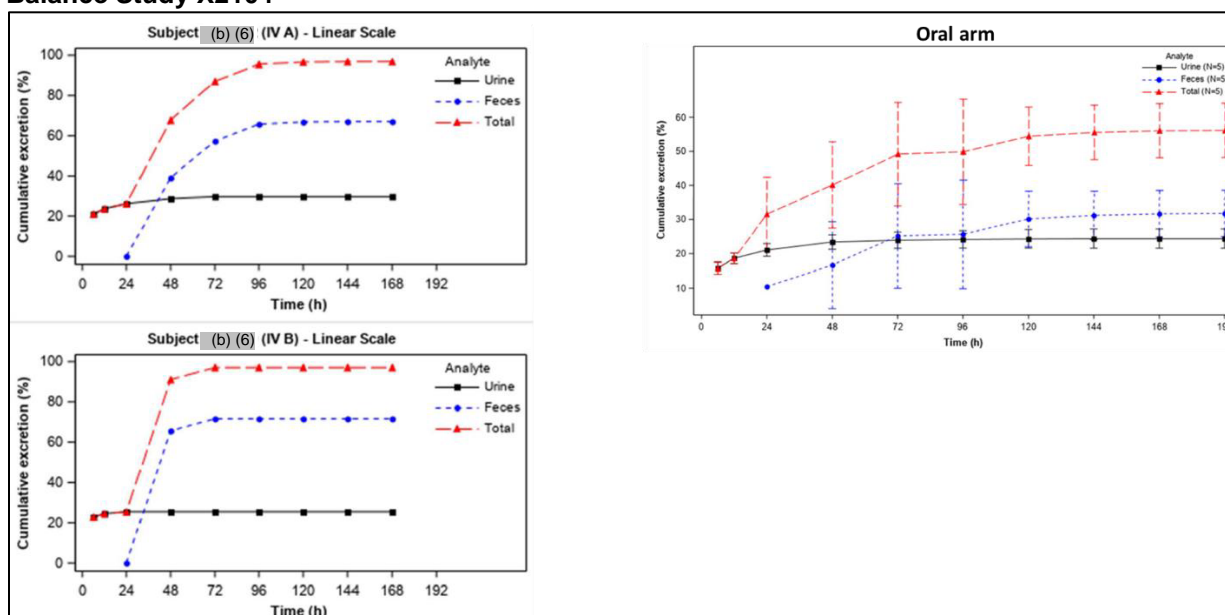
- The metabolic profiles in blood, urine, and feces obtained after oral and intravenous administration were comparable.
- The relative contributions of clearance pathways were also comparable between oral and IV administration.
- No long-lasting radioactivity was detected in blood or excreta.
- No volatile radioactivity was detected in exhaled air after oral administration, which would have suggested the formation of volatile metabolites or CO₂.

IV Arm

The recovery of the administered dose of [¹⁴C]-remibrutinib was 96.8% in IV Arm A and 97.2% in IV Arm B. Fecal excretion accounted for 67.1% of the dose in IV Arm A, with 57.4% recovered within the first 72 hours. In IV Arm B, fecal excretion was 71.7%, with 65.7% of this amount recovered within the first 48 hours ([Figure 27](#) and [Table 46](#)). Urinary excretion constituted 29.7% of the dose in IV Arm A and 25.5% in IV Arm B, the majority of which was recovered within the first 12 to 24 hours. The percentage of unchanged remibrutinib recovered in urine was 2.2% for IV Arm A and 5% for IV Arm B.

Note that as near-complete recovery of radioactivity was obtained after IV dosing, it is not likely that the missing radioactivity after oral dosing was retained within the body. The data further support that technical issues contributed to incomplete recovery of radioactivity after oral dosing.

Figure 27. Arithmetic Mean (SD) Total Radioactivity Recovery in Urine and Feces in ADME-Mass Balance Study X2104



Source: Study X2104 Clinical Report, Figure 11-1 and 11-2

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; h, hour; IV, intravenous; SD, standard deviation

Table 46. Summary Statistics of Total Radioactivity Excretion in Urine and Feces and Remibrutinib in ADME-Mass Balance Study X2104

Subject ID/ Statistic	Total [¹⁴ C]Radioactivity			LOU064	
	Fe(urine) (%)	Fe(feces) (%)	Fe(total) (%)	Fe(urine) (%)	CLr (L/h)
Treatment arm:100 mg LOU064 + 100 mg [¹⁴C]LOU064 Oral arm					
n	5	5	5	5	5
Mean (SD)	24.4 (2.80)	31.8 (6.75)	56.2 (7.95)	4.1 (1.72)	0.9 (0.42)
CV (%) mean	11.5	21.3	14.2	41.4	45.5
Median	25.4	30.1	57.1	4.2	0.8
[Min, Max]	[20.3, 27.2]	[24.7, 42.1]	[48.0, 68.3]	[1.8, 6.5]	[0.5, 1.5]
Treatment arm:100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-A					
n	1	1	1	1	1
Mean (SD)	29.7 (-)	67.1 (-)	96.8 (-)	2.2 (-)	2.1 (-)
CV (%) mean					
Median					
[Min, Max]					
Treatment arm:100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-B					
n	1	1	1	1	1
Mean (SD)	25.5 (-)	71.7 (-)	97.2 (-)	5.0 (-)	6.7 (-)
CV (%) mean					
Median					
[Min, Max]					

Source: Study X2104 Clinical Report, Table 11-1

The excretion of total radioactivity in urine and feces as presented in the bioanalytical reports, were calculated using the amount of radioactivity measured in Bq divided by the (actual) radioactivity dose in Bq. For the mass balance results reported in the CSR, the percent excreted was derived from the concentrations in ng-eq/mL or ng-eq/g multiplied by the volume (or weight) of the sample, divided by the (actual) administered dose of [¹⁴C]-remibrutinib. Differences in rounding at several steps during these calculations resulted in small differences between the (mean) cumulative excretion results reported in the bioanalytical reports and the CSR.

CV% = coefficient of variation (%) = SD/mean*100

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CLr, renal clearance; CSR, clinical study report; Fe, iron; ID, identifier; IV, intravenous; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; SD, standard deviation

Pharmacokinetics of Total Radioactivity in Plasma and Whole Blood

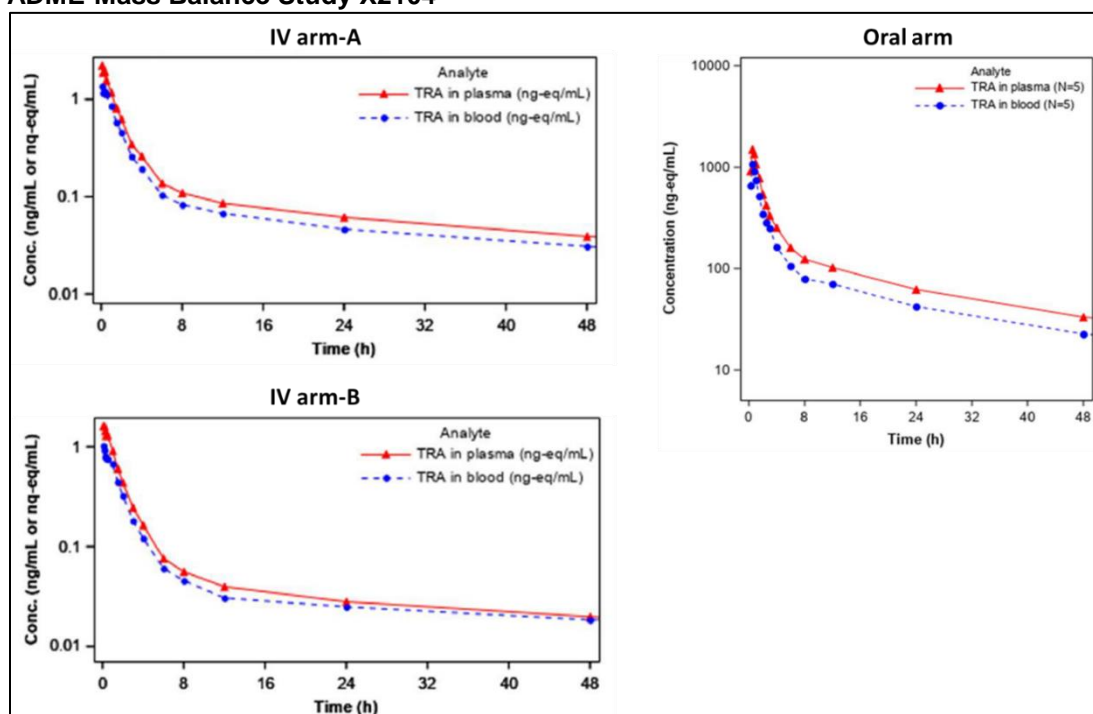
Oral Arm

Following administration of [¹⁴C]-remibrutinib, total radioactivity concentrations were quantifiable in plasma for up to 312 to 600 hours and in whole blood for up to 216 to 408 hours postdose. The AUC_{0-inf} of total radioactivity in plasma was marginally higher than that in whole blood (14900 h*ng-eq/mL versus 12700 h*ng-eq/mL) ([Table 47](#) and [Table 48](#), as well as [Figure 28](#)). The median elimination t_{1/2} of [¹⁴C]-remibrutinib was 250 hours in whole blood and 288 hours in plasma.

IV Arm

Total radioactivity concentrations were quantifiable in both plasma and whole blood up to 408 hours postdose. In IV Arm A and IV Arm B, the total radioactivity, as measured by AUC_{0-inf}, in whole blood and plasma were comparable (AUC_{0-inf} 16.9 versus 18.5 h*ng-eq/mL, respectively, in IV Arm A and 13.2 versus 12.8 h*ng-eq/mL, respectively, in IV Arm B), suggesting an equal distribution of total radioactivity between plasma and red blood cells ([Table 47](#), [Table 48](#), and [Figure 28](#)). The elimination t_{1/2} of total radioactivity in whole blood was 374 hours in IV Arm A and 435 hours in IV Arm B. The elimination t_{1/2} of total radioactivity in plasma was 291 hours in IV Arm A and 363 hours in IV Arm B.

Figure 28. Plasma and Whole Blood Concentration-Time Profiles of Total Radioactivity in the ADME-Mass Balance Study X2104



Source: Study X2104 Clinical Report, Figure 11-3 and 11-4

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; conc., concentration; h, hour; IV, intravenous; N, number of subjects in this analysis set; TRA, total radioactivity

Table 47. Summary Statistics of Total Radioactivity in Whole Blood in the ADME-Mass Balance Study X2104

Statistic	C _{max} (ng-eq/mL)	T _{max} (h)	AUC _{last} (h.ng-eq/mL)	AUC _{inf} (h.ng-eq/mL)	T _{1/2} (h)
Treatment arm: 100 mg LOU064 + 100 mg [¹⁴C]LOU064 Oral arm					
n	5	5	5	5	5
Mean (SD)	1140 (403)		8040 (2330)	12700 (7000)	366 (377)
CV (%) mean	35.3		28.9	55.3	103.0
Geo-mean	1090		7700	11200	257
CV (%) geo-mean	35.6		36.4	59.7	110.2
Median	1040	0.50	8190	11100	250
[Min, Max]	[712, 1750]	[0.50, 0.75]	[4200, 10000]	[5130, 24100]	[117, 1020]
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-A					
n	1	1	1	1	1
Mean (SD)	1.37 (-)		10.2 (-)	16.9 (-)	374 (-)
CV (%) mean					
Geo-mean					
CV (%) geo-mean					
Median		0.08			
[Min, Max]					
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-B					
n	1	1	1	1	1
Mean (SD)	1.03 (-)		7.37 (-)	13.2 (-)	435 (-)
CV (%) mean					
Geo-mean					
CV (%) geo-mean					
Median		0.13			
[Min, Max]					

Source: Study X2104 Clinical Report, Table 11-2

CV% = coefficient of variation (%) = (SD/mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)-1)* 100; geo-mean = geometric mean

For T_{max}, only median, min and max are displayed.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; C_{max}, maximum plasma concentration; geo, geometric; IV, intravenous; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Table 48. Summary Statistics of Total Radioactivity in Plasma in the ADME-Mass Balance Study X2104

Statistic	C _{max} (ng-eq/mL)	T _{max} (h)	AUC _{last} (h.ng-eq/mL)	AUC _{inf} (h.ng-eq/mL)	T _{1/2} (h)
Treatment arm: 100 mg LOU064 + 100 mg [¹⁴C]LOU064 Oral arm					
n	5	5	5	5	5
Mean (SD)	1600 (507)		11400 (3380)	14900 (3820)	275 (42.8)
CV (%) mean	31.7		29.6	25.7	15.6
Geo-mean	1540		11000	14500	272
CV (%) geo-mean	32.1		31.3	27.2	17.4
Median	1430	0.50	11400	15500	288
[Min, Max]	[1070, 2290]	[0.50, 0.75]	[7590, 15400]	[10100, 19600]	[201, 311]
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-A					
n	1	1	1	1	1
Mean (SD)	2.24 (-)		13.2 (-)	18.5 (-)	291 (-)
CV (%) mean					
Geo-mean					
CV (%) geo-mean					
Median		0.08			
[Min, Max]					
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-B					
n	1	1	1	1	1
Mean (SD)	1.62 (-)		8.29 (-)	12.8 (-)	363 (-)
CV (%) mean					
Geo-mean					
CV (%) geo-mean					
Median		0.13			
[Min, Max]					

Source: Study X2104 Clinical Report, Table 11-3

CV% = coefficient of variation (%) = (SD/mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)-1) * 100.; geo-mean = geometric mean

For T_{max}, only median, min and max are displayed.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; C_{max}, maximum plasma concentration; IV, intravenous; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration

Pharmacokinetics of Remibrutinib in Blood

After the administration of remibrutinib at a dose of 100 mg BID, steady-state conditions were achieved by Day 4 with an elimination t_{1/2} of 3.29 hours in the oral arm, 1.85 hours in IV Arm A and 2.06 hours in IV Arm B. A summary of the pharmacokinetic parameters of remibrutinib at steady state in blood is presented in [Table 49](#).

Table 49. Summary Statistics of Remibrutinib Concentrations in Plasma in the ADME-Mass Balance Study X2104

Statistic	C _{max,ss} (ng/mL)	T _{max,ss} (h)	C _{min,ss} (ng/mL)	C _{trough} (ng/mL)	AUC _{tau} (h.ng/mL)	T _{1/2} (h)	CL _{ss/F} (L/h)	V _{z/F} (L)	CL _r (L/h)
Treatment arm: 100 mg LOU064 + 100 mg [¹⁴C]LOU064 Oral									
n	5	5	5	5	5	5	5	5	5
Mean (SD)	745 (116)		3.42 (1.10)	3.42 (1.10)	901 (258)	3.29 (1.02)	118 (33.9)	576 (264)	0.917 (0.416)
CV (%) mean	15.5		32.0	32.0	28.6	31.0	28.6	45.7	45.3
Geo-mean	739		3.27	3.27	872	3.17	115	524	0.841
CV (%) geo-mean	14.4		34.5	34.5	29.4	30.4	29.4	53.5	49.8
Median	700	0.50	3.55	3.55	926	3.00	108	590	0.846
[Min, Max]	[662, 947]	[0.25, 0.50]	[2.17, 4.78]	[2.17, 4.78]	[600, 1280]	[2.42, 4.82]	[78.3, 167]	[274, 906]	[0.479, 1.47]
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-A									
n	1	1	1		1	1	1	1	1
Mean (SD)	89.5 (-)		3.88 (-)		266 (-)	1.85 (-)	376 (-)	1000 (-)	2.05 (-)
Geo-mean									
Median		1.33							
[Min, Max]									
Treatment arm: 100 mg LOU064 + 100 µg [¹⁴C]LOU064 IV arm-B									
n	1	1	1		1	1	1	1	1
Mean (SD)	59.3 (-)		1.65 (-)		140 (-)	2.06 (-)	713 (-)	2120 (-)	6.66 (-)
Geo-mean									
Median		1.13							
[Min, Max]									

Source: Study X2104 Clinical Report, Table 11-3

CV% = coefficient of variation(%) = (SD/mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)-1) * 100; geo-mean = geometric mean

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{tau}, area under the concentration-time curve over the dosing interval; CL_r, renal clearance; CL_{ss/F}, apparent oral clearance at steady state; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; geo, geometric; C_{trough}, trough concentration; IV, intravenous; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetics; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_{z/F}, apparent volume of distribution during terminal phase after oral administration

Metabolic Profile of Remibrutinib in Human Subjects

Metabolite patterns in blood, urine and feces were evaluated as AUC_{0-12h} (IV) or AUC_{0-24h} (oral) in blood, for up to 48 hours in urine, and for up to 96 (IV) or 144 hours (oral) in feces. The pool covering the period from 0 to 48 hours postdose in urine represented 95% of the mean total radioactivity excreted in urine in the oral arm (~24% of the dose) and 98% of that in the IV arms (~28% of the dose). The pool covering the period from 0 to 144 hours postdose in feces in the oral arm represented 94% of the mean total radioactivity excreted in feces (~32% of the dose). The pool covering the period from 24 to 96 hours postdose in feces in the IV arms represented 99% of the mean total radioactivity excreted in feces (~69% of the dose).

Oral Arm

Upon oral administration of 100-mg [¹⁴C]-remibrutinib, the parent remibrutinib was the predominant species in blood, constituting 16.7% of the blood ¹⁴C-AUC_{0-24h} (Table 50). Metabolic profiling in healthy subjects revealed that remibrutinib is metabolized into 18 distinct metabolites in blood, with none of these metabolites accounting for ≥10% of the total. The most abundant metabolites, accounting for a total of 11.2% of blood AUC_{0-24h}, were a mixture of two diastereomers, M68a and M68b. As the diastereomers are present in a 3:1 ratio, neither metabolite is considered major (i.e., accounts for >10% of total exposure). Remaining metabolites accounted for ≤6.3% of blood AUC_{0-24h}. The unchanged remibrutinib in excreta represented 1.86% of the administered dose.

NDA 218436
RHAPSIDO (remibrutinib, LOU064)

In urine, a total of 31 metabolites were identified, with metabolite M24 being the most abundant, comprising 3.49% of the dose (refer to Table 6-7, Study X2104 clinical study report Amendment 3). The amount of unchanged remibrutinib excreted in urine was 0.65% of the dose, suggesting negligible renal excretion of remibrutinib.

In feces, a total of 21 metabolites were detected, with M24 being the most prevalent, representing 7.22% of the dose (refer to Table 6-7, Study X2104 clinical study report Amendment 3). The amount of unchanged remibrutinib in feces was 1.21% of the dose, suggesting near complete absorption of remibrutinib ($F_a > 98\%$, assuming the compound is stable in the intestine) and extensive metabolism.

Table 50. Metabolic Profile of Remibrutinib in Blood Following Oral Administration in the ADME-Mass Balance Study X2104

Sample collection time (h)	AUC _{0-24h}	AUC _{0-24h}
Component ^{a)}	(ng·eq·h/mL) ^{c)}	% ^{b)}
Front Peak	196	6.08
M1	57.5	1.78
M70	133	4.14
M68a, M68b (EHT330)	360	11.2 ^{f)}
M2 (LSX574)	159	4.95
M69 (ETV952)	20.4	0.634
M6	24.2	0.752
M7 + M57	115	3.57
P1	33.3	1.03
P2	53.7	1.67
M15	74.1	2.30
M58	15.4	0.479
M19	60.3	1.87
M22 (LTP763)	22.1	0.686
M24 (DWC499)	204	6.33
M25	36.1	1.12
M28	98.3	3.05
M50	17.3	0.538
M31 (LQT456)	58.7	1.82
LOU064	540	16.7
Sum of additional components	97.6	3.03
Total detected	2380	73.7
Lost during sample processing ^{d)}	242	7.50
Lost during chromatography ^{e)}	605	18.8
Total radiolabeled components in original sample	3220	100

Source: Study X2104 Clinical Report- Amendment no. 3, Table 6-5

^{a)} Unknown components P1 and P2 accounted for 1.10 and 1.77% AUC_{0-24h} of RA, respectively.

^{b)} Percent of total radiolabeled components in original sample.

^{c)} Concentrations and AUCs rounded to three significant digits.

^{d)} Combined losses due to sample extraction and reconstitution.

^{e)} Losses observed in a HPLC column recovery experiment.

^{f)} Total exposure of both diastereoisomers (ratio 3/1 derived from human urine pool 0 to 48 hours).

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; h, hour; HPLC, high-performance liquid chromatography; LOU064, remibrutinib; RA, radioactivity

IV Arm

Following intravenous administration of 100- μ g [^{14} C]-remibrutinib, the parent compound remibrutinib was the most abundant component in blood, constituting 21.7% of the blood ^{14} C-AUC_{0-12h}. Thirteen metabolites were identified in the blood, with none representing $\geq 10\%$ of the total radioactivity (Table 51). Notably, metabolites M68a and M68b were detected and accounted for 6.8% of total radioactive components.

A total of 27 metabolites were detected in urine, with none exceeding 10% of the total radioactivity (refer to Table 6-8, Study X2104 clinical study report Amendment 3). The amount of unchanged remibrutinib excreted in urine was 2.93% of the administered dose.

In feces, a total of 21 metabolites were characterized, with M24 being the most prevalent, accounting for 16.9% of the dose. The remaining metabolites in feces each represented less than 10% of the dose (refer to Table 6-8, Study X2104 clinical study report Amendment 3). Unchanged remibrutinib was not detected in feces, indicating that remibrutinib is primarily eliminated through metabolic pathways.

Table 51. Metabolic Profile of Remibrutinib in Blood Following Intravenous Administration in the ADME-Mass Balance Study X2104

Subject #	(b) (6)		(b) (6)		Mean	
Sample collection time (h)	AUC _{0-12h}					
Component ^{a)}	(ng-eq·h/mL) ^{c)}	% ^{b)}	(ng-eq·h/mL) ^{c)}	% ^{b)}	(ng-eq·h/mL) ^{c)}	% ^{b)}
Front Peak	0.115	8.31	0.147	7.71	0.131	8.01
M70	0.0209	1.51	0.0342	1.79	0.0275	1.65
M68a, M68b (EHT330)	0.0830	5.99	0.145	7.58	0.114	6.79 ^{e)}
M2 (LSX574)	0.0339	2.45	0.0568	2.97	0.0453	2.71
M69 (ETV952)	0.0208	1.51	0.00625	0.327	0.0135	0.916
M6	0.0254	1.83	0.0124	0.648	0.0189	1.24
M7 + M57	0.0227	1.64	0.0362	1.89	0.0295	1.77
P1	0.00688	0.497	0.0174	0.912	0.0122	0.705
P2	0.0373	2.69	0.0500	2.62	0.0437	2.66
M15	0.108	7.84	0.0682	3.57	0.0883	5.70
M19	0.0492	3.55	0.0738	3.86	0.0615	3.71
M24 (DWC499)	0.0224	1.62	0.0889	4.65	0.0557	3.13
M28	0.00791	0.571	0.0285	1.49	0.0182	1.03
M31 (LTQ456)	0.00707	0.511	0.0245	1.28	0.0158	0.897
LOU064	0.310	22.4	0.401	21.0	0.356	21.7
Sum of additional components	0.513	4.27	0.721	0.616	0.617	2.44
Total detected	1.38	67.2	1.91	62.9	1.65	65.1
Lost during sample processing ^{d)}	0.676	32.8	1.13	37.1	0.902	35.0
Total radiolabeled components in original sample	2.06	100	3.04	100	2.55	100

Source: Study X2104 Clinical Report- Amendment no. 3, Table 6-6

^{a)} Unknown components P1 and P2 accounted for 0.705 and 2.66 AUC_{0-12h} of RA (mean across the subjects), respectively.

^{b)} Percent of total radiolabeled components in original sample.

^{c)} Concentrations and AUCs rounded to three significant digits.

^{d)} Combined losses due to sample extraction and reconstitution.

^{e)} Total exposure of both diastereomers (ratio 3/1 derived from human urine pool 0 to 48 hours).

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; h, hour; LOU064, remibrutinib; RA, relative availability

The fraction of the dose cleared by various metabolic pathways was estimated by assessing the data determined in excreta. A small fraction of the dose was recovered in unchanged remibrutinib in excreta. Therefore, remibrutinib is primarily cleared via metabolism. It is estimated that remibrutinib is primarily metabolized through oxidative pathways, with a lesser contribution from glutathione conjugation, as detailed in [Table 52](#).

Table 52. Contributions of the Various Metabolic Pathways in the Elimination of Remibrutinib in the ADME-Mass Balance Study X2104

Route of administration	p.o.	i.v.
% of administered dose analyzed in the combined urine and feces samples	53.1	95.8
Metabolic pathway	Fraction of the % of dose analyzed (%)	
Oxidative pathways	65.7	64.2
GSH pathway	15.6	12.7
Unchanged LOU064	3.50	3.06
Unknown ¹⁾	15.3	20.2

Source: Study X2104 Clinical Report—Amendment no. 3, Table 2-1; Study X2104 Clinical Report—Amendment no. 3, Figure 7-41

¹⁾ Includes unidentified components and losses due to sample preparation, extraction and reconstitution.

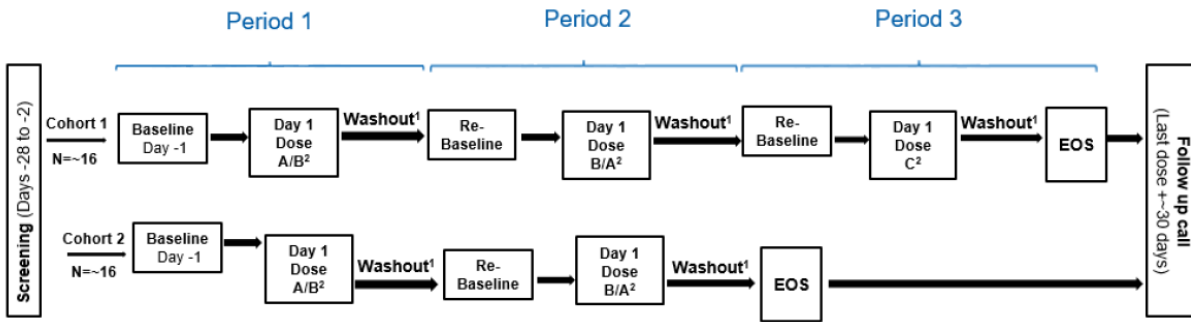
Abbreviations: ADME, absorption, distribution, metabolism, and excretion; GSH, glutathione; i.v., intravenous; p.o., oral administration

14.2.3. Relative Bioavailability Study Comparing HGC and FCT Drug Products, Study X2105

Study X2105 was a randomized, open-label, three-period study designed to evaluate the relative bioavailability of two formulations of remibrutinib: a FCT and a HGC ([Figure 29](#)). The HGC formulation was utilized in phase 1 and phase 2 clinical studies of remibrutinib. The selected FCT variant (variant selected [VS]) was employed in phase 3 trials and was compared against the HGC formulation. The FCT (VS) contains remibrutinib that was (b) (4) (b) (4) range as that in the HGC. Additionally, this study assessed the bioavailability of FCT (VS), with a particle size of approximately (b) (4) nM, in comparison to an alternative FCT variant (variant alternative [VA]), with a particle size of approximately (b) (4) nM. This comparison aimed to determine whether minor differences in the manufacturing process, specifically (b) (4), could influence the absorption rate and extent of remibrutinib.

All three remibrutinib formulations were administered to healthy adult subjects (aged 18 to 55 years) in the fasted state as a single oral dose of 100 mg (2x50 mg). Subjects were randomized 1:1 to one of two treatment sequences that varied the order of administering remibrutinib HGC and FCT (VS). Pharmacokinetic samples were collected in each period at predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, and 48 hours postdose. Bioequivalence between FCT (VS) and HGC remibrutinib 100 mg was established if the least-squares geometric mean ratio and its 90% CI fell within the predefined bioequivalence range of 80% to 125%. A washout period of 7 to 14 days separated each treatment period.

Figure 29. Study Design, Study X2105



Source: Study X2105 Clinical Report, Figure 9-1

¹ Minimum washout of at least 7 days beginning after the single oral morning dose in each period.

² Treatments:

A: single morning oral dose of 100-mg remibrutinib FCT (VS)

B: single morning oral dose of 100-mg remibrutinib HGC

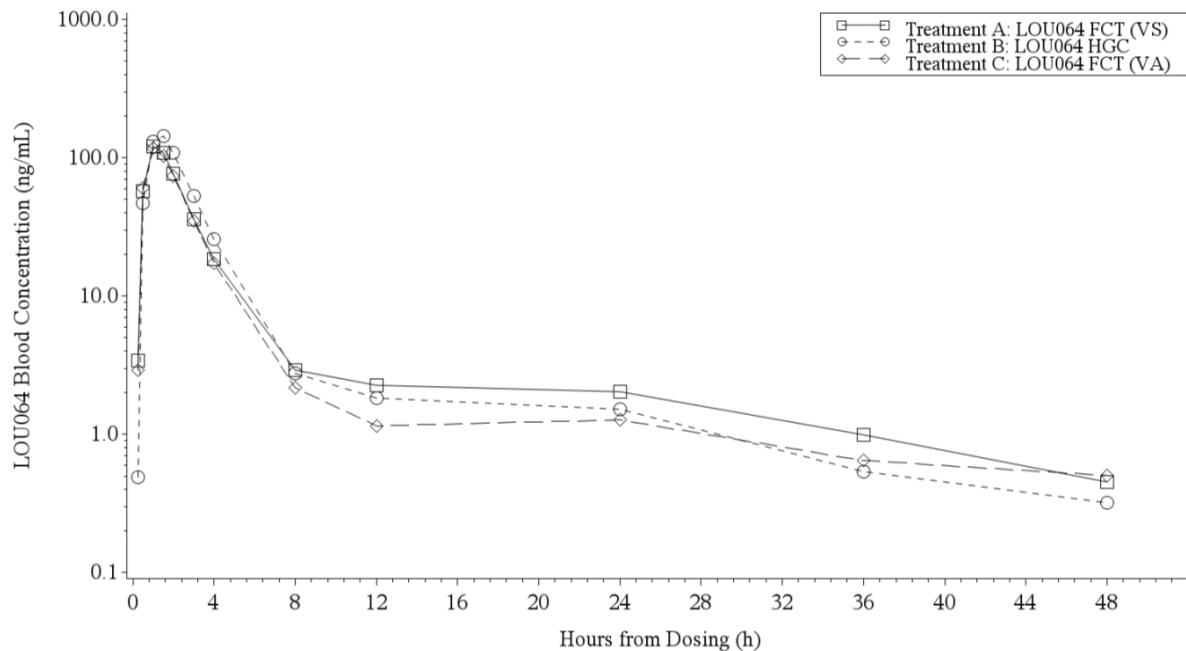
C: single morning oral dose of 100-mg remibrutinib FCT (VA)

Abbreviations: EOS, end of study; FCT, film-coated tablet; HGC, hard gelatin capsule; N, number of subjects; VA, variant alternative; VS, variant selected

Results

The blood concentration-time profiles of remibrutinib, along with a summary of pharmacokinetic parameters, following the administration of a single 100-mg dose of FCT (VS), FCT (VA), and HGC formulations, are presented in [Figure 30](#) and [Table 53](#).

Figure 30. Arithmetic Mean Blood Concentration-Time Profiles of Remibrutinib, Semilog Scale, Study X2105



Source: Study X2105 Clinical Report, Figure 11-2

Abbreviations: FCT, film-coated tablet; h, hour; HGC, hard gelatin capsule; N, number of subjects; VA, variant alternative; VS, variant selected

Table 53. Summary Statistics of Remibrutinib PK Parameters Following the Administration of 100 mg as FCT or HGC Formulations, Study X2104

Treatment	Statistic	C _{max} (ng/mL)	T _{max} (h)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	T _{1/2} (h)	CL/F (L/h)	V _z /F (L)
A	n	32	32	32	24	24	24	24
	Mean (SD)	140 (107)	.	347 (194)	383 (213)	11.6 (5.67)	373 (278)	6040 (4500)
	CV% mean	76.5	.	55.8	55.7	49.0	74.5	74.5
	Geo-mean	103	.	300	326	10.6	307	4680
	CV% geo-mean	102.7	.	61.2	67.1	43.0	67.1	84.5
	Median	106	1.00	303	339	9.55	295	4760
	[Min;Max]	[18.0, 421]	[0.500, 4.01]	[69.0, 912]	[71.3, 916]	[5.56, 25.2]	[109, 1400]	[1450, 19200]
B	n	31	31	31	24	24	24	24
	Mean (SD)	176 (98.5)	.	408 (191)	444 (203)	9.93 (5.59)	297 (190)	4190 (3270)
	CV% mean	56.1	.	46.9	45.8	56.2	64.0	78.1
	Geo-mean	148	.	364	393	8.63	254	3170
	CV% geo-mean	68.6	.	54.0	58.1	62.4	58.1	91.3
	Median	170	1.03	383	443	8.44	226	3180
	[Min;Max]	[32.6, 405]	[0.500, 2.04]	[115, 821]	[117, 822]	[1.36, 29.5]	[122, 853]	[553, 12300]
C	n	16	16	16	6	6	6	6
	Mean (SD)	140 (80.5)	.	309 (166)	310 (168)	10.7 (5.30)	434 (263)	7550 (7080)
	CV% mean	57.4	.	53.7	54.3	49.5	60.6	93.9
	Geo-mean	122	.	274	269	9.70	372	5200
	CV% geo-mean	57.5	.	53.4	66.9	51.5	66.9	121.5
	Median	126	1.00	255	310	8.63	334	5450
	[Min;Max]	[49.9, 349]	[0.499, 2.02]	[118, 749]	[126, 551]	[5.42, 17.7]	[181, 796]	[1840, 20300]

Source: Study X2105 Clinical Report, Table 11-1

Treatment: A = remibrutinib FCT (VS), B = remibrutinib HGC, C = remibrutinib FCT (VA)

CV% = coefficient of variation(%) = (SD/mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)-1) * 100.

For T_{max}, only median, min and max are displayed.

. = Value missing or not reportable

Blood remibrutinib concentrations were quantifiable in all subjects from 0.5 hours to 24 hours postdose following Treatments A and C and in all subjects from 0.5 hours to 12 hours postdose following Treatment B. Blood concentrations of remibrutinib remained quantifiable in 23/32 following remibrutinib FCT (VS) (Treatment A) and 17/31 following remibrutinib HGC (Treatment B) at 48 hours postdose. Blood concentrations of remibrutinib remained quantifiable in 15/16 subjects at 36 hours postdose and were quantifiable for 7/16 subjects with samples collected at 48 hours postdose following remibrutinib FCT (VA) (Treatment C).

The linear trapezoidal rule was used for AUC calculation. AUC_{0-inf} was not included in the statistical analysis when AUC%Extrap is >20%.

The PK parameters AUC_{0-inf}, AUC%Extrap, Lambda_z, t_{1/2}, CL/F, and Vz/F was not determined for 18 subjects in either treatment period, 8 subjects in Treatment A, 7 subjects in Treatment B, and 10 subjects in Treatment C, because they did not exhibit a terminal elimination phase or had an adjusted R² value of the regression analysis of the terminal phase <0.75

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time;; CL/F, apparent clearance; C_{max}, maximum plasma concentration; FCT, film-coated tablet; geo, geometric; HGC, hard gelatin capsule; max, maximum; min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; VA, variant alternative; VS, variant selected; Vz/F, apparent volume of distribution during terminal phase after oral administration

Statistical analysis of the pharmacokinetic parameters of remibrutinib revealed that the C_{max}, AUC_{last}, and AUC_{0-inf} of the remibrutinib FCT (VS) formulation were 28%, 16%, and 20% lower, respectively, compared to those of the remibrutinib HGC formulation ([Table 54](#) and [Table 55](#)). Additionally, the AUC_{last} and AUC_{0-inf} of the remibrutinib FCT (VS) formulation were 26.8% and 7.2% higher, respectively, while the C_{max} was 4.6% lower compared to the remibrutinib FCT (VA) formulation ([Table 54](#) and [Table 55](#)). Notably, the elimination phase was determined for only six subjects who received the FCT (VA) formulation. It was also noted that for nine subjects who received the FCT (VA) formulation, the 48-hour postdose PK sample was missing as blood collection tubes were not available. As a result, the AUC_{last} determined for the FCT (VA) formulation may have been underestimated, especially as blood concentrations at 48 hours postdose were quantifiable in the seven subjects from whom samples were collected. No change in median T_{max} was observed between the three formulations (about 1 hour for all formulations).

Table 54. Statistical Analysis of Remibrutinib Blood PK Parameter Values for Remibrutinib FCT (VS) vs. Remibrutinib HGC, Study X2105

Parameter	FCT (VS) (Test)		HGC (Reference)		GMR%	90% CI	Intrasubject CV%
	Geometric LSMs	n	Geometric LSMs	n			
C _{max} (ng/mL)	107	31	148	31	72.01	58.42-88.77	51.45
AUC _{last} (ng*hr/mL)	304	31	363	31	83.61	73.34-95.31	31.05
AUC _{0-inf} (ng*hr/mL)	301	23	374	24	80.47	68.34-94.75	28.99

Source: Study X2105 Clinical Report, Table 11-2

Intrasubject CV% was calculated as $100 \times \text{square root}(\exp[\text{MSE}]-1)$, where MSE = Residual variance from ANOVA.

The mixed-effects model for analysis of FCT (VS) versus HGC includes treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect.

The analysis of FCT (VS) versus HGC include subjects in the PK set with evaluable PK parameters for FCT (VS) versus HGC in Cohorts 1 and 2. Subject (b) (6) was excluded since this subject was dropped by the investigator on Day -1 of Period 2.

Abbreviations: ANOVA, analysis of variance; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FCT, film-coated tablet; GMR, geometric mean ratio; HGC, hard gelatin capsule; LSM, least-squares mean; MSE, mean square error; n, number of subjects; PK, pharmacokinetic; VS, variant selected

Table 55. Statistical Analysis of Remibrutinib Blood PK Parameter Values for Remibrutinib FCT (VS) vs. Remibrutinib FCT (VA), Study X2105

Parameter	FCT (VS) (Test)		FCT (VA) (Reference)		GMR%	90% CI	Intrasubject CV%
	Geometric LSMs	n	Geometric LSMs	n			
C _{max} (ng/mL)	117	16	122	16	95.4	66.50-136.8	63.52
AUC _{last} (ng*hr/mL)	294	16	274	16	107.21	79.65-144.3	50.84
AUC _{0-inf} (ng*hr/mL)	305	11	241	6	126.84	66.14-243.23	79.17

Source: Study X2105 Clinical Report, Table 11-3

Intrasubject CV% was calculated as $100 \times \text{square root}(\exp[\text{MSE}]-1)$, where MSE = Residual variance from ANOVA.

The mixed-effects model includes treatment and sequence as fixed effects and subject nested within sequence as a random effect.

This analysis includes subjects from the PK Set with evaluable PK parameters.

Abbreviations: ANOVA, analysis of variance; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; FCT, film-coated tablet; GMR, geometric mean ratio; LSM, least-squares mean; MSE, mean square error; n, number of subjects; PK, pharmacokinetic; VA, variant alternative; VS, variant selected

Overall, the systemic exposure to remibrutinib following oral administration of 100 mg of the FCT (VS) formulation was lower than that following administration of the HGC formulation. However, high variability in the PK parameters was observed. The AUC of the FCT (VS) formulation was greater than that observed with the FCT (VA) formulation. Results should be interpreted with caution due to missing samples among subjects who received the FCT (VA) formulation and inability to characterize the terminal elimination phase in most subjects. Although the magnitude of effect is unclear, differences in particle size due to changes in the manufacturing process do not appear to yield substantial differences in the systemic exposure.

14.2.4. Food-Effect Study Following Multiple Doses of Remibrutinib, Study A02104

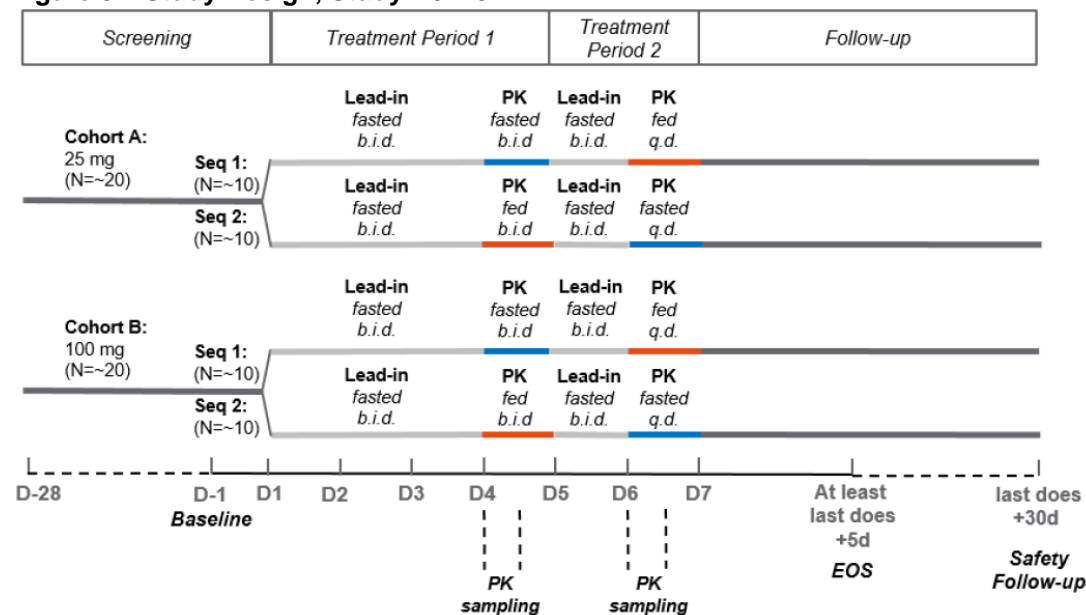
Study A02104 was a randomized, open-label, two-cohort, two-period, two-sequence, crossover study designed to evaluate the effect of food on the steady-state pharmacokinetics of multiple

doses of remibrutinib FCT 25 mg and 100 mg in healthy Chinese adult subjects. Although the exclusion criteria did not restrict the gender of enrolled subjects, only male subjects were enrolled. The study design is illustrated in [Figure 31](#). Subjects were randomized to one of two cohorts divided by dose (i.e., 25 mg or 100 mg). Within each cohort, subjects were randomized to one of two treatment sequences that varied the timing of prandial states. Remibrutinib was administered BID from Days 1 to 5. On Day 6, only the morning dose was administered. The test drug was provided as remibrutinib FCT 25 mg and 100 mg.

In the fed state, subjects received a high-fat, high-calorie breakfast (800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively). Remibrutinib was administered within 5 minutes after completion of the meal. For drug administration on Day 4 under fed conditions, only the morning dose of remibrutinib FCT 25 mg and 100 mg was taken after a standard high-fat breakfast. The evening dose was taken following a fast of at least 2 hours. For fasted and fed administration, subjects fasted for at least 10 hours before the morning dose (or the high-fat breakfast), and for at least 2 hours before the evening dose.

PK samples were collected after the Day 4 morning dose and the Day 6 dose, with PK sampling conducted up to 24 hours postdose.

Figure 31. Study Design, Study A02104



Source: Study A02104 Clinical Report, Figure 9-1

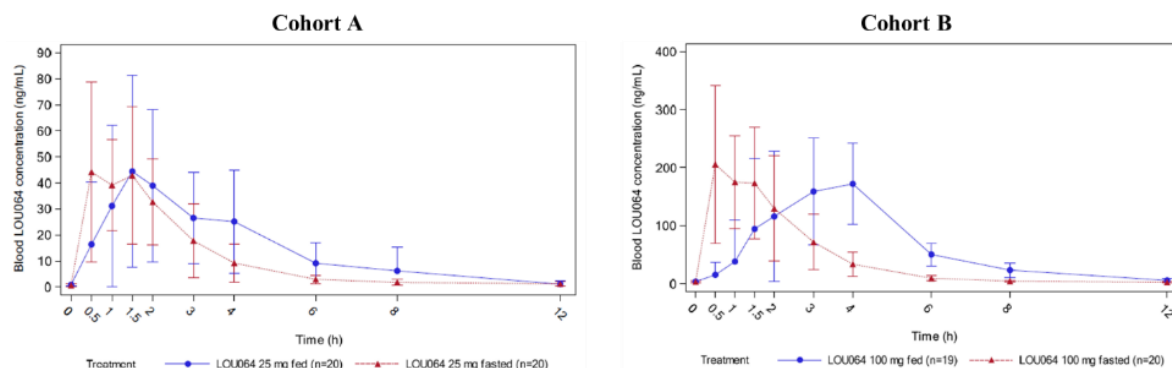
Per Study A02104 protocol, the breakfast was high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories), derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

Abbreviations: b.i.d., twice daily; D, day; EOS, end of study; N, number of subjects; PK, pharmacokinetic; q.d., once daily

Results

The concentration-time profiles of remibrutinib and its pharmacokinetic parameters, under both fasted and fed conditions, following the administration of remibrutinib at dosages of 25 mg BID and 100 mg BID, are presented in [Figure 32](#) and [Table 56](#). The PK data collected on Day 4 and Day 6 were pooled across treatment sequences.

Figure 32. Arithmetic Mean (SD) Blood Concentration-Time Profiles of Remibrutinib in Fasted and Fed States by Dose Cohort, Study A02104



Source: Study A02104 Clinical Report, Figure 11-1 and 11-2
Abbreviations: h, hour; LOU064, remibrutinib; n, number of subjects; SD, standard deviation

Table 56. Summary Statistics of Remibrutinib PK Parameters Concentrations in Blood in Fasted and Fed State, Study A02104

Parameter	Statistics	LOU064 25 mg fed	LOU064 25 mg fasted	LOU064 100 mg fed	LOU064 100 mg fasted
C _{max} (ng/mL)	n	20	20	19	20
	Mean (SD)	66.6 (30.1)	65.8 (24.7)	246 (76.8)	285 (91.0)
	CV%	45.2	37.6	31.2	31.9
	Geo-mean	58.9	61.9	233	268
	Geo-CV%	59.9	36.4	37.1	40.0
	Median	59.6	57.7	253	283
Min-Max		14.5-131	35.8-121	79.6-386	90.6-425
AUC _{0-12h} (h*ng/mL)	n	20	20	19	20
	Mean (SD)	178 (63.9)	133 (53.1)	760 (190)	534 (185)
	CV%	35.8	40.0	25.0	34.6
	Geo-mean	167	125	737	502
	Geo-CV%	42.3	33.6	26.2	38.4
	Median	167	118	707	484
Min-Max		43.6-368	72.3-315	439-1100	219-941
AUC _{0-4h} (h*ng/mL)	n	20	20	19	20
	Mean (SD)	114 (58.1)	110 (43.6)	407 (209)	464 (162)
	CV%	50.8	39.6	51.3	34.9
	Geo-mean	88.2	104	343	435
	Geo-CV%	128.0	35.3	76.2	39.3
	Median	119	100	323	417
Min-Max		2.80-206	58.2-249	54.6-754	181-837
CL/F (L/h)	n	18	18	18	20
	Mean (SD)	146 (27.7)	186 (47.2)	139 (38.0)	208 (82.9)
	CV%	19.0	25.3	27.3	39.8
	Geo-mean	143	180	135	195
	Geo-CV%	19.9	30.3	26.8	36.9
	Median	144	199	139	199
Min-Max		92.6-197	77.5-272	87.4-224	106-445
T _{max} (h)	n	20	20	19	20
	Median	2.00	1.00	3.00	0.500
	Min-Max	0.500-6.00	0.500-2.00	1.50-4.00	0.500-2.00

Source: Study A02104 Clinical Report, Table 11-1

n = number of subjects with corresponding evaluable PK parameters. CV% = (SD/arithmetic mean)

* 100; Geo-CV% = sqrt (variance for log-transformed data)-1) * 100.

Concentrations below the LLOQ were reported as "zero" and missing data were labeled as such

Abbreviations: AUC_{0-4h}, area under the concentration-time curve from time 0 to 4 hours; AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo-CV, geometric coefficient of variation; Geo-mean, geometric mean; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum plasma concentration

Upon administration of remibrutinib at a dose of 25 mg BID in the fed state to healthy Chinese adult male subjects, the C_{max} decreased by 5%, while the AUC_{0-12h} increased by 33%, and median T_{max} was extended by 1 hour compared to the fasted state (2 hours versus 1 hour, respectively). Similarly, when remibrutinib was administered at a dose of 100 mg BID in the fed state, the C_{max}

decreased by 15%, the AUC_{0-12h} increased by 43%, and the median T_{max} was prolonged by 2.5 hours relative to the fasted state (3 hours versus 0.5 hours, respectively). (Table 57).

Table 57. Statistical Analysis of Remibrutinib Blood PK Parameter Values for Remibrutinib 25 mg BID and Remibrutinib 100 mg BID in Fasted (Reference) and Fed (Test) States, Study A02104

Parameter	Treatment	Adjusted Geometric Mean	GMR (90% CI)
Remibrutinib 25 mg BID			
C _{max} (ng/mL) (N=20)	Fasted	61.9	0.951 (0.763-1.19)
	Fed	58.9	
AUC _{0-12h} (h.ng/mL) (N=20)	Fasted	125	1.33 (1.19-1.49)
	Fed	167	
Remibrutinib 100 mg BID			
C _{max} (ng/mL) (N=19)	Fasted	278	0.845 (0.723-0.988)
	Fed	235	
AUC _{0-12h} (h.ng/mL) (N=19)	Fasted	515	1.43 (1.22-1.69)
	Fed	739	

Source: Reviewer's generated table based on Study A02104 Clinical Report, Table 11-2 and 11-3

Model: Log-transformed remibrutinib primary PK parameters (C_{max}, AUC_{0-12h}) were analyzed using a mixed-effect model including treatment (fed versus fasted), period, sequence as fixed effects, and subject nested within sequence as random effect. The estimated treatment mean difference and corresponding 90% CI for the difference (fed versus fasted) were back-transformed to obtain geometric mean ratio (fed versus fasted) and corresponding 90% CI for the ratio.

Abbreviations: AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; N, number of observations used for analysis; PK, pharmacokinetic

14.2.5. Hepatic Impairment Study A2101

Study A2101 was an open-label study designed to evaluate the pharmacokinetics, safety, and tolerability of remibrutinib administered at a dose of 25 mg twice daily in adult subjects with mild (Child-Pugh Class A, score 5 to 6), moderate (Child-Pugh Class A, score 7 to 9), and severe (Child-Pugh Class A, score 10 to 15) HI compared to matched healthy adult subjects with normal hepatic function. The study also aimed to assess the plasma protein binding (unbound fraction [f_u]) of remibrutinib in subjects with mild, moderate, or severe HI and in matched healthy control subjects to investigate the potential impact of reduced plasma protein binding on the pharmacokinetics of remibrutinib.

An exploratory objective of this study was to examine the relationship between remibrutinib PK parameters and baseline measures of impaired hepatic function (e.g., prothrombin time, INR, bilirubin, albumin, AST, and Child-Pugh score, as appropriate) using a linear regression model.

The study was conducted in two parts:

- Part 1: Enrolled subjects with mild (Group 1) and moderate (Group 2) HI and matched healthy control subjects with normal hepatic function (Group 4)
- Part 2: Enrolled subjects with severe HI (Group 3) and matched healthy control subjects with normal hepatic function (Group 4)

Each subject in the healthy control group was matched with respect to gender, age (± 10 years), and body weight ($\pm 20\%$) to at least one and up to three evaluable subjects in the HI groups. Each control subject in Group 4 could be matched to any HI group (Groups 1, 2, and 3) but could not be matched to more than one subject from the same HI group.

Key inclusion criteria included males and females between 18 and 70 years of age (inclusive). Subjects with an estimated glomerular filtration rate of <45 mL/min/1.73 m² were excluded from Groups 1, 2, and 3 (i.e., HI groups).

All subjects received remibrutinib 25 mg (1x25 mg) BID orally under fasting conditions on Day 1 and Day 2, and a morning oral dose of remibrutinib 25 mg on Day 3 to achieve steady state. The PK samples were collected on Day 3 at predose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose. Blood collection for the determination of unbound drug was performed at 1 hour postdose on Day 3.

The PK parameters $C_{\max,ss,u}$, $AUC_{\tau,u}$, and $AUC_{\text{last},ss,u}$ were calculated using unbound plasma remibrutinib concentrations. The total plasma concentration of remibrutinib was calculated based on the measured blood concentrations of remibrutinib and the blood-to-plasma partitioning ratio of 0.955 determined at clinically relevant concentrations (refer to Section 14.1). The unbound plasma concentrations were calculated from the total plasma concentration multiplied by the fraction unbound determined from samples collected 1 hour postdose on Day 3.

Results

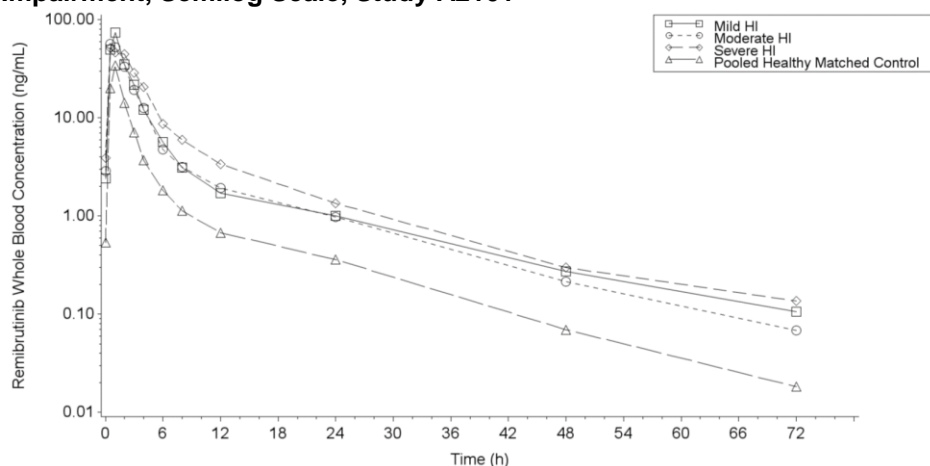
The study enrolled eight subjects with mild HI, eight subjects with moderate HI, seven subjects with severe HI, and 15 matched controls with normal hepatic function. All subjects completed the study. Among subjects with HI, the median (min, max) Child-Pugh scores were as follows:

- Mild HI: 5 (5, 6)
- Moderate HI: 7 (7, 8)
- Severe HI: 10 (10, 11)

Whole Blood Remibrutinib Pharmacokinetics

The blood concentration-time profiles of remibrutinib following the administration of remibrutinib 25 mg BID in subjects with normal hepatic function, and subjects with mild, moderate, or severe HI are illustrated in [Figure 33](#). The blood PK parameters of remibrutinib on Day 3 for all study groups is presented in [Table 58](#). The $C_{\max,ss}$ values were elevated in all HI groups (65, 57, and 60.8 ng/mL for mild, moderate, and severe HI subjects, respectively) compared to the normal hepatic function group (30.1 ng/mL). Notably, $C_{\max,ss}$ values were comparable among the three HI groups. Similarly, the geometric means AUC_{τ} and AUC_{last} were higher in all HI groups compared to the normal hepatic function group. Specifically, AUC_{τ} values were 60.5, 151, 147, and 204 ng·h/mL for subjects with normal hepatic function, and subjects with mild, moderate, and severe HI, respectively ([Table 58](#)). The $T_{\max}$, ranging from 0.42 to 2 hours, was comparable across all hepatic function groups. It is noteworthy that the arithmetic mean predose blood concentrations of remibrutinib on Day 3 were 0.539 ng/mL in subjects with normal hepatic function and 2.41 ng/mL, 2.88 ng/mL, and 3.93 ng/mL in subjects with mild, moderate, and severe HI, respectively. Furthermore, the terminal $t_{1/2}$ appeared to be prolonged, and the apparent oral clearance at steady state (CL_{ss}/F) and apparent volume of distribution at steady state (V_{ss}/F) were elevated in the HI groups compared to the normal hepatic function group.

Figure 33. Arithmetic Mean Remibrutinib Whole Blood Concentration-Time Profiles in Hepatic Impairment, Semilog Scale, Study A2101



Source: Study A2101 Clinical Report, Figure 11-3
Blood remibrutinib remained quantifiable in 2/15 healthy matched control subjects, 2/8 mild HI subjects, 3/7 moderate HI subjects, and 6/7 severe HI subjects at 72 hours postdose.
Abbreviations: h, hour; HI, hepatic impairment

Table 58. Summary Statistics of Blood Remibrutinib PK Parameters in Hepatic Impairment, Study A2101

Group	Statistic	C _{max,ss} (ng/mL)	T _{max,ss} (h)	AUC _{tau} (ng·h/mL)	AUC _{last,ss} (ng·h/mL)	T _{1/2} (h)	CL _{ss} /F (L/h)	V _z /F (L)
Pooled Healthy Matched Control	n	15	15	15	15	12	15	12
	Mean (SD)	36.7 (19.1)	.	71.6 (36.6)	82.5 (45.8)	9.70 (5.56)	544 (569)	5330 (4850)
	CV% mean	52.1	.	51.1	55.5	57.3	104.5	91.0
	Geo-mean	30.1	.	60.5	69.4	8.15	413	4240
	CV% geo-mean	88.1	.	76.4	75.2	71.9	76.4	71.4
	Median	39.9	0.98	79.9	87.2	9.87	313	3670
[Min, Max]	[4.23, 70.2]	[0.42, 2.00]	[10.2, 148]	[12.2, 196]	[3.13, 21.4]	[169, 2460]	[1870, 19800]	
Mild HI	n	8	8	8	8	7	8	7
	Mean (SD)	77.5 (49.2)	.	180 (127)	214 (152)	13.9 (5.71)	192 (113)	3830 (3260)
	CV% mean	63.5	.	70.7	71.0	41.2	58.8	85.1
	Geo-mean	65.0	.	151	179	12.6	165	2960
	CV% geo-mean	72.2	.	66.8	66.6	54.2	66.8	86.7
	Median	63.4	0.96	139	154	14.0	180	2640
[Min, Max]	[21.7, 176]	[0.78, 1.00]	[57.2, 467]	[74.5, 543]	[4.81, 21.1]	[53.6, 437]	[1230, 10600]	
Moderate HI	n	7	7	7	7	6	7	6
	Mean (SD)	67.3 (40.3)	.	163 (77.1)	195 (81.8)	14.8 (6.86)	188 (95.7)	3060 (970)
	CV% mean	60.0	.	47.4	41.9	46.2	51.0	31.7
	Geo-mean	57.0	.	147	179	13.6	170	2920
	CV% geo-mean	70.7	.	51.4	48.2	47.6	51.4	37.0
	Median	61.7	0.92	152	203	12.5	164	3040
[Min, Max]	[23.1, 128]	[0.42, 1.95]	[66.8, 306]	[80.9, 338]	[8.44, 24.5]	[81.6, 374]	[1530, 4550]	
Severe HI	n	7	7	7	7	7	7	7
	Mean (SD)	62.3 (15.9)	.	208 (48.4)	261 (59.3)	16.9 (9.75)	125 (25.5)	3020 (1890)
	CV% mean	25.6	.	23.2	22.7	57.8	20.4	62.6
	Geo-mean	60.8	.	204	256	14.9	123	2630
	CV% geo-mean	23.9	.	22.2	23.1	56.6	22.2	58.9
	Median	54.8	0.53	188	246	13.4	133	2780
[Min, Max]	[48.3, 92.1]	[0.48, 2.00]	[165, 278]	[192, 341]	[8.67, 33.2]	[89.9, 151]	[1350, 6910]	

Source: Study A2101 Clinical Report, Table 11-1
CV% = coefficient of variation (%) = (SD/Mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)⁻¹) * 100.
For T_{max,ss}, only median, minimum and maximum are displayed.
One subject with mild HI, one subject with moderate HI and three healthy subjects did not have a terminal elimination phase and therefore t_{1/2} and V_z/F could not be calculated for these subjects.
Subject (b) (6) (Moderate HI) was excluded from the PK set due to protocol deviations involving sample processing that impacted PK and did not have at least one calculable primary PK parameter.
Abbreviations: AUC_{last,ss}, area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau}, area under the concentration-time curve over the dosing interval; CL_{ss}/F, apparent oral clearance at steady state; C_{max,ss}, maximum plasma concentration at steady state; geo-mean, geometric mean; HI, hepatic impairment; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max,ss}, time to maximum plasma concentration at steady state; V_z/F, apparent volume of distribution during terminal phase after oral administration

Based on whole blood remibrutinib concentrations, the geometric mean ratios for mild, moderate, and severe HI compared to controls with normal hepatic function were determined as

follows: for $C_{max,ss}$, the ratios were 1.85, 1.65, and 1.99, respectively; for AUC_{tau} , the ratios were 2.15, 2.07, and 3.12, respectively; and for $AUC_{last,ss}$, the ratios were 2.33, 2.3, and 3.49, respectively ([Table 59](#)).

Table 59. Statistical Analysis of Remibrutinib Blood PK Parameter Values for Remibrutinib 25 mg BID Between Healthy Subjects and Subjects With Hepatic Impairment, Study A2101

Comparison	Parameter (unit)	Test		Reference		GMR	90% CI	Group Inter-Participant CV%	
		Geometric LSMS	n	Geometric LSMS	n			Test	Reference
Mild HI (Test) vs Pooled Healthy Matched Control (Reference)	$C_{max,ss}$ (ng/mL)	62.0	8	33.6	15	1.85	1.22 - 2.80	36.00	86.19
	AUC_{tau} (ng·h/mL)	147	8	68.4	15	2.15	1.53 - 3.04	35.43	62.39
	$AUC_{last,ss}$ (ng·h/mL)	177	8	75.9	15	2.33	1.56 - 3.48	45.39	66.85
Moderate HI (Test) vs Pooled Healthy Matched Control (Reference)	$C_{max,ss}$ (ng/mL)	55.4	7	33.6	15	1.65	0.93 - 2.92	72.31	86.19
	AUC_{tau} (ng·h/mL)	141	7	68.4	15	2.07	1.37 - 3.12	46.76	62.39
	$AUC_{last,ss}$ (ng·h/mL)	175	7	75.9	15	2.30	1.53 - 3.46	42.38	66.85
Severe HI (Test) vs Pooled Healthy Matched Control (Reference)	$C_{max,ss}$ (ng/mL)	66.9	7	33.6	15	1.99	1.24 - 3.19	34.09	86.19
	AUC_{tau} (ng·h/mL)	214	7	68.4	15	3.12	1.98 - 4.94	49.98	62.39
	$AUC_{last,ss}$ (ng·h/mL)	265	7	75.9	15	3.49	2.27 - 5.37	39.17	66.85

Source: Study A2101 Clinical Report, Table 11-4

Natural log (ln)-transformed PK parameters ($C_{max,ss}$, AUC_{tau} , and $AUC_{last,ss}$) were analyzed using an analysis of covariance (ANCOVA) model with group as fixed factor and gender, age, and weight as covariates to compare each of the HI groups (mild, moderate, and severe) to the pooled healthy control group (healthy subjects). A model was run for each PK parameter. Least-squares means (LSMs) for each group as well as the difference between each HI group and the pooled healthy control group along with the corresponding 90% confidence interval (CI) on the ln-scale were calculated for each PK parameter.

Geometric Mean Ratio = Test/Reference

Group intersubject CV% was calculated as $100 \times \text{square root}(\exp[\text{MSE}] - 1)$, where MSE = Group specific residual variance from ANCOVA.

Subject (b) (6) (Moderate HI) was excluded from the PK set due to protocol deviations involving sample processing that impacted PK and did not have at least one calculable primary PK parameter.

Abbreviations: $AUC_{last,ss}$, area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau} , area under the concentration-time curve over the dosing interval; BID, twice daily; CI, confidence interval; $C_{max,ss}$, maximum plasma concentration at steady state; CV, coefficient of variation; GMR, geometric mean ratio; HI, hepatic impairment; LSM, least-squares mean; MSE, mean square error; n, number of subjects; PK, pharmacokinetic

Unbound Remibrutinib Plasma Pharmacokinetics

The plasma protein binding of remibrutinib was determined by ultrafiltration. Radiolabeled [^{14}C]-remibrutinib was added ex vivo to clinical samples and the concentrations were determined by liquid scintillation counting. The mean f_u of remibrutinib, measured at the 1-hour postdose time point on Day 3, was found to be comparable across subjects with normal hepatic function ($f_u = 0.0472$) and subjects with mild ($f_u = 0.0465$), moderate ($f_u = 0.0474$), and severe ($f_u = 0.0438$) HI. Similar to what was observed based on total blood pharmacokinetics, the PK parameters of unbound remibrutinib in plasma, including $C_{max,ss,u}$, $AUC_{tau,u}$, and $AUC_{last,ss,u}$, were elevated in all HI groups compared to subjects with normal hepatic function ([Table 60](#)). Based on unbound plasma remibrutinib concentrations, the geometric mean ratios for mild, moderate, and severe HI compared to healthy controls were as follows: 1.9, 1.63, and 1.76 for $C_{max,ss,u}$; 2.14, 2.0, and 2.78 for $AUC_{tau,u}$; and 2.29, 2.2, and 3.09 for $AUC_{last,ss,u}$, respectively ([Table 61](#)).

Table 60. Summary Statistics of Unbound Remibrutinib Plasma PK Parameters in Hepatic Impairment, Study A2101

Group	Statistic	C _{max,ss,u} (ng/mL)	AUC _{tau,u} (ng·h/mL)	AUC _{last,ss,u} (ng·h/mL)
Pooled Healthy Matched Control	n	15	15	15
	Mean (SD)	1.75 (0.897)	3.45 (1.86)	3.99 (2.36)
	CV% mean	51.2	53.9	59.0
	Geo-mean	1.47	2.95	3.39
	CV% geo-mean	78.3	69.1	69.1
Mild HI	Median	1.90	2.96	3.86
	[Min, Max]	[0.257, 3.36]	[0.618, 7.84]	[0.741, 10.4]
	n	8	8	8
	Mean (SD)	4.04 (3.47)	9.60 (9.38)	11.4 (11.0)
	CV% mean	85.9	97.7	96.6
Moderate HI	Geo-mean	3.12	7.27	8.62
	CV% geo-mean	85.8	84.1	84.8
	Median	2.97	6.47	7.23
	[Min, Max]	[1.04, 12.0]	[2.74, 31.7]	[3.57, 36.9]
	n	7	7	7
Severe HI	Mean (SD)	2.95 (1.31)	7.49 (2.66)	9.08 (2.99)
	CV% mean	44.5	35.6	32.9
	Geo-mean	2.73	7.06	8.59
	CV% geo-mean	43.8	39.9	39.2
	Median	2.35	7.16	9.42
Severe HI	[Min, Max]	[1.70, 5.01]	[3.43, 12.3]	[4.15, 13.6]
	n	7	7	7
	Mean (SD)	2.79 (0.580)	9.72 (3.77)	12.0 (4.21)
	CV% mean	20.8	38.8	35.0
	Geo-mean	2.73	9.15	11.5
Severe HI	CV% geo-mean	24.8	38.3	34.1
	Median	2.98	9.19	11.7
	[Min, Max]	[1.63, 3.35]	[5.64, 17.0]	[7.06, 20.3]

Source: Study A2101 Clinical Report, Table 11-3

CV% = coefficient of variation (%) = (SD/Mean)*100; CV% geo-mean = sqrt (exp(variance for log-transformed data)-1) * 100.

Subject (b) (6) (Moderate HI) was excluded from the PK set due to protocol deviations involving sample processing that impacted pharmacokinetics and did not have at least 1 calculable primary PK parameter.

Abbreviations: AUC_{last,ss,u}, unbound area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau,u}, unbound area under the concentration-time curve over the dosing interval; C_{max,ss,u}, unbound maximum plasma concentration at steady state; geo-mean; geometric mean; HI, hepatic impairment; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation

Table 61. Statistical Analysis of Unbound Remibrutinib Plasma PK Parameter Values for Remibrutinib 25 mg BID Between Healthy Subjects and Subjects With Hepatic Impairment, Study A2101

Comparison	Parameter (unit)	Test		Reference		GMR	90% CI	Group Inter-Participant CV%	
		Geometric LSMs	n	Geometric LSMs	n			Test	Reference
Mild HI (Test) vs Pooled Healthy Matched Control (Reference)	C _{max,ss,u} (ng/mL)	3.04	8	1.60	15	1.90	1.20 - 3.00	55.04	72.49
	AUC _{tau,u} (ng·h/mL)	7.13	8	3.34	15	2.14	1.44 - 3.17	51.54	53.52
	AUC _{last,ss,u} (ng·h/mL)	8.52	8	3.73	15	2.29	1.46 - 3.57	60.41	58.65
Moderate HI (Test) vs Pooled Healthy Matched Control (Reference)	C _{max,ss,u} (ng/mL)	2.62	7	1.60	15	1.63	1.05 - 2.55	47.28	72.49
	AUC _{tau,u} (ng·h/mL)	6.67	7	3.34	15	2.00	1.35 - 2.95	43.65	53.52
	AUC _{last,ss,u} (ng·h/mL)	8.20	7	3.73	15	2.20	1.47 - 3.29	43.34	58.65
Severe HI (Test) vs Pooled Healthy Matched Control (Reference)	C _{max,ss,u} (ng/mL)	2.83	7	1.60	15	1.76	1.13 - 2.75	36.39	72.49
	AUC _{tau,u} (ng·h/mL)	9.29	7	3.34	15	2.78	1.67 - 4.65	64.03	53.52
	AUC _{last,ss,u} (ng·h/mL)	11.5	7	3.73	15	3.09	1.93 - 4.96	52.06	58.65

Source: Study A2101 Clinical Report, Table 11-5

Natural log (ln)-transformed PK parameters (C_{max,ss,u}, AUC_{tau,u}, and AUC_{last,ss,u}) were analyzed using an analysis of covariance (ANCOVA) model with group as fixed factor and gender, age, and weight as covariates to compare each of the HI groups (mild, moderate, and severe) to the pooled healthy control group (healthy subjects). A model was run for each PK parameter. Least-squares means (LSMs) for each group as well as the difference between each HI group and the pooled healthy control group along with the corresponding 90% confidence interval (CI) on the ln-scale were calculated for each PK parameter.

Geometric mean ratio = Test/Reference

Group intersubject CV% was calculated as 100 x square root (exp[MSE]-1), where MSE = Group specific residual variance from ANCOVA.

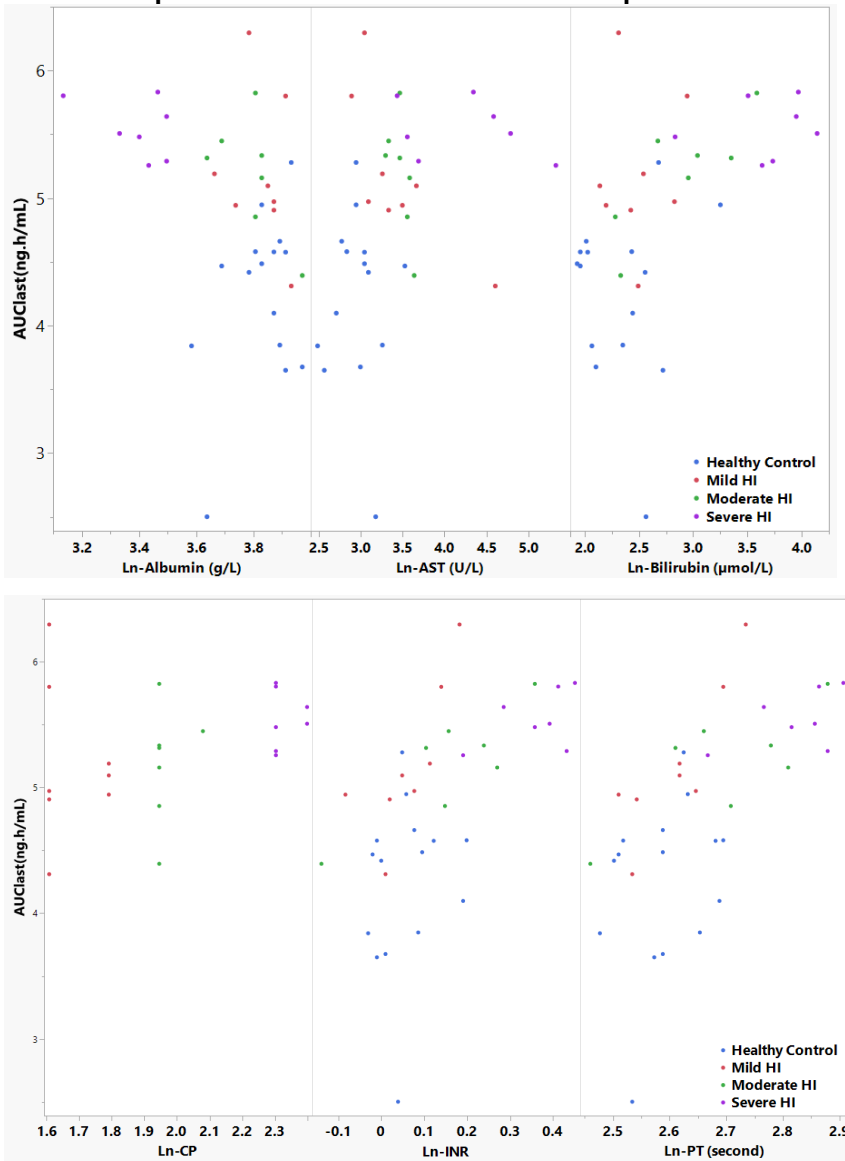
Subject (b) (6) (Moderate HI) was excluded from the PK set due to protocol deviations involving sample processing that impacted pharmacokinetics and did not have at least 1 calculable primary PK parameter.

Abbreviations: AUC_{last,ss,u}, unbound area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau,u}, unbound area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max,ss,u}, unbound maximum plasma concentration at steady state; CV, coefficient of variation; GMR, geometric mean ratio; HI, hepatic impairment; LSM, least-squares mean; MSE, mean square error; n, number of subjects; PK, pharmacokinetic

Relationship Between Remibrutinib Blood PK Parameters and Hepatic Function Parameters

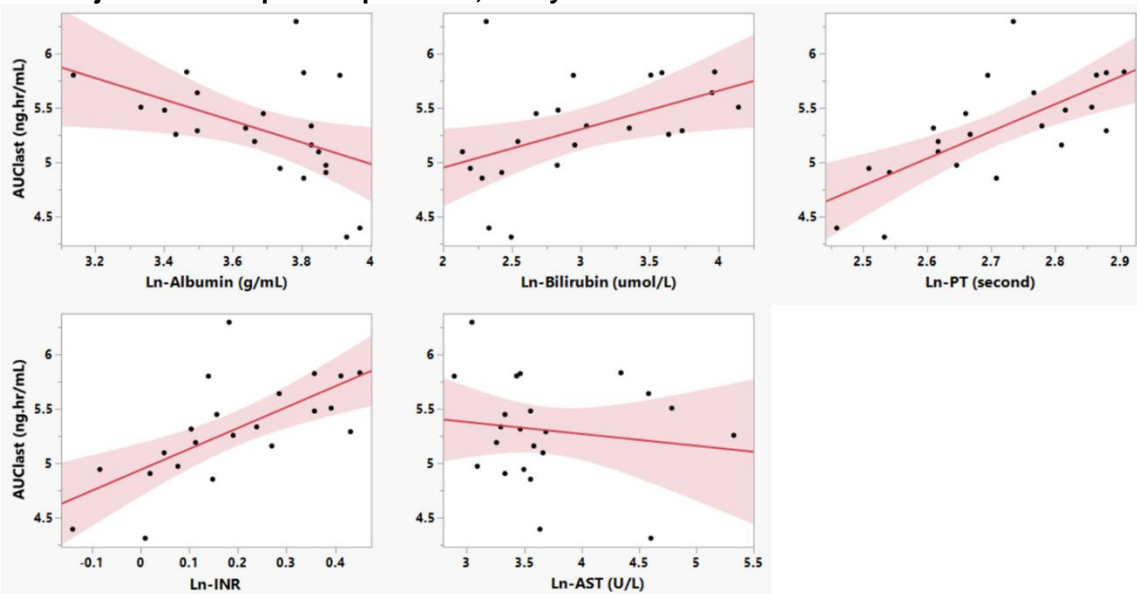
The associations between blood remibrutinib exposure and hepatic function parameters were explored using a linear regression model to predict the natural logarithm-transformed $AUC_{last,ss}$ based on logarithm-transformed baseline hepatic function measures. The hepatic function measures included baseline prothrombin time, albumin, bilirubin, AST, and INR. The exploratory analysis showed an apparent relationship between remibrutinib $AUC_{last,ss}$ and different hepatic function measures (Figure 34 and Figure 35).

Figure 34. Scatter Plots of Blood Ln-Transformed $AUC_{last,ss}$ of Remibrutinib and Ln-Transformed Baseline Hepatic Function Measures for Each Hepatic Function Group, Study A2101



Source: Reviewer's analysis using ADPC.xpt and ADPP.xpt data
Abbreviations: AST, aspartate aminotransferase; AUC, area under the concentration-time curve; CP, Child-Pugh; HI, hepatic impairment; INR, international normalized ratio; PT, prothrombin time

Figure 35. Linear Regression Plot With Two-Sides 95% Confidence Interval of Blood Ln-Transformed $AUC_{last,ss}$ of Remibrutinib and Ln-Transformed Baseline Hepatic Function Measures for Subjects With Hepatic Impairment, Study A2101



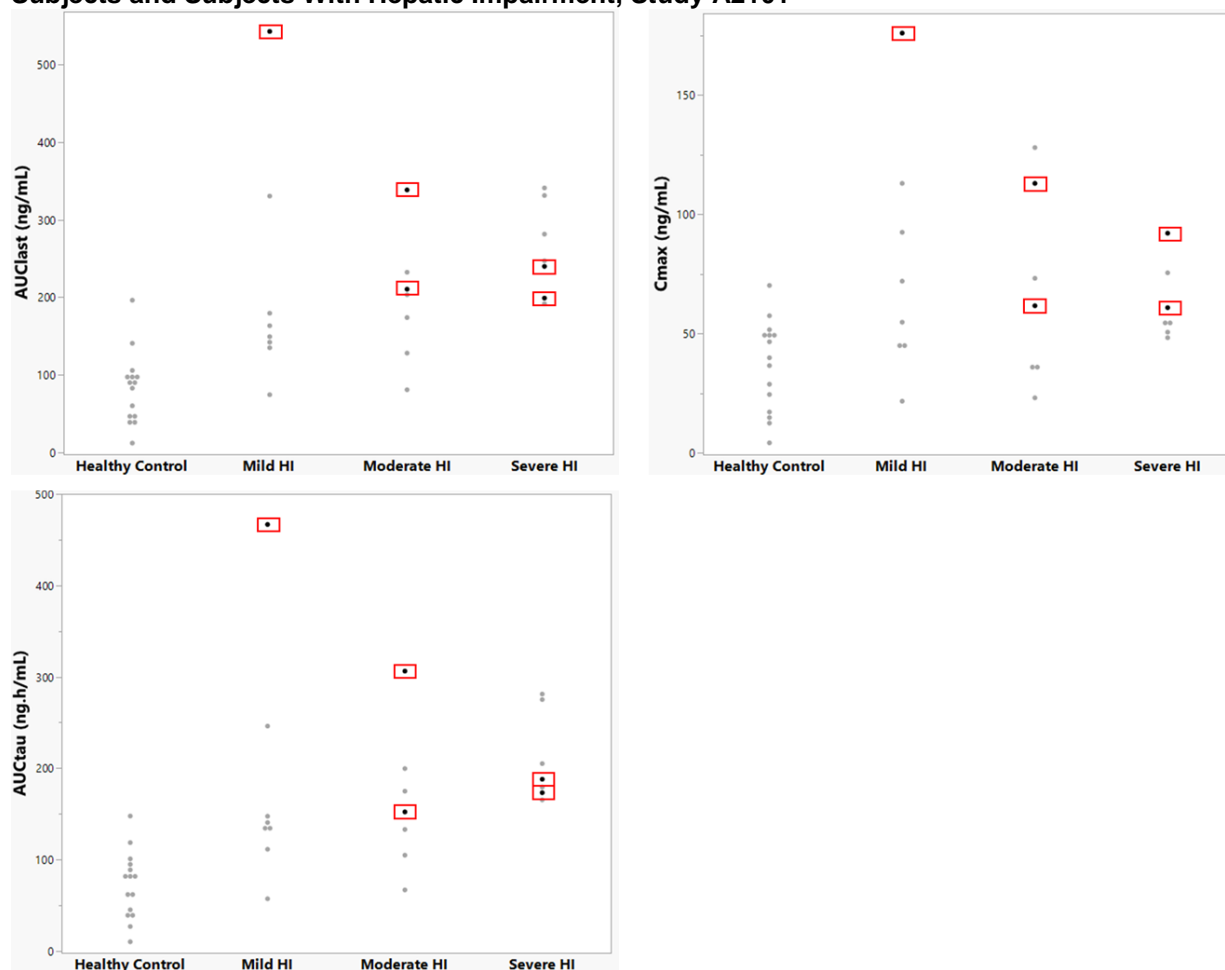
Source: Reviewer's analysis using ADPC.xpt and ADPP.xpt data Study A2101

Abbreviations: $AUC_{last,ss}$, area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; HI, hepatic impairment; INR, international normalized ratio; PT, prothrombin time

Impact of Concomitant Treatment

The Applicant restricted the enrollment of subjects on Legalon, a phytopharmaceutical preparation derived from *Silybum marianum* (L.) (an extract of milk thistle). Per the European Medicines Agency Committee on Herbal Medicinal Products, milk thistle fruit can be used to support liver function. Notably, Study A2101 enrolled subjects from a single site in Hungary. Thus, use of milk thistle products among subjects with HI was possible. The restriction on Legalon usage in Study A2101 was implemented following an observation of elevated remibrutinib exposure in subjects who coadministered remibrutinib with Legalon. Specifically, one subject (b) (6) with mild HI, two subjects (b) (6) with moderate HI, and two subjects (b) (6) with severe HI coadministered Legalon. Notably, subject (b) (6) with mild HI showed significantly higher C_{max} and AUC of remibrutinib compared to other subjects within the same group. One of the two subjects with moderate HI on Legalon exhibited higher remibrutinib exposure compared to other subjects within the same HI group (Figure 36). It is important to note that the exposure to remibrutinib in the two subjects with severe HI and one subject with moderate HI fell within the range observed in other subjects within their respective HI groups (Figure 36). The Applicant hypothesized that the increased exposure to remibrutinib when coadministered with Legalon could be attributed to the inhibition of CYP3A4 as remibrutinib was identified as a substrate of CYP3A4. Based on literature reports, in vitro studies have indicated that milk thistle may decrease CYP3A4 activity by 50% (Venkataramanan et al. 2000). However, clinical studies reported in the literature indicated that silymarin products do not alter midazolam exposure (Gurley et al. 2006; Kawaguchi-Suzuki et al. 2014).

Figure 36. Scattered Plot of Blood $AUC_{last,ss}$, AUC_{tau} , and $C_{max,ss}$ of Remibrutinib in Healthy Control Subjects and Subjects With Hepatic Impairment, Study A2101



Source: Reviewer Analysis using ADPC.xpt data

Black dots in red squares represent subjects on Legalon.

Abbreviations: AUC_{last} , area under the concentration-time curve from time zero to the last measurable concentration sampling time; $AUC_{last,ss}$, area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau} , area under the concentration-time curve over the dosing interval; $C_{max,ss}$, maximum plasma concentration at steady state; HI, hepatic impairment

Given the potential for milk thistle products to inhibit CYP3A4 activity, it is possible that the true effect of HI on the pharmacokinetics of remibrutinib may have been overestimated. Elevated remibrutinib exposure relative to remaining subjects in the respective HI group was only observed in one subject with mild HI and one subject with moderate HI, both of whom were concomitantly taking Legalon. Thus, conclusions for subjects with mild HI and subjects with moderate HI may have been impacted. The magnitude of increase in C_{max} , AUC_{last} , and AUC_{tau} was higher in mild HI versus moderate HI when compared to subjects with normal hepatic function. This observation may be attributed to the higher exposure observed in Subject (b) (6) in the mild HI group. For the remaining subjects on Legalon, although remibrutinib exposure was comparable to that in other subjects with a similar HI severity, it is still possible that PK parameters were elevated. However, given that there is conflicting evidence regarding the impact of milk thistle products on CYP3A4 activity, the impact of HI on remibrutinib exposure will consider data from all subjects irrespective of use of milk thistle products.

14.2.6. Drug-Drug Interaction

14.2.6.1. CYP3A4 Inhibitors (Ritonavir and Grapefruit Juice), Study X2103

In vitro investigations demonstrated that the primary clearance pathway of remibrutinib is oxidative metabolism mediated by CYP3A4. Study X2103 was designed as an open-label, single-sequence, crossover study to assess the impact of ritonavir (RTV), a strong inhibitor of both intestinal and hepatic CYP3A4/P-gp, and grapefruit juice (GFJ), a moderate to strong inhibitor of intestinal CYP3A4, on the exposure to oral remibrutinib in healthy adult subjects under fasted conditions. Secondary objectives of this study included the determination of the fraction of oral remibrutinib that escapes gut metabolism (F_{gut}).

A detailed description of the study design is provided in [Figure 37](#).

Period 1 (Reference Period)

Day 1 and 2 (Lead-In)

Single oral dose of remibrutinib 50 mg was administered on the morning of Day 1 and Day 2, after an overnight fast of at least 10 hours. The remibrutinib doses on Day 1 and Day 2 were given 24 hours apart.

Day 3

Subjects were given approximately 240 mL of 10% glucose (to mimic GFJ caloric content) after an overnight fast of at least 9 hours. One hour later, a single oral dose of remibrutinib 50 mg was administered, followed by IV bolus administration of 100 μg stable-isotope-labeled (SIL)-remibrutinib 2 hours after the oral dose. Blood samples were collected for up to 24 hours for remibrutinib and SIL-remibrutinib measurements.

Period 2 (GFJ Period)

Day 4 (Baseline and Lead-In)

Following baseline assessment, a single 50-mg oral remibrutinib dose was administered in the morning of Day 4 after an overnight fast of at least 9 hours. GFJ was given orally to the subjects 15 hours postremibrutinib intake, on the evening of Day 4.

Day 5

A total of 240-mL GFJ was given in the morning after an overnight fast of at least 9 hours. A single 20-mg oral remibrutinib dose was administered 1 hour later. Blood samples were collected for up to 24 hours after the oral remibrutinib dosing, for remibrutinib measurements.

Period 3 (RTV Period)

Day 6 (Baseline and Lead-In)

Following baseline assessment, a single 50-mg oral remibrutinib dose was administered in the morning of Day 6 after an overnight fast of at least 9 hours. This was followed by a single 100-mg oral dose of RTV 15 hours after the oral remibrutinib dose.

Day 7

RTV 100 mg was administered with approximately 240 mL 10% w/v glucose in water on the morning of Day 7 after an overnight fast of at least 9 hours. One hour later, a single 20-mg oral remibrutinib dose was administered. At 2 hours after the oral dose, subjects received IV bolus administration of 100- μ g SIL-remibrutinib. On the evening of Day 7, about 12 hours post the morning RTV dose, another oral RTV 100-mg dose was given. Blood samples were collected up to 48 hours for remibrutinib and SIL-remibrutinib measurements.

Day 8

An oral dose of RTV 100 mg was administered in the morning after an overnight fast of at least 9 hours followed by a second dose of RTV 100 mg 12 hours postmorning RTV dose.

The remibrutinib dose of 50 mg once daily was given orally in Period 1 and Period 2 to achieve near-complete BTK receptor occupancy and steady-state conditions, thereby minimizing the influence of target-mediated drug disposition on remibrutinib PK measurements. In the first-in-human Study X2101, once-daily dosing of remibrutinib at 25 mg and above resulted in almost complete BTK occupancy beginning on Day 1. This level of occupancy persisted with administration of subsequent daily doses until about 48 hours after the last dose on Day 12 (refer to Section [14.2.1.1](#)). PK results from Study X2101 indicated that remibrutinib accumulates following administration of multiple doses despite a short apparent half-life at doses $\leq$ 100 mg. The reason for this accumulation is likely due to the influence of target binding on remibrutinib disposition rather than incomplete clearance of remibrutinib prior to administration of the next dose. Given the short apparent half-life, it is not expected that administration of higher doses (i.e., 50 mg) will influence the pharmacokinetics following administration of the 20-mg dose used to evaluate the impact of CYP3A4 inhibition. Therefore, it is reasonable for the Applicant to administer lead-in doses of 50-mg remibrutinib prior to probing the impact of CYP3A4 inhibition on remibrutinib exposure.

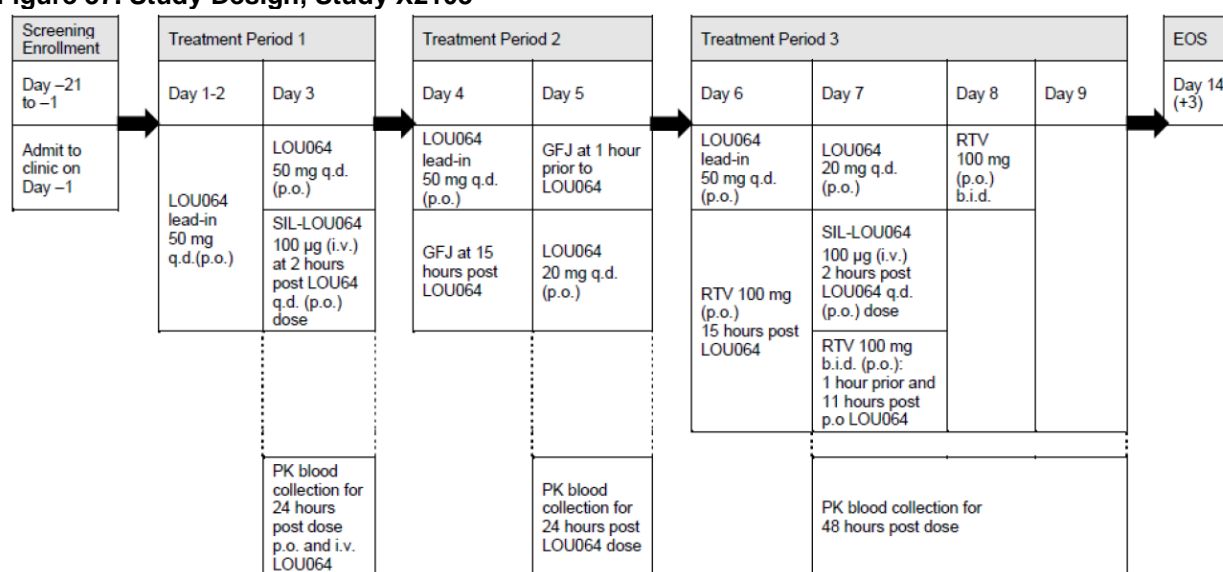
RTV and GFJ are mechanism-based inhibitors of CYP3A4, exhibiting time- and concentration-dependent enzyme inactivation that is irreversible ([Bailey et al. 2013](#); [Loos et al. 2022](#)). Consequently, a complete washout (minimum of 2 to 3 weeks) of RTV or GFJ between treatment periods is not feasible, as it would require the full de novo synthesis of the CYP3A enzyme pool. A washout of 24 hours between all periods was selected to separate remibrutinib dosing. The washout period is acceptable for clearance of remibrutinib prior to administration of the next dose. As GFJ is expected to impact only intestinal CYP3A4, while RTV will impact both intestinal and hepatic CYP3A4, the sequence of administration is reasonable. As an additive effect between GFJ and RTV is not expected, full washout to accommodate resynthesis of the CYP3A enzyme pool between the GFJ and RTV treatment periods is not required.

The dose of ritonavir to be used in the study is 100 mg administered twice daily. This dosage is the same as that approved for use in combination with lopinavir for the treatment of HIV-1 infection (Kaletra) and the same as that approved for use in combination with nirmatrelvir for the treatment of mild-to-moderate COVID-19 (Paxlovid). Notably, at this dosage, ritonavir is used to inhibit CYP3A-mediated metabolism of the concomitant treatment.

Administration of SIL-remibrutinib as an IV bolus dose was intended to support determination of the fractional contribution of CYP3A to overall clearance. The dose of SIL-remibrutinib of 100 µg is 0.5% of the lowest oral remibrutinib dose of 20 mg.

Remibrutinib for oral administration was supplied as HGCs in 20-mg and 50-mg strengths. Remibrutinib for intravenous administration was supplied in vials containing SIL-remibrutinib (a stable labeled isotope of remibrutinib) 100-µg powder for solution for injection.

Figure 37. Study Design, Study X2103



Source: Study X2103 Clinical Report, Figure 9-1

On the morning of Day 3, subjects were administered 240 mL of 10% w/v glucose in water after at least 9 hours of fasting and oral remibrutinib was administered thereafter 1 hour later.

Subjects were administered RTV with approximately 240 mL 10%w/v glucose in water on the morning of Day 7 after approximately 9 hours of overnight fasting.

Abbreviations: EOS, end of study; GFJ, grapefruit juice; i.v., intravenous; LOU064, remibrutinib; PK, pharmacokinetic; p.o., oral administration; q.d., once daily; RTV, ritonavir

Results

DDI With Ritonavir and Grapefruit Juice

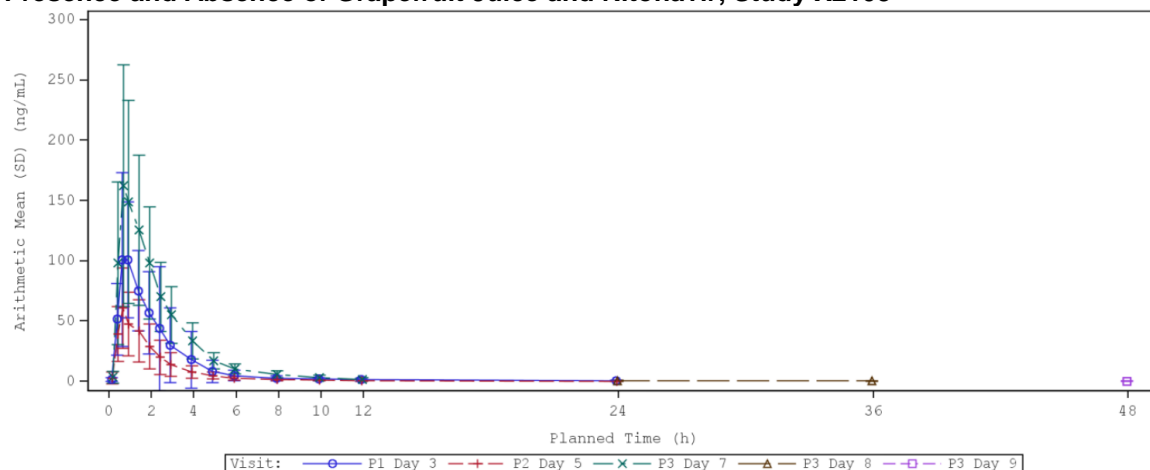
The blood concentration-time profiles and pharmacokinetic parameters for remibrutinib following the administration of 20-mg and 50-mg doses with and without 100-mg RTV or 240-mL GFJ, are illustrated in [Figure 38](#) and summarized in [Table 62](#). Dose-normalized PK parameters were used to assess the impact of CYP3A4 inhibitors on the pharmacokinetics of remibrutinib as 50-mg remibrutinib was administered in Treatment Period 1, while 20-mg remibrutinib was administered in Treatment Periods 2 and 3. Based on Study X2101, following administration of multiple once-daily doses of remibrutinib, exposure increased in a less than dose-proportional manner between doses of 10 mg and 600 mg (refer to [Section 14.2.1.1](#)).

Therefore, it is unclear whether comparing dose-normalized PK parameters will be appropriate. Based on PK data from Study X2101, between dosages of 10 mg QD and 50 mg QD at steady state, median C_{max} appeared to increase in an approximately dose-proportional manner (17.2 ng/mL and 100 ng/mL, respectively), while median AUC_{last} increased in a greater than dose-proportional manner (22.4 ng.h/mL and 179 ng.h/mL, respectively) (refer to [Table 41](#)). However, between dosages of 25 mg QD and 50 mg QD, C_{max} increased in a less than dose-proportional manner, while AUC_{last} increased in an approximately dose-proportional manner. On the other hand, remibrutinib $C_{max,ss}$ and AUC_{tau} increase in a dose-proportional manner between dosages of 10 mg BID, 25 mg BID, and 100 mg BID in Study A2201 (see Section [14.2.7](#)). Specifically, the geometric mean $C_{max,ss}$ values following the administration of 10 mg BID, 25 mg BID, and 100 mg BID were 26.8, 56.6, and 188 ng/mL, respectively while geometric mean AUC_{tau} values were 65.1, 162, and 677 ng.h/mL, respectively. Therefore, the use of dose-normalized parameters is acceptable.

Median (min-max) T_{max} values of remibrutinib when administered alone was 1 hour (0.52 hour to 2.5 hours), 0.73 hours (0.5 hours to 2 hours) when remibrutinib was coadministered with GFJ, and 0.715 hours (0.5 hours to 1.5 hours) when remibrutinib was coadministered with RTV. The mean elimination $t_{1/2}$ was comparable for remibrutinib alone (6.58 hours) and when coadministered with GFJ (7.13 hours) but was increased when remibrutinib was coadministered with RTV (12.1 hours).

GFJ elevated the dose-normalized C_{max} , AUC_{last} , and AUC_{0-inf} of orally administered remibrutinib by 1.24-, 1.33- and 1.28-fold, respectively. RTV has a greater impact on remibrutinib pharmacokinetics. Dose-normalized C_{max} , AUC_{last} , and AUC_{0-inf} of orally administered remibrutinib increased by 3.32-, 4.5-, and 4.31-fold, respectively ([Table 63](#)).

Figure 38. Arithmetic Mean (SD) Oral Remibrutinib Blood Concentration-Time Profiles in the Presence and Absence of Grapefruit Juice and Ritonavir, Study X2103



Source: Study X2103 Clinical Report, Figure 11-2

Treatment P1: Single p.o. 50-mg remibrutinib dose on Days 1, 2, and 3. Single IV 100- μ g SIL-remibrutinib on Day 3.

Treatment P2: Single p.o. 50-mg remibrutinib dose and 240-mL GFJ on Day 4. Single p.o. 20-mg remibrutinib dose and 240-mL GFJ on Day 5.

Treatment P3: Single p.o. 50-mg remibrutinib dose and single p.o. 100-mg RTV on Day 6. Single p.o. 100-mg RTV, single p.o. 20-mg remibrutinib dose, and single IV 100- μ g SIL-remibrutinib on Day 7. Two p.o. 100-mg RTV doses on Day 8.

Abbreviations: GFJ, grapefruit juice; h, hour; IV, intravenous; p.o., oral administration; SIL, stable-isotope-labeled; RTV, ritonavir; SD, standard deviation

Table 62. Summary of PK Parameters for Oral Remibrutinib in the Presence and Absence of Grapefruit Juice and Ritonavir, Study X2103

Period/ Treatment/ Day	Statistic	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng ² h/mL)	AUC _{last} (ng ² h/mL)	AUC _{inf} (ng ² h/mL)	T _{max} (h)	Lambda z (1/h)	T _{1/2} (h)	MRT (h)	CL/F (L/h)	V _z /F (L)
Period 1/ LOU064 Alone (50 mg)/ Day 3	n	17	16	17	11	17	11	11	11	11	11
	mean (SD)	139 (68.9)	244 (118)	237 (118)	265 (139)	-	0.115 (0.0390)	6.58 (1.77)	3.61 (1.54)	221 (81.0)	2060 (874)
	CV%	49.7	48.4	49.7	52.5	-	34.1	26.9	42.6	36.7	42.4
	Geo-mean	123	227	219	243	-	0.110	6.33	3.38	206	1880
	CV% Geo-mean	56.4	38.5	40.1	42.6	-	31.3	31.2	38.0	42.5	48.3
	Median	119	233	230	239	1.00	0.0911	7.61	3.24	209	2020
	Min; Max	48.1; 260	118; 649	118; 648	122; 660	0.520; 2.50	0.0831; 0.201	3.46; 8.35	2.14; 7.50	75.8; 410	832; 3460
Period 2/ LOU064 (20 mg)+GFJ /Day 5	n	16	16	16	8	16	8	8	8	8	8
	mean (SD)	65.4 (31.4)	126 (63.9)	125 (63.9)	112 (31.0)	-	0.0989 (0.0139)	7.13 (1.07)	3.75 (1.10)	189 (46.5)	1930 (492)
	CV%	47.9	50.8	50.9	27.6	-	14.0	15.0	29.4	24.6	25.5
	Geo-mean	59.1	115	115	109	-	0.0980	7.07	3.61	184	1870
	CV% Geo-mean	49.1	43.0	43.0	26.4	-	14.6	14.6	28.8	26.5	26.1
	Median	59.6	109	109	103	0.730	0.0985	7.04	3.52	195	1950
	Min; Max	25.7; 150	50.8; 336	50.7; 336	74.7; 171	0.500; 2.00	0.0754; 0.117	5.93; 9.19	2.61; 5.78	117; 268	1290; 2740
Period 3/ LOU064 (20 mg)+RTV /Day 7	n	16	16	16	12	16	12	12	12	12	12
	mean (SD)	180 (96.7)	406 (170)	416 (172)	427 (190)	-	0.0602 (0.0141)	12.1 (2.82)	4.67 (1.40)	53.5 (18.5)	929 (403)
	CV%	53.8	41.8	41.4	44.4	-	23.4	23.3	29.9	34.6	43.4
	Geo-mean	159	380	389	398	-	0.0587	11.8	4.51	50.3	858
	CV% Geo-mean	54.7	37.7	37.2	39.5	-	23.8	23.8	27.4	39.5	42.9
	Median	155	388	399	432	0.715	0.0608	11.4	4.43	46.3	803
	Min; Max	75.8; 436	223; 913	230; 932	233; 947	0.500; 1.50	0.0425; 0.0849	8.16; 16.3	3.06; 8.26	21.1; 85.7	472; 1730

Source: Study X2103 Clinical Report, Table 11-1

CV%=sd/mean*100. CV% Geo-mean = sqrt (exp(variance for log-transformed data)-1)*100. For T_{max} only median, min, and max are displayed.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; geo-mean, geometric mean; GFJ, grapefruit juice; LOU064, remibrutinib; Max, maximum; Min, minimum; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; RTV, ritonavir; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution during terminal phase after oral administration

Table 63. Statistical Comparisons of Remibrutinib Dose-Normalized PK Parameters After Administration of Remibrutinib Alone vs. Coadministration of Grapefruit Juice and Ritonavir, Study X2103

Parameter	Treatment	Adjusted Geometric	
		Mean (90% CI)	GMR (90%CI)
C _{max} (ng/mL/mg)	Remibrutinib alone (Reference) (N=17)	2.45 (1.99, 3.02)	
	Remibrutinib + GFJ (Test 1) (N=16)	3.03 (2.45, 3.75)	1.24 (1.05, 1.46)
	Remibrutinib + Ritonavir (Test 2) (N=16)	8.15 (6.59, 10.1)	3.32 (2.81, 3.93)
AUC _{0-24h} (h.ng/mL/mg)	Remibrutinib alone (Reference) (N=16)	4.49 (3.83, 5.26)	
	Remibrutinib + GFJ (Test 1) (N=16)	5.80 (4.95, 6.80)	1.29 (1.16, 1.43)
	Remibrutinib + Ritonavir (Test 2) (N=16)	19.2 (16.4, 22.5)	4.27 (3.84, 4.74)

Parameter	Treatment	Adjusted Geometric	
		Mean (90% CI)	GMR (90%CI)
AUC _{last} (h*ng/mL/mg)	Remibrutinib alone (Reference) (N=17)	4.37 (3.73, 5.13)	
	Remibrutinib + GFJ (Test 1) (N=16)	5.80 (4.93, 6.81)	1.33 (1.19, 1.47)
	Remibrutinib + Ritonavir (Test 2) (N=16)	19.7 (16.7, 23.1)	4.50 (4.05, 4.99)
AUC _{0-inf} (h*ng/mL/mg)	Remibrutinib alone (Reference) (N=11)	4.66 (3.92, 5.54)	
	Remibrutinib + GFJ (Test 1) (N=8)	5.98 (4.97, 7.19)	1.28 (1.09, 1.51)
	Remibrutinib + Ritonavir (Test 2) (N=12)	20.1 (16.9, 23.8)	4.31 (3.76, 4.94)

Source: Study X2103 Clinical Report, Table 11-8

The linear-log trapezoidal method was used for AUC calculation. If the adjusted R-square value of the regression analysis of the terminal phase was less than 0.75, no values were reported for AUC_{inf}.

All drug concentrations below the LLOQ were reported as "zero" and were treated as zero in summary statistics and linear concentration-time profiles and for PK parameters calculation.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CI, confidence interval; C_{max}, maximum plasma concentration; GFJ, grapefruit juice; GMR, geometric mean ratio; LLOQ, lower limit of quantification; N, number of subjects; PK, pharmacokinetic

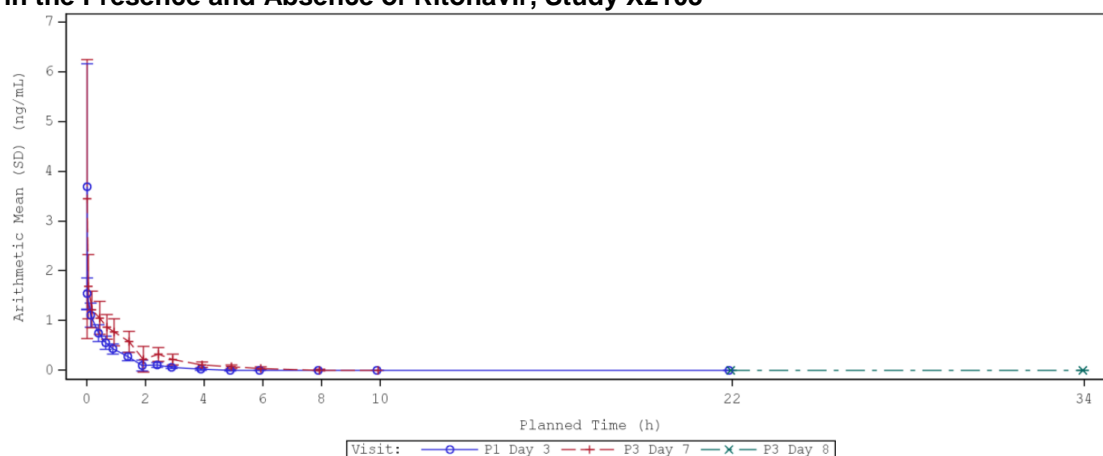
Pharmacokinetics of Intravenous SIL-Remibrutinib and Bioavailability of Remibrutinib

The blood concentration-time profiles and PK parameters of SIL-remibrutinib, following the administration of a 100-µg IV dose with and without ritonavir, are presented in [Figure 39](#) and [Table 64](#). The mean CL, t_{1/2}, and V_c for intravenous remibrutinib were determined to be 70.1 L/h, 0.725 hours, and 72.4 L, respectively.

The mean dose-normalized pharmacokinetic parameters for SIL-remibrutinib, when administered alone, were as follows: C_{max}, 0.0389 ng/mL/mg; AUC_{0-24h}, 14.5 h*ng/mL/mg; AUC_{last}, 14.3 h*ng/mL/mg; and AUC_{0-inf}, 14.7 h*ng/mL/mg. When administered with ritonavir on Day 7, the corresponding values were: C_{max}, 0.0365 ng/mL/mg; AUC_{0-24h}, 24.8 h*ng/mL/mg; AUC_{last}, 24.4 h*ng/mL/mg; and AUC_{0-inf}, 25.3 h*ng/mL/mg.

Based on the dose-normalized AUC_{0-24h} values for SIL-remibrutinib when administered alone and in the presence of ritonavir, the estimated fraction of SIL-remibrutinib metabolized by CYP3A4 (f_m) was determined to be 0.42 (i.e., 1 – [14.5/24.8]).

Figure 39. Arithmetic Mean (SD) Intravenous SIL-Remibrutinib Blood Concentration-Time Profiles in the Presence and Absence of Ritonavir, Study X2103



Source: Study X2103 Clinical Report, Figure 11-2

Treatment P1: Single p.o. 50-mg remibrutinib dose on Days 1, 2, and 3. Single IV 100-µg SIL-remibrutinib on Day 3.

Treatment P3: Single p.o. 50-mg remibrutinib dose and single p.o. 100-mg RTV on Day 6. Single p.o. 100-mg RTV, single p.o. 20-mg remibrutinib dose, and single IV 100-µg-SIL-remibrutinib on Day 7. Two p.o. 100-mg RTV doses on Day 8.

Abbreviations: h, hour; IV, intravenous; p.o., oral administration; SIL, stable-isotope-labeled; RTV, ritonavir; SD, standard deviation

Table 64. Summary of PK Parameters for SIL-Remibrutinib in the Presence and Absence of Ritonavir, Study X2103

Period/ Treatment/ Day	Statistic	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	T _{max} (h)	Lambda z (1/h)	T _{1/2} (h)	CL (L/h)	V _c (L)	V _{ss} (L)	MRT (h)
Period 1/ SIL-LOU064 Alone (100 µg)/ Day 3	n	17	17	17	14	17	14	14	14	14	14	14
	mean (SD)	3.89 (2.24)	1.45 (0.317)	1.43 (0.319)	1.47 (0.256)	-	1.00 (0.230)	0.725 (0.151)	70.1 (12.8)	72.4 (16.5)	63.1 (16.9)	0.900 (0.145)
	CV%	57.6	21.9	22.4	17.4	-	23.0	20.8	18.2	22.8	26.8	16.1
	Geo-mean	3.26	1.42	1.39	1.45	-	0.978	0.709	69.1	70.7	61.3	0.887
	CV% Geo- mean	71.3	21.8	22.3	17.9	-	22.3	22.2	18.0	22.8	24.2	17.7
	Median	3.62	1.43	1.40	1.48	0.0500	0.888	0.782	67.8	70.2	58.6	0.928
	Min; Max	1.15; 8.31	0.992; 2.17	0.958; 2.15	1.03; 1.89	0.0200; 0.150	0.705; 1.42	0.489; 0.983	52.9; 97.1	44.1; 107	46.3; 110	0.570; 1.13
Period 3/ SIL-LOU064 (100 µg)+RTV/ Day 7	n	16	16	16	13	16	13	13	13	13	13	13
	mean (SD)	3.65 (2.60)	2.48 (0.786)	2.44 (0.777)	2.53 (0.863)	-	0.565 (0.110)	1.27 (0.232)	43.6 (13.6)	78.2 (25.4)	69.8 (21.5)	1.63 (0.332)
	CV%	71.2	31.7	31.9	34.2	-	19.4	18.3	31.2	32.4	30.8	20.3
	Geo-mean	2.89	2.37	2.33	2.40	-	0.555	1.25	41.6	75.0	66.9	1.61
	CV% Geo- mean	81.6	31.0	31.0	33.3	-	18.8	18.7	33.4	29.8	30.8	18.9
	Median	2.90	2.26	2.23	2.25	0.0500	0.542	1.28	44.5	69.9	63.8	1.58
	Min; Max	1.03; 9.87	1.45; 4.48	1.44; 4.43	1.50; 4.56	0.0500; 1.03	0.385; 0.828	0.837; 1.80	21.9; 66.8	53.8; 137	41.1; 114	1.27; 2.50

Source: Study X2103 Clinical Report, Table 11-3

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL, clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo-mean, geometric mean; LOU064, remibrutinib; Max, maximum; Min, minimum; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; RTV, ritonavir; SIL, stable-isotope-labeled; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_c, central volume of distribution; V_{ss}, volume of distribution at steady state

Fraction of Remibrutinib Absorbed From the Gut

The F_{gut} was determined using dose-normalized AUC_{0-24h} values. These values were 4.89 h*ng/mL/mg for remibrutinib administered alone and 6.28 h*ng/mL/mg when coadministered with GFJ. The estimated F_{gut} value of 0.78 indicates a relatively lower contribution of gut CYP3A4 to the metabolism of remibrutinib compared to hepatic CYP3A4.

14.2.6.2. CYP3A4 Inducers (Carbamazepine), P-gp Substrates (Digoxin), OATP1B1 Substrates (Coproporphyrin), and BCRP/OATP1B1 Substrate (Rosuvastatin), Study A02103

Study A02103 was an open-label, two-part study to investigate the impact of carbamazepine (a strong CYP3A4 inducer) 300 mg BID on the exposure to remibrutinib 100 mg BID, and the impact of remibrutinib 100 mg BID on the exposure to digoxin (P-gp substrate) 0.25-mg single-dose tablet and rosuvastatin (BCRP and OATP1B substrate) 10-mg single-dose tablet in healthy adult subjects.

Part 1

Part 1 was a two-period, single-sequence study in which remibrutinib 100 mg (2x50 mg) BID was administered alone (Period 1, Days 1 to 3), followed by coadministration of remibrutinib 100 mg (2x50 mg) BID (Period 2, Days 23 to 25) and the CYP3A4 inducer, carbamazepine (Period 2, Days 4 to 25). Remibrutinib was administered BID on Days 1, 2, 23, and 24, and in

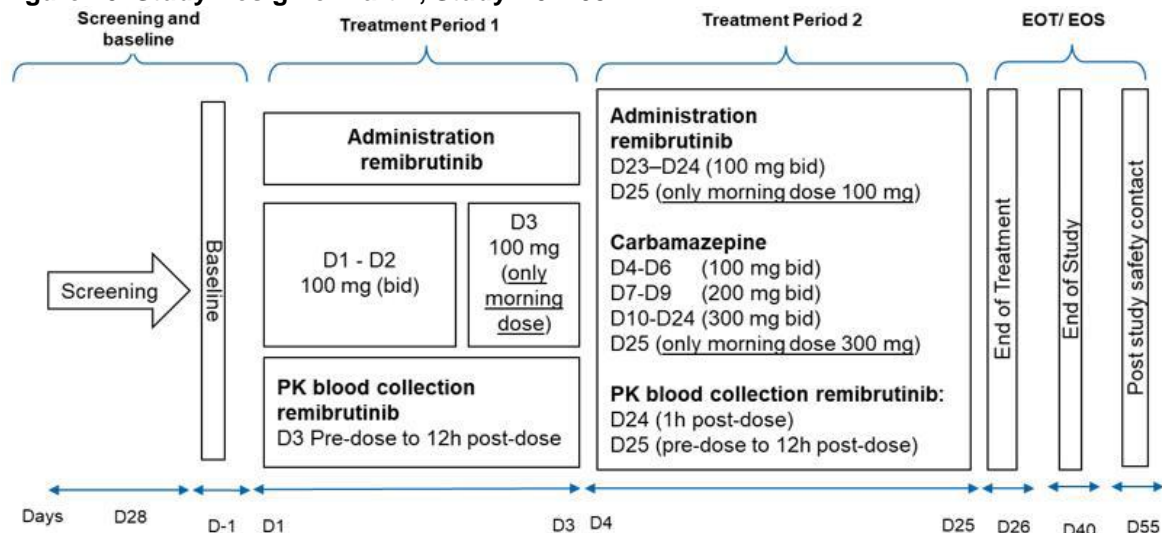
the morning only on Days 3 and 25. Remibrutinib was administered in Period 1 and 2 following an overnight fast of at least 10 hours. On Days 1, 2, 23, and 24, subjects remained fasted 1 hour postmorning dose and kept fasted for at least 1 hour prior to evening dose. On Days 3 and 25, subjects remained fasted until 4 hours postmorning dose.

During the carbamazepine up-titration, subjects received oral doses of carbamazepine 100 mg BID from Day 4 to Day 6, followed by carbamazepine 200 mg BID from Day 7 to Day 9, and carbamazepine target maintenance dose of 300 mg BID from Day 10 to Day 25 (on Day 25, morning dose only).

On Days 3 and 25, PK samples were collected up to 12 hours either alone (Day 3) or under CYP3A4 induction by carbamazepine (Day 25). Remibrutinib PK blood concentration was also measured on Day 24 at 1 hour postdose.

A comprehensive description of the study design and pharmacokinetic sampling times for Part 1 is illustrated in [Figure 40](#).

Figure 40. Study Design of Part 1, Study A02103



Source: Study A02103 Clinical Report, Figure 9-1

Remibrutinib was provided in 50 mg strength hard gelatin capsule (Batch # 2044228).

Day 3: remibrutinib PK samples were obtained at predose, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose. Day 24: remibrutinib PK sample was obtained 1 hour postdose. Day 25: remibrutinib PK samples were obtained at predose and 0.5, 1, 2, 3, 4, 6, 8, 12 hours postdose.

Abbreviations: bid, twice daily; D, day; EOS, end of study; EOT, end of treatment; h, hour; PK, pharmacokinetic

Remibrutinib was administered as 50-mg HGCs. Carbamazepine was administered as 100, 200, or 300 mg extended-release capsules. The maintenance dose of carbamazepine of 300 mg BID is within the range of approved doses per the approved labeling for carbamazepine (Carbatrol). Administration of carbamazepine for 14 days prior to coadministration with remibrutinib is acceptable to ensure sufficient time for CYP3A4 induction.

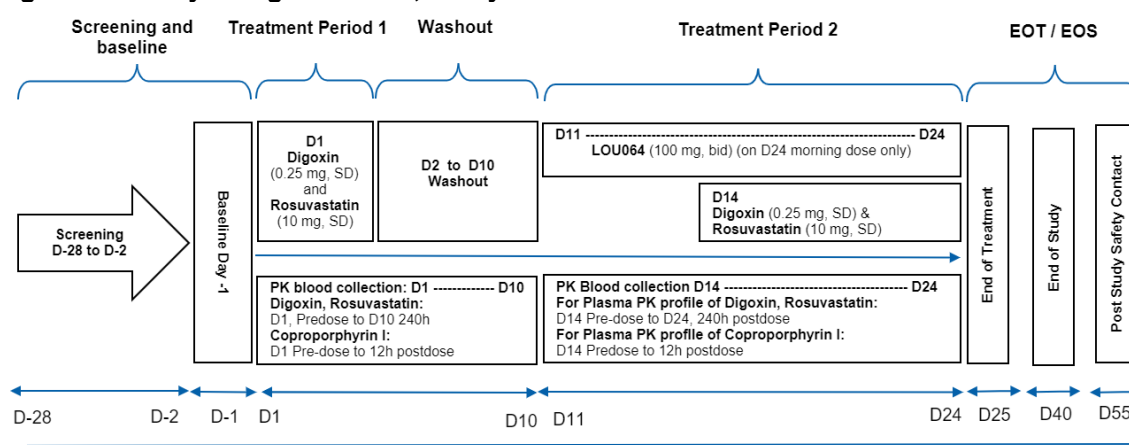
Part 2

Part 2 was a two-period, single-sequence study in which a drug cocktail containing digoxin and rosuvastatin was administered alone (Period 1, Day 1), followed by coadministration of the same cocktail (Period 2, Day 14) with remibrutinib (Period 2, Days 11 to 24). On Day 1, subjects

received a single dose of digoxin (0.25-mg tablet) and rosuvastatin (10-mg tablet) after an overnight fast of at least 10 hours and remained fasted until 4 hours postdose. From Day 11 to Day 24, subjects were administered oral doses of remibrutinib 100 mg BID (only the morning dose was administered on Day 24). On Day 14, subjects received a single dose of digoxin (0.25 mg) and rosuvastatin (10 mg) after an overnight fast of 10 hours and remained fasted until 4 hours postdose. A comprehensive description of the study design and PK sampling times for Part 2 is illustrated in [Figure 41](#).

To differentiate between BCRP and OATP1B1 inhibition, the endogenous OATP1B1 substrate coproporphyrin I was measured. Additionally, the renal clearance of rosuvastatin, a process mediated by OAT3 at the renal tubule level, was monitored to assess the inhibitory potential of remibrutinib on OAT3 transport.

Figure 41. Study Design of Part 2, Study A02103



Note:

Participants will be domiciled from D-1 (baseline) until discharge on D25

For Digoxin and Rosuvastatin: D1 (0.5h pre-dose) up to D10 (240h post dose) and D14 (0.5h pre-dose) up to D24 (240h post-dose)

For Coproporphyrin I: D1 (0.5 pre-dose) to D2 (24h post-dose) and D14 (0.5h pre-dose) up to D15 (24h post-dose)

PK Urine collection for Rosuvastatin: D1 and D14: 0h-24h, 24h-48h, 48h-72h, 72h-96h

Source: Study A02103 Clinical Report, Figure 9-2

Abbreviations: D, day; EOS, end of study; EOT, end of treatment; LOU064, remibrutinib; PK, pharmacokinetic; SD, standard deviation

Remibrutinib was administered as 50-mg HGCs. Digoxin was administered as a 0.25-mg tablet. Rosuvastatin was administered as a 10-mg tablet.

PK Results

The statistical analysis evaluating the impact of carbamazepine on the exposure to remibrutinib, as well as the assessment of the effect of remibrutinib on the plasma exposure to rosuvastatin, digoxin, and coproporphyrin I, and on urine rosuvastatin levels, is detailed in [Table 65](#).

Table 65. Statistical Comparisons of Blood Remibrutinib PK Parameters When Administered With and Without Carbamazepine and the Comparison of Plasma PK Parameters of Rosuvastatin, Digoxin, and Coproporphyrin I and Urine Rosuvastatin With and Without the Coadministration of Remibrutinib, Study A02103

Parameter	Treatment	Adjusted Geometric Mean (90% CI)	GMR 90% (CI)	Intrasubject CV%
<i>Effect of carbamazepine on remibrutinib</i>				
$C_{max,ss}$ (ng/mL)	Remibrutinib alone (Reference) (N=24)	124.61 (100.25, 154.9)	0.26 (0.21, 0.33)	47.08
	Remibrutinib + carbamazepine (Test) (N=22)	32.97 (26.33, 41.30)		
$AUC_{last,ss}$ (h*ng/mL)	Remibrutinib alone (Reference) (N=24)	274.25 (223.8, 336.07)	0.22 (0.18, 0.27)	39.08
	Remibrutinib + carbamazepine (Test) (N=22)	60.68 (49.22, 74.80)		
AUC_{tau} (h*ng/mL)	Remibrutinib alone (Reference) (N=24)	276.26 (225.82, 337.95)	0.23 (0.19, 0.28)	39.52
	Remibrutinib + carbamazepine (Test) (N=20)	63.68 (51.36, 78.94)		
<i>Effect of remibrutinib on digoxin</i>				
C_{max} (ng/mL)	Digoxin alone (Reference) (N=22)	0.92 (0.83, 1.02)	2.08 (1.81, 2.40)	28.01
	Remibrutinib + digoxin (Test) (N=22)	1.92 (1.72, 2.14)		
AUC_{last} (h*ng/mL)	Digoxin alone (Reference) (N=22)	13.77 (12.49, 15.17)	1.45 (1.36, 1.54)	11.87
	Remibrutinib + digoxin (Test) (N=22)	19.90 (18.05, 21.94)		
AUC_{inf} (h*ng/mL)	Digoxin alone (Reference) (N=21)	15.44 (14.07, 16.94)	1.40 (1.32, 1.49)	11.18
	Remibrutinib + digoxin (Test) (N=22)	21.61 (19.71, 23.70)		
<i>Effect of remibrutinib on pharmacokinetics of plasma rosuvastatin</i>				
C_{max} (ng/mL)	Rosuvastatin alone (Reference) (N=22)	3.60 (2.98, 4.33)	1.56 (1.35, 1.81)	28.42
	Remibrutinib + rosuvastatin (Test) (N=22)	5.63 (4.67, 6.78)		
AUC_{last} (h*ng/mL)	Rosuvastatin alone (Reference) (N=22)	38.57 (30.90, 48.14)	1.65 (1.47, 1.84)	22.03
	Remibrutinib + rosuvastatin (Test) (N=22)	63.54 (50.90, 79.31)		
AUC_{inf} (h*ng/mL)	Rosuvastatin alone (Reference) (N=21)	42.11 (33.92, 52.27)	1.56 (1.41, 1.73)	19.22
	Remibrutinib + rosuvastatin (Test) (N=21)	65.77 (52.98, 81.64)		

NDA 218436
RHAPSIDO (remibrutinib, LOU064)

Parameter	Treatment	Adjusted Geometric Mean (90% CI)	GMR 90% (CI)	Intrasubject CV%
<i>Effect of remibrutinib on renal CL of rosuvastatin</i>				
CLr (L/h)	Rosuvastatin alone (Reference) (N=22)	10.00 (8.78, 11.40)	1.06 (1.00, 1.12)	10.84
	Remibrutinib + rosuvastatin (Test) (N=22)	10.63 (9.32, 12.11)		
<i>Effect of remibrutinib on the pharmacokinetics of baseline uncorrected plasma coproporphyrin I</i>				
C _{max} (pg/mL)	Digoxin + rosuvastatin alone (Reference) (N=22)	413.54 (386.83, 442.10)	1.02 (0.95, 1.09)	13.46
	Digoxin + rosuvastatin + remibrutinib (Reference) (N=22)	420.88 (393.70, 449.95)		
AUC _{last} (h*pg/mL)	Digoxin + rosuvastatin alone (Reference) (N=22)	4370.54 (4075.29, 4687.19)	0.98 (0.93, 1.04)	11.61
	Digoxin + rosuvastatin + remibrutinib (Reference) (N=22)	4293.61 (4003.55, 4604.69)		

Source: Study A02103 Clinical Report, Table 11-2, 11-4, 11-6, 11-8, and 11-10

The linear trapezoidal rule (linear-linear) was used for AUC calculation. Regression analysis of the terminal plasma or blood elimination phase for the determination of t_{1/2} included at least 3 data points after C_{max}. If the adjusted R² value of the regression analysis of the terminal phase was less than 0.75 and if the %AUC_{inf,extrap} was >20%, no values were reported for AUC_{inf}.

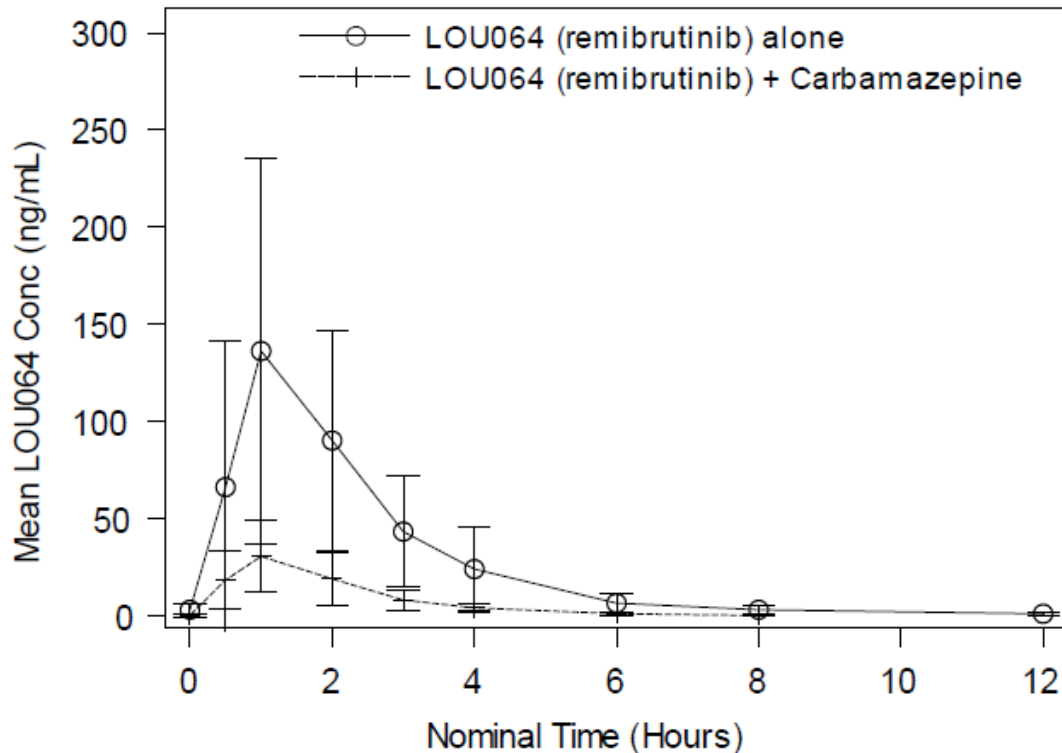
Log-transformed primary blood PK parameters of remibrutinib (C_{max,ss}, AUC_{last,ss} and AUC_{tau}), log-transformed primary plasma and urine (rosuvastatin only) PK parameters of rosuvastatin, digoxin and coproporphyrin I (C_{max}, AUC_{last}, and/or AUC_{inf}, and CLr [rosuvastatin only]) were analyzed using mixed-effect model with treatment as a fixed effect and subject as a random effect.

Abbreviations: AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; AUC_{last,ss}, area under the concentration-time curve from time zero to the last measurable concentration sampling time at steady state; AUC_{tau}, area under the concentration-time curve over the dosing interval; CI, confidence interval; CLr, renal clearance; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady state; CV, coefficient of variation; GMR, geometric mean ratio; N, number of subjects; PK, pharmacokinetic; t_{1/2}, half-life

Part 1: Effect of Carbamazepine (Strong CYP3A4 Inducer) on Remibrutinib

The coadministration of remibrutinib at a dose of 100 mg BID with carbamazepine resulted in significant reductions in the PK parameters of remibrutinib. Specifically, $C_{max,ss}$, AUC_{tau} , and $AUC_{last,ss}$ were reduced by 74%, 77%, and 78%, respectively. Additionally, carbamazepine decreased the CL_{ss}/F and V_{ss}/F of remibrutinib from 1540 L/h to 362 L/h and from 2720 L to 1100 L, respectively (Table 66 and Figure 42). Notably, there was no significant impact on the T_{max} of remibrutinib.

Figure 42. Arithmetic Mean ($\pm$ SD) Blood Concentration-Time Profiles of Remibrutinib in the Presence and Absence of Carbamazepine, Study A02103



Source: Study A02103 Clinical Report, Figure 11-1
Abbreviations: LOU064, remibrutinib; SD, standard deviation

Table 66. Summary of Blood PK Parameters of Remibrutinib in the Presence and Absence of Carbamazepine, Study A02103

Treatment	Statistics	C _{max,ss} (ng/mL)	T _{max,ss} (h)	AUC _{tau} (h*ng/mL)	AUC _{last,ss} (h*ng/mL)	T _{1/2,ss} (h)	CL _{ss/F} (L/h)	V _{ss/F} (L)
Remibrutinib alone (N=24)	n	24	24	24	24	24	24	24
	Mean (SD)	154 (99.3)		331 (208)	330 (208)	2.44 (1.49)	502 (695)	1600 (1770)
	CV% mean	64.4		62.7	63.0	61.1	138.4	111.0
	Geo-mean	125		276	274	2.10	362	1100
	CV% geo-mean	84.6		77.2	79.2	58.2	77.2	97.5
	Median	129	1.01	323	323	1.99	310	855
	(Min; Max)	(14.0; 484)	(0.50; 2.00)	(27.3; 1120)	(25.1; 1120)	(1.05; 6.92)	(89.4; 3660)	(194; 7470)
Remibrutinib + Carbamazepine (N=22)	n	22	22	20	22	19	19	19
	Mean (SD)	37.7 (17.5)		70.8 (29.3)	68.2 (28.0)	1.28 (0.395)	1700 (815)	3010 (1340)
	CV% mean	46.4		41.3	41.1	30.8	47.9	44.4
	Geo-mean	33.7		64.8	62.4	1.23	1540	2720
	CV% geo-mean	52.8		46.8	46.2	31.3	48.2	50.0
	Median	31.2	1.01	62.6	61.7	1.29	1550	3520
	(Min; Max)	(15.2; 65.5)	(0.49; 3.02)	(29.8; 123)	(28.1; 121)	(0.718; 2.21)	(816; 3360)	(1460; 5430)

Source: Study A02103 Clinical Report, Table 11-1

For T_{max,ss}, only n, median, minimum, and maximum are presented.

Subjects (b) (6) and (b) (6) were discontinued in Period 2 and hence PK parameters from treatment Period 1 is included in this table.

For Subjects (b) (6) and (b) (6) PK parameters AUC_{tau}, CL_{ss/F}, t_{1/2,ss} and V_{ss/F} are excluded from the summary statistics calculation for treatment Period 2 due to number of PK points to calculate λz <3. For Subject (b) (6), PK parameters CL_{ss/F}, t_{1/2,ss}, and V_{ss/F} are excluded from the summary statistics calculation for treatment Period 2 due to Adj R²<0.75.

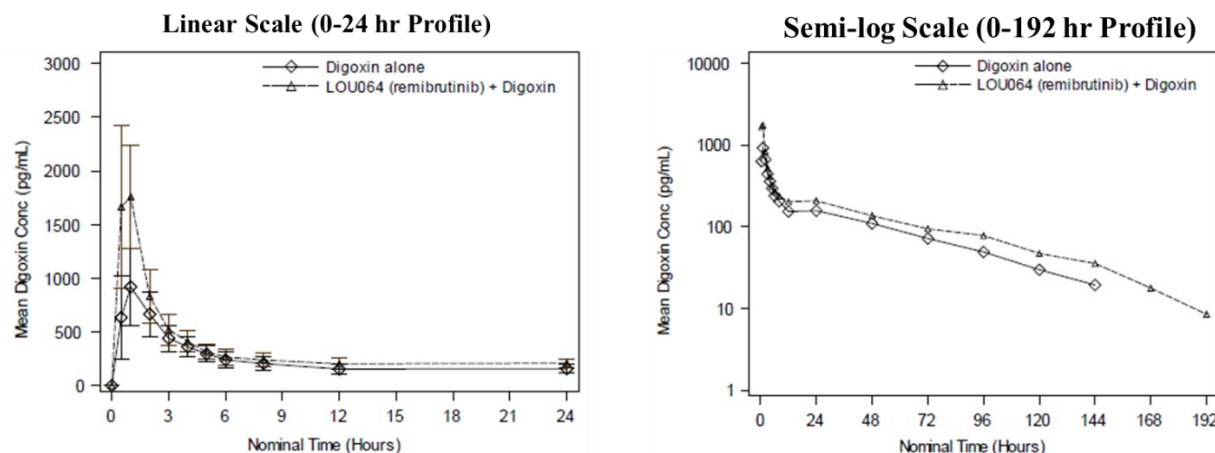
CV%, coefficient of variation (%) =100*(SD/arithmetic mean); CV% Geo-mean = sqrt (exp (variance for log-transformed data)-1)) * 100

Abbreviations: AUC_{last,ss}, the AUC from time zero to the last measurable concentration sampling time (t_{last}) at steady state (mass*time*volume⁻¹); AUC_{tau}, area under the concentration-time curve over the dosing interval; CL_{ss/F}, the total body clearance of drug from the blood after oral administration(volume x time⁻¹) at steady state; C_{max,ss}, the maximum (peak) steady-state blood drug concentration during a dosage interval; Geo, geometric; Max, maximum; Min, minimum; N, number of subjects in the pharmacokinetic analysis set in respective treatment; n, number of subjects with evaluable values in the pharmacokinetic analysis set in respective treatment; PK, pharmacokinetic; SD, standard deviation; T_{1/2,ss}, the elimination half-life associated with the terminal slope (λz) of a semilogarithmic concentration-time curve (time) at steady state; T_{max,ss}, the time to reach maximum (peak) blood drug concentration after single-dose administration (time) at steady state; V_{ss/F}, apparent volume of distribution at steady state after oral administration

Part 2: Effect of Remibrutinib on Digoxin (P-gp Substrate)

The plasma concentration-time profiles and PK parameters of a single dose of a 0.25-mg digoxin tablet, both when administered alone and in the presence of remibrutinib 100 mg BID, are presented in [Figure 43](#) and [Table 67](#). The coadministration of remibrutinib 100 mg BID with digoxin 0.25 mg resulted in a 2.08-fold increase in C_{max}, a 1.45-fold increase in AUC_{last}, and a 1.4-fold increase in AUC_{0-inf} of digoxin, as detailed in [Table 65](#).

Figure 43. Arithmetic Mean ($\pm$ SD) Plasma Concentration-Time Profiles of Digoxin in the Presence and Absence of Remibrutinib, Study A02103



Source: Study A02103 Clinical Report, Figure 11-3 and 11-4
Abbreviations: hr, hour; LOU064, remibrutinib; SD, standard deviation

Table 67. Summary of Plasma PK Parameters of Digoxin in the Presence and Absence of Remibrutinib, Study A02103

Treatment	Statistics	C _{max} (ng/mL)	T _{max} (h)	AUC _{last} (h*ng/mL)	AUC ₀₋₉₆ (h*ng/mL)	AUC _{inf} (h*ng/mL)	T _{1/2} (h)	CL/F (L/h)	V _z /F (L)
Digoxin alone (N=22)	n	22	22	22	22	21	21	21	21
	Mean (SD)	0.963 (0.325)		14.3 (3.92)	12.8 (3.14)	15.9 (4.18)	44.2 (11.1)	16.9 (4.92)	1050 (265)
	CV% mean	33.8		27.4	24.6	26.3	25.0	29.1	25.3
	Geo-mean	0.920		13.8	12.4	15.3	43.1	16.3	1010
	CV% geo-mean	30.6		29.4	25.3	28.1	22.4	28.1	26.2
	Median (Min; Max)	0.906 (0.538; 2.08)	1.01 (0.49; 2.01)	14.8 (7.77; 22.6)	12.8 (7.77; 20.7)	16.3 (9.24; 24.3)	41.3 (26.7; 75.2)	15.3 (10.3; 27.1)	1020 (560; 1600)
Remibrutinib + Digoxin (N=22)	n	22	22	22	22	22	22	22	22
	Mean (SD)	2.00 (0.550)		20.5 (4.92)	17.2 (3.78)	22.2 (5.00)	48.0 (9.10)	11.9 (2.81)	814 (199)
	CV% mean	27.6		24.0	22.0	22.6	18.9	23.7	24.4
	Geo-mean	1.92		19.9	16.8	21.6	47.3	11.6	789
	CV% geo-mean	30.5		25.0	22.4	23.5	17.2	23.5	26.6
	Median (Min; Max)	1.93 (0.997; 3.04)	0.76 (0.49; 2.00)	21.4 (13.3; 30.5)	17.3 (11.8; 24.5)	23.4 (14.7; 32.0)	46.4 (38.1; 78.3)	10.7 (7.81; 17.0)	839 (481; 1140)

Source: Study A0213 Clinical Report, Table 11-3

For T_{max}, only n, median, minimum, and maximum are presented.

For Subject (b) (6) PK parameters AUC_{inf}, CL/F, t_{1/2}, V_z/F has been excluded from the summary statistics calculation for treatment period 1 due to Adj R²<0.75, AUC_{inf,extrap}>20%.

CV% = coefficient of variation (%) = 100*(SD/arithmetic mean); CV% Geo-mean = sqrt (exp (variance for log-transformed data)-1) * 100

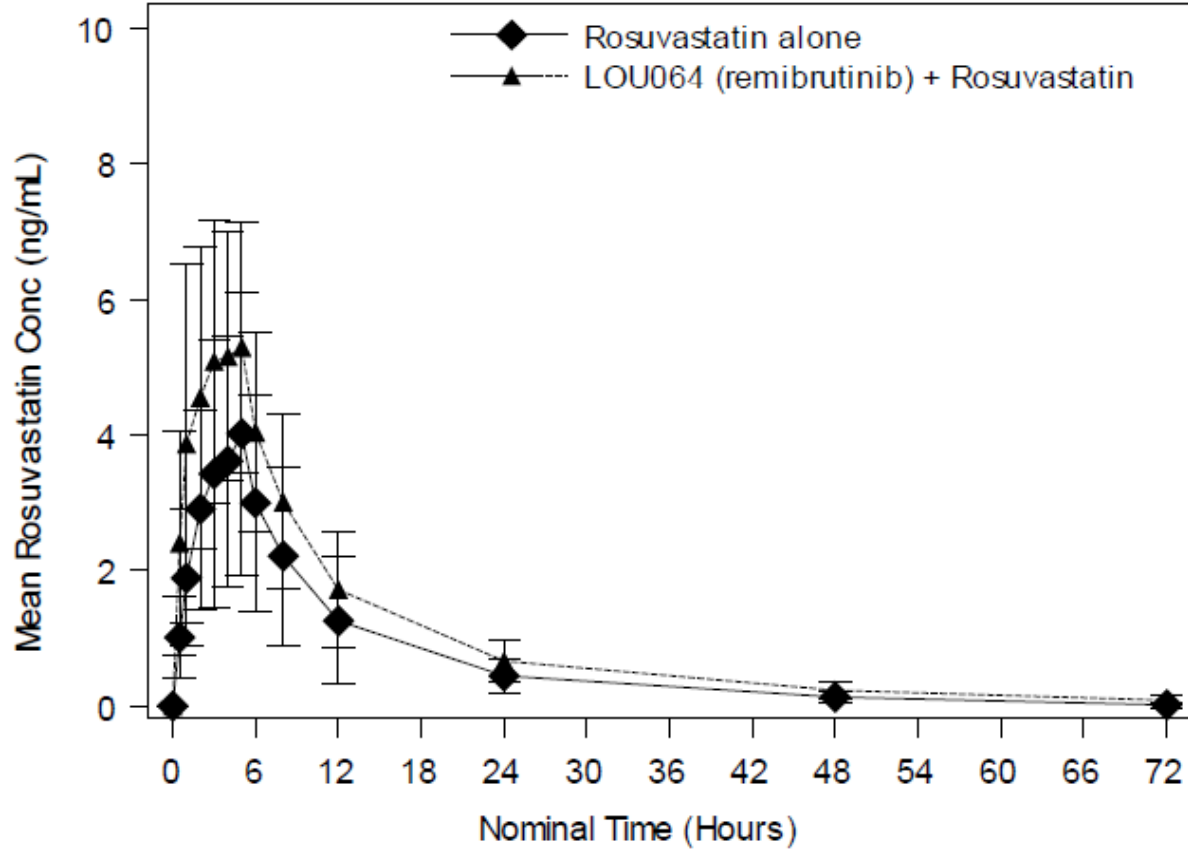
Abbreviations: AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; AUC_{inf}, the AUC from time zero to infinity (mass x time x volume⁻¹); AUC_{last}, the AUC from time zero to the last measurable concentration sampling time (t_{last}) (massxtimexvolume⁻¹); CL/F, the total body clearance of drug from the plasma after oral administration (volume x time⁻¹); C_{max}, maximum plasma concentration; Geo, geometric; Max, maximum; Min, minimum; N, number of subjects in the pharmacokinetic analysis set in respective treatment; n, number of subjects with evaluable values in the pharmacokinetic analysis set in respective treatment; PK, pharmacokinetic; SD, standard deviation; t_{1/2}, the elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve (time); T_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase after oral administration

Part 2: Effect of Remibrutinib on Rosuvastatin (BCRP and OATP1B1 Substrate)

The plasma concentration-time profiles and PK parameters of a single dose of rosuvastatin 10 mg, administered both alone and in conjunction with remibrutinib 100 mg BID, are presented in [Figure 44](#) and [Table 68](#). The coadministration of remibrutinib 100 mg BID with a single dose

of rosuvastatin 10 mg resulted in a 1.56-fold increase in C_{max} , a 1.65-fold increase in AUC_{last} , and a 1.56-fold increase in AUC_{0-inf} of rosuvastatin, as detailed in [Table 65](#).

Figure 44. Arithmetic Mean ($\pm$ SD) Plasma Concentration-Time Profiles of Rosuvastatin in the Presence and Absence of Remibrutinib, Study A02103



Source: Study A02103 Clinical Report, Figure 11-7
Abbreviation: conc, concentration; LOU064, remibrutinib; SD, standard deviation

Table 68. Summary of Plasma PK Parameters of Rosuvastatin in the Presence and Absence of Remibrutinib, Study A02103

Treatment	Statistics	C _{max} (ng/mL)	T _{max} (h)	AUC _{last} (h*ng/mL)	AUC _{0-96h} (h*ng/mL)	AUC _{inf} (h*ng/ml)	T _{1/2} (h)	CL/F (L/h)	V _z /F (L)
Rosuvastatin alone (N=22)	n	22	22	22	22	21	21	21	21
	Mean (SD)	4.18 (2.20)		46.8 (27.1)	49.0 (27.3)	50.9 (27.2)	11.5 (4.92)	288 (219)	4040 (2030)
	CV% mean	52.5		57.9	55.8	53.5	42.9	76.2	50.3
	Geo-mean	3.60		38.6	41.1	43.1	10.6	232	3550
	CV% geo-mean	64.8		76.9	72.4	70.9	41.0	70.9	58.0
	Median	3.79	5.00	43.8	45.5	47.3	10.4	211	3640
	(Min; Max)	(1.05; 9.11)	(1.00; 8.03)	(9.97; 109)	(11.2; 111)	(11.3; 111)	(5.43; 25.8)	(90.2; 888)	(1060; 8810)
Remibrutinib + Rosuvastatin (N=22)	n	22	22	22	22	21	21	21	21
	Mean (SD)	6.11 (2.54)		70.8 (28.5)	73.0 (28.7)	75.9 (28.9)	16.0 (7.48)	169 (119)	3230 (1240)
	CV% mean	41.6		40.3	39.3	38.1	46.8	70.3	38.3
	Geo-mean	5.63		63.5	65.9	68.7	14.4	146	3020
	CV% geo-mean	44.3		56.1	54.0	54.5	51.6	54.5	38.5
	Median	6.08	4.50	78.5	79.3	84.5	15.4	118	2990
	(Min; Max)	(2.22; 14.0)	(1.02; 5.03)	(15.9; 114)	(17.2; 117)	(17.2; 119)	(5.48; 38.1)	(84.0; 581)	(1510; 6450)

Source: Study A02103 Clinical Report, Table 11-5

For T_{max}, only n, median, minimum, and maximum are presented. For subject identifier, (b) (6) PK parameters AUC_{inf}, CL/F, t_{1/2}, V_z/F has been excluded from the summary statistics calculation for treatment period 1 due to AUC_{extrap} >20% and For Subject (b) (6), PK parameters AUC_{inf}, CL/F, t_{1/2}, V_z/F has been excluded from the summary statistics calculation for treatment period 2 due to Adj R²<0.75.

CV% = coefficient of variation (%) = 100*(SD/arithmetic mean); CV% Geo-mean = sqrt (variance for log-transformed data-1) * 100

Abbreviations: AUC_{0-96h}, area under the concentration-time curve from time 0 to 96 hours; AUC_{inf}, the AUC from time zero to infinity (mass x time x volume-1); AUC_{last}, the AUC from time zero to the last measurable concentration sampling time (t_{last}) (mass x time x volume-1); CL/F, the total body clearance of drug from the plasma after oral administration(volume x time-1); C_{max}, the maximum (peak) observed plasma drug concentration after single-dose administration (mass x volume-1); Geo, geometric; Max, maximum; Min, minimum; N, number of subjects in the pharmacokinetic analysis set in respective treatment; n, number of subjects with evaluable values in the pharmacokinetic analysis set in respective treatment; PK, pharmacokinetic; SD, standard deviation; t_{1/2}, the elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve (time); T_{max}, the time to reach maximum (peak) plasma drug concentration after single-dose administration (time); V_z/F, apparent volume of distribution during terminal phase after oral administration

Rosuvastatin Urine Pharmacokinetics

A summary of the PK data for rosuvastatin in urine, both in the presence and absence of remibrutinib, is presented in [Table 69](#). The geometric mean CL_r of rosuvastatin exhibited a 6% increase when coadministered with remibrutinib, rising from 10.0 L/h to 10.6 L/h. As renal clearance of rosuvastatin is primarily mediated by OAT3, this observation suggests that remibrutinib does not inhibit OAT3.

Table 69. Summary of Urine PK Parameters of Rosuvastatin in the Presence and Absence of Remibrutinib, Study A02103

Treatment	Statistics	Ae0-24 (µg)	Ae0-48 (µg)	Ae0-72 (µg)	Ae0-96 (µg)	CLr (L/h)
Rosuvastatin alone (N=22)	n	22	22	22	22	22
	Mean (SD)	388 (193)	436 (209)	457 (215)	466 (219)	10.6 (3.48)
	CV% mean	49.6	47.8	47.2	47.1	32.8
	Geo-mean	335	382	402	411	10.0
	CV% geo-mean	65.5	61.1	58.8	58.4	39.4
	Median (Min; Max)	398 (82.4; 685)	453 (106; 761)	478 (120; 805)	492 (123; 836)	10.3 (3.06; 18.8)
Remibrutinib + Rosuvastatin (N=22)	n	22	22	22	22	22
	Mean (SD)	604 (200)	692 (233)	727 (243)	743 (248)	11.2 (3.83)
	CV% mean	33.2	33.6	33.5	33.4	34.2
	Geo-mean	569	652	684	701	10.6
	CV% geo-mean	37.7	38.0	37.9	37.7	34.6
	Median (Min; Max)	610 (261; 983)	705 (301; 1180)	743 (314; 1240)	754 (321; 1260)	10.6 (4.50; 23.0)

Source: Study A02103 Clinical Report, Table 11-7

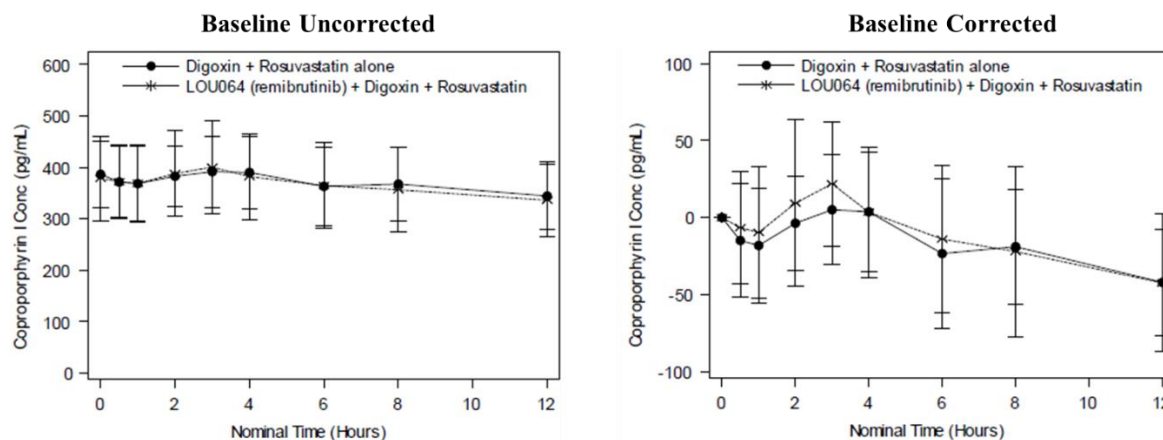
CV%, coefficient of variation (%) = 100*(SD/arithmetic mean); CV% Geo-mean = sqrt (exp (variance for log-transformed data)-1)) × 100

Abbreviations: Ae_{0-t}, cumulative amount of unchanged drug excreted into the urine from time 0 to time t; CLr, absolute amount of drug excreted in urine-Ae/AUC; Geo, geometric; N, number of subjects in the pharmacokinetic analysis set in respective treatment; n, number of subjects with evaluable values in the pharmacokinetic analysis set in respective treatment; Max, maximum; Min, minimum; PK, pharmacokinetic; SD, standard deviation

Part 2: Effect of Remibrutinib on Plasma Coproporphyrin I (OATP1B1 Substrate)

Rosuvastatin was employed as a substrate for BCRP and OATP1B to investigate potential drug interactions. To distinguish between the inhibition of OATP1B and BCRP, changes in coproporphyrin I, a potential endogenous biomarker of OATP1B1 activity, were measured in the absence and presence of remibrutinib. The plasma concentration-time profiles and PK parameters of coproporphyrin I following the administration of digoxin (0.25 mg) and rosuvastatin (10 mg) with remibrutinib (100 mg BID) were compared to those following the administration of digoxin (0.25 mg) and rosuvastatin (10 mg) alone. These data are presented in [Figure 45](#) and [Table 70](#). Overall, C_{max} of uncorrected coproporphyrin I increased by 2%, while AUC_{last} decreased by 2% in the presence of remibrutinib ([Table 65](#)). These findings suggest that remibrutinib may not have the potential to inhibit the hepatic uptake transporter OATP1B1.

Figure 45. Arithmetic Mean (± SD) Concentration-Time Profiles of Baseline-Uncorrected and Baseline-Corrected Coproporphyrin I in the Presence and Absence of Remibrutinib, Study A02103



Source: Study A02103 Clinical Report, Figure 11-10

Abbreviations: LOU064, remibrutinib; SD, standard deviation

Table 70. Summary of Plasma PK Parameters of Uncorrected Coproporphyrin I in the Presence and Absence of Remibrutinib, Study A02103

Treatment	Statistics	C _{max} (pg/mL)	T _{max} (h)	AUC _{last} (h*pg/mL)
Digoxin + Rosuvastatin alone (N=22)	n	22	22	22
	Mean (SD)	419 (65.9)		4440 (772)
	CV% mean	15.7		17.4
	Geo-mean	414		4370
	CV% geo-mean	16.4		18.2
	Median (Min; Max)	435 (310; 523)	3.01 (0.00; 12.03)	4580 (3160; 5830)
Remibrutinib + Digoxin + Rosuvastatin (N=22)	n	22	22	22
	Mean (SD)	430 (90.6)		4380 (914)
	CV% mean	21.1		20.9
	Geo-mean	421		4290
	CV% geo-mean	20.7		20.8
	Median (Min; Max)	405 (251; 691)	2.50 (0.00; 8.00)	4120 (2670; 6540)

Source: Study A02103 Clinical Report, Table 11-9

For T_{max}, only n, median, minimum, and maximum are presented. Only baseline uncorrected PK parameters are presented in this table. All Subjects for treatment period 1 and treatment period 2, PK parameters AUC_{inf} has been excluded from the summary statistics calculation due to Adj R²<0.75, AUC_{inf,extrap} >20% and number of PK points to calculate λ_z <3.

For AUC_{inf}, most subjects were excluded from summary and analysis for failing to meet the acceptability criterion (Adj R²<0.75) or there were not 3 points following C_{max} in the elimination phase.

CV% = coefficient of variation (%) = 100*(SD/arithmic mean); Geo = geometric; CV% Geo-mean = sqrt (exp (variance for log-transformed data)-1)) * 100

Abbreviations: AUC_{last}, the AUC from time zero to the last measurable concentration sampling time (T_{last}) (mass x time x volume⁻¹); C_{max}, the maximum (peak) observed plasma drug concentration after single-dose administration (mass x volume⁻¹); Max, maximum; Min, minimum; N, number of subjects in the pharmacokinetic analysis set in respective treatment; n, number of subjects with evaluable values in the pharmacokinetic analysis set in respective treatment; PK, pharmacokinetic; SD, standard deviation; T_{max}, the time to reach maximum (peak) plasma drug concentration after single-dose administration (time)

14.2.6.3. CYP3A4 Substrates (Oral Contraceptives and Midazolam), CYP1A2 Substrates (Caffeine) and CYP2C9 Substrates (Tolbutamide), Study X2102

In vitro studies have demonstrated that remibrutinib possesses the potential to both inhibit and induce CYP3A4, CYP1A2, and CYP2C9. Study X2102 was designed as an open-label, three-period, single-sequence, crossover study in healthy female subjects of nonchild-bearing potential to investigate the impact of remibrutinib 100 mg (administered as 1x100-mg HGC) BID for 18 days on the exposure to a single dose of an OC containing EE and LVG, which are substrates of CYP3A and CYP2C. Additionally, the study examined the impact of remibrutinib on single oral doses of midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), and tolbutamide (CYP2C9 substrate).

The study design is outlined as follows ([Figure 46](#)).

Period 1 (Day 1)

Subjects were administered a single dose of a probe cocktail containing 2 mg of midazolam, 200 mg of caffeine, and 500 mg of tolbutamide. This was followed by a washout period of at least 72 hours and not exceeding 7 days.

Period 2 (Day 9)

Subjects received a single oral dose of a combined OC containing 30 µg of EE and 150 µg of LVG. This was followed by a washout period of at least 5 days and not exceeding 7 days.

Period 3

Subjects were administered daily doses of remibrutinib 100 mg BID for 18 days (Day 16 to Day 33). On Day 18 and Day 26, subjects received a single dose of the probe cocktail containing 2 mg of midazolam, 200 mg of caffeine, and 500 mg of tolbutamide approximately 30 minutes after the morning dose of remibrutinib. On Day 30, subjects received a single oral dose of the combined OC (EE 30 µg and LVG 150 µg) approximately 30 minutes after the morning dose of remibrutinib.

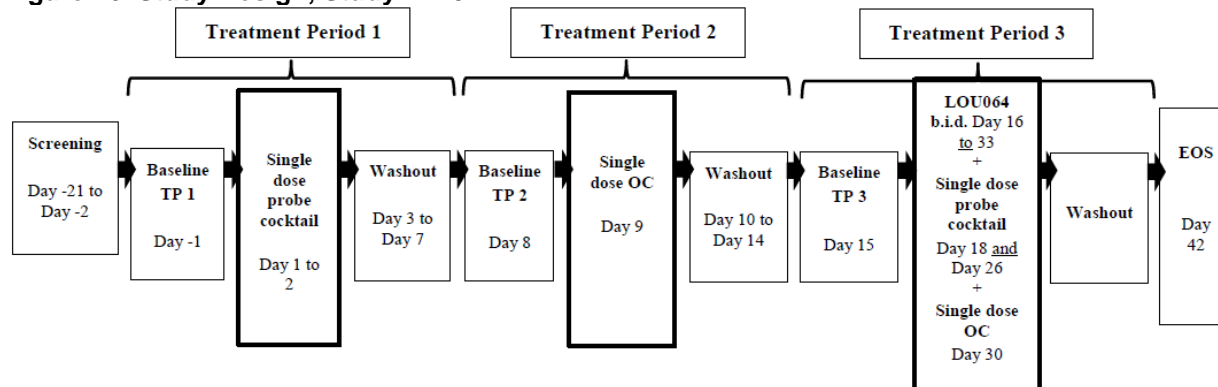
The Applicant assumed that the within-subject variability in the PK parameters for EE and LVG would be lower than the between-subject variability. Consequently, a lower sample size was used for this single-sequence crossover design relative to the sample size that may have been needed for a parallel group design.

Blood sampling timepoints were collected as follows:

- Midazolam: Days 1, 18, and 26 (at predose and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose)
- Tolbutamide: Days 1, 18, and 26 (at predose and 24 hours postdose)
- Caffeine: Days 1, 18, and 26 (at predose and 6 hours postdose)
- EE/LVG: Days 9 and 30 (at predose and 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours postdose)
- Remibrutinib: Days 16 and 17 (at predose and 6.5 hours postdose); Days 18 and 26 (at predose and 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours postdose); Days 22 and 25 (at 6.5 hours postdose); Day 30 (at predose and 6 hours postdose)

The Applicant utilized tolbutamide C24h and caffeine C6h to assess drug interactions between remibrutinib and tolbutamide and caffeine. The Applicant's rationale for measuring tolbutamide and caffeine concentrations at a single time point is based on prior studies in the literature, which have suggested that tolbutamide C24h levels may reflect CYP2C9 activity ([Fuhr et al. 1996](#); [Jetter et al. 2004](#)). Similarly, caffeine C6h levels may reflect CYP1A2 activity ([Fuhr et al. 1996](#)). Additionally, the paraxanthine/caffeine C6h ratio may also reflect CYP1A2 activity ([Fuhr et al. 1996](#)).

Figure 46. Study Design, Study X2102



Source: Study X2102 Clinical Report, Figure 9-1

Probe cocktail: single oral dose of 2-mg midazolam, 200-mg caffeine, and 500-mg tolbutamide.

OC: single oral dose of the combined OC (EE 30 µg and LVG 150 µg).

Abbreviations: b.i.d., twice daily; EE, ethinylestradiol; EOS, end of study; LOU064, remibrutinib; LVG, levonorgestrel; OC, oral contraceptive; TP, treatment period

Results

The plasma concentration-time profiles in the presence and absence of remibrutinib for EE, LVG, midazolam, tolbutamide, caffeine, and paraxanthine are illustrated in [Figure 47](#).

The statistical analysis evaluating the impact of multiple oral doses of remibrutinib 100 mg BID on the exposure of EE 30 µg, LVG 150 µg and single-dose probe cocktails containing midazolam (2 mg), caffeine (200 mg), and tolbutamide (500 mg) is presented in [Table 71](#).

Table 71. Statistical Comparisons of Plasma PK Parameters of Oral Contraceptives (Ethinylestradiol + Levonorgestrel), Midazolam, Tolbutamide, and Caffeine/Paraxanthine With and Without the Coadministration of Multiple Oral Doses of Remibrutinib, Study X2102

Parameter	Treatment	Adjusted Geometric Mean	
		(90% CI)	GMR 90% (CI)
C _{max} (ng/mL)	Ethinyl estradiol (Reference, N=30)	0.0636 (0.0574, 0.0704)	1.28 (1.19, 1.39)
	Ethinyl estradiol + remibrutinib (Test, N=27)	0.0816 (0.0735, 0.0906)	
AUC _{0-inf} (h*ng/mL)	Ethinyl estradiol (Reference, N=8)	0.928 (0.773, 1.11)	1.00 (0.80, 1.25)
	Ethinyl estradiol + remibrutinib (Test, N=12)	0.927 (0.795, 1.08)	
AUC _{0-24h} (h*ng/mL)	Ethinyl estradiol (Reference, N=30)	0.509 (0.468, 0.553)	1.16 (1.10, 1.22)
	Ethinyl estradiol + remibrutinib (Test, N=27)	0.591 (0.543, 0.643)	
AUC _{0-48h} (h*ng/mL)	Ethinyl estradiol (Reference, N=30)	0.619 (0.561, 0.683)	1.18 (1.12, 1.25)
	Ethinyl estradiol + remibrutinib (Test, N=27)	0.731 (0.662, 0.808)	
C _{max} (ng/mL)	Levonorgestrel (Reference, N=30)	2.98 (2.67, 3.33)	1.36 (1.24, 1.50)
	Levonorgestrel + remibrutinib (Test, N=27)	4.06 (3.62, 4.56)	
AUC _{0-inf} (h*ng/mL)	Levonorgestrel (Reference, N=12)	45.9 (40.4, 52.3)	1.39 (1.25, 1.55)
	Levonorgestrel + remibrutinib (Test, N=14)	63.9 (56.4, 72.5)	
AUC _{0-24h} (h*ng/mL)	Levonorgestrel (Reference, N=30)	18.2 (16.2, 20.4)	1.39 (1.30, 1.49)
	Levonorgestrel + remibrutinib (Test, N=26)	25.2 (22.4, 28.4)	
AUC _{0-48h} (h*ng/mL)	Levonorgestrel (Reference, N=30)	26.6 (23.6, 30.1)	1.41 (1.32, 1.51)
	Levonorgestrel + remibrutinib (Test, N=26)	37.6 (33.2, 42.6)	
C _{max} (ng/mL)	Midazolam (Reference, N=30)	8.56 (7.86, 9.33)	1.36 (1.26, 1.47)
	Midazolam + remibrutinib (Test, N=28)/Day 18	11.6 (10.7, 12.7)	
	Midazolam + remibrutinib (Test, N=27)/Day 26	10.9 (9.99, 11.9)	
AUC _{0-inf} (h*ng/mL)	Midazolam (Reference, N=30)	32.4 (29.3, 35.8)	1.45 (1.36, 1.54)
	Midazolam + remibrutinib (Test, N=26)/Day 18	46.9 (42.4, 52.0)	
	Midazolam + remibrutinib (Test, N=26)/Day 26	46.5 (42.0, 51.5)	
AUC _{0-24h} (h*ng/mL)	Midazolam (Reference, N=30)	30.6 (27.7, 33.7)	1.43 (1.35, 1.51)
	Midazolam + remibrutinib (Test, N=28)/Day 18	43.7 (39.5, 48.3)	
	Midazolam + remibrutinib (Test, N=27)/Day 26	43.7 (39.5, 48.3)	

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Parameter	Treatment	Adjusted Geometric Mean	
		(90% CI)	GMR 90% (CI)
C24h (ng/mL)	Tolbutamide (Reference, N=30)	9220 (7900, 10800)	
	Tolbutamide + remibrutinib (Test, N=28)/Day 18	11700 (10000, 13700)	1.27 (1.18, 1.36)
	Tolbutamide + remibrutinib (Test, N=27)/Day 26	12000 (10200, 14000)	1.30 (1.21, 1.39)
Paraxanthine/Caffeine ratio C6h	Caffeine (Reference, N=30)	0.408 (0.365, 0.456)	
	Caffeine + remibrutinib (Test, N=28)/Day 18	0.396 (0.354, 0.443)	0.970 (0.92, 1.02)
	Caffeine + remibrutinib (Test, N=27)/Day 26	0.360 (0.322, 0.402)	0.881 (0.84, 0.93)

Source: Study X2102 Clinical Report, Table 11-7 and 11-8

The effect of remibrutinib on the EE, LVG, midazolam, tolbutamide and caffeine drug exposure was analyzed using an analysis of variance model for the primary PK parameters that included study treatment as a fixed effect and subject as a random effect.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{0-48h}, area under the concentration-time curve from time 0 to 48 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C6h, plasma concentration measured at 6 hours postdose; C24h, plasma concentration measured at 24 hours postdose; C, concentration; CI, confidence interval; C_{max}, maximum plasma concentration; EE, ethinylestradiol; GMR, geometric mean ratio; LVG, levonorgestrel; N, number of subjects; PK, pharmacokinetic

Impact of Remibrutinib on OC

The PK parameters of EE and LVG following a single dose of OC administered with and without remibrutinib 100 mg twice daily are summarized in [Table 72](#) and [Table 73](#), respectively. The coadministration of remibrutinib 100 mg BID with a single dose of OC resulted in a 1.28-fold increase in C_{max} , a 1.16-fold increase in AUC_{0-24h} , and a 1.18-fold increase in AUC_{0-48h} for EE. For LVG, the increases were 1.36-fold in C_{max} , 1.39-fold in AUC_{0-inf} , 1.39-fold in AUC_{0-24h} , and 1.41-fold for AUC_{0-48h} ([Table 71](#)).

Despite these increases, the interaction between remibrutinib and OC does not indicate a clinically significant impact on the safety and efficacy of OC when coadministered with remibrutinib.

Table 72. Summary of Plasma PK Parameters of Ethinylestradiol in the Presence and Absence of Remibrutinib, Study X2102

Period/Treatment/Day	Statistic	Cmax (ng/mL)	Tmax (hours)	AUC0-24h (ng·h/mL)	AUC0-48h (ng·h/mL)	AUClast (ng·h/mL)	AUCinf (ng·h/mL)	CL/F (mL/h)	Vz/F (mL)	T1/2 (hours)
Treatment Period 2 Single dose OC Day 9	n	30	30	30	30	30	8	8	8	28
	mean (SD)	0.0680	-	0.531 (0.158)	0.657 (0.229)	0.634 (0.242)	1.06 (0.262)	30400	715000	19.3 (5.78)
	CV%	(0.0259) 38.1	-	29.7	34.9	38.2	24.7	(10400)	(91200) 12.8	30.0
	Geo-mean; CV% Geo-mean	0.0636; 39.2	-	0.509; 30.5	0.619; 36.6	0.590; 40.5	1.03; 29.5	29200; 29.5	710000; 12.7	18.6; 26.9
	Median	0.0644	1.50	0.517	0.612	0.593	1.06	28500	696000	18.0
Treatment Period 3 LOU064+single dose OC Day 30	Min; Max	0.0245; 0.157	0.730; 6.00	0.270; 0.913	0.270; 1.16	0.242; 1.16	0.553; 1.35	54300	589000; 850000	10.6; 39.1
	n	27	27	27	27	27	12	12	12	26
	mean (SD)	0.0841	-	0.607 (0.154)	0.761 (0.224)	0.741 (0.250)	0.977 (0.353)	34200	731000	18.4 (5.44)
	CV%	(0.0234) 27.8	-	25.4	29.5	33.7	36.1	(10900)	(112000) 15.3	29.6
	Geo-mean; CV% Geo-mean	0.0810; 28.6	-	0.590; 24.3	0.732; 28.9	0.705; 32.8	0.924; 35.5	32500; 35.4	723000; 15.9	17.6; 31.8
Median	0.0852	1.50	0.580	0.718	0.699	0.841	35700	737000	18.6	
Min; Max	0.0430; 0.136	0.750; 2.00	0.377; 0.987	0.411; 1.29	0.370; 1.37	0.572; 1.58	19000; 52400	519000; 941000	9.51; 28.0	

Source: Study X2102 Clinical Report, Table 11-1

CV%=Coefficient of variation (%)=sd/mean*100; CV% Geo-mean = sqrt (exp(variance for log-transformed data)-1)*100.

For T_{max} only median, min and max are displayed.

Plasma concentrations of EE 30 µg were below the LLOQ (5 pg/mL) in all subjects but one subject by 72 hours postdose when OC was given with remibrutinib. Plasma concentrations of LVG 150 µg were below LLOQ (100 pg/mL) in 11 of 27 subjects by 96 hours postdose when OC given alone.

The log-linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $t_{1/2}$ included at least 3 data points after C_{max} . If the adjusted R-square value of the regression analysis of the terminal phase was less than 0.75, no values were reported for $t_{1/2}$, AUC_{inf} , CL/F and Vz/F. When the proportion of extrapolation that contributed to AUC_{inf} exceeded 20% AUC_{inf} was not reported.

Concentration data below the LLOQ were treated as "zero" for PK parameter calculation as well as for summary statistics.

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 hours; AUC_{0-48h} , area under the concentration-time curve from time 0 to 48 hours; AUC_{inf} , area under the concentration-time curve from time zero to infinity; AUC_{last} , area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F, apparent clearance; C_{max} , maximum plasma concentration; geo-mean, geometric mean; EE, ethinylestradiol; LLOQ, lower limit of quantification; LVG, levonorgestrel; max, maximum; min, minimum; n, number of subjects; OC, oral contraceptive; PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase after oral administration

Table 73. Summary of Plasma PK Parameters of Levonorgestrel in the Presence and Absence of Remibrutinib, Study X2102

Period/Treatment/Day	Statistic	C _{max} (ng/mL)	T _{max} (hours)	AUC _{0-24h} (ng·h/mL)	AUC _{0-48h} (ng·h/mL)	AUC _{last} (ng·h/mL)	AUC _{inf} (ng·h/mL)	CL/F (mL/h)	Vz/F (mL)	T _{1/2} (hours)
Treatment Period 2 Single dose OC Day 9	n	30	30	30	30	30	12	12	12	28
	mean (SD)	3.18 (1.13)	-	19.3 (6.72)	28.5 (10.3)	36.8 (15.0)	52.6 (9.44)	2940 (521)	145000	42.5 (12.7)
	CV%	35.6	-	34.8	36.0	40.7	18.0	17.7	(33100)	22.9
	Geo-mean; CV% Geo-mean	2.98; 38.9	-	18.2; 38.2	26.6; 39.4	33.8; 45.7	51.8; 17.8	2900; 17.7	141000; 26.7	40.8; 29.2
	Median	3.08	1.00	19.6	29.9	38.6	51.1	2940	152000	41.2
	Min; Max	1.48; 5.56	0.480; 2.07	7.38; 36.2	10.5; 53.3	10.5; 68.8	35.9; 74.8	2010; 4180	75200; 187000	25.6; 77.3
Treatment Period 3 LOU064+single dose OC Day 30	n	27	27	26	26	27	14	14	14	23
	mean (SD)	4.29 (1.41)	-	27.1 (9.73)	41.0 (15.5)	51.4 (23.1)	65.4 (22.8)	2550 (856)	145000	45.0 (10.8)
	CV%	32.9	-	35.8	37.7	45.0	34.9	33.6	(54300)	37.4
	Geo-mean; CV% Geo-mean	4.06; 36.5	-	25.4; 40.8	38.0; 43.5	43.7; 82.4	62.0; 35.0	2420; 35.0	136000; 38.3	44.0; 21.4
	Median	4.24	1.00	27.0	40.2	53.6	65.3	2300	134000	44.2
	Min; Max	1.61; 7.40	0.730; 2.02	9.00; 48.6	12.7; 75.7	2.78; 102	36.0; 119	1260; 4170	67200; 266000	29.2; 82.7

Source: Study X2102 Clinical Report, Table 11-2

CV% = Coefficient of variation (%) = $\text{sd}/\text{mean} \times 100$; CV% Geo-mean = $\sqrt{\text{exp}(\text{variance for log-transformed data}) - 1} \times 100$.

For T_{max} only median, min and max are displayed.

LVG in plasma was quantifiable in 19 of 21 subjects at 96 hours postdose when OC was given with multiple doses of remibrutinib 100 mg.

The log-linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of t_{1/2} included at least 3 data points after C_{max}. If the adjusted R-square value of the regression analysis of the terminal phase was less than 0.75, no values were reported for t_{1/2}, AUC_{inf}, CL/F and Vz/F. When the proportion of extrapolation that contributed to AUC_{inf} exceeded 20% AUC_{inf} was not reported.

Concentration data below the LLOQ were treated as "zero" for PK parameter calculation as well as for summary statistics.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{0-48h}, area under the concentration-time curve from time 0 to 48 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; geo-mean, geometric mean; LLOQ, lower limit of quantification; LVG, levonorgestrel; max, maximum; min, minimum; n, number of subjects; OC, oral contraceptive; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase after oral administration

Impact of Remibrutinib on Midazolam (CYP3A4 Substrate)

The PK parameters of midazolam following the administration of a single dose of a probe cocktail, with and without coadministration of remibrutinib 100 mg BID, are summarized in [Table 74](#). On Day 18, the coadministration of remibrutinib 100 mg BID with a single dose of the probe cocktail, which included midazolam 2 mg, resulted in a 1.36-fold increase in C_{max}, a 1.45-fold increase in AUC_{0-inf}, and a 1.43-fold increase in AUC_{0-24h} for midazolam compared to when midazolam was administered alone. Similarly, on Day 26, the coadministration of remibrutinib 100 mg BID with a single dose of the probe cocktail led to a 1.27-fold increase in C_{max}, a 1.43-fold increase in AUC_{0-inf}, and a 1.43-fold increase in AUC_{0-24h} for midazolam compared to when midazolam was administered alone.

In vitro studies have demonstrated that remibrutinib acts as a reversible and time-dependent inhibitor and inducer of CYP3A4. Consequently, the net effect of remibrutinib on CYP3A4 function may exhibit time-dependent characteristics. For example, reversible inhibition is likely to be more pronounced at the initiation of treatment, while the induction effect may be most evident following multiple days of treatment. Based on the observed effects of remibrutinib on midazolam exposure on Days 18 (3 days following the administration of remibrutinib) and 26 (11 days following administration of remibrutinib), remibrutinib has low potential to inhibit or induce CYP3A4. Time-dependent changes in CYP3A4 activity were not observed as midazolam exposure was comparable on Days 18 and 26.

Table 74. Summary of Plasma PK Parameters of Midazolam in the Presence and Absence of Remibrutinib, Study X2102

Period/Treatment/Day	Statistic	C _{max} (ng/mL)	T _{max} (hours)	AUC _{0-24h} (ng ^h /mL)	AUC _{last} (ng ^h /mL)	AUC _{inf} (ng ^h /mL)	CL/F (mL/h)	Vz/F (mL)	T _{1/2} (hours)
Treatment Period 1 Probe cocktail Day 1	n	30	30	30	30	30	30	30	30
	mean (SD)	8.84 (2.45)	-	32.0 (9.76)	31.8 (9.93)	34.0 (10.7)	64500 (19500)	576000 (182000)	6.38 (1.48)
	CV%	27.7	-	30.5	31.2	31.5	30.2	31.6	23.3
	Geo-mean; CV% Geo-mean	8.56; 25.4	-	30.6; 31.2	30.3; 32.1	32.4; 31.7	61700; 31.6	554000; 28.2	6.23; 22.6
	Median	8.42	0.750	30.1	30.1	31.2	64200	549000	6.00
Min; Max	5.58; 17.2	0.480; 1.98	15.1; 50.3	14.8; 50.3	17.1; 54.8	36500; 117000	324000; 1300000	4.19; 10.9	
Treatment Period 3 LOU064+probe cocktail Day 18	n	28	28	28	28	26	26	26	27
	mean (SD) CV%	12.3 (3.78)	-	46.5 (15.3)	46.0 (15.2)	50.3 (16.1)	43400 (12500)	467000 (142000)	7.79 (1.93)
	Geo-mean; CV% Geo-mean	11.7; 32.1	-	44.1; 34.2	43.7; 34.5	48.1; 30.9	41600; 30.9	445000; 33.2	7.57; 24.1
	Median	11.5	0.750	45.7	45.2	49.2	40700	475000	7.00
	Min; Max	6.00; 19.8	0.420; 1.97	18.9; 81.5	18.0; 80.7	28.2; 88.2	22700; 71000	213000; 800000	4.95; 13.3
Treatment Period 3 LOU064+probe cocktail Day 26	n	27	27	27	27	26	26	26	27
	mean (SD) CV%	11.3 (3.11)	-	46.0 (15.4)	45.6 (15.2)	48.1 (15.1)	46400 (17500)	504000 (168000)	8.37 (3.31)
	Geo-mean; CV% Geo-mean	10.9; 28.5	-	43.5; 35.0	43.2; 35.0	45.7; 34.6	43800; 34.6	482000; 30.5	7.88; 35.0
	Median	10.8	0.550	43.4	43.0	46.4	43100	474000	7.99
	Min; Max	6.86; 18.0	0.500; 2.02	18.6; 86.4	18.1; 85.1	18.8; 80.7	24800; 106000	263000; 1130000	3.76; 18.5

Source: Study X2102 Clinical Report, Table 11-3

CV% = Coefficient of variation (%) = $\text{sd}/\text{mean} \times 100$; CV% Geo-mean = $\sqrt{\text{exp}(\text{variance for log-transformed data}) - 1} \times 100$.

For T_{max} only median, min and max are displayed.

Plasma concentrations of midazolam 2 mg were below LLOQ (0.1 ng/mL) in 9 of 30 subjects by 24 hours when the probe cocktail was given alone. When the probe cocktail was given with multiple doses of remibrutinib 100 mg, only one subject showed midazolam concentration below the LLOQ at 24 hours after dosing on Days 18 and 26.

The log-linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of t_{1/2} included at least 3 data points after C_{max}. If the adjusted R-square value of the regression analysis of the terminal phase was less than 0.75, no values were reported for t_{1/2}, AUC_{inf}, CL/F and Vz/F. When the proportion of extrapolation that contributed to AUC_{inf} exceeded 20% AUC_{inf} was not reported.

Concentration data below the LLOQ were treated as "zero" for PK parameter calculation as well as for summary statistics.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; AUC_{0-48h}, area under the concentration-time curve from time 0 to 48 hours; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; geo-mean, geometric mean; LLOQ, lower limit of quantification; max, maximum; min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; T_{max}, time to maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase after oral administration

Impact of Remibrutinib on Caffeine (CYP1A2 Substrate)

The C_{6h} of caffeine and its metabolite paraxanthine showed no significant difference when the probe cocktail was administered with or without remibrutinib 100 mg BID (Table 75). The coadministration of remibrutinib 100 mg BID with 200 mg of caffeine, resulted in a 3% and 12% decrease in the paraxanthine/caffeine C_{6h} ratio on Days 18 and 26, respectively (Table 71). These findings suggest that multiple oral doses of remibrutinib 100 mg are unlikely to impact the exposure to a single dose of caffeine.

Based on the observed effects of remibrutinib on the paraxanthine/caffeine C_{6h} ratio on Days 18 and 26 (3 and 11 days, respectively, after the initiation of remibrutinib dosing), remibrutinib has low potential to inhibit or induce CYP1A2.

Table 75. Summary of Plasma PK Parameters of Caffeine and Paraxanthine in the Presence and Absence of Remibrutinib, Study X2102

Period/Treatment/Day Statistic		Ratio Paraxanthine/Caffeine C6h	Caffeine C6h (ng/mL)	Paraxanthine C6h (ng/mL)
Treatment Period 1 Probe cocktail Day 1	n	30	30	30
	mean (SD) CV%	0.433 (0.141) 32.5	3200 (690) 21.5	1310 (276) 21.1
	Geo-mean; CV%	0.408; 38.5	3130; 23.0	1280; 25.9
	Geo-mean			
	Median	0.428	3140	1350
Min; Max	0.119; 0.822	1900; 4400	490; 1760	
Treatment Period 3 LOU064+probe cocktail Day 18	n	28	28	28
	mean (SD) CV%	0.418 (0.143) 34.2	3210 (723) 22.5	1260 (259) 20.5
	Geo-mean; CV%	0.394; 36.7	3140; 22.9	1240; 22.2
	Geo-mean			
	Median	0.403	3230	1270
Min; Max	0.150; 0.758	1950; 4740	641; 1730	
Treatment Period 3 LOU064+probe cocktail Day 26	n	27	27	27
	mean (SD) CV%	0.384 (0.135) 35.2	3430 (808) 23.5	1230 (268) 21.8
	Geo-mean; CV%	0.360; 39.1	3330; 25.5	1200; 23.2
	Geo-mean			
	Median	0.381	3330	1230
Min; Max	0.140; 0.707	1670; 4670	627; 1840	

Source: Study X2102 Clinical Report, Table 11-4

CV%=Coefficient of variation (%)=sd/mean*100. CV% Geo-mean = sqrt (exp(variance for log-transformed data)-1)*100.

Abbreviations: C6h, plasma concentration measured at 6 hours postdose; Geo-mean, geometric mean; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation

Impact of Remibrutinib on Tolbutamide (CYP2C9 Substrate)

The C24h of tolbutamide of the probe cocktail showed no significant differences when tolbutamide was administered with and without remibrutinib 100 mg BID ([Table 76](#)). The coadministration of remibrutinib 100 mg BID with a single dose of tolbutamide 500 mg resulted in 1.27- and 1.3-fold increases in tolbutamide C24h on Days 18 and 26, respectively ([Table 71](#)).

While PK parameters such as C_{max} and AUC are commonly used to evaluate drug interactions in clinical studies, the Applicant utilized tolbutamide C24h to assess the drug interaction between remibrutinib and tolbutamide. Studies in the literature suggest that tolbutamide C24h may reflect CYP2C9 activity ([Fuhr et al. 1996](#); [Jetter et al. 2004](#)). [Jetter et al. \(2004\)](#), proposed using the natural logarithm of tolbutamide C24h as a metric for CYP2C9 activity because it is strongly correlated with clearance. Tolbutamide C24h was found to be able to differentiate between CYP2C9 *1/*1 and *1/*2 genotypes from *1/*3 and *2/*2 genotypes. The natural logarithm of tolbutamide C24h for CYP2C9 *1/*3 and *2/*2 genotypes was approximately 2-fold higher than that for CYP2C9 *1/*1. However, there was no significant difference between CYP2C9 *1/*1 and *1/*3 or *2/*2 genotypes based on C_{max} , and only a 1.45-fold difference based on AUC_{0-inf} . Consequently, tolbutamide C24h may overestimate the magnitude of drug interaction between remibrutinib and tolbutamide compared to that determined when using C_{max} and AUC. As multiple oral doses of remibrutinib 100 mg yielded an approximate 30% increase in tolbutamide C24h, a lower magnitude may have been observed based on C_{max} and AUC. This is further supported by in vitro data. Although remibrutinib was identified as a CYP2C9 inhibitor in vitro, an in vivo DDI risk is not predicted at clinical concentrations following administration of the recommended dose.

Based on the observed effects of remibrutinib on tolbutamide exposure (C24h) on Days 18 and 26 (3 and 11 days, respectively, following the initiation of remibrutinib treatment), remibrutinib has low potential to inhibit or induce CYP2C9.

Table 76. Summary of Plasma PK Parameters of Tolbutamide in the Presence and Absence of Remibrutinib, Study X2102

Period/Treatment/Day	Statistic	C24h (ng/mL)
Treatment Period 1 Probe cocktail Day 1	n	30
	mean (SD) CV%	10700 (5760) 54.0
	Geo-mean; CV% Geo-mean	9220; 60.1
	Median	9500
	Min; Max	3460; 23800
Treatment Period 3 LOU064+probe cocktail Day 18	n	28
	mean (SD) CV%	13400 (6140) 45.7
	Geo-mean; CV% Geo-mean	12100; 50.7
	Median	12500
	Min; Max	4770; 27000
Treatment Period 3 LOU064+probe cocktail Day 26	n	27
	mean (SD) CV%	13700 (5760) 42.0
	Geo-mean; CV% Geo-mean	12600; 45.6
	Median	12700
	Min; Max	5470; 24700

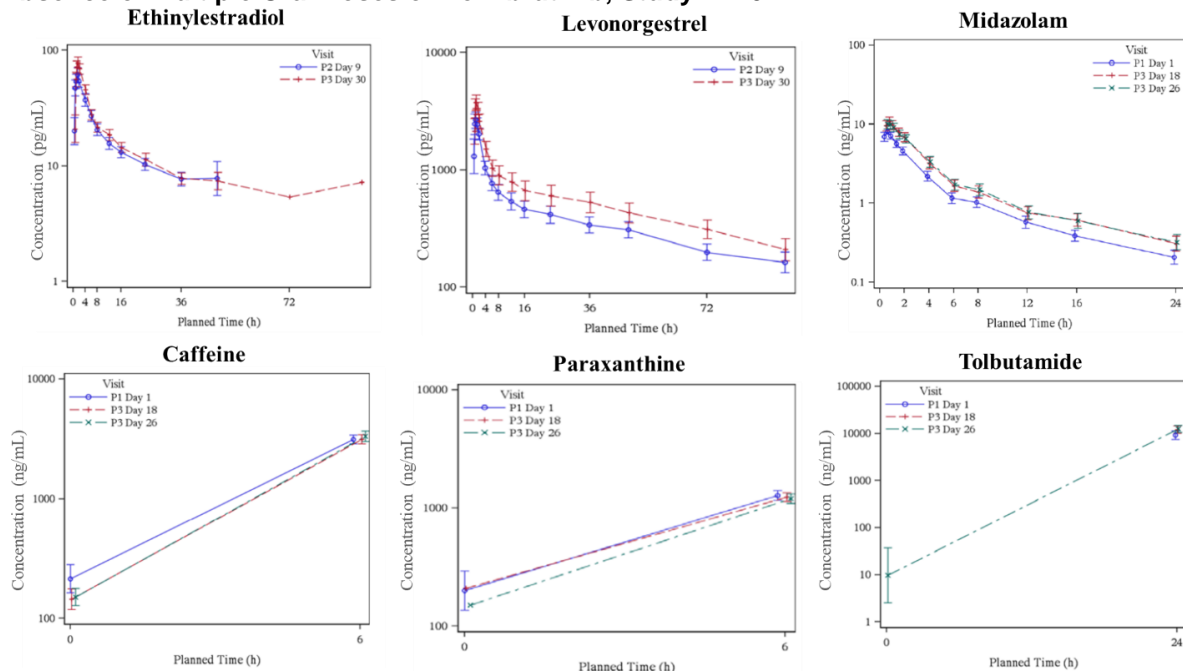
Source: Study X2102 Clinical Report, Table 11-5

CV%=Coefficient of variation (%)=sd/mean*100.

CV% Geo-mean = sqrt (exp(variance for log-transformed data)-1)*100.

Abbreviations: C24h, plasma concentration measured at 24 hours postdose; Geo-mean, geometric mean; LOU064, remibrutinib; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; SD, standard deviation

Figure 47. Geometric Mean (90% CI) Plasma Concentration-Time Profiles of Ethinylestradiol, Levonorgestrel, Midazolam, Caffeine, Paraxanthine, and Tolbutamide in the Presence and Absence of Multiple Oral Doses of Remibrutinib, Study X2102



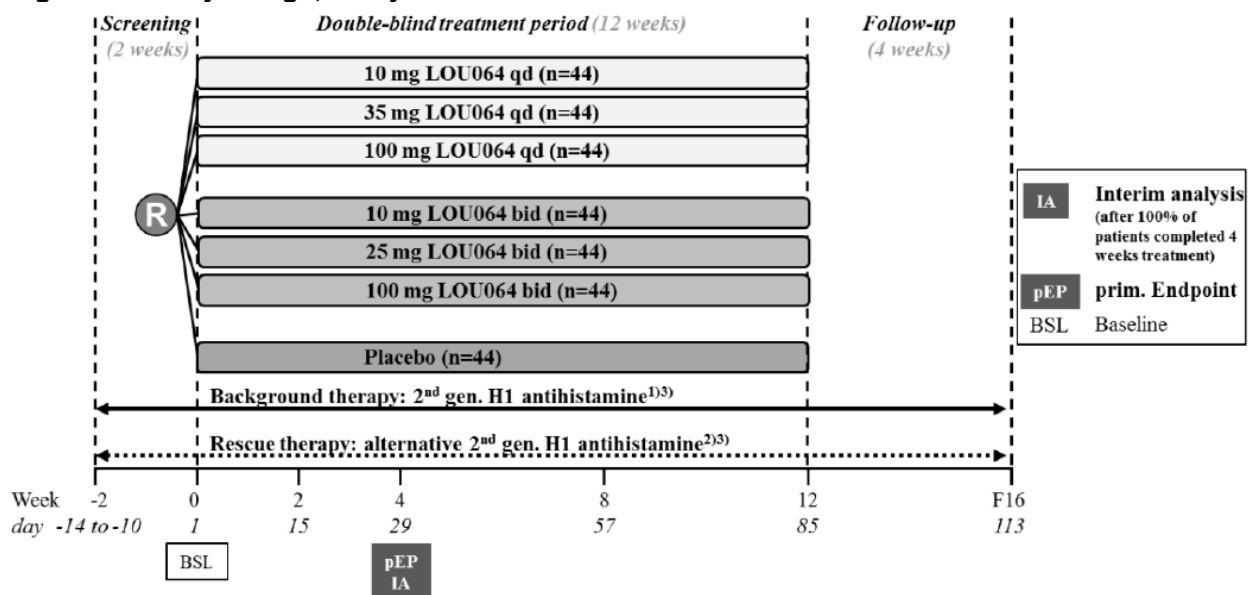
Source: Study X2102 Clinical Report, Figure 11-1, 11-2, 11-3, 11-4, 11-5, and 11-6.

Abbreviations: CI, confidence interval; h, hour; P, period

14.2.7. Dose-Ranging in Subjects With CSU, Study A2201

Study A2201 was a phase 2b, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of six different dosing regimens of oral remibrutinib in adult subjects with CSU that remained inadequately controlled despite treatment with second-generation H1-antihistamines. The study design and treatment arms are illustrated in Figure 48. Subjects were randomized equally to one of six remibrutinib treatment arms or placebo for 12 weeks. Dosages of remibrutinib ranged from 10 mg QD up to 100 mg BID. Remibrutinib was administered in the form of hard gelatin capsules, available in strengths of 10 mg, 25 mg, and 50 mg. Randomization was stratified by prior exposure to anti-IgE biologics (including omalizumab and ligelizumab), limited to 40% of the total study population, and by geographical region. The primary objective of the study was to characterize the dose-response relationship of remibrutinib administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4.

Figure 48. Study Design, Study A2201



Source: Study A2201 Clinical Report, Figure 9-1

¹⁾ Background therapy was a second generation H1-antihistamine at a locally approved licensed posology that was administered every day with a stable treatment regimen throughout the study (from Day -14 until Day 113).

²⁾ Rescue therapy was a second generation H1-antihistamine at a locally approved licensed posology that was eliminated primarily via renal excretion (e.g., cetirizine, levocetirizine or bilastine). The rescue H1-antihistamine had to be different from the background H1-antihistamine and could be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis throughout the study (from Day -14 until Day 113).

³⁾ H1-antihistamines used for background therapy and rescue therapy was not changed throughout the study.

remibrutinib 10 mg (Batch #1010020203, 1010018765, and 1010024908), remibrutinib 25 mg (Batch #1010020204, 1010018766, and 1010024915), and remibrutinib 50 mg (Batch #1010020206, 1010020205, 1010018767, 1010019287, 1010024299, 1010024909, 1010024910) were used in Study A2201.

Abbreviations: BSL, baseline; CSU, chronic spontaneous urticaria; LOU064, remibrutinib; n, number of subjects; qd, once daily

Efficacy and Dose-Response

Primary Endpoint (UAS7 Score Change From Baseline at Week 4)

The primary objective of this study was to establish a dose-response relationship and characterize the dose-response curve for remibrutinib administered either QD or BID at doses of 10 mg, 35 mg, and 100 mg QD, and 10 mg, 25 mg, and 100 mg BID, in comparison to placebo. The primary endpoint was the change from baseline in UAS7 at Week 4.

At the studied doses, a dose-response relationship was not observed. Based on the analysis of changes in UAS7 scores from baseline at Week 4, all remibrutinib treatment arms demonstrated greater reductions compared to the placebo (as detailed in and [Table 77](#)). The most substantial LS mean treatment difference (90% CI; p-value) relative to placebo was observed in the remibrutinib 25-mg BID arm (-14.58, 90% CI: -18.43, -10.73; nominal p<0.0001). Notably, the LS means of treatment differences compared to placebo for the remibrutinib 10 mg QD and 30 mg QD arms were similar to those of the remibrutinib 25-mg BID arm. Specifically, the LS mean treatment difference for the remibrutinib 10 mg QD arm was -13.66 (90% CI: -17.51, -9.81; nominal p<0.0001), and for the remibrutinib 30 mg QD arm, it was -13.64 (90% CI: -17.49, -9.78; nominal p<0.0001). These results indicate a flat dose-response relationship at dosages of 10 mg QD and above.

Table 77. UAS7 Score Change From Baseline at Week 4 Estimated With a Mixed-Effect Repeated Measurement Analysis of UAS7 Score Change From Baseline, Study A2201

Analysis visit	Treatment group	n	Within treatment			Treatment contrast in LS mean (Change)			
			LS Mean Change	(SE)	Comparison	LS Mean	(SE)	(90% CI)	One-sided p-value
Week 4	LOU064 10 mg q.d. (N =44)	44	-19.10	(1.686)	vs. Placebo	-13.66	(2.334)	(-17.51,-9.81)	<0.0001
	LOU064 35 mg q.d. (N =44)	43	-19.08	(1.690)	vs. Placebo	-13.64	(2.336)	(-17.49,-9.78)	<0.0001
	LOU064 100 mg q.d. (N =47)	47	-14.65	(1.624)	vs. Placebo	-9.21	(2.277)	(-12.97,-5.45)	<0.0001
	LOU064 10 mg b.i.d. (N =44)	44	-15.99	(1.686)	vs. Placebo	-10.55	(2.319)	(-14.38,-6.72)	<0.0001
	LOU064 25 mg b.i.d. (N =43)	42	-20.02	(1.708)	vs. Placebo	-14.58	(2.334)	(-18.43,-10.73)	<0.0001
	LOU064 100 mg b.i.d. (N =45)	41	-18.06	(1.691)	vs. Placebo	-12.62	(2.327)	(-16.45,-8.78)	<0.0001
	Placebo (N =42)	40	-5.44	(1.739)					

Source: Study A2201 Clinical Report, Table 11-3

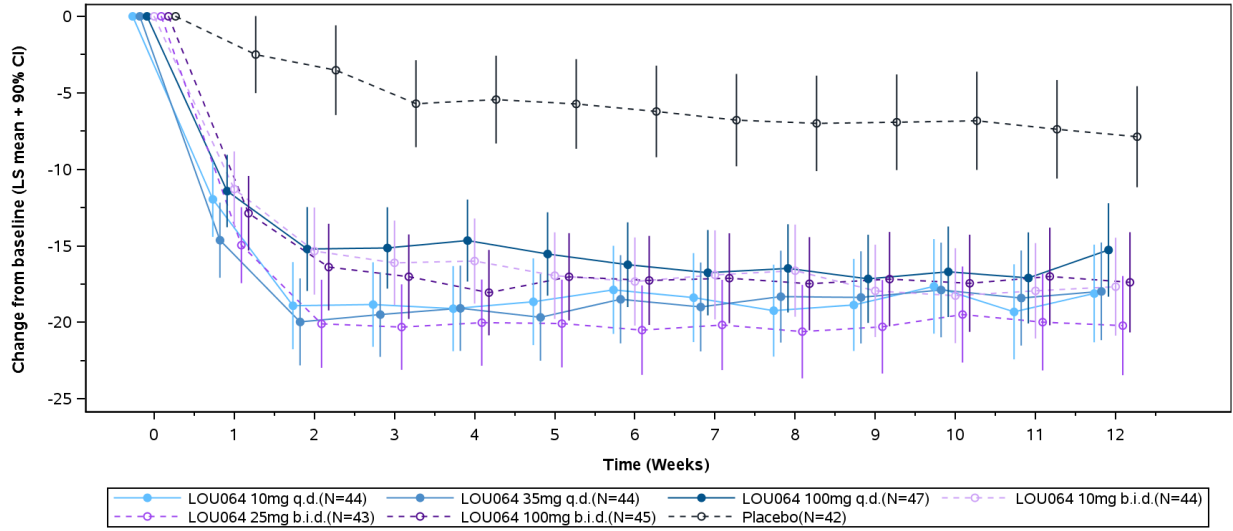
Baseline UAS7 score is comprised of the 7 days prior to Day 1 (Day -7 to Day -1).

MMRM: change from baseline in UAS7 score = treatment + baseline UAS7 score + prior exposure to anti-IgE biologics + geographical region + week + baseline UAS7 score*week + treatment group*week.

Abbreviations: CI, confidence interval; LOU064, remibrutinib; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; n, number of subjects with observed value at the visit; q.d., once daily; SE, standard error; UAS7, weekly urticaria activity score

Similar results were observed for the secondary endpoints of change from baseline to Week 12 in UAS7, the proportion of subjects achieving a UAS7 score of 0 at Week 12, and the proportion of subjects achieving a UAS7 score ≤6 at Week 12. Although all groups performed better relative to placebo, the most pronounced change for all endpoints was observed with the 25-mg BID dosage (refer to Tables 11-4 and 11-5, clinical study report for Study A2201). The change in UAS7 over the treatment period was similar across all treatment groups ([Figure 49](#)).

Figure 49. Mixed-Effect Repeated Measurement Analysis of UAS7 Score Change From Baseline Over 12 Weeks, Study A2201



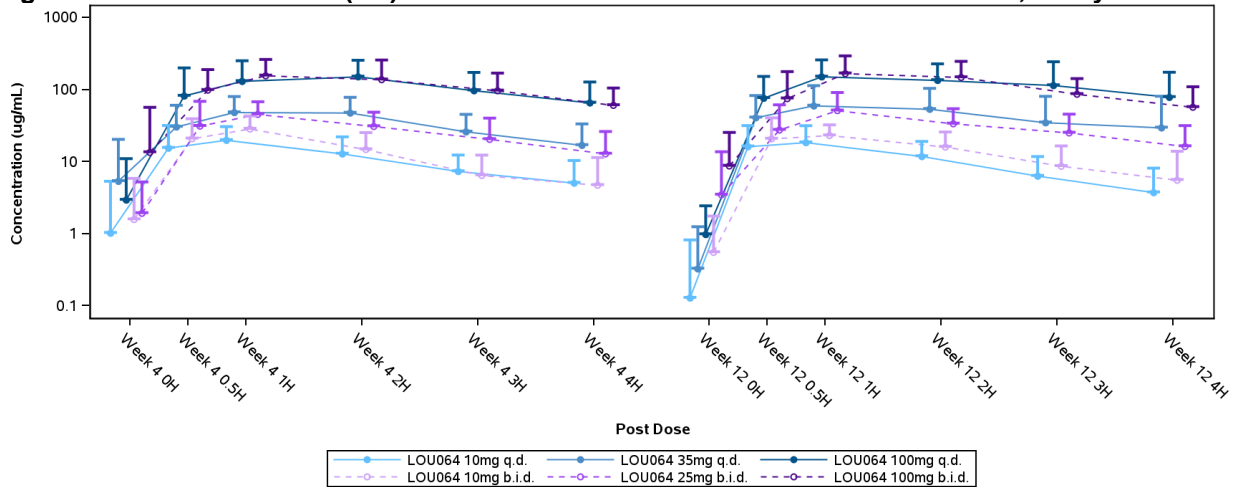
Source: Study A2201 Clinical Report, Figure 11-2

Abbreviations: b.i.d., twice daily; CI, confidence interval; LOU064, remibrutinib; LS, least squares; N, number of subjects; q.d., once daily; UAS7, weekly urticaria activity score

Pharmacokinetic Results

The whole blood concentration-time profiles and PK parameters of remibrutinib for all doses at Week 4 and Week 12 are illustrated in [Figure 50](#) and [Table 78](#). At steady state, the systemic exposure to QD dosing is relatively comparable to that of twice daily dosing for the 10-mg and 100-mg doses. This is expected given the short elimination half-life of remibrutinib.

Figure 50. Arithmetic Mean (SD) Remibrutinib Blood Concentration Time-Profiles, Study A2201



Source: Study A2201 Clinical Report, Figure 11-5

Abbreviations: b.i.d., twice daily; H, hour; LOU064, remibrutinib; q.d., once daily; SD, standard deviation

Table 78. Summary of PK Parameters of Remibrutinib in Blood, Study A2201

Parameter (unit)	Visit	Summary Statistics	LOU064 10 mg q.d. N= 44	LOU064 35 mg q.d. N= 44	LOU064 100 mg q.d. N= 47	LOU064 10 mg b.i.d. N= 44	LOU064 25 mg b.i.d. N= 43	LOU064 100 mg b.i.d. N= 45
AUC _{tau} (hr*ng/mL)	Week 4	n	6	6	15	26	19	17
		Mean (SD)	70.0 (32.3)	229 (115)	942 (780)	65.3 (36.8)	183 (97.5)	685 (368)
		CV(%) mean	46.2	50.4	82.8	56.4	53.3	53.7
		Geo-mean	62.8	197	639	57.5	164	611
		CV(%) geo-mean	58.5	73.1	129.1	53.4	49.2	51.2
		Median	72.0	273	722	55.8	145	585
		Min-Max	24.9 - 120	80.9 - 348	89.4 - 2680	24.9 - 185	80.2 - 482	239 - 1730
AUC _{tau} (hr*ng/mL)	Week 12	n	9	7	11	21	14	17
		Mean (SD)	49.6 (15.2)	184 (104)	779 (465)	70.7 (30.7)	195 (126)	761 (357)
		CV(%) mean	30.6	56.7	59.7	43.5	64.4	46.9
		Geo-mean	47.6	163	630	65.1	162	677
		CV(%) geo-mean	30.8	54.7	88.8	43.3	71.8	56.6
		Median	47.1	152	753	68.7	157	709
		Min - Max	32.8 - 74.3	95.6 - 379	110 - 1630	27.1 - 160	46.4 - 488	189 - 1580
AUC _{clast} (4hr) (hr*ng/mL)	Week 4	n	32	30	30	35	32	28
		Mean (SD)	45.2 (18.4)	131 (65.4)	427 (314)	55.9 (32.3)	107 (56.8)	418 (246)
		CV(%) mean	40.7	49.9	73.4	57.9	53.2	58.8
		Geo-mean	43.8	111	325	50.7	93.4	343
		CV(%) geo-mean	38.7	73.6	93.8	52.9	114.7	83.3
		Median	41.0	126	337	47.9	101	374
		Min - Max	0 - 81.8	15.6 - 268	68.1 - 1420	0 - 147	0 - 222	27.7 - 1210
AUC _{clast} (4hr) (hr*ng/mL)	Week 12	n	33	28	29	34	29	24
		Mean (SD)	41.8 (19.5)	159 (151)	441 (313)	54.4 (29.4)	118 (66.6)	469 (240)
		CV(%) mean	46.7	95.4	71.0	54.0	56.2	51.2
		Geo-mean	36.3	116	386	46.2	107	387
		CV(%) geo-mean	98.0	109.2	77.6	79.0	58.6	88.5
		Median	40.1	139	336	53.6	111	443
		Min - Max	0 - 97.4	8.33 - 857	0 - 1340	2.19 - 171	0 - 304	28.7 - 1060
C _{max} (ng/mL)	Week 4	n	32	30	30	35	32	28
		Mean (SD)	27.6 (13.7)	67.2 (32.7)	194 (142)	32.2 (18.7)	55.5 (34.7)	196 (144)
		CV(%) mean	49.8	48.7	73.2	58.0	62.5	73.4
		Geo-mean	25.8	57.0	147	28.8	49.0	152
		CV(%) geo-mean	47.4	74.5	95.3	57.8	89.2	94.4
		Median	26.6	71.0	169	27.3	51.9	166
		Min - Max	0 - 67.4	7.96 - 129	22.0 - 610	0 - 91.5	0 - 159	12.1 - 718
C _{max} (ng/mL)	Week 12	n	33	28	29	35	29	25
		Mean (SD)	26.1 (14.5)	80.3 (53.9)	199 (137)	31.2 (16.0)	64.9 (42.3)	219 (125)
		CV(%) mean	55.5	67.1	69.0	51.2	65.2	57.0
		Geo-mean	22.6	64.0	179	26.8	56.6	188
		CV(%) geo-mean	82.3	89.2	69.6	71.6	65.9	90.6
		Median	24.4	76.5	185	28.2	55.3	213
		Min - Max	0 - 63.9	6.32 - 279	0 - 659	1.95 - 74.7	0 - 175	0 - 510

Parameter (unit)	Visit	Summary Statistics	LOU064 10 mg q.d. N= 44	LOU064 35 mg q.d. N= 44	LOU064 100 mg q.d. N= 47	LOU064 10 mg b.i.d. N= 44	LOU064 25 mg b.i.d. N= 43	LOU064 100 mg b.i.d. N= 45
Time of C _{max} (hr)	Week 4	n	32	30	30	35	32	28
		Mean (SD)	1.33 (1.15)	1.54 (0.905)	1.52 (0.843)	0.900 (0.447)	1.15 (0.872)	1.52 (0.929)
		CV(%) mean	86.0	58.7	55.7	49.6	75.9	60.9
		Geo-mean	1.05	1.37	1.28	0.840	1.06	1.33
		CV(%) geo-mean	84.5	62.1	68.7	47.3	66.5	68.1
		Median	1.00	1.19	1.14	1.00	1.00	1.08
Time of C _{max} (hr)	Week 12	Min - Max	0 – 4.00	0 – 4.00	0.500 – 3.00	0 – 2.00	0 – 3.02	0 – 3.08
		n	33	28	29	35	29	25
		Mean (SD)	1.17 (0.956)	1.48 (1.03)	1.61 (1.15)	1.17 (0.767)	1.32 (0.929)	1.39 (0.859)
		CV(%) mean	81.9	69.2	71.8	65.4	70.4	61.8
		Geo-mean	0.965	1.19	1.41	0.980	1.22	1.18
		CV(%) geo-mean	70.5	77.4	73.5	65.6	58.2	64.7
		Median	1.00	1.09	1.07	1.00	1.00	1.03
		Min - Max	0 – 4.08	0.500 – 4.00	0 – 4.00	0.500 – 4.00	0 – 4.00	0.500 – 4.00

Source: Study A2201 Clinical Report, Table 11-9.

Blood samples were collected at Week 4 and Week 12 to evaluate the pharmacokinetic of remibrutinib. The linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal elimination phase in blood for the determination of $t_{1/2}$ included at least 3 data points after C_{max} . If the adjusted R² value of the regression analysis of the terminal phase was less than 0.75, no values were to be reported for $t_{1/2}$, AUC_{inf} , Vz/F and CL/F . Therefore, and due to the limited sampling up to 4 hours, these PK parameters might be determined as feasible.

Abbreviations: AUC_{last} , area under the concentration-time curve from time zero to the last measurable concentration sampling time; AUC_{0-t} , area under the concentration-time curve over the dosing interval; b.i.d., twice daily; CL/F , apparent clearance; C_{max} , maximum plasma concentration; CV, coefficient of variation; geo-mean, geometric mean; hr, hour; Max, maximum; Min, minimum; N, number of subjects; n, number of subjects with specific parameters; q.d., once daily; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; Vz/F , apparent volume of distribution during terminal phase after oral administration

14.2.8. Phase 3, Remibrutinib (25 mg BID) in Adult Subjects With CSU, Trial A2301

Trial A2301 was a randomized, double-blind, placebo-controlled study designed to establish the efficacy, safety, and tolerability of remibrutinib 25 mg administered twice daily in adult subjects with CSU inadequately controlled by H1-antihistamines, in comparison to a placebo. For full details of the study design and efficacy results, refer to Section 6.

Sparse pharmacokinetic blood samples were collected at Week 2, Week 12, and Week 52, with sampling limited to two time points at each visit to characterize peak exposures of remibrutinib (45 minutes and 90 minutes postdose).

Pharmacokinetic Results

In the remibrutinib arm, the geometric mean coefficient of variation (CV%) blood concentrations of remibrutinib at 45 minutes and 90 minutes postdose were as follows:

- Week 2: 41 (142) ng/mL (N=266) and 36.4 (97) ng/mL (N=264)
- Week 12: 39.4 (145) ng/mL (N=252) and 35.5 (97) ng/mL (N=253)
- Week 52: 34.1 (149) ng/mL (N=219) and 32.4 (113) ng/mL (N=218), respectively

Remibrutinib concentrations remained consistent across all visits.

14.2.9. Phase 3, Remibrutinib (25 mg BID) in Adult Subjects With CSU, Trial A2302

Trial A2302 mirrors the design and methodology of Trial A2301, with the additional inclusion of a subpopulation of Chinese subjects to assess the exposure to remibrutinib. For full details on the study design and efficacy results, refer to Section [6](#).

Pharmacokinetic Results

The pharmacokinetic analysis revealed that remibrutinib concentrations remained consistent, across all visits, mirroring the findings from Trial A2301.

Sparse pharmacokinetic blood samples were collected at Week 2, Week 12, and Week 52, with sampling limited to two time points at each visit to characterize peak exposures of remibrutinib (45 minutes and 90 minutes postdose). The geometric mean (CV%) blood concentrations of remibrutinib at 45 minutes and 90 minutes postdose were as follows:

- Week 2: 41.3 (113) ng/mL (N=251) and 39 (91) ng/mL (N=250)
- Week 12: 37.9 (154) ng/mL (N=237) and 38 (101) ng/mL (N=232)
- Week 52: 37.2 (144) ng/mL (N=191) and 36 (76) ng/mL (N=193), respectively

Overall, the exposure to remibrutinib is comparable between Trials A2301 and A2302 with high variability in PK data. Note that the primary difference between Trials A2301 and A2302 is the inclusion of Chinese subjects with CSU in Trial A2302.

14.2.10. Phase 3, Remibrutinib (25 mg BID) in Adult Japanese Subjects With CSU, Study A1301

Study A1301 was an open-label study designed to evaluate the safety, tolerability, and efficacy of remibrutinib administered at a dose of 25 mg twice daily in adult Japanese subjects with CSU who were inadequately controlled by H1-antihistamine therapy. The pharmacokinetic sampling methodology employed in this study was the same as that used in Trials A2301 and A2302 (i.e., at 45 and 90 minutes postdose at Weeks 2, 12, and 52).

Pharmacokinetic Results

The geometric mean (CV%) blood concentrations of remibrutinib at 45 minutes and 90 minutes postdose were as follows:

- Week 2: 53.9 (96) ng/mL (N=70) and 44.6 (64) ng/mL (N=69)
- Week 12: 50.8 (110) ng/mL (N=71) and 47.2 (60) ng/mL (N=71)
- Week 52: 43.5 (150) ng/mL (N=68) and 45.7 (62) ng/mL (N=68), respectively

In comparison to Trials A2301 and A2302, the exposure to remibrutinib in Japanese subjects with CSU in Study A1301 is slightly higher. However, a definitive conclusion on exposure comparison can't be made due to the observed high variability in PK data.

14.3. Bioanalytical Method Validation and Performance

14.3.1. Quantification of Remibrutinib

The Applicant developed and validated several bioanalytical methods to determine the concentrations of remibrutinib within the clinical pharmacology program. A summary of these bioanalytical methods, along with the studies supported by each method for the determination of remibrutinib, is presented in [Table 79](#).

Table 79. Summary of Analytical Methods Used To Quantify Remibrutinib in Clinical Trials

Analyte	Matrix	LLOQ (ng/mL)	Method validation report	BA site	Study	BA data report
LOU064	Blood	1.00	DMPK R1600407	(b) (4)	X2101	DMPK RCLOU064X2101 DMPK RCLOU064X2101-01
LOU064	Urine	1.00	DMPK R1600408		X2101	DMPK RCLOU064X2101
LOU064	Blood	1.00	DMPK R1600407		X2102	DMPK RCLOU064X2102
LOU064	Blood	0.100	DMPK R1800081		X2103	DMPK RCLOU064X2103
LOU064- [¹³ C ₃ , ¹⁵ N]	Blood	0.03	DMPK R1800080		X2103	DMPK RCLOU064X2103
LOU064	Blood	0.100	DMPK R1800081		X2104	DMPK RCLOU064X2104 DMPK RCLOU064X2104-01
LOU064	Urine	1.00	DMPK R1600408		X2104	DMPK RCLOU064X2104
LOU064	Blood	0.100	DMPK R1800081		X2105	DMPK RCLOU064X2105
LOU064	Blood	1.00	DMPK R1600407		X1101	DMPK RCLOU064X1101
LOU064	Urine	1.00	DMPK R1600408		X1101	DMPK RCLOU064X1101
LOU064	Blood	1.00	DMPK R1600407		A1301	DMPK RCLOU064A1301
LOU064	Blood	0.100	DMPK R1800081		A2101	DMPK RCLOU064A2101
LOU064	Blood	1.00	DMPK R1600407		A2201	DMPK RCLOU064A2201
LOU064	Blood	1.00	DMPK R1600407		A2301	DMPK RCLOU064A2301
LOU064	Blood	1.00	DMPK R1600407		A2302	DMPK RCLOU064A2302 DMPK RCLOU064A2302-01
LOU064	Blood	0.100	DMPK R1900112a		A2302	DMPK RCLOU064A2302a
LOU064	Blood	0.100	DMPK R1800081		A2201E1	DMPK RCLOU064A2201E1
LOU064	Blood	1.00	DMPK R1600407		A02103	DMPK RCLOU064A02103
LOU064	Blood	0.100	DMPK R1900112a		A02104	DMPK RCLOU064A02104 DMPK RCLOU064A02104-01

Source: NDA 218436, Module 2.7.1, Summary of Biopharmaceutic Studies, Table 1-6

Study A2201E1 was an open-label, single arm, multicenter, long-term safety and tolerability as well as efficacy extension study in adult subjects with CSU inadequately controlled by H1-antihistamine who completed Study A2201. In Study A2201E1, subjects were treated with 100-mg remibrutinib BID as HGC for 52 weeks. Remibrutinib exposure in subjects was monitored by measuring trough levels before dosing at selected sites.

Abbreviations: BA, bioanalytical; BID, twice daily; CSU, chronic spontaneous urticaria; DMPK, drug metabolism and pharmacokinetics; HGC, hard gelatin capsule; LLOQ, lower limit of quantification; LOU064, remibrutinib

14.3.1.1. Quantification of Remibrutinib in Human Blood

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical assay was developed and validated for the quantification of remibrutinib concentrations in human blood including methods DMPK R1600407, DMPK R1800081, and DMPK R1900112a. Method DMPK R1800080 was developed and validated for the quantification of remibrutinib- $^{13}\text{C}_3,^{15}\text{N}$ (i.e., SIL-remibrutinib) concentrations in human blood from Study X2103 (refer to Section 14.2.6.1). A summary of the method validations for remibrutinib in blood is presented in Table 80. The method validation for remibrutinib- $^{13}\text{C}_3,^{15}\text{N}$ in human blood is shown in Table 81. The methods were deemed acceptable for the determination of remibrutinib in human blood samples.

For most studies (except for Studies X2104 and X2105), the number of samples used for incurred sample reanalysis (ISR) fell below the number recommended in the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) (i.e., 10% of the first 1000 samples plus 5% of the number of samples that exceed 1000). Nevertheless, across studies, the ISR pass rate was at least 86%. In addition, for all trials with samples analyzed using method 1800081, the total number of samples used for ISR and their pass rates are adequate to meet the guidance-recommended criteria (refer to Table 2.2a in the Applicant's Information Request Response dated June 10, 2025). Given that Methods 1800081 and 1600407 were developed at the same laboratory (i.e., (b) (4)) and are based on the same assay principle (i.e., LC-MS/MS), the available data are adequate to establish reliability of the bioanalytical methods.

14.3.1.2. Quantification of Remibrutinib in Human Urine

Method DMPK R1600408 was developed and validated utilizing LC-MS/MS at the (b) (4) bioanalytical site in (b) (4) for the quantification of remibrutinib concentrations in human urine in Studies X2101, X1101, and X2104. A summary of the method validation for remibrutinib in urine is presented in Table 81. The method was deemed acceptable for the determination of remibrutinib in human urine samples.

Table 80. Summary of Bioanalytical Method Validation Reports To Measure Remibrutinib in Human Blood

Method ID	DMPK R1600407/DMPK R1600407-01/DMPK R1800424	DMPK R1800081/DMPK R1800081-01	DMPK R1900112a/DMPK R1900112a-01
Bioanalytical sites	(b) (4)	(b) (4)	(b) (4)
Bioanalytical assay	LC-MS/MS		
Analyte	Remibrutinib in human blood		
Calibration curve	8 points, 1 to 1000 ng/mL	8 points, 0.1 to 100 ng/mL	8 points, 0.1 to 100 ng/mL
Cumulative accuracy (%bias)	3 to 2.2%	-3.10 to 2.50%	-4.60 to 3.00%
Cumulative precision (%CV)	3.69-7.05%	2.31 to 3.91%	1.60 to 4.10%
Regression model & weighting	$y = ax + b$, linear regression with a weighting factor of $1/x^2$		
QCs performance	QCs: 1, 3, 30, 800 ng/mL	QCs: 0.1, 0.3, 30, 80 ng/mL	QCs: 0.1, 0.3, 3, 30, 80 ng/mL
Cumulative accuracy (%bias)	-5.1 to -0.33%	-6.60 to -4.13%	-5.40 to 0.30%
Interbatch %CV	6.32 to 10.16%	3.22 to 12.74%	2.60 to 5.60%
Selectivity	No significant chromatographic peaks in six lots of blank matrices (blood) for remibrutinib or internal standard (IS)		
Matrix effect (Matric factor, MF)	Remibrutinib (<i>obtained on areas</i>) • MF at QC low (3 ng/mL) =0.99 • MF at QC high (800 ng/mL) =0.97 Remibrutinib (<i>obtained on peak area ratios</i>) • MF at QC low (3 ng/mL) =0.98 • MF at QC high (800 ng/mL) =1.03 Internal standard (IS) • MF at QC low (3 ng/mL) =1.02 • MF at QC high (800 ng/mL) =0.94	Remibrutinib (<i>obtained on areas</i>) • MF at QC low (0.3 ng/mL) =0.98 • MF at QC high (80 ng/mL) =0.99 Remibrutinib (<i>obtained on peak area ratios</i>) • MF at QC low (0.3 ng/mL) =1.02 • MF at QC high (80 ng/mL) =1.02 Internal Standard • MF at 30 ng/mL concentration with QC low (0.3 ng/mL) =0.96	Remibrutinib • MF at QC low (0.3 ng/mL) =1.07 to 1.10 • MF at QC high (80 ng/mL) =1.03 to 1.10 Internal standard • MF at QC low (0.3 ng/mL) =0.982 to 1.04 • MF at QC high (80 ng/mL) =0.972 to 1.04

		MF at 30 ng/mL concentration with QC high (80 ng/mL) =0.97	
Recovery	Remibrutinib 3 ng/mL, overall mean =89.77%, 4.24% CV 30 ng/mL, overall mean =93.35%, 7.59% CV 800 ng/mL, overall mean =97.59%, 6.54% CV Internal standard 300 ng/mL, overall mean =101.57%, 6.65% CV	Remibrutinib 0.3 ng/mL, overall mean =72.85%, 1.43% CV 30 ng/mL, overall mean =69.77%, 2.05% CV 80 ng/mL, overall mean =74.38%, 4.99% CV Internal standard 30 ng/mL, overall mean =75.23%, 2.38% CV	Remibrutinib 0.3 ng/mL, overall mean =103.8%, 3.9% CV 30 ng/mL, overall mean =102%, 3.7% CV 80 ng/mL, overall mean =104.2, 3.50% CV Internal standard 30 ng/mL, overall mean =101%, 3.9% CV
Dilution linearity	High concentration QC sample spiked with 5000 ng/mL of remibrutinib was diluted 1:10. Mean bias: -7.80%, CV: 2.93% (n=6)	High concentration QC sample spiked with 800 ng/mL of remibrutinib was diluted 1:10. Mean bias: -3.63%, CV: 6.33% (n=6)	High concentration QC sample spiked with 1000 ng/mL of remibrutinib was diluted 1:10. Mean bias: 5%, CV: 2.5% (n=6)
Specificity	No significant interference from blank human blood on remibrutinib or IS <u>Specificity against coproporphyrin I, coproporphyrin III, rosuvastatin, and digoxin</u> Coproporphyrin I (1 ng/mL), coproporphyrin III (1 ng/mL), digoxin (1.3 ng/mL) and rosuvastatin (9 ng/mL) were added to blank matrix (n=6) without addition of remibrutinib and its internal standard. No peaks at the retention times of each of the nonspiked analyte were present with a peak signal which was greater than 20% of the mean LLOQ calibration standard	No significant interference from blank human blood on remibrutinib or IS <u>Specificity against ritonavir or eltrombopag olamine</u> Ritonavir (15.0µM) or eltrombopag olamine (20 µg/mL) was added to blank matrix (n=6) without remibrutinib or IS. No peaks at the retention times of the nonspiked analyte were present which represented a peak signal which was greater than 20% of the mean LLOQ calibration standard peak	No significant interference from blank human blood on remibrutinib or IS

	peak signals and 5% of the mean internal standard peak signals.	signals and 5% of the mean internal standard peak signals	
Short-term stability	Stability in spiked human blood samples on an ice bath has been demonstrated for 2 hours • QC 3 ng/mL, bias: -0.09%, CV: 2.58% • QC 800 ng/mL, bias: -3.73%, CV: 2.79%	Stability in spiked human blood samples on an ice bath has been demonstrated for 4 hours • QC 0.3 ng/mL, bias: -14.67%, CV: 3.54%. • QC 80.0 ng/mL, bias: -5.88%, CV: 1.94%.	Stability in spiked human blood samples on an ice bath has been demonstrated for 6 hours • QC 0.3 ng/mL, bias: -4.3%, CV: 3.30% • QC 80 ng/mL, bias: -9.5%, CV: 1.00% Stability in spiked human blood samples at room temperature has been demonstrated for 2 hours • QC 0.3 ng/mL, bias: -3%, CV: 4.1% • QC 80 ng/mL, bias: -2.9%, CV: 2.3%
Process stability	Postpreparative stability in 10°C for 192 hours: • QC 3 ng/mL, bias: 2.67%, CV: 7.27% • QC 800 ng/mL, bias: -2.75%, CV: 6.08% Reinjection reproducibility in 10°C for 192 hours: • QC 1 ng/mL, bias: -11.4%, CV: 10.21% • QC 3 ng/mL, bias: -7%, CV: 6.77% • QC 30 ng/mL, bias: -10%, CV: 3.2% • QC 800 ng/mL, bias: -9.13%, CV: 5.05%	Postpreparative stability in 10°C for 89 hours: • QC 0.1 ng/mL, bias: -1.8%, CV: 9.37% • QC 0.3 ng/mL, bias: 8%, CV: 2.98% • QC 30 ng/mL, bias: 4.33%, CV: 2.23% • QC 80 ng/mL, bias: 4.25%, CV: 3.44% Reinjection reproducibility in 10°C for 85 hours: • QC 0.1 ng/mL, bias: -0.80%, CV: 3.86% • QC 0.3 ng/mL, bias: 4%, CV: 4.10% • QC 30 ng/mL, bias: 4.33%, CV: 1.67%	Postpreparative stability at 5°C ±3°C for 98 hours: • QC 0.3 ng/mL, bias: -4.3%, CV: 2.1% • QC 80 ng/mL, bias: -12.9%, CV: 2.1%

		• QC 80 ng/mL, bias: 6.5%, CV: 5.85%	
Freeze-thaw stability	Three freeze-thaw cycles (at $-24\pm 6^{\circ}\text{C}$) • QC 3 ng/mL, bias: -8.33%, CV: 4.15% • QC 800 ng/mL, bias: -11.25%, CV: 5.52% • Three freeze-thaw cycles (at $-75\pm 10^{\circ}\text{C}$) • QC 3 ng/mL, bias: -8.67%, CV: 3.23% • QC 800 ng/mL, bias: -3.5%, CV: 5.73%	Two freeze-thaw cycles (at $-75\pm 10^{\circ}\text{C}$) • QC 0.3 ng/mL, bias: -12%, CV: 1.47%. • QC 80 ng/mL, bias: -2.13%, CV: 4.61%.	Five freeze-thaw cycles (at $-20\pm 10^{\circ}\text{C}$) • QC 0.3 ng/mL, bias: -3.7%, CV: 3.40% • QC 80 ng/mL, bias: -9.1%, CV: 2.40% Five freeze-thaw cycles (at $-75\pm 10^{\circ}\text{C}$) • QC 0.3 ng/mL, bias: -2.3%, CV: 2.80% • QC 80 ng/mL, bias: -9%, CV: 0.90%
Long-term stability	34 days (at $-24\pm 6^{\circ}\text{C}$) • QC 3 ng/mL, bias: -8.67%, CV: 6.64% • QC 800 ng/mL, bias: -15%, CV: 1.57% 743 days (at $-75\pm 10^{\circ}\text{C}$) • QC 3 ng/mL, bias: 8%, CV: 3.64% • QC 800 ng/mL, bias: 14.5%, CV: 2.43%	192 days (at $-75\pm 10^{\circ}\text{C}$) • QC 0.3 ng/mL, bias: -3.67%, CV: 2.75% • QC 80 ng/mL, bias: -4.88%, CV: 3.94% 586 days (at $-75\pm 10^{\circ}\text{C}$) in human blood using incurred stability samples from study X2104.	43 days (at -10 to -30°C) • QC 0.3 ng/mL, bias: -5.70%, CV: 2.20%. • QC 80 ng/mL, bias: -8.90%, CV: 2.10%. 512 days (at -60 to -80°C) • QC 0.3 ng/mL, bias: -3%, CV: 5.5% • QC 80 ng/mL, bias: -1.9%, CV: 1.7%
In-study performance	The in-study performance for Studies X2101 (42 samples), X2102 (21 samples), X1101 (21 samples), A2201 (81 samples), A02103 (21 samples), A1301 (21 samples), A2301 (21 samples), and A2302 (21 samples) was deemed acceptable. At least 85.7% of these samples meeting the prespecified criteria.	The in-study performance for Studies X2103 (21 samples), X2104 (21 samples), X2105 (105 samples), A2201E1 (21 samples), and A2101 (21 samples) was deemed acceptable. At least 71.4% met the prespecified criteria.	The in-study performance for Studies A02104 (24 samples) and A2302 (32 samples) was deemed acceptable. This assessment included evaluations of standard curve performance, QC performance, method reproducibility (with at least 24 study samples analyzed, and at least 95.8% of samples meeting the

prespecified criteria), and sample analysis within the established stability period.

- Carry over
- <20% of the mean of the LLOQ calibration standard peak signals for remibrutinib
  - <5% of the mean of the LLOQ calibration standard peak signals for IS

Source: Reviewer-generated table based on the bioanalytical methods validation reports and summary of biopharmaceutical studies and associated analytical methods DMPK R1800424 used to report additional specificity, matrix effect, carryover, and stability data.

DMPK R1800081-01 used to report additional stability assessments specificity assessments, cross-validations data and to document the change of internal standard from remibrutinib-[D₇, ¹³C] to remibrutinib-D₄. Six lots of blank matrices were tested for the selectivity assessment due to the change of labeled internal standard from remibrutinib-[D₇, ¹³C] to remibrutinib-[D₄]. There were no significant chromatographic peaks detected at the mass transitions and expected retention times of remibrutinib or at the internal standard remibrutinib-D₄ that would interfere with quantitation in all the six lots tested.

Abbreviations: CV, coefficient of variance; DMPK, drug metabolism and pharmacokinetics; LC-MS-MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; n, number of subjects; QC, quality control

Table 81. Summary of Bioanalytical Method Validation Reports To Measure Remibrutinib in Human Urine and Remibrutinib-[¹³C₃,¹⁵N] in Human Blood

Method ID	DMPK R1600408/DMPK R1600408a-01	DMPK R1800080
Bioanalytical sites	(b) (4)	(b) (4)
Analyte	Remibrutinib in human urine	Remibrutinib-[¹³ C ₃ , ¹⁵ N] in human blood
Calibration curve	8 points, 1 to 1000 ng/mL	8 points, 0.03 to 20 ng/mL
Cumulative accuracy (%bias)	-3.50 to 3.50%	-2.80 to 3.40%%
Cumulative precision (%CV)	2.19 to 4.90%	1.62 to 8.93%
Regression model & weighting	y = ax + b, linear regression with a weighting factor of 1/x ²	y = ax + b, linear regression with a weighting factor of 1/x
QCs performance	QCs: 1, 3, 30, 800 ng/mL	QCs: 0.03, 0.09, 6, 15 ng/mL
Cumulative accuracy (%bias)	-14.70 to -0.33%	-7 to 3.33%
Interbatch %CV	1.19 to 5.45%	3.96 to 12.58%
Selectivity	No significant chromatographic peaks in 6 lots of blank matrices for remibrutinib or internal standard (IS)	No significant chromatographic peaks in 6 lots of blank matrices (blood) for remibrutinib or internal standard (IS)
Matrix effect (matric factor, MF)	-	<i>Remibrutinib-[¹³C₃,¹⁵N] (obtained on areas)</i> • MF at QC low (0.09 ng/mL) =1.03, CV: 2.12% • MF at QC high (15 ng/mL) =1.01, CV%: 2.1 <i>Remibrutinib-[¹³C₃,¹⁵N] (obtained on peak areas)</i> • MF at QC low (0.09 ng/mL) =1.03, CV: 2.12%

Method ID	DMPK R1600408/DMPK R1600408a-01	DMPK R1800080
		- MF at QC high (15 ng/mL) =1.01, CV%: 2.1 <i>Internal standard (obtained on areas)</i> - MF at QC low (0.09 ng/mL) =1.02, CV%: 2.12 - MF at QC high (80 ng/mL) =1.01, CV%: 2.09
Recovery	<i>Remibrutinib</i> 3.00 ng/mL, overall mean =80.91%, 4.36% CV 30.0 ng/mL, overall mean =81.88%, 1.64% CV 800 ng/mL, overall mean =84.81%, 2.98% CV <i>Internal Standard</i> 300 ng/mL, overall mean =87.94%, 3.81% CV	<i>Remibrutinib</i> 0.09 ng/mL, overall mean =70.49%, 2.06% CV 6 ng/mL, overall mean =69.83%, 2.16% CV 15 ng/mL, overall mean =73.62%, 1.84% CV <i>Internal standard</i> 8 ng/mL, overall mean =78.91%, 2.91% CV
Dilution linearity		High concentration QC sample spiked with 200 ng/mL of remibrutinib was diluted 1:20. Mean bias: -3%, CV: 1.86% (n=6)
Specificity		No significant interference from blank human blood on remibrutinib-[¹³C₃,¹⁵N] or IS <u>Specificity against ritonavir:</u> Ritonavir (15μM) was added to blank matrix (n=6) without remibrutinib-[¹³C₃,¹⁵N] or IS. Interference with ritonavir was not observed. <u>Specificity against remibrutinib</u> In human blood spiked with 2000 ng/mL remibrutinib, a peak higher than 20% (29.35%) of the remibrutinib-[¹³C₃,¹⁵N] mean peak area at LLOQ was detected at the retention time on the transition of remibrutinib[¹³C₃,¹⁵N]. According to the Applicant, this result can be explained by the purity of the reference material for

Method ID	DMPK R1600408/DMPK R1600408a-01	DMPK R1800080
		remibrutinib as approximately the same result (24.49%) was observed when pure solution of remibrutinib was injected. In Study X2103, the highest mean (SD) C _{max} observed was 180 (96.7) ng/mL. As this is well below the tested condition of 2000 ng/mL, significant interference with measurement of remibrutinib [¹³ C ₃ , ¹⁵ N] is not expected.
Short-term stability	Stability in spiked human urine samples on an ice bath has been demonstrated for 4 hours • QC 3 ng/mL, bias: 3%, CV: 3.22% • QC 800 ng/mL, bias: -5.13%, CV: 2.61% Stability in spiked human urine samples at 5±5°C has been demonstrated for 24 hours • QC 3 ng/mL, bias: -2%, CV: 2.18%. • QC 800 ng/mL, bias: -9.75%, CV: 1.66%	Stability in spiked human blood samples on an ice bath has been demonstrated for 2 hours and 20 minutes • QC 0.09 ng/mL, bias: -11.56%, CV: 2.09% • QC 15 ng/mL, bias: -4%, CV: 1.88% Stability was not demonstrated after 3.5 hours or 4.5 hours.
Process stability	Postpreparative stability in 10°C for 74 hours: • QC 3 ng/mL, bias: -11.67%, CV: 4.04% • QC 800 ng/mL, bias: -8.25%, CV: 1.32% Reinjection reproducibility in 10°C for 90 hours: • QC 1 ng/mL, bias -7.10%, CV: 3.97% • QC 3 ng/mL, bias: -7.00%, CV: 2.96%. • QC 30 ng/mL, bias -2.67%, CV: 0.73% • QC 800 ng/mL, bias: -9%, CV: 1.58%	Postpreparative stability in 10°C for 120 hours: • QC 0.03 ng/mL, bias: -2%, CV: 6.46% • QC 0.09 ng/mL, bias: 6%, CV: 4.86% • QC 6 ng/mL, bias: 11.17%, CV: 2.89% • QC 15 ng/mL, bias: 10%, CV: 2.26% Reinjection reproducibility in 10°C for 116 hours: • QC 0.03 ng/mL, bias: -1.67%, CV: 7.02% • QC 0.09 ng/mL, bias: 3.89%, CV: 2.29% • QC 6 ng/mL, bias: 10.33%, CV: 2.22% • QC 15 ng/mL, bias: 8.67%, CV: 2.68%
Freeze-thaw stability	Three freeze-thaw cycles (at -24±6°C) • QC 3 ng/mL, bias: 2%, CV: 5.95% • QC 800 ng/mL, bias: -5.25%, CV: 1.77%	Two freeze-thaw cycles (at -24±6°C) • QC 0.09 ng/mL, bias: -14.33%, CV: 5.73% • QC 15 ng/mL, bias: -2.67%, CV: 2.65%

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Method ID	DMPK R1600408/DMPK R1600408a-01	DMPK R1800080
	Three freeze-thaw cycles (at $-75\pm 10^{\circ}\text{C}$) • QC 3 ng/mL, bias: 12.33%, CV: 3.50% • QC 800 ng/mL, bias: -3%, CV: 2.51%	Two freeze-thaw cycles (at $-75\pm 10^{\circ}\text{C}$) • QC 0.09 ng/mL, bias: -12.11%, CV: 2.68% • QC 15 ng/mL, bias: -2%, CV: 2.72%
Long-term stability	1002 days (at $-24\pm 6^{\circ}\text{C}$) • QC 3 ng/mL, bias: 2.33%, CV: 6.09% – QC 800 ng/mL, bias: 1%, CV: 2%	188 days (at $-75\pm 10^{\circ}\text{C}$) • QC 0.09 ng/mL, bias: -9.22%, CV: 4.44% • QC 15 ng/mL, bias: 0%, CV: 1.98%
	1002 days (at $-75\pm 10^{\circ}\text{C}$) • QC 3 ng/mL, bias: 2.33%, CV: 5.47% • QC 800 ng/mL, bias: -2.5%, CV: 5.62%	Stability was not demonstrated after 117 and 188 days of storage at $-24^{\circ}\text{C} \pm 6^{\circ}\text{C}$
In-study performance	The in-study performance for Studies X2101, X2104 (21 samples), and X1101 (21 samples) was deemed acceptable. At least 81% met the prespecified criteria.	The in-study performance for Study X2103 (21 samples) was deemed acceptable across several key metrics with 95.2% met the prespecified criteria
Carryover	• <20% of the mean of the LLOQ calibration standard peak signals for remibrutinib • <5% of the mean of the LLOQ calibration standard peak signals for IS	

Source: Reviewer-generated table based on the bioanalytical methods validation reports and summary of biopharmaceutic studies and associated analytical methods
 Abbreviations: C_{max} , maximum plasma concentration; CV, coefficient of variation; DMPK, drug metabolism and pharmacokinetics; LLOQ, lower limit of quantification; QC, quality control; SD, standard deviation

14.3.2. Cross-Validation of Analytical Sites

Cross-validation between (b) (4) and (b) (4) was conducted by analyzing 20 spiked QC samples, with each sample tested in quintuplicate at both sites. Additionally, cross-validation of analytical methods for each site was performed using 30 incurred samples from Trial A2302. A summary of the cross-validation results is presented in the accompanying [Table 82](#).

Table 82. Summary of Cross-Validation Results Between (b) (4) and (b) (4)

Validation Parameters	(b) (4) (DMPK R1600407) vs. (b) (4) (DMPK R1900112)	(b) (4) (DMPK R1800081) vs. (b) (4) (DMPK R1900112a)
<i>Remibrutinib in human blood</i>		
20 spiked QC samples (5 replicates at each level of concentration) from (b) (4) (reference laboratory) and were analyzed blindly in (b) (4)	For the lower limit of quantification (LLOQ) at 1 ng/mL, low quality control (QC) at 3 ng/mL, mid QC at 30 ng/mL, and high QC at 800 ng/mL, the normalized differences (%) between (b) (4) and (b) (4) were 0.23% and -5.09%, -5.89% and -10.35%, respectively. The range of bias was from -13.7% to 4.13%, and the range of coefficient of variation (CV%) was from 2.01% to 12.4%	For the LLOQ at 0.1 ng/mL, low QC at 0.3 ng/mL, mid QC at 30 ng/mL, and high QC at 80 ng/mL, the normalized differences (%) between (b) (4) and (b) (4) were 3.64% and -7.04%, -0.32% and 9.46%, respectively. The range of bias was observed to be from -10.63% to 12%, while the range of coefficient of variation (CV%) was between 2.45% and 4.7%.
Validation Parameters	(b) (4) (DMPK R1600407) vs. (b) (4) (DMPK R1800081)	(b) (4) (DMPK R1900112) vs. (b) (4) (DMPK R1900112a)
30 incurred samples from Trial A2302 were tested	Of the samples analyzed in Trial A2302, 29 out of 30 (96.6%) with concentrations ranging from 3 to 72 ng/mL met the acceptance criteria	Of the samples analyzed in Trial A2302, 30 out of 30 (100%) with concentrations ranging from 3 to 80 ng/mL met the acceptance criteria, demonstrating a bias within ±20%.

Source: Reviewer-generated table based on the bioanalytical methods validation reports and summary of biopharmaceutical studies and associated analytical methods
Abbreviations: CV, coefficient of variation; DMPK, drug metabolism and pharmacokinetics; LLOQ, lower limit of quantification; QC, quality control

14.3.3. Quantitation of Radiation From [¹⁴C]-Remibrutinib in Human Blood, Plasma, Urine, and Feces

Plasma and Whole Blood

The concentrations of total radioactivity in whole blood, plasma, urine, fecal and expired air samples obtained from Study X2104 were determined using accelerator mass spectrometry (AMS). Initially, urine and feces samples were analyzed using liquid scintillation counting (LSC); when the radioactivity concentrations by LSC dropped below the LLOQ, AMS was used to measure total radioactivity in urine and fecal samples.

A reference standard sucrose-8542 ($C_{12}H_{22}O_{11}$) with a certified $^{14}C/^{12}C$ isotope ratio was used as system suitability sample with $^{14}C/^{12}C$ ratio = 1.5061×10^{-12} dpm/g, C = 20.42, and Bq/g C = 0.3403786. The sucrose was always analyzed at the start of each run of samples (in triplicate). When the measured $^{14}C/^{12}C$ ratio (average of at least 2) deviated >15% from the certified ratio, the run was rejected, and the samples were reprocessed and reanalyzed.

Two AMS QC samples were included in triplicate in each analysis. These QC samples were blank pooled plasma spiked with a known amount of ^{14}C -paracetamol. Thereafter, the $^{14}C/^{12}C$ ratio (nominal ratio) was determined using AMS analysis. The average $^{14}C/^{12}C$ ratio of the QC samples in an analytical run must be within 85 to 115% of the nominal ratio. In addition, the CV should be $\leq 15\%$. The QC results fulfilled the requirements for all analytical runs.

All homogenized feces samples were analyzed in triplicate; if the CV is >30%, the sample was reanalyzed. All plasma, blood and urine samples were analyzed in duplicate; if the CV is >20%, the sample is reanalyzed. Thirty-seven samples (one urine, three plasma and thirty-three blood samples of the oral arm and two blood samples of the intravenous arm) with CV% >20% were reanalyzed. For a number of blood samples, the CV remained >20% after multiple reanalyses and were reported, as agreed as not reportable. Overall, the AMS analytical runs met the acceptance criteria.

Urine and Feces

The [^{14}C] radioactivity concentrations in urine, feces, and vomitus (if applicable) were determined using LSC (for feces and urine) or AMS (when radioactivity concentrations by LSC dropped below the LLOQ). All samples and stock solutions and dilutions thereof were stored at a nominal $-20^{\circ}C$.

All QC samples (50, 5000, and 40000 dpm/g) in human urine were prepared by spiking human urine with a reference standard [1-methyl- ^{14}C]-caffeine. QC samples (100, 6400, and 128000 dpm/g) in human feces were prepared by spiking human feces homogenate with the reference standard. For each run, the absolute bias had to be $\leq 10\%$ of the nominal value ($\leq 15\%$ at the lowest level using the low-level count mode, LLCM) for at least four out of six QC samples. At least one QC result had to be accepted for each QC level. The validated range for the analysis of urine and feces samples using LSC is 10 to 1000000 dpm/mL and 40 to 1000000 dpm/g, respectively.

Measurements of urine samples were performed in duplicate and feces samples were analyzed in triplicate. The samples were placed in the LSC for at least 30 minutes before counting. The CV over the duplicate/triplicate analysis had to be $\leq 15\%$ for samples with an activity level >250 dpm/g or $\leq 20\%$ for samples with an activity level ≤ 250 dpm/g. When the criteria for CV over the duplicate/triplicate analysis were not reached, the duplicate/triplicate results were rejected, and the samples were reanalyzed in duplicate. These criteria did not apply for study samples with results below the LLOQ, as these samples were analyzed using AMS.

The method was acceptable for assessment of [^{14}C]-remibrutinib in human urine and feces in clinical samples obtained from Study X2104.

14.3.4. Quantification of Other Species in DDI Studies

In drug-drug interaction trials, a number of coadministered drugs or endogenous biomarkers (i.e., coproporphyrin I) were analyzed. These compounds include tolbutamide, ethinylestradiol, levonorgestrel, midazolam, 1-hydroxymidazolam, caffeine, and paraxanthine in Study X2102; and coproporphyrin I, rosuvastatin, and digoxin in Study A02103. The bioanalytical methods and method performance for the coadministered drugs in the DDI studies are summarized in [Table 83](#). The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* ([November 2022](#)).

Table 83. Summary of Analytical Methods Performance and In-Study Analysis for Other Species in DDI, Studies X2102 and A02103

Compound	Method #	Analytical Method	Standard Calibration Range	Accuracy of Standard Calibration	Precision of Standard Calibration	Long-Term Stability	Freeze-Thaw Cycles	Incurred-Samples Reanalysis
Tolbutamide in plasma	1701042	LC-MS/MS	5 to 5000 ng/mL	-5.6% to 3%	≤4.51%	171 days at -75°C	Three cycles at -75°C	100% of 21 samples met the prespecified criteria
Ethinylestradiol in plasma	CP055373	LC-MS/MS	5 to 500 ng/mL	-3.2% to 5%	≤4.71%	23 weeks at -24°C	Three cycles at -24°C	85.7% of 21 samples met the prespecified criteria
Levonorgestrel in plasma		LC-MS/MS	0.1 to 20 ng/mL	-2% to 1.6%	≤3.67%			81% of 21 samples met the prespecified criteria
Midazolam in plasma	CP065442 and CP 035127	LC-MS/MS	0.1 to 100 ng/mL	-3.4% to 2%	≤6.95%	12 months at -24°C	Three cycles at -24°C	95.2% of 21 samples met the prespecified criteria
Hydroxymidazolam in plasma				-1.4% to 2%	≤5.52%			
Caffeine in plasma	CP085106	LC-MS/MS	100 to 50000 ng/mL	1.6% to 1.2%	≤5.9%	137 at -75°C	Three cycles at -75°C	100% of 21 samples met the prespecified criteria
Paraxanthine in plasma				-2% to 1.6%	≤3.46%			95.2% of 21 samples met the prespecified criteria
Rosuvastatin in plasma	VIN-BRD-MV-1056-03	LC-ESI-MS/MS	0.1 to 50000 ng/mL	-1.4% to 0.9%	≤4.84%	261 days at -78°C	Five cycles at -78°C	100% of 30 samples met the prespecified criteria
Rosuvastatin in urine	DMPK R2101281	LC-ESI-MS/MS	1 to 2000 ng/mL	-4.5% to 3.5%	≤5.7%	266 days at -78°C	Five cycles at -78°C	100% of 20 samples met the prespecified criteria

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Compound	Method #	Analytical Method	Standard Calibration Range	Accuracy of Standard Calibration	Precision of Standard Calibration	Long-Term Stability	Freeze-Thaw Cycles	Incurred-Samples Reanalysis
Digoxin in plasma	VIN-BRD-MV-1463-01	LC-ESI-MS/MS	20 to 4000 pg/mL	-3.2% to 3.7%	≤5.62%	265 days at -78°C	Five cycles at -78°C	100% of 30 samples met the prespecified criteria
Coproporphyrin I in plasma	VIN-BRD-MV-1466	LC-ESI-MS/MS	50 to 5000 pg/mL	-2.15% to 2.78%	≤4.67%	207 days in unaltered matrix at -78°C	Three cycles at -78°C	80% of 20 samples met the prespecified criteria

Source: Reviewer-generated table based on the Applicant's response to the Information Request (dated April 8, 2025), SEQ 0009, SDN 0009, Modules 1.11.3 and 5.3.3.1.

LC-ESI-MS/MS: liquid chromatography—electrospray ionization—mass spectrometry/mass spectrometry

Abbreviations: DDI, drug-drug interaction; DMPK, drug metabolism and pharmacokinetics; LC-ESI-MS/MS, liquid chromatography—electrospray—tandem mass spectrometry; LC-MS/MS, liquid chromatography with tandem mass spectrometry

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Population Pharmacokinetics

14.5.1.1. Review Summary

In general, the Applicant’s population PK analysis is considered acceptable for the purpose of describing the pharmacokinetics of remibrutinib and providing exposure metrics for E-R analyses. The Applicant’s analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in [Table 84](#).

Table 84. Specific Comments on Applicant’s Final Population PK Model

Utility of the Final Model		Reviewer’s Comments
Support Applicant’s proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Based on population PK analysis in clinical studies, no significant differences in the pharmacokinetics of remibrutinib were observed in subjects ≥ 65 years of age versus younger adult subjects.
		A popPK analysis was conducted on remibrutinib data from 1152 subjects showed that there was no clinically relevant effect in the pharmacokinetics of remibrutinib based on age (18 to 80 years), sex (63.5% females and 36.5% males), race/ethnicity (59.3% non-Asian, 8.8% Mainland Chinese, 12.2% Japanese, and 19.7% other Asian) and body weight (range 39 to 162 kg).
		Based on the data from clinical trials (including Trial A2301 and REMIX-2 phase 3 trials) as well as popPK and exposure-response analyses, race/ethnicity had no clinically relevant effect on
		Acceptable
		The statement is acceptable. Age and gender are not significant covariates in the final model.
		The effect of body weight on clearance and volume parameters, and Asian race on clearance is not clinically relevant (Table 88 , Table 89).
		The statement is acceptable. The effect of race/ethnicity on remibrutinib clearance is not clinically relevant (Table 88).

Utility of the Final Model		Reviewer's Comments
		remibrutinib pharmacokinetics. Therefore, no dose adjustment is required.
		Following an oral dose of 25-mg remibrutinib twice daily, there are no clinically relevant differences in the pharmacokinetics of remibrutinib in subjects with mild (estimated glomerular filtration rate (eGFR) 60 to <90 mL/min/1.73 m ²), moderate (eGFR 45 to <60 mL/min/1.73 m ²) or severe (eGFR 15 to <45 mL/min/1.73 m ²) renal impairment when compared to subjects with normal renal function.
	Pharmacokinetics	Based on pooled data from population pharmacokinetic (popPK) analysis, the volume of distribution at steady state was 58 liters (central compartment) and 1180 liters (peripheral compartment).
Derive exposure metrics for exposure-response analyses	$C_{avg,ss}$	The exposure metric was calculated based on individual PK parameters. Given the moderate level of shrinkage for apparent clearance in the final model, the Applicant's final model is generally acceptable for generating this exposure metric for exposure-response analyses (Table 87).

Source: Module 5.3.3.5, Population Pharmacokinetic Analysis Report
Abbreviations: $C_{avg,ss}$, average plasma concentration at steady state; eGFR, estimated glomerular filtration rate; n, number of subjects; PK, pharmacokinetic; popPK, population pharmacokinetic

14.5.1.2. Introduction

The primary objectives of the Applicant’s analysis were to:

- To characterize the remibrutinib pharmacokinetics in subjects with CSU for total daily dose between 10 mg and 200 mg using pooled concentration data at steady state from healthy volunteers and adult subjects with CSU.
- To assess the effects of baseline covariates (age, weight, race/region, creatinine clearance) and usage of PPIs/antacids on the pharmacokinetics of remibrutinib in the studied population.

14.5.1.3. Model Development

14.5.1.3.1. Data

The PK analyses for remibrutinib were based on PK data from three phase 1 studies in healthy subjects, one phase 2 study in subjects with CSU, and three phase 3 studies in subjects with CSU. Brief descriptions of the studies included are presented in [Table 85](#).

The overall percent of BLQ samples for remibrutinib was 12.6%. These observations were included in the population PK analysis as interval-censored. The final NONMEM data file for remibrutinib model development contained 7088 observations from 1152 subjects. [Table 86](#) provides summary statistics of the baseline demographic covariates in the PK analysis dataset.

Table 85. Summary of Studies With PK Sampling Included in Population PK Analysis

Study	Description	Dose/regimen	Sampling time at steady state
X1101	A randomized, patient blinded, placebo-controlled study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending doses and a multiple dose of LOU064 in Japanese healthy patients.	Part A: Single doses of 5; 30; 100; 200 or 400 mg LOU064 Part B: 100 mg LOU064 twice daily for 5 days	Part B: Day 4: 2 (h) Day 5: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 (h)
X2101	A 6-part FIH study of LOU064 consisting of a 4-part randomized, double-blind, placebo-controlled SAD and MAD study to investigate the safety and tolerability in healthy volunteers, patients with atopic diathesis and patients with atopic dermatitis; an open-label food effect study; and a double-blind cross-over design formulation effect study in healthy volunteers.	Part 1: Single doses of 0.5; 1.5; 5; 15; 30; 60; 100; 200; 400 or 600 mg LOU064 Part 2: 10; 25; 50; 100; 400 or 600 mg LOU064 q.d. for 12 days Part 3: Two single administrations of 60 mg LOU064 (fasted or fed) separated by 18 days Part 4: 100 or 200 mg LOU064 b.i.d. for 12 days Part 5: Two single administrations of 50 mg LOU064 (wet-milled- or micronized formulation) separated by 18 days Part 6: 100 mg LOU064 or Placebo b.i.d. over 4 weeks	Part 2 MAD/q.d.: Day 5: 0 (h) Day 7: 0, 2 (h) Day 9: 0 (h) Day 12: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12; 24, 36, 48, 72, 96, 168 (h) Part 4 MAD/b.i.d.: Day 5: 0 (h) Day 7: 0, 2 (h) Day 9: 0 (h) Day 12: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 168 (h)
A2201	A multicenter, randomized, double-blind, placebo- controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult CSU patients inadequately controlled by H1-antihistamines	10 mg q.d. 35 mg q.d. 100 mg q.d. 10 mg b.i.d. 25 mg b.i.d. 100 mg b.i.d. Placebo All for 12 weeks	Week 4: 0, 0.5, 1, 2, 3, 4 (h) Week 12: 0, 0.5, 1, 2, 3, 4 (h)

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A1301	A multicenter, open label Phase 3 study of remibrutinib (LOU064) to investigate the safety, tolerability and efficacy for 52 weeks in adult Japanese CSU patients inadequately controlled by H1-antihistamines.	25 mg b.i.d. for 52 weeks	Week 2 (Day 15), 0.75, 1.5 (h) Week 12 (Day 85), 0.75, 1.5 (h) Week 52 (Day 365)/Study discontinuation, 0.75, 1.5 (h)
A2301	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 CSU patients inadequately controlled by H1-antihistamines	25 mg b.i.d. for 52 weeks Placebo for 24 weeks followed by 25 mg b.i.d.	Week 2 (Day 15), 0.75, 1.5 (h) Week 12 (Day 85), 0.75, 1.5 (h) Week 52 (Day 365)/Study discontinuation, 0.75, 1.5 (h)
A2302	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 CSU patients inadequately controlled by H1-antihistamines	25 mg b.i.d. for 52 weeks Placebo for 24 weeks followed by 25 mg b.i.d.	Week 2 (Day 15), 0.75, 1.5 (h) Week 12 (Day 85), 0.75, 1.5 (h) Week 52 (Day 365)/Study discontinuation, 0.75, 1.5 (h)
A02104	A randomized, open-label, two-cohort, two-period, two-sequence, cross-over study to evaluate the effect of food on the steady-state pharmacokinetics of LOU064 (remibrutinib) film coated tablet (FCT) in Chinese healthy participants	Cohort A: 25 mg b.i.d./q.d. (fasted or fed) Cohort B: 100 mg b.i.d./q.d. (fasted or fed)	Day 4 (Period 1): 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (h) Day 6 (Period 2): 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 (h)

Source: Applicant's Population PK report, Tables 5-1

Abbreviations: b.i.d., twice daily; CSU, chronic spontaneous urticaria; FCT, film coated tablet; FIH, first in human; h, hour; LOU064, remibrutinib; MAD, multiple-ascending dose; PK, pharmacokinetic; q.d., once daily; SAD, single-ascending dose

Table 86. Summary of Baseline Continuous and Categorical Covariates for PK Analysis

	X1101 N = 6	X2101 N = 30	A2201 N = 224	A1301 N = 71	A2301 N = 403	A2302 N = 378	A02104 N = 40	Overall N = 1152
Age (year)								
No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	29.2 (6.97)	38.5 (13.31)	45.0 (14.81)	43.5 (12.52)	45.1 (14.12)	42.0 (14.46)	27.0 (4.10)	43.1 (14.44)
Median	28.5	33.0	45.0	43.0	45.0	41.0	26.0	43.0
IQR	23 – 35	29 – 51	33 – 56	34 – 52	35 – 55	30 – 51	25 – 29	31 – 54
Range	22 – 38	23 – 63	18 – 78	19 – 70	18 – 79	18 – 80	20 – 37	18 – 80
Age group – n(%)								
AGE < 65	6 (100.0%)	30 (100.0%)	203 (90.6%)	66 (93.0%)	364 (90.3%)	348 (92.1%)	40 (100.0%)	1057 (91.8%)
AGE >= 65	0 (0.0%)	0 (0.0%)	21 (9.4%)	5 (7.0%)	39 (9.7%)	30 (7.9%)	0 (0.0%)	95 (8.2%)
Gender – n(%)								
Female	0 (0.0%)	0 (0.0%)	164 (73.2%)	54 (76.1%)	271 (67.2%)	242 (64.0%)	0 (0.0%)	731 (63.5%)
Male	6 (100.0%)	30 (100.0%)	60 (26.8%)	17 (23.9%)	132 (32.8%)	136 (36.0%)	40 (100.0%)	421 (36.5%)
Weight (kg)								
No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	74.2 (10.85)	79.2 (9.64)	78.2 (18.44)	59.5 (11.70)	76.9 (20.03)	74.0 (19.35)	65.1 (6.86)	74.8 (19.07)
Median	76.6	78.4	76.7	57.3	72.6	70.7	64.6	71.3
IQR	64 – 83	72 – 85	65 – 90	50 – 68	63 – 87	60 – 83	61 – 69	61 – 85
Range	62 – 85	63 – 102	43 – 137	42 – 100	42 – 162	39 – 160	51 – 80	39 – 162

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BMI (kg/m²)

No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	24.4 (4.04)	24.3 (2.50)	28.1 (6.20)	22.6 (3.49)	28.0 (6.56)	26.8 (6.21)	22.7 (1.85)	27.0 (6.23)
Median	25.2	24.1	27.2	22.2	27.0	25.5	22.9	25.7
IQR	21 – 28	23 – 26	23 – 32	20 – 25	23 – 31	23 – 30	21 – 24	23 – 30
Range	20 – 28	19 – 29	17 – 48	17 – 33	16 – 58	15 – 53	20 – 26	15 – 58

Fat free mass (kg)

No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	57.3 (4.33)	61.4 (5.49)	49.0 (10.56)	40.9 (9.39)	48.8 (11.24)	48.2 (11.04)	52.0 (4.24)	48.6 (11.01)
Median	58.1	61.2	47.6	38.3	46.5	46.5	51.7	47.3
IQR	53 – 61	58 – 66	41 – 57	34 – 45	40 – 56	39 – 55	49 – 55	40 – 56
Range	52 – 62	51 – 72	30 – 77	29 – 67	29 – 84	28 – 90	43 – 61	28 – 90

Fat mass (kg)

No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	16.9 (6.55)	17.8 (4.76)	29.2 (12.21)	18.7 (5.33)	28.1 (13.05)	25.8 (12.54)	13.1 (2.99)	26.1 (12.55)
Median	18.1	17.5	26.9	17.7	26.0	23.0	12.9	23.2
IQR	11 – 23	14 – 21	20 – 36	15 – 21	19 – 35	17 – 31	11 – 16	17 – 31
Range	9 – 23	9 – 29	7 – 75	7 – 33	5 – 96	5 – 86	8 – 19	5 – 96

**Creatinine
clearance (mL/min)**

No. obs.	6	30	224	71	403	378	40	1152
Mean (SD)	145.3 (14.34)	125.9 (29.85)	116.0 (34.33)	100.8 (24.25)	117.4 (36.92)	115.5 (32.47)	107.4 (16.96)	115.5 (33.81)
Median	141.9	122.2	110.0	101.1	111.8	112.1	106.4	111.1
IQR	136 – 147	103 – 143	92 – 136	86 – 114	93 – 135	95 – 132	97 – 116	93 – 133
Range	133 – 172	81 – 221	52 – 258	59 – 179	23 – 269	51 – 275	75 – 151	23 – 275

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**Renal impairment
classification – n
(%)**

Severe (15 - 30 mL/min)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Mild to Moderate (45 – 60 mL/min)	0 (0.0%)	0 (0.0%)	6 (2.7%)	1 (1.4%)	11 (2.7%)	7 (1.9%)	0 (0.0%)	25 (2.2%)
Mild (60 – 90 mL/min)	0 (0.0%)	3 (10.0%)	43 (19.2%)	24 (33.8%)	75 (18.6%)	72 (19.0%)	5 (12.5%)	222 (19.3%)
Normal (>= 90 mL/min)	6 (100.0%)	27 (90.0%)	175 (78.1%)	46 (64.8%)	316 (78.4%)	299 (79.1%)	35 (87.5%)	904 (78.5%)

Race – n (%)

Non-Asian	0 (0.0%)	29 (96.7%)	183 (81.7%)	0 (0.0%)	276 (68.5%)	195 (51.6%)	0 (0.0%)	683 (59.3%)
Japanese	6 (100.0%)	0 (0.0%)	37 (16.5%)	71 (100.0%)	27 (6.7%)	0 (0.0%)	0 (0.0%)	141 (12.2%)
Mainland Chinese	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	61 (16.1%)	40 (100.0%)	101 (8.8%)
Other Asian	0 (0.0%)	1 (3.3%)	4 (1.8%)	0 (0.0%)	100 (24.8%)	122 (32.3%)	0 (0.0%)	227 (19.7%)

**PPI usage during
treatment – n (%)**

Yes	0 (0.0%)	0 (0.0%)	24 (10.7%)	6 (8.5%)	53 (13.2%)	45 (11.9%)	0 (0.0%)	128 (11.1%)
No	6 (100.0%)	30 (100.0%)	200 (89.3%)	65 (91.5%)	350 (86.8%)	333 (88.1%)	40 (100.0%)	1,024 (88.9%)

**Antacid usage
during treatment –
n (%)**

Yes	0 (0.0%)	0 (0.0%)	27 (12.1%)	15 (21.1%)	75 (18.6%)	51 (13.5%)	0 (0.0%)	168 (14.6%)
No	6 (100.0%)	30 (100.0%)	197 (87.9%)	56 (78.9%)	328 (81.4%)	327 (86.5%)	40 (100.0%)	984 (85.4%)

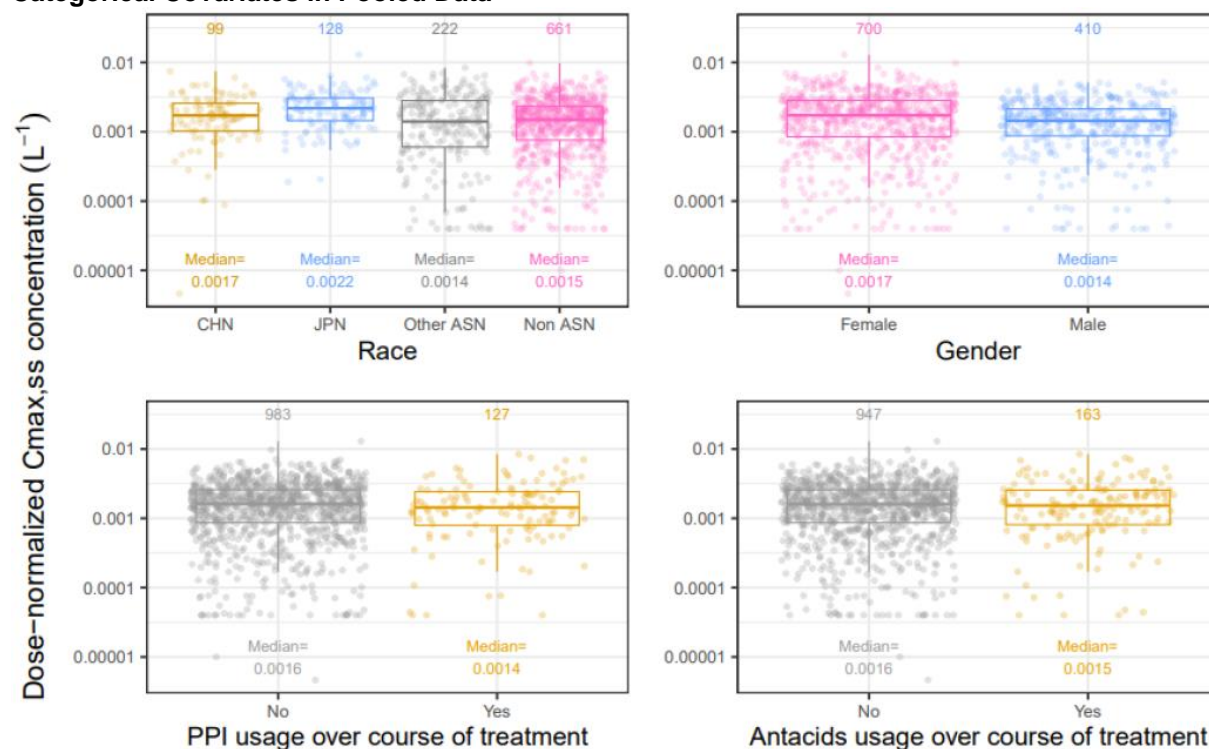
**H2 receptor usage
during treatment –
n (%)**

Yes	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (1.4%)	4 (1.0%)	2 (0.5%)	0 (0.0%)	8 (0.7%)
No	6 (100.0%)	30 (100.0%)	223 (99.6%)	70 (98.6%)	399 (99.0%)	376 (99.5%)	40 (100.0%)	1,144 (99.3%)

Source: Applicant's Population PK Report, Table 7-2

Abbreviations: BMI, body mass index; IQR, interquartile range; N, number of subjects; n, number of subjects with specific parameter; PK, pharmacokinetic; PPI, proton-pump inhibitors; SD, standard deviation

Figure 51. Plot of Remibrutinib Dose-Normalized Observed $C_{max,ss}$ Concentrations (Log Scale) vs. Categorical Covariates in Pooled Data



Source: Applicant's Population PK Report, Figure 7-8

$C_{max,ss}$ refers to the averaged concentration at time after dose between 0.75 hours and 1.25 hours.

Abbreviations: ASN, Asian; CHN, Chinese; $C_{max,ss}$, maximum plasma concentration at steady state; JPN, Japanese; PK, pharmacokinetic; PPI, proton-pump inhibitor

14.5.1.3.2. Base Model

The population PK model was developed using a nonlinear mixed-effects modeling approach with the stochastic approximation expectation-maximization algorithm implemented in MONOLIX (version 2021R2).

A population PK model for remibrutinib was previously developed based on pooled steady-state data of Studies X2101 and A2201 with total daily dose between 10 mg and 200 mg. The model was described as a two-compartment, first-order absorption model with a lag time and linear elimination. The previous structural popPK model was used in the current popPK model based on the new pooled dataset and with full reevaluation of the correlation matrix.

Interindividual variability was modelled assuming a log-normal distribution for patient level random effects. Residual variability was described using proportional error model. The quality of the model fit was assessed by diagnostic plots.

14.5.1.3.3. Covariate Analysis

The effect of body size covariates (e.g., body weight, body mass index, FFM, and FM) on apparent clearance (CL/F) or apparent central volume of distribution (V_1/F) was evaluated as part of the base model. Weight with both estimated allometric scaling and fixed allometric scaling of 0.75 for clearances and 1 for volumes was tested. The impact of other prespecified

covariates were investigated: age (on CL/F), gender (on CL/F), race/region (on CL/F), renal impairment (assessed as creatinine clearance on CL/F), and usage of PPI/antacids (on CL/F, V_1/F , apparent intercompartmental clearance and apparent peripheral volume of distribution [V_2/F]). The significance of the covariates after inclusion of the body size effect was assessed using a full covariate modeling approach. The impact of usage of PPI/antacids was explored graphically as inclusion of the PPI/antacid usage as time-dependent covariate led to unstable models. Hepatic impairment was not assessed as a covariate in the model. According to Applicant's response to Information Request, subjects with hepatic impairment were not enrolled in the studies included in the population PK analysis. In the full modeling dataset, a small fraction of subjects showed mildly elevated levels of ALT (n=94, 8%), AST (n=34, 3%) or INR (n=34, 3%) in the overall dataset, and only one subject had total bilirubin $\geq 1.5 \times$ ULN.

Primary covariates evaluated in the development of PK model was included in [Table 86](#).

14.5.1.4. Final Model

A two-compartment model with first-order absorption with fixed lag time and constant clearance described the PK data of remibrutinib ([Figure 52](#), [Figure 53](#)). Statistically significant covariate effects on PK model parameters were the followings: FFM and FM on CL/F, race effect on CL/F, and FM effect on V_1/F . Age, gender, and mild renal impairment are not significant covariates. Based on the graphical exploration of observed data, the use of PPI/antacids does not appear to have effect on remibrutinib exposure ([Figure 51](#)).

The parameter estimates for the final covariate model are listed in [Table 87](#). The RSE for all parameters was $<40\%$. The intersubject variability for PK parameters was generally high especially for V_1/F , the apparent intercompartmental clearance, and V_2/F , which ranges from 127% to 4386%. Moderate to high eta-shrinkage was observed for PK parameters. According to the Applicant, the high intersubject variability is due to large variability observed in PK concentrations.

The effects of FFM, FM, Mainland Chinese subjects, Japanese subjects, and other Asian subjects, on the AUC of remibrutinib are explored in [Table 88](#). The effects of evaluated intrinsic factors (FFM, FM, Mainland Chinese subjects, Japanese subjects, and other Asian subjects) are generally small (20 to 30%). According to the Applicant, potential explanation for the effect of FFM and FM on remibrutinib may be remibrutinib is a lipophilic compound ($\text{LogP} \sim 3$), which can distribute into human fat tissue and result in body composition as an important factor for drug distribution and metabolism. The effect of body weight was small based on the results of simulated AUC in subjects with weight of 49 kg (5th percentile) and 109 kg (95th percentile) assuming the ratio of FFM to FM of 2:1. As the FDA requested, the Applicant performed additional simulation to assess the effect of body weight on remibrutinib exposure by using resampled demographic characteristics from the population PK data, which keeps the natural correlations among body fat percentage, body weight, and gender and variability in body composition. The results confirmed that the impact of body weight on remibrutinib exposures is not clinically relevant ([Table 89](#)). Given the high intersubject variability of remibrutinib pharmacokinetics, the effect of explored intrinsic factors is unlikely to be clinically meaningful.

Table 87. Parameter Estimates From Final PopPK Model

Parameter (unit)	Estimate (RSE in %)	Shrinkage	CV%
Structural Parameters			
Tlag (h)	0.26 (FIX)	55.5%	
k _a (1/h)	0.86 (1.7)	-	
CL/F (L/h)	160 (3.4)	31.5%	
FFM on CL/F	0.79 (12.2)		
FM on CL/F	-0.28 (18.9)		
Mainland Chinese on CL/F	-0.19 (38.7)		
Japanese on CL/F	-0.18 (35)		
Other Asian on CL/F	-0.26 (22.5)		
V ₁ /F (L)	58 (6.83)	65.7%	
FM on V ₁ /F	0.48 (22.5)		
Q/F (L/h)	43 (12)	54.5%	
V ₂ /F (L)	1180 (20.8)	73.2%	
Inter-individual variability, standard deviations			
IIV Tlag	0.71 (FIX)		81%
IIV CL	0.65 (3.8)		73%
IIV V ₁	0.98 (5.4)		127%
IIV Q	1.94 (5.3)		649%
IIV V ₂	2.75 (4.8)		4386%
Correlation			
corr_CL_Q	-0.66 (6.7)		
corr_V ₂ _CL	-0.31 (21)		
corr_V ₂ _Q	0.57 (11.2)		
Residual Variability			
Proportional error (b)	0.47 (1.2)		
Objective Function			
OFV=-2LL	58313.91		
cBIC	58458.75		

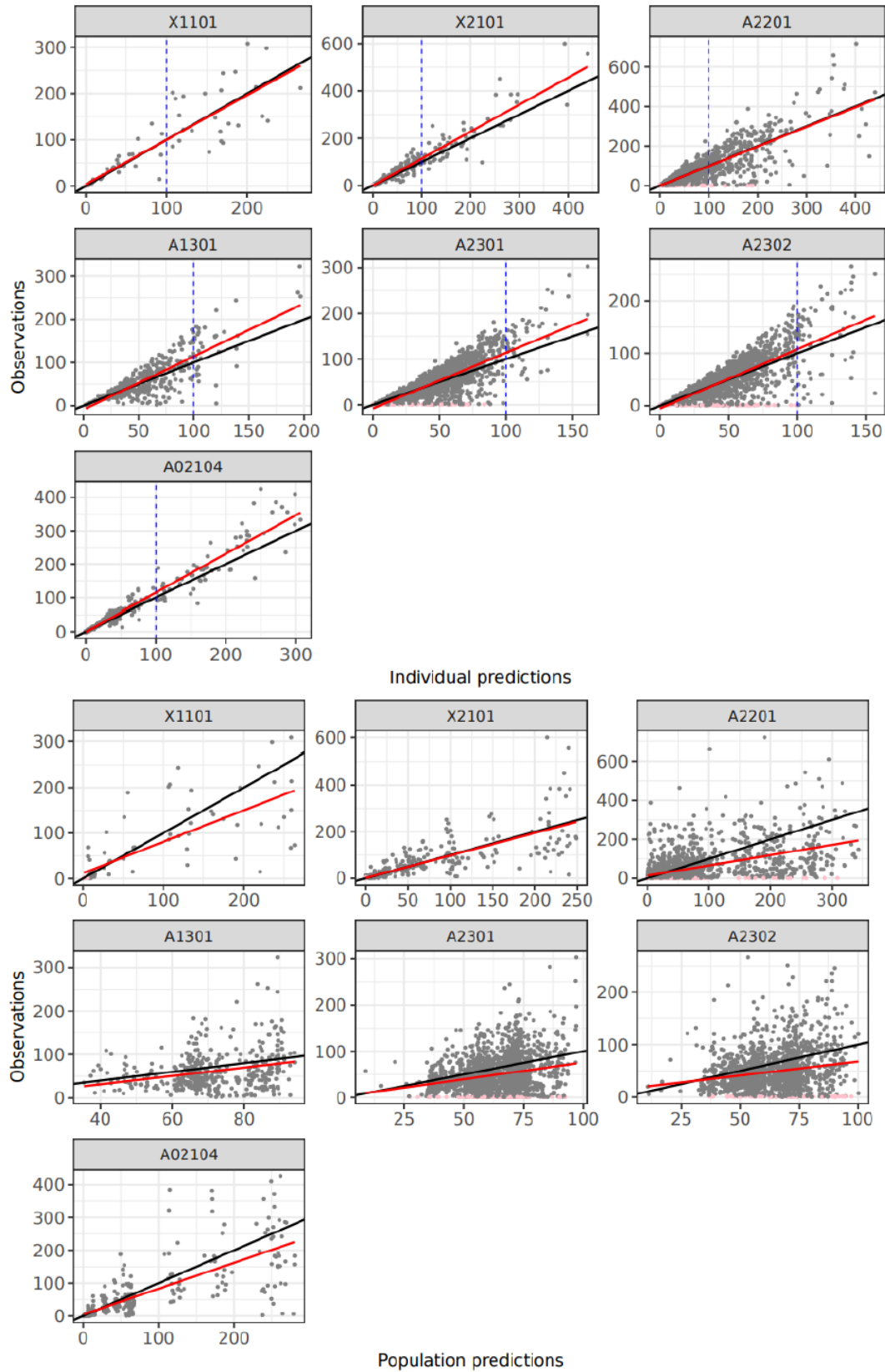
Source: Applicant's Response to FDA Information Request dated April 23, 2025, Table 3-1

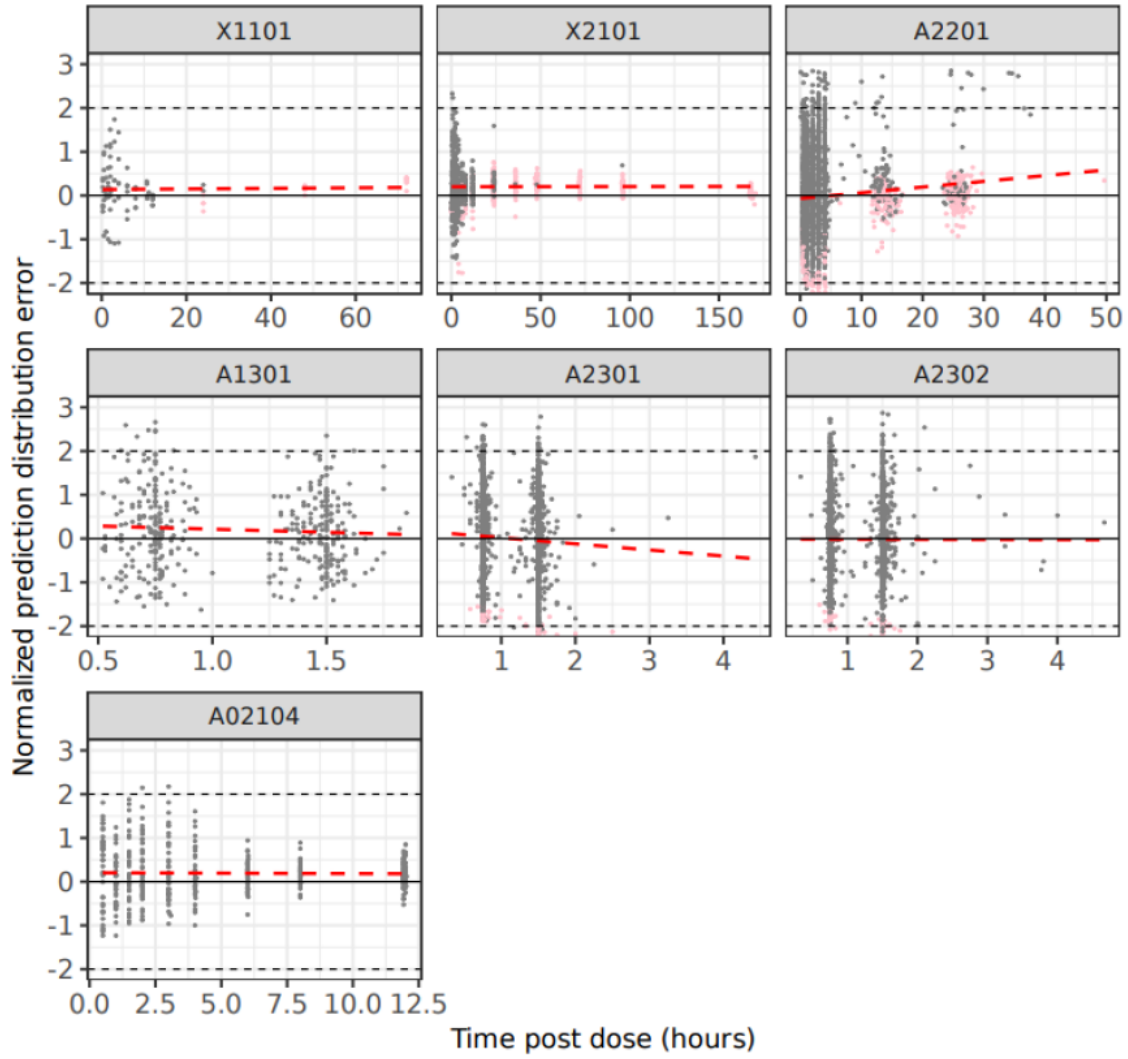
Estimates of structural PK parameters are for a typical non-Asian CSU subject with FFM of 47 kg and FM of 23 kg

The coefficient of variation (CV%) for interindividual variability (IIV) was calculated as $100\% \cdot \sqrt{\exp(\omega^2) - 1}$, where ω is the standard deviation of IIV.

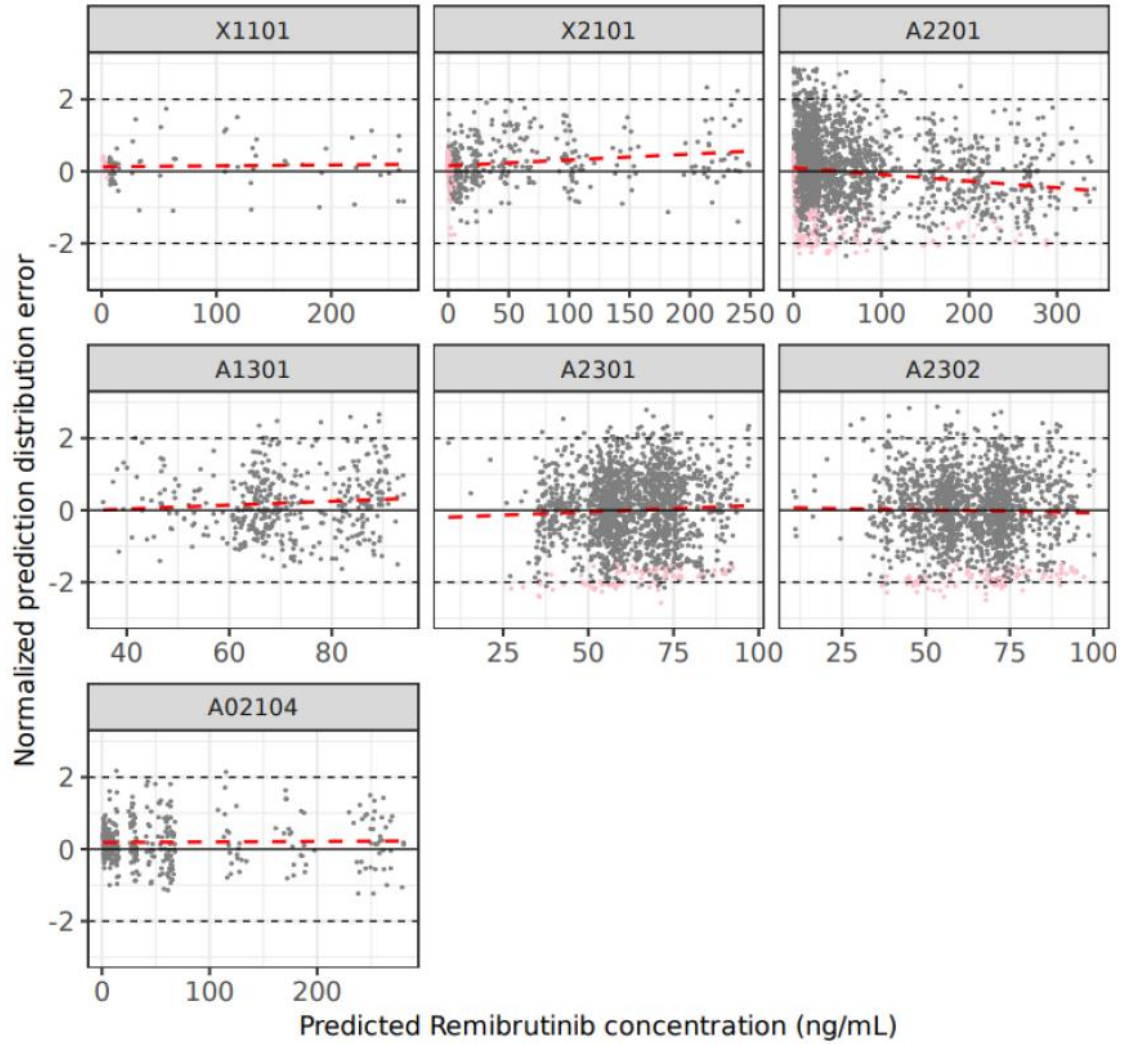
Abbreviations: cBIC, corrected Bayesian Information Criteria; CL, clearance; CL/F, apparent clearance; corr, correlation; CSU, chronic spontaneous urticaria; FFM, fat-free mass; FM, fat mass; k_a, absorption rate constant; OFV, objective function; PK, pharmacokinetic; popPK, population pharmacokinetics; Q, a short term for Q/F, which is apparent intercompartmental clearance; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Tlag, lag time; V₁/F, apparent central volume of distribution; V₂/F, apparent peripheral volume of distribution

Figure 52. Goodness-of-Fit Plots for Final Population PK Model for Observations of Remibrutinib



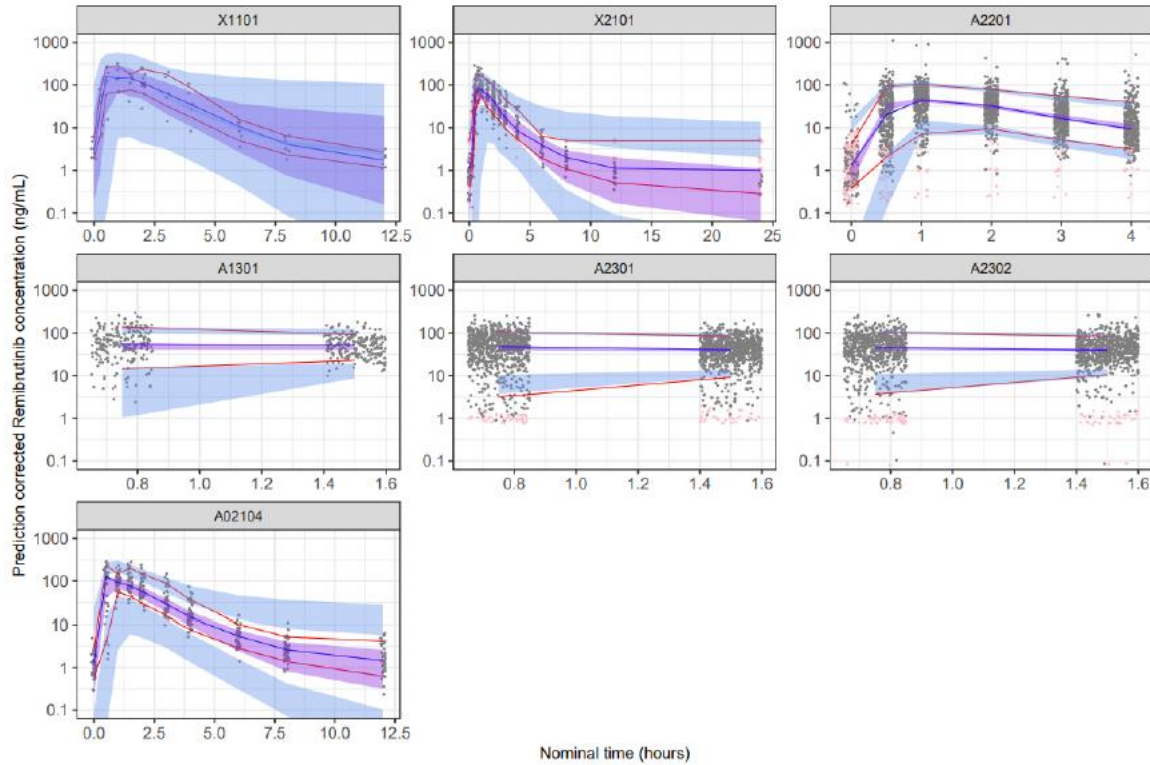


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Source: Applicant's Population PK Report, Figures 7-11 and 7-12
Pink dots represent simulated BLOQ values. Black solid line is identity line. Red solid curve is linear regression line. Red dashed line = linear regression line.
Abbreviation: PK, pharmacokinetic

Figure 53. Visual Predictive Check for Observations of Remibrutinib From Final Population PK Model



Source: Applicant's Population PK Report, Figure 7-14

The lines represent the 10th, 50th, and 90th percentiles of observed data. Shaded areas are 95th prediction intervals for the 10th, 50th, and 90th percentiles. Pink dots are simulated BLOQ values.

Abbreviations: BLOQ, below the limit of quantification; PK, pharmacokinetic

Table 88. Simulated AUC at Steady State for 25 mg BID by Race and Fat Mass Group

	Median (90% PI)	Mean (SD)
Typical Non-Asian patient	155 (54, 459)	193 (136)
Non-Asian patient with FM 23kg and FFM 34kg (5th percentile)	201 (70, 592)	249 (175)
Non-Asian patient with FM 23kg and FFM 68kg (95th percentile)	116 (40, 343)	144 (101)
Non-Asian patient with FFM 47kg and FM 12kg (5th percentile)	130 (45, 383)	161 (113)
Non-Asian patient with FFM 47kg and FM 50kg (95th percentile)	193 (67, 570)	239 (168)
Typical Mainland Chinese patient	189 (66, 558)	234 (165)
Typical Japanese patient	187 (65, 552)	232 (163)
Typical Other Asian patient	202 (70, 595)	250 (176)

Source: Applicant's Population PK Report, Table 7-10.

The typical non-Asian, Mainland Chinese, Japanese, Other Asian subject has FFM of 47 kg and FM of 23 kg.

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; FFM, fat-free mass; FM, fat mass; PK, pharmacokinetic; PI, prediction interval; SD, standard deviation

Table 89. Simulated PK Parameters at Steady State for 25 mg BID by Body Weight Distribution Subgroups Corresponding to <10th, 45th to 55th, >90th Percentile in the Reference Population

Parameter	Summary statistics	42-60kg	77.1-82.2kg	107-161.6kg
AUC (ng*h/mL)	Median (90% PI)	173.7 (58 - 515.1)	152.5 (48.1 - 451.9)	155.6 (51.2 - 490.8)
	Difference in median	13.9%	ref	2.0%
	Geom Mean (SD)	173.5 (155.5)	154.9 (145)	156 (146.1)
C_{avg} (ng/mL)	Median (90% PI)	14.5 (4.8 - 42.9)	12.7 (4 - 37.7)	13 (4.3 - 40.9)
	Difference in median	14.2%	ref	2.4%
	Geom Mean (SD)	14.5 (13)	12.9 (12.1)	13 (12.2)
C_{max} (ng/mL)	Median (90% PI)	57.8 (24.3 - 119)	50.9 (22.1 - 106.1)	47.4 (19.9 - 97.2)
	Difference in median	13.6%	ref	-6.9%
	Geom Mean (SD)	56.1 (29.5)	49.8 (27.1)	46.2 (25)
C_{min} (ng/mL)	Median (90% PI)	1.4 (0 - 23.4)	1.3 (0 - 20.4)	1.4 (0 - 21)
	Difference in median	7.7%	ref	7.7%
	Geom Mean (SD)	0.9 (9)	0.8 (8.4)	0.9 (8.7)

Source: Applicant's response to IR dated April 23, 2025, Table 2-2

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{avg}, average concentration; C_{max}, maximum plasma concentration; C_{min}, minimum concentration; Geom mean, geometric mean; IR, Information Request; PK, pharmacokinetic; PI, prediction interval; SD, standard deviation

14.5.2. Exposure-Response Analysis

14.5.2.1. Review Summary

There was a positive E-R relationship for both continuous and categorical efficacy endpoints (UAS7, ISS7, and HSS7 response) with plateau of response achieved at the proposed remibrutinib dose regimen.

The E-R analysis for safety did not identify a significant relationship between remibrutinib exposure and AEs and AEs of special interest. The E-R analysis for remibrutinib and safety laboratory and vital sign parameters is considered exploratory due to the limited range of exposure from one dose level. Among the subjects with chronic spontaneous urticaria who received remibrutinib 25 mg twice daily, there was no clinically relevant association between remibrutinib exposure and changes in laboratory parameters of blood chemistry, selected blood cell counts, immunoglobulin concentrations, selected coagulation panel parameters, diastolic and systolic blood pressure (BP).

14.5.2.2. Introductions

The primary objectives of the Applicant's E-R analysis were to:

- To explore the exposure-response relationship between remibrutinib concentrations and UAS7, ISS7, and HSS7 in adult subjects with chronic spontaneous urticaria at selected time points.
- To explore the effect of selected intrinsic and extrinsic factors on clinical outcome (UAS7, ISS7, and HSS7 response) in adult subjects with CSU.

- To develop nonlinear mixed effects models characterizing the exposure-response relationship to remibrutinib for efficacy and describing longitudinal changes in UAS7 (and possibly ISS7/HSS7) in adult subjects with CSU.
- To explore the exposure-response relationship between remibrutinib concentrations and safety in adult subjects with CSU based on the selected adverse events and changes in selected laboratory and vital sign parameters.

PK exposure metrics including average concentration at steady state ($C_{avg,ss}$), and individual empirical Bayes estimates were predicted based on post hoc parameter estimates from the final population PK model. Of note, 18% of subjects included in the current analyses did not have any PK measurements and $C_{avg,ss}$ in those individuals were imputed based on population CL/F estimate adjusted for individual covariate values. A sensitivity analysis for the key exposure- efficacy and exposure-safety was conducted by excluding individuals with missing PK measurements, and the interpretation of its results was in line with the analyses presented in this report.

14.5.2.3. E-R Analysis for Efficacy

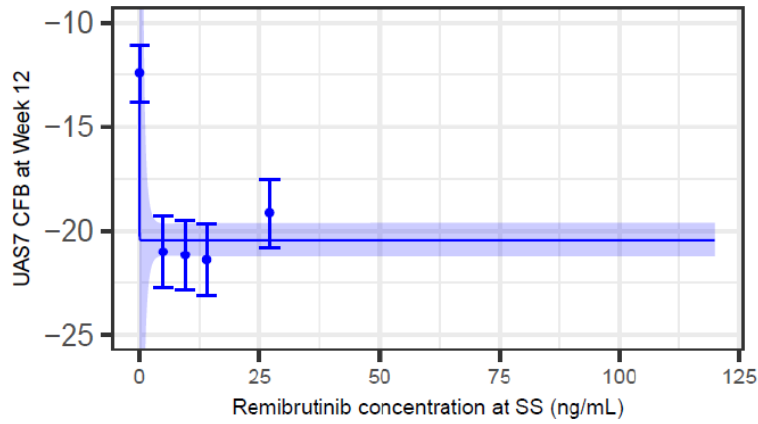
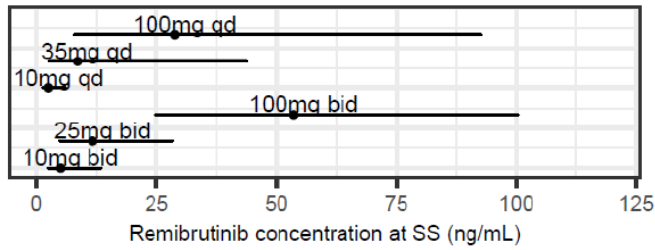
The efficacy E-R analysis was based on data from one phase 2 (A2201) and two phase 3 trials (A2301 and A2302). The primary efficacy endpoints explored in the analysis include the followings: absolute change from baseline in HSS7, absolute change from baseline in ISS7, absolute change from baseline in UAS7, achievement of complete absence of itch and hives ($UAS7 = 0$), and achievement of disease activity control ($UAS7 \leq 6$).

The analysis data included 45230 measurements for each efficacy endpoint from 1221 subjects. MONOLIX (version 2021R2) and R software (version 4.1.0) were used for the E-R analysis for efficacy.

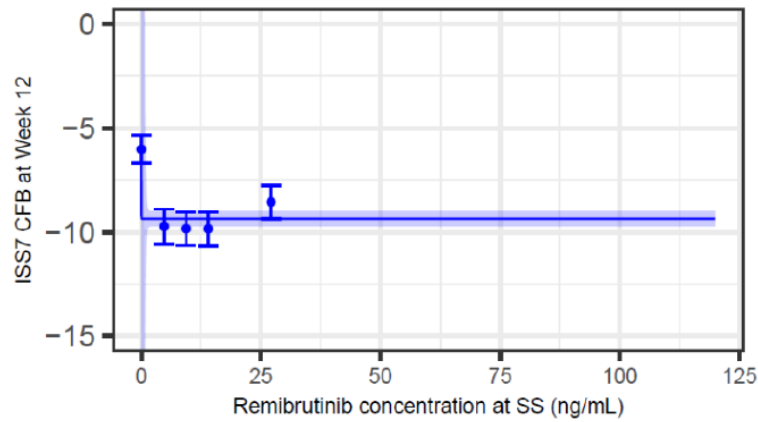
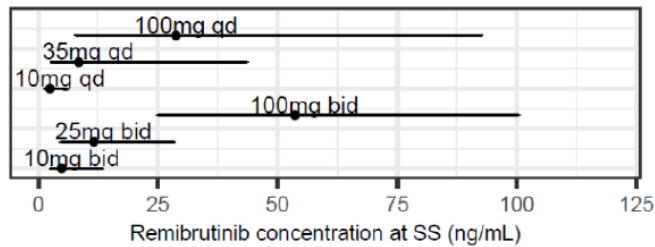
For continuous efficacy endpoints (changes from baseline in UAS7, ISS7, and HSS7), the results from a nonlinear model with sigmoidal E_{max} function of exposure metrics and baseline value as a covariate suggested a positive E-R relationship. The plateau of response was achieved at low remibrutinib exposures, and the remibrutinib dose regimen investigated in phase 3 studies (25 mg BID) provided PK exposures in the plateau range of the E-R relationship ([Figure 54](#)). Similarly, for binomial efficacy variables, the results from a logistic regression model with sigmoidal E_{max} function suggested that the remibrutinib dose regimen investigated in phase 3 studies (25 mg BID) provided PK exposures in the plateau range of the exposure-response relationship ([Figure 55](#)). Longitudinal nonlinear mixed effects exposure-response model for UAS7 was attempted but not developed due to issues with model convergence and identifiability of parameters estimates.

Figure 54. Exposure-Response Relationship for Change From Baseline in UAS7, ISS7, and HSS7 at Week 12 vs. $C_{avg,ss}$ Based on Pooled Data Across Trials A2201, A2301, and A2302

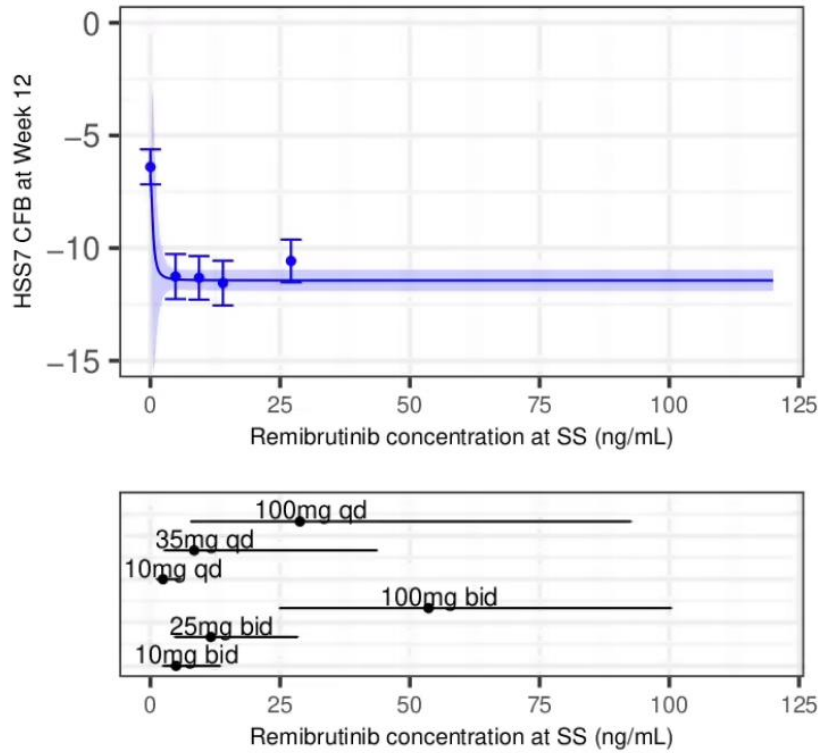
A: Change From Baseline in UAS7



B: Change From Baseline in ISS7



C: Change From Baseline in HSS7



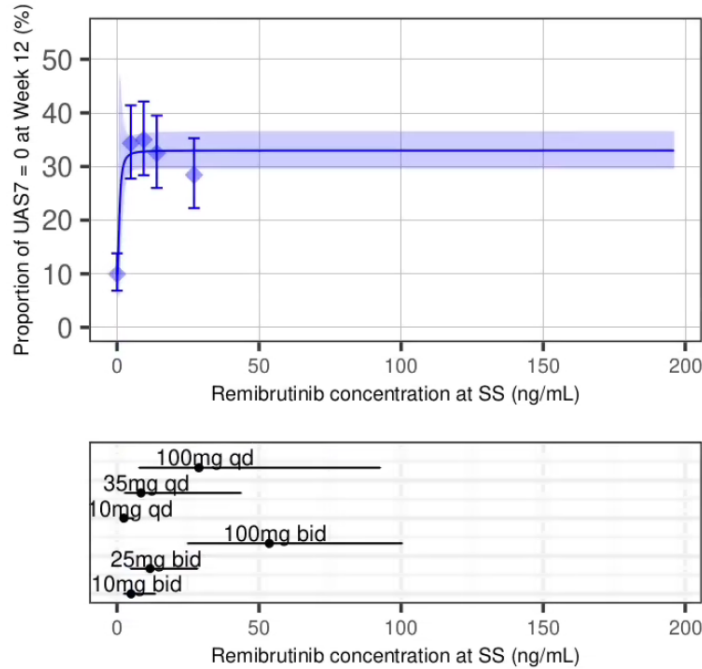
Source: Applicant's E-R report, Figures 7-14, 7-15, and 7-16

Top panel: Blue line is the model predicted response with 95% CI (shaded area). Blue dots with error bars represent mean with 95% CI of the observed response by quartile of positive $C_{avg,ss}$ distribution, and a separate bin for placebo response (plotted at $C_{avg,ss}=0$).

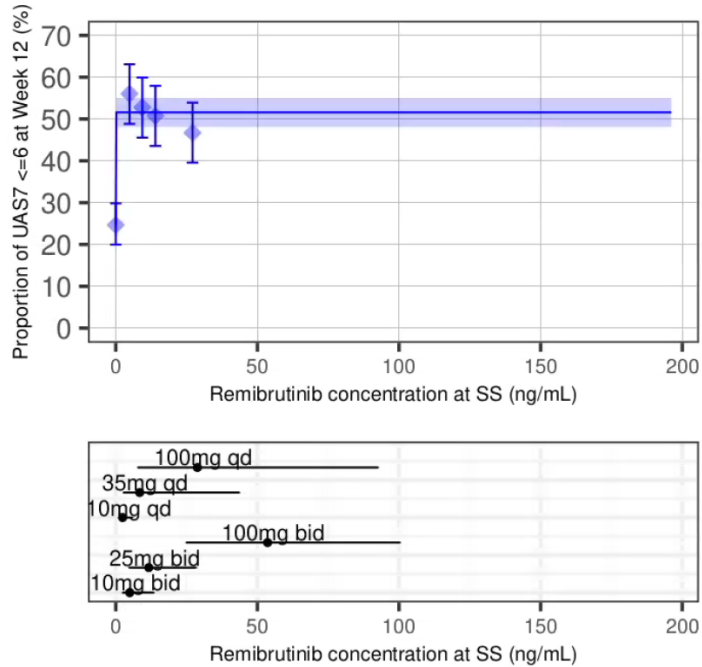
Bottom panel: Summary of individual $C_{avg,ss}$ by dosing regimen: median and the 5th to 95th percentiles of distribution for each dosing regimen are represented with the dot and the horizontal bar.

Abbreviations: bid, twice daily; CFB, change from baseline; CI, confidence interval; $C_{avg,ss}$, average concentration at steady state; CFB, change from baseline; E-R, exposure-response; HSS7, weekly hives severity score; ISS7, weekly itch severity score; qd, once daily; SS, steady state; UAS7, weekly urticaria activity score

Figure 55. Exposure-Response Relationship for Proportion of Subjects Achieving UAS7 =0 and UAS ≤6 at Week 12 vs. $C_{avg,ss}$ Based on Pooled Data Across Trials A2201, A2301, and A2302
A: Proportion of Subjects Achieving UAS7 =0



B: Proportion of Subjects Achieving UAS ≤6



Source: Applicant's E-R report, Figures 7-17, and 7-18

Top panel: Predicted response rate with 95% confidence interval (shaded area). Blue dots with error bars represent proportion with 95% CI of the observed response by quartile of positive $C_{avg,ss}$ distribution, and a separate bin for placebo response (plotted at $C_{avg,ss} = 0$).

Bottom panel: Summary of individual $C_{avg,ss}$ by dosing regimen: median and the 5th to 95th percentiles of distribution for each dosing regimen are represented with the dot and the horizontal bar.

Abbreviations: bid, twice daily; CI, confidence interval; $C_{avg,ss}$, average concentration at steady state; E-R, exposure-response; qd, once daily; SS, steady state; UAS, urticaria activity score; UAS7, weekly urticaria activity score

14.5.2.4. E-R Analysis for Safety

The safety E-R analysis was based on data from one phase 2 (A2201) and two phase 3 trials (A2301 and A2302). The safety endpoints included AEs monitoring, physical examinations, monitoring of laboratory markers in blood and urine, and vital signs. The AEs of special interest included infections, bleeding, and cytopenias. The laboratory and vital sign parameters included laboratory parameters of blood chemistry panel, blood cell counts, immunoglobulin concentrations, selected parameters of coagulation, diastolic BP, and systolic BP. R software (version 4.1.0) were used for the E-R analysis for safety.

For AEs, three data pools were created based on differences in the design of the analyzed studies, in particular duration of treatment and the placebo-controlled period. Logistic regression with log-transformed $C_{avg,ss}$ were conducted to test the influence of exposure on AEs in subjects on active treatment in the three pooled safety datasets. Individual remibrutinib $C_{avg,ss}$ were comparable between subjects with and without occurrence of any AEs across all three E-R safety data pools. Logistic regression fitted to all three E-R safety data pools did not show a statistically significant relationship for occurrence of any AEs with increasing remibrutinib $C_{avg,ss}$. Similar results were observed for occurrence of SAEs which had rates below 5%. Logistic regression fitted to all three E-R safety data pools did not show a statistically significant relationship for occurrence of AESIs (bleeding, cytopenia, and infection) with increasing remibrutinib $C_{avg,ss}$ (Figure 56).

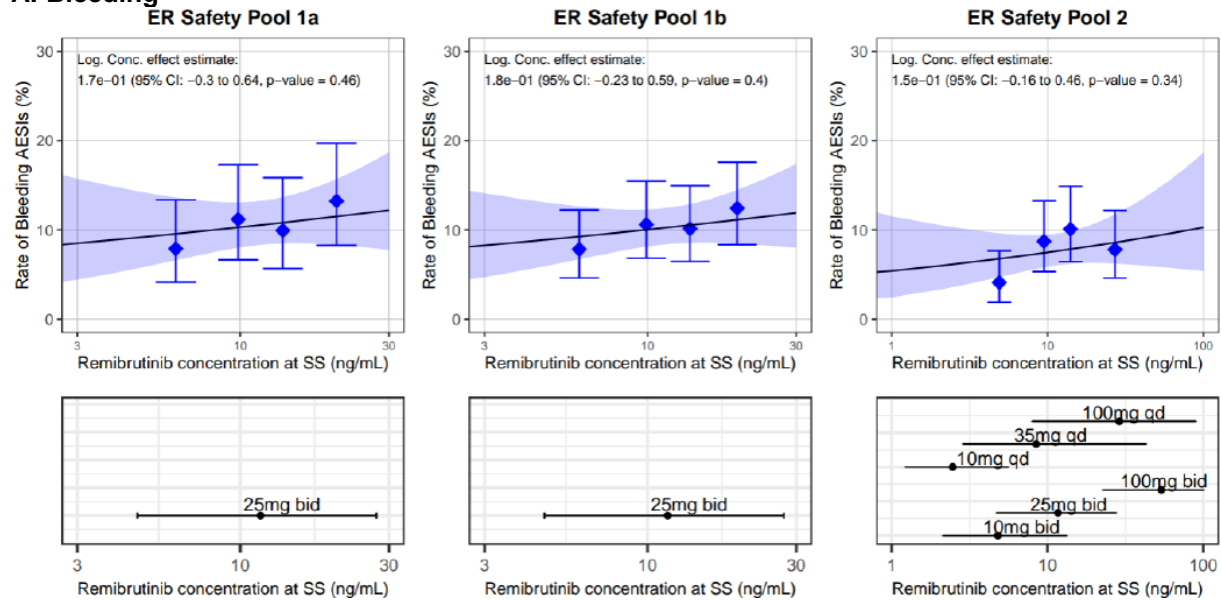
For laboratory and vital-sign parameters, two data pools from Trials A2301 and A2302 with one included placebo group and one excluded placebo group were explored. Exploratory and MMRM analyses indicated no clear evidence of a relationship between remibrutinib PK exposures ($C_{avg,ss}$) and changes in laboratory parameters of blood chemistry panel (ALT, amylase, alkaline phosphatase, AST, bilirubin, creatine kinase, creatinine, gamma-glutamyl transferase, and lipase), selected blood cell counts (erythrocytes, leukocytes, lymphocytes, neutrophils, and platelets), IgE concentrations, selected laboratory parameters from coagulation panel (activated partial thromboplastin time, prothrombin INR, and prothrombin time), diastolic and systolic BP in Trials A2301 and A2302.

The absolute bilirubin levels, erythrocyte counts, creatinine and creatine kinase levels were higher in subjects with low remibrutinib $C_{avg,ss}$ (in 1st quartile of distribution) than in subjects with higher remibrutinib $C_{avg,ss}$ (2nd to 4th quartile) or placebo. According to the Applicant, this could be attributed to confounding factors of body size (e.g., fat mass or fat free mass) which affect both remibrutinib pharmacokinetics and listed safety parameters.

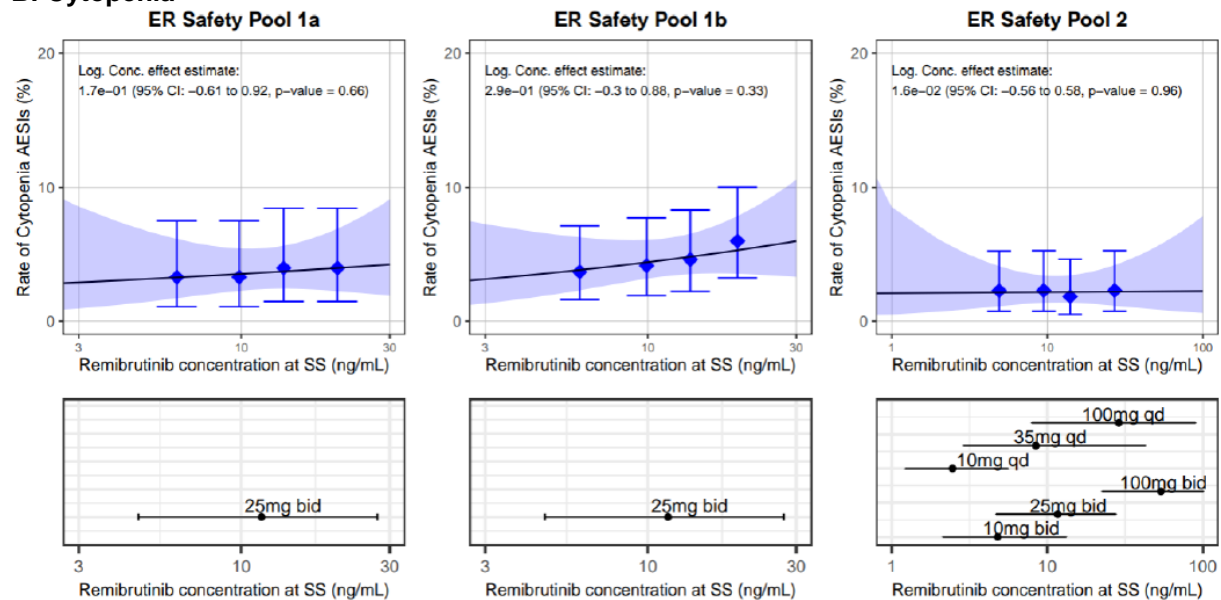
The trend of elevations in median lymphocyte counts and decrease in platelet counts with increasing remibrutinib exposure is of limited clinical relevance given the transient character and small magnitude of change with median levels remaining within limits of normal, and no signal for AEs of lymphocytosis and bleeding AESIs. Similarly, the trend of elevation in median bilirubin concentrations, and decrease in creatinine concentrations and neutrophil counts with increasing remibrutinib exposure is of no clinical relevance given the marginal magnitude of these changes. The observed trends for positive correlation between $C_{avg,ss}$ and change from baseline in IgA and IgG concentrations, and a negative correlation with change from baseline in IgM concentration is of limited clinical relevance, given small magnitude of observed changes, inconsistent direction of the remibrutinib $C_{avg,ss}$ effect on those globulins and no increase in infection rates in remibrutinib arms in Trials A2301 and A2302.

Figure 56. Logistic Regression for Occurrence of AESIs (Bleeding, Cytopenia, Infection) in E-R Safety Pool 1a, E-R Safety Pool 1b, and E-R Safety Pool 2

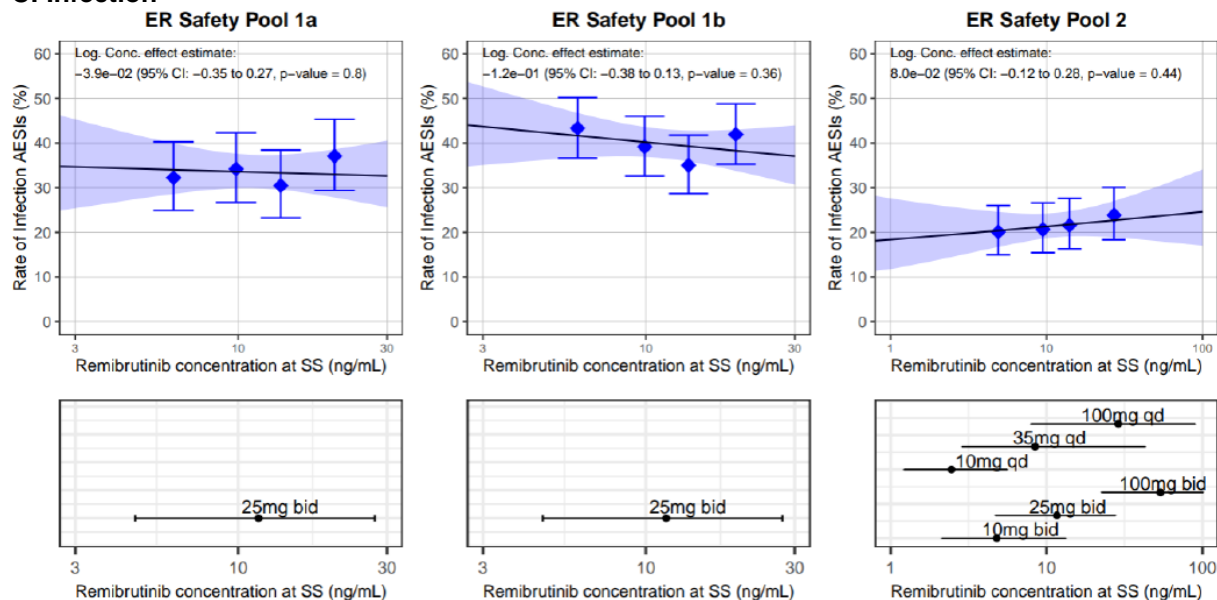
A: Bleeding



B: Cytopenia



C: Infection



Source: Applicant's E-R report, Figures 7-24, 7-26, and 7-28

Top: The regression curve and the shaded area represent the event rate and 95% CI as a function of log of the individual average remibrutinib concentrations at steady state, as predicted from the logistic regression models. The diamonds and the vertical bars represent the observed event rate and 95% CI presented by quartiles of average remibrutinib concentration at steady state in the corresponding data pool.

"Conc. effect estimate" = estimated average change in the logit (log-odds) of the outcome per one unit (ng/mL) increase in the remibrutinib $C_{avg,ss}$.

Bottom: Summary of individual average remibrutinib concentrations at steady state by dosing regimen: median and the 5th to 95th percentiles of distribution for each dosing regimen are represented with the dot and the horizontal bar.

Abbreviations: AESI, adverse event of special interest; bid, twice daily; CI, confidence interval; conc, concentration; E-R, exposure-response; qd, once daily; SS, steady state

14.5.3. PBPK Modeling

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK modeling analyses to predict the following:

- The effect of strong (ketoconazole, itraconazole, and ritonavir), moderate (fluconazole, erythromycin), and weak (fluvoxamine) CYP3A inhibitors on the pharmacokinetics of remibrutinib at doses of 25 mg BID.
- The effect of strong (carbamazepine and rifampicin), moderate (efavirenz), and weak (dexamethasone) CYP3A4 inducers on the pharmacokinetics of remibrutinib at doses of 25 mg BID.
- The effect of multiple doses of remibrutinib 25 mg BID on the pharmacokinetics of substrates of CYP3A (midazolam), P-gp (digoxin), and BCRP (rosuvastatin).

The Divisions of Inflammation and Immune Pharmacology and Pharmacometrics have reviewed the PBPK submission (Report DMPK R2301014, modeling and simulation files, and response to Information Requests dated March 24, 2025 (supporting document number [SDN] 0007) and March 14, 2025 (SDN 0005)) to conclude the following:

- Simulations predicted 3.21- to 3.65-fold increase in AUC of remibrutinib when multiple doses of remibrutinib 25 mg BID were coadministered with multiple doses of strong CYP3A4 inhibitors.
- Simulations predicted 1.89- to 2.27-fold increase in AUC of remibrutinib when multiple doses of remibrutinib 25 mg BID were coadministered with multiple doses of moderate CYP3A4 inhibitors.
- Simulations predicted 74.3% to 90.5% reduction in AUC of remibrutinib when multiple doses of remibrutinib 25 mg BID were coadministered with multiple doses of strong CYP3A4 inducers. Simulations predicted 64% reduction in AUC of remibrutinib when multiple doses of remibrutinib 25 mg BID were coadministered with multiple doses of moderate CYP3A4 inducers.
- Simulations, in combination with clinical DDI results, suggest a low potential for a clinically relevant effect of remibrutinib 25 mg BID on CYP3A4 substrates.
- The magnitude of the interaction effect of remibrutinib 25 mg BID on the pharmacokinetics of substrates of P-gp and BCRP could not be confidently predicted by PBPK.

PBPK Model for Remibrutinib

Background

Remibrutinib binds to the BTK protein, thereby inhibiting its enzymatic activity. Notably, remibrutinib demonstrates TMDD at lower doses, a characteristic that influences its pharmacokinetic profile and therapeutic efficacy.

Remibrutinib is predominantly metabolized by CYP3A4, with an estimated fractional contribution of CYP3A4 (f_m CYP3A4) of approximately 0.43. Other non-CYP-mediated pathways appear to also contribute to remibrutinib metabolic clearance, while renal clearance is minimal (<2%).

In vitro studies have demonstrated that remibrutinib acts as a CYP3A-reversible inhibitor ($K_{i,u} = 14.1 \mu\text{M}$) and time-dependent inhibitor ($K_{I,u} = 6.9 \mu\text{M}$, $K_{inact} = 0.612 \text{ 1/h}$). Furthermore, in vitro investigations have revealed that remibrutinib induces CYP3A4.

Remibrutinib exhibits high passive permeability at concentrations of $50 \mu\text{M}$ and above, while at lower concentrations, its permeability is diminished due to an apically directed P-gp-mediated efflux process. This efflux is not significantly influenced by BCRP or multidrug resistance-associated protein 2. Additionally, remibrutinib is not a substrate for the hepatic uptake transporters OATP1B1 and OATP1B3. As a precipitant, remibrutinib demonstrates clinically relevant potential to inhibit intestinal P-gp ($K_{i,u} = 0.382 \mu\text{M}$, $R = 1.02$ [hepatic], $R = 517$ [intestinal]), and BCRP ($K_{i,u} = 0.467 \mu\text{M}$, $R = 1.01$ [hepatic], $R = 423$ [intestinal]), The R value denotes the static DDI risk assessment for remibrutinib at a dosage of 25 mg twice daily (see Section [8.2](#)).

Multiple oral doses of remibrutinib at 100 mg BID did not significantly alter the PK parameters of a single oral dose of combined OCs containing EE 30 µg and LVG 150 µg. Similarly, remibrutinib did not significantly impact the PK parameters of midazolam (a CYP3A4 substrate) or rosuvastatin (a substrate for BCRP, OATP1B1, and OAT3) (see Section [14.2.6.2](#) and Section [14.2.6.3](#)). The increases in PK parameters for these substrates were less than 1.7-fold when compared to their administration alone. However, coadministration of remibrutinib 100 mg BID with digoxin 0.25 mg resulted in a 2.08-fold increase in C_{max} , a 1.45-fold increase in AUC_{last} , and a 1.4-fold increase AUC_{0-inf} of digoxin (see Section [14.2.6.2](#)). Additionally, remibrutinib did not exhibit the potential to inhibit the hepatic uptake of coproporphyrin I, a biomarker for OATP1B1 substrate.

Grapefruit juice, a moderate to strong inhibitor of gut CYP3A4, did not increase the exposure to remibrutinib (Study 2103). The F_{gut} was estimated from the dose-normalized AUC_{0-24h} values of 4.89 h*ng/mL/mg and 6.28 h*ng/mL/mg for remibrutinib when administered alone and in the presence of grapefruit juice, respectively. The F_{gut} was estimated to be 0.78, indicating a lesser contribution of gut CYP3A4 in the metabolism of remibrutinib compared to hepatic CYP3A4 (see Section [14.2.6.1](#)).

Ritonavir, a strong inhibitor of both gut and hepatic CYP3A4/P-gp, significantly increased the dose-normalized C_{max} and AUC_{0-24h} of orally administered remibrutinib by 3.32-fold and 4.27-fold, respectively. Conversely, carbamazepine, a strong inducer of CYP3A4, decreased $C_{max,ss}$, $AUC_{tau,ss}$, and $AUC_{last,ss}$ of remibrutinib 100 mg BID by 74%, 77%, and 78%, respectively (see Sections [14.2.6.1](#) and [14.2.6.2](#)).

Method

Software

Simcyp Population-based Simulator, version 21, release 1 (V21R1) and Simcyp® In Vitro Data Analysis (SIVA) Toolkit® version 4 (Certara UK Limited, Sheffield, United Kingdom) was used for the simulations.

Model Development

The input parameters for the remibrutinib PBPK model are detailed in [Table 90](#). The foundational remibrutinib base model was developed utilizing available in vitro absorption, ADME data, along with clinical DDI data with ritonavir (Study X2103). Remibrutinib is formulated as a FCT (b) (4). Thus, the oral absorption of remibrutinib was predicted through a mechanistic approach, considering both the biopharmaceutic properties of the drug substance and formulation effect, using the advanced dissolution, absorption, and metabolism model within the Simcyp Simulator.

Table 90. Inputs Parameters for Remibrutinib PBPK Model

Parameter	Mean Value	Reference
Molecular weight (g/mol)	507.5	DSP2R5003387-0009056892
LogP _{o:w}	3.24	DSP2R5003387-0009056892
Compound type	Monoprotic base	Estimated from aqueous media solubility – see details in Section 3.2.2.3
Pka1	3.822	DMPK R1400850
B/P	0.813	DMPK R1400850
f _{u,p}	0.0465	DMPK R1400850

Absorption

(b) (4)

Parameter	Mean Value	Reference
(b) (4)		
Distribution		
Distribution model	Full PBPK	
V _{ss} prediction method	Method 2	
V _{ss} (L/kg)	0.637	Predicted
K _p scalar	0.17	Optimized to recover the observed IV data (CLOU064X2103)
Elimination		
Target CL _{IV} (L/h)	70.1	Clearance based on CLOU064X2103
CYP3A4 V _{max} (pmol/min/pmol of isoform)	3.9	Target f _m CYP3A4=0.43 (CLOU064X2103)
CYP3A4 K _{m,u} (μM)	1.5	DMPK R1600559
CL _r (L/h)	1.224	CLOU064X2101 (based on 50 mg QD dose)
Additional systemic clearance (L/h)	37.5	Corresponding to ~53% of systemic clearance attributed to non-CYP-mediated metabolic pathways
Active hepatic uptake scalar	1	DMPK R1500097
Interactions		
CYP1A2		
K _{i,u} (μM)	35.3	DMPK R1500083
IndC ₅₀ (μM)	4.55±0.75	DMPK R1600703
Ind _{max}	5.47±2.24	
CYP2B6		
K _{i,u} (μM)	23.7±2.4	DMPK R1500083
IndC ₅₀ (μM)	5.47±0.12	DMPK R1600703
Ind _{max}	5.45±2.04	
CYP2C9		
K _{i,u} (μM)	0.025	Optimized from in vitro value of 7.7±0.5μM (DMPK R1500083) to best match the DDI with tolbutamide (CLOU064X2102)
IndC ₅₀ (μM)	5.1±0.64	DMPK R1600703
Ind _{max}	3.02±0.98	

Parameter	Mean Value	Reference
CYP3A4/5		
$K_{i,u}$ (μM)	14.1 $\pm$ 1.4	DMPK R1500083
IndC ₅₀ (μM)	5.08	DMPK R1600703
Ind _{max}	22.6	DMPK R1600703-The in vitro estimated Indmax (28-fold) was calibrated using rifampicin positive control (E_{max} =19.48-fold)
$K_{i,u}$ (μM)	1.38	Optimized for midazolam DDI (CLOU064X2102) from the in vitro value of 6.9 (+/-2.2) μM (DMPK R1500083)
K_{inact} h ⁻¹	0.612 $\pm$ 0.06	DMPK R1500083
Transporters		
$K_{i,u}$ (P-gp) (μM)	0.382	DMPK R2301196
$K_{i,u}$ (μM) (MATE1)	1.7	DMPK R2000485
$K_{i,u}$ (μM) (BCRP)	0.467	DMPK R2301196
$K_{i,u}$ (μM) (OATP1B1)	2.36	DMPK R2000485
$K_{i,u}$ (μM) (OATP1B3)	7.55	DMPK R2000485
$K_{i,u}$ (μM) (OAT1)	9.87	DMPK R2000485
$K_{i,u}$ (μM) (OAT3)	1.09	DMPK R2000485
$K_{i,u}$ (μM) (OCT1)	7.19	DMPK R1700782
$K_{i,u}$ (μM) (OCT2)	68.7	DMPK R1700782
PD basic		
PK compartment	Plasma – Free concentration	Lua script
Response model (μM)	Custom	
K_{syn} ($\mu\text{M}/\text{h}$)	0.045	Optimized to best fit pharmacokinetics of Day 1 especially at low doses for which no full target saturation is expected
K_{deg} (1/h)	0.01	LOU064X2101 Modeling report
K_{irr} (1/ $\mu\text{M}\cdot\text{h}$)	500	Optimized top down from initial estimate using preclinical rat value of 18 (RD-2014-00816)

Source: Reviewer-generated table based on Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Table 6-1

Abbreviations: BCRP, breast cancer resistance protein; CL_{IV} , clearance following intravenous dosing; CL_r , renal clearance; CSR, critical supersaturation ratio; CYP, cytochrome P450; DMPK, drug metabolism and pharmacokinetics; $f_{u,\text{gut}}$, fraction unbound in the gut; $f_{u,p}$, fraction unbound in plasma; IndC₅₀, substrate concentration that induce enzyme by 50%; Ind_{max}, maximal fold induction of an enzyme or gene expression; K_{deg} , degradation constant; $K_{i,u}$, unbound inhibition constant (reversible inhibition); K_{inact} , enzyme inactivation constant; K_{irr} , irreversible binding constant; $K_{m,u}$, the unbound concentration of substrate which permits the enzyme to achieve half V_{max} ; k_{out} , first order rate constants out of the single adjusting compartment; K_{syn} , synthesis constant; LOU064, remibrutinib; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PD, pharmacodynamic; P_{eff} , effective permeability; $P_{\text{eff,man}}$, effective permeability in man; P-gp, P-glycoprotein; PK, pharmacokinetic; P_{Ka} , acid dissociation constant; PRC, precipitation rate constant; SIVA, Simcyp® In Vitro Data Analysis; V_{max} , the maximum rate of reaction achieved when an enzyme is completely saturated with substrate; V_{ss} , volume of distribution at steady state

PK Data for Remibrutinib Model Development and Validation

The Applicant has used PK data from different studies to develop and validate remibrutinib PBPK model as summarized in [Table 91](#).

Table 91. Summary of Clinical Studies Used by the Applicant To Develop and Validate the PBPK Model of Remibrutinib

Study No.	Study Description	Roles in PBPK Analyses
X2103	Clinical DDI study with ritonavir and grapefruit juice and IV remibrutinib micro tracer. • Period 1: remibrutinib 50 mg on Day 1 to 3; and remibrutinib 100 µg IV QD on Day 3 • Period 2: remibrutinib 50 mg and grapefruit juice on Day 4; remibrutinib 20 mg QD and grapefruit juice on Day 5 • Period 3: remibrutinib 50 mg and ritonavir 100 mg on Day 6; remibrutinib 20 mg, remibrutinib 100 µg IV QD, and ritonavir 100 mg BID on Day 7; and ritonavir 100 mg BID on Day 8	Confirm IV clearance and volume of distribution at steady state. Confirm f_mCYP3A4 after IV and oral dosing
X2101	• Single-rising dose: 0.5, 1.5, 5, 15, 30, 60, 100, 200, 400, and 600 mg • Multiple-rising dose: 10, 25, 50, 100, 400, and 600 mg single dose for 12 days • Food effect: 60-mg single dose • Multiple-rising dose: 100 mg and 200 mg BID for 12 days	Model development and adjustment of TMDD parameters k_{irr} and k_{syn} and supersaturation ratio at 400- and 600-mg dose only
A2201	Remibrutinib 25 mg BID for 4 weeks in subjects with CSU	External model validation to extrapolate model predictive capacity in subjects
A02103	Clinical DDI study • Remibrutinib 100 mg BID • Carbamazepine 100 mg BID for Day 1 to 3; 200 mg BID for Day 4 to 6; 300 mg BID Day 7 to 22 (a.m.) • Digoxin: 0.25-mg single dose on Day 4 • Rosuvastatin: 10-mg single dose on Day 4	Confirm f_mCYP3A4, OATP1B1, BCRP, and P-gp inhibition
X2102	Remibrutinib: 100 mg BID for 14 days + single doses of caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate), midazolam (CYP3A4 substrate), or ethinyl estradiol (CYP3A4 substrate)	Sensitivity analysis for adjustment of K_i for CYP3A4 and CYP2C9 Confirmation of CYP1A2 and CYP3A4 interaction properties.

Source: Reviewer-generated table based on Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Table 2-1

Abbreviations: a.m., in the morning; BCRP, breast cancer resistance protein; BID, twice daily; CSU, chronic spontaneous urticaria; CYP, cytochrome P450; DDI, drug-drug interaction; f_m CYP3A4, fractional contribution of CYP3A4; IV, intravenous; k_{irr} , irreversible binding constant; k_{syn} , synthesis rate constant; K_i , time-dependent inhibition constant; OATP, organic anion transport protein; QD, once daily; P-gp, P-glycoprotein; TMDD, target-mediated drug disposition

(b) (4)

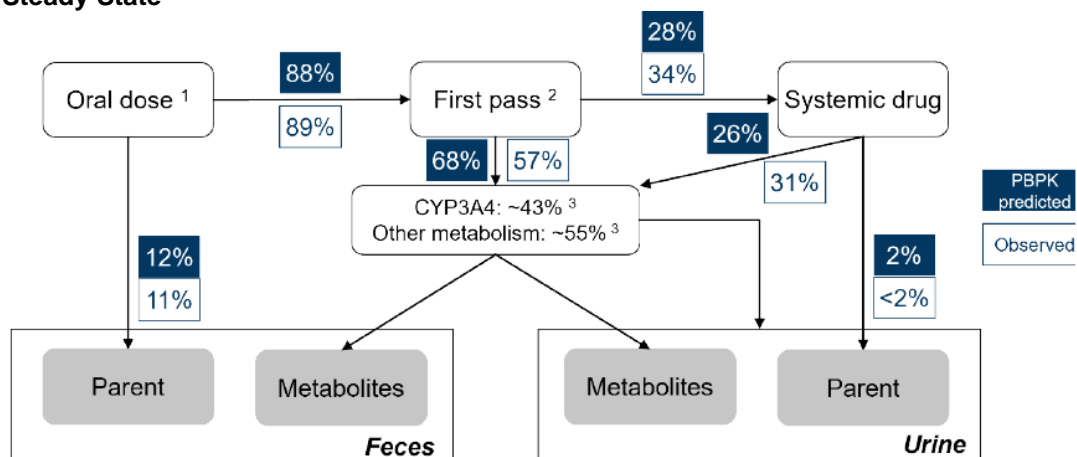
Distribution, Metabolism, and Clearance

The full PBPK model was used to describe the distribution of remibrutinib. The scalar for the tissue-partition coefficient was optimized from 1 to 0.17, resulting in a final V_{ss} of 0.63 L/kg. This value is generally comparable to the V_{ss} of 0.81 ± 0.22 L/kg observed following IV administration in Study X2103.

CYP3A4 was estimated to contribute to 97.8% of the oxidative hepatic metabolism of remibrutinib based on findings from the study in human liver microsomes (DMPK R1600559). Clinically, the remibrutinib f_m CYP3A4 was determined to be 43% at steady-state exposure based on the findings from the clinical DDI with ritonavir (see Section [14.2.6.1](#)). Additionally, following IV administration in the human ADME study, 40% of the detected drug-related material in the excreta (urine and feces) were identified as oxidative metabolites, while approximately 17% were classified as mixed metabolites from glucuronidation, hydrolysis, or glutathione conjugation with an oxidative metabolism step (unknown as primary and/or secondary step) (see Section [14.2.2](#)).

The retrograde method was employed to calculate the CYP3A4-mediated intrinsic clearance, utilizing a f_m CYP3A4 value of 0.43 and an estimated IV CL of 72 L/h. This approach predicted a steady-state IV clearance of 70.1 L/h (uninhibited IV CL) in Study X2103. To consider the potential for CYP3A4 saturation, the parameters $V_{max} = 3.9$ pmol/min/pmol of CYP3A4 and $K_{m,u} = 1.5$ μ M were used in the model instead of the intrinsic clearance value. The CLR was estimated to be approximately 1.224 L/h based on Study X2101. The remaining clearance attributed to non-CYP3A4 metabolic pathways (hydrolysis and glutathione conjugation) was entered into the model as additional systemic clearance. The disposition scheme of remibrutinib, with estimates for pathways contribution (observed and predicted) at steady state (50-mg daily oral dose) is shown in [Figure 57](#).

Figure 57. Observed and Predicted Estimates for the Disposition Pathways of Remibrutinib at Steady State



Observed pathway contributions to overall systemic clearance at steady state, white boxes; Resultant PBPK model predicted pathway contributions to overall systemic clearance at steady state, blue boxes

¹ Oral absorption of remibrutinib was estimated to be approximately 89% based on [CLOU064X2103](#)

² Measured bioavailability: 34% [CLOU064X2103](#)

³ Fractional contribution of CYP enzymes based on clinical DDI data ([CLOU064X2103](#))

Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Figure 3-1
Abbreviations: CYP, cytochrome P450; DDI, drug-drug interaction; PBPK, physiologically based pharmacokinetic

TMDD

Remibrutinib is an inhibitor of BTK and exhibits TMDD. The PBPK model for remibrutinib was integrated with a PD model (scripted in Lua within the Simcyp Simulator v 21R1) to account for the time-dependent changes in systemic clearance of remibrutinib due to target binding saturation following repeated dosing. This PD model represents the "net effect" of the irreversible binding of remibrutinib to BTK, aggregating binding events and target expression across all tissues within the systemic compartment. This semimechanistic approach describes the increased clearance of remibrutinib on Day 1 due to TMDD and the target saturation observed at steady state and/or at higher remibrutinib doses. Importantly, the PD model was implemented to describe the TMDD process and its effect on the pharmacokinetics of remibrutinib but was not designed to elucidate remibrutinib-BTK binding kinetics across tissues or to be linked to remibrutinib efficacy due to its limited parameters. The PD model is described by the following equations:

Equation 1. PD Model

$$\frac{dTarget}{dt} = k_{syn} - k_{deg} * Target - k_{irr} * C_{blood} * Target \quad (3)$$

$$\frac{dComplex}{dt} = k_{irr} * C_{blood,free} * Target - k_{deg} * Complex \quad (4)$$

$$\% Target_{occ} = 100 * \frac{Complex}{(Target + Complex)} \quad (5)$$

where Target, Complex and Target_{occ} represent the concentrations of BTK and BTK-remibrutinib complex as well as the BTK occupancy, respectively; k_{syn} is the zero order target synthesis rate ($\mu\text{M}/\text{h}$); k_{deg} (h^{-1}) is the target turnover; k_{irr} is the irreversible binding constant ($1/\mu\text{M}^*\text{h}$) and $C_{blood,free}$ is the unbound blood concentration of remibrutinib.

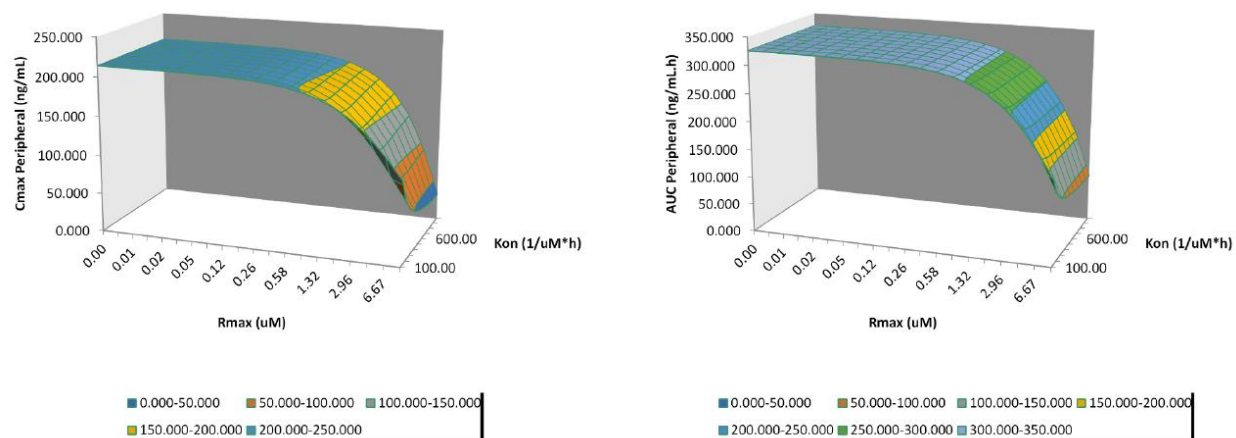
Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib
Abbreviations: BTK, Bruton's tyrosine kinase; $C_{blood,free}$ unbound blood concentration of remibrutinib; dComplex, change in BTK-remibrutinib complex; dt, change in time; dTarget, change in the concentrations of BTK; k_{deg} , target turnover; k_{irr} , irreversible binding constant; k_{syn} , zero order target synthesis rate; Target_{occ},

In response to an FDA request (dated March 12, 2025) to justify the necessity of accounting for the TMDD process in the remibrutinib PBPK model, the Applicant clarified that the exposure differences between Day 1 and Day 12 in Study X2101 were up to 4.86-fold at the dose of 10 mg once daily, which then decreased to 1.14-fold at the higher dose of 600 mg once daily (see Section 14.2.1.1) due to the time-dependent changes in systemic clearance of remibrutinib by target binding saturation following repeated dosing.

The FDA also requested the Applicant to demonstrate the performance of the PD model for different sets of PD parameters evaluated within the model. The initial TMDD parameters (degradation constant [k_{deg}], irreversible binding constant [k_{irr}], and synthesis rate constant [k_{syn}]) were manually adjusted in a “top-down” manner to predict remibrutinib pharmacokinetics in Study X2101 after a single dose at 1.5, 5, 15, 30, 60, and 100 mg, and subsequently the PK parameters after 10 and 25 mg once daily. The degradation rate constant (k_{deg}) was maintained at 0.01 h^{-1} , consistent with the estimated k_{deg} value of 0.00976 h^{-1} obtained from the PK/PD analysis of Study X2101. The PBPK input values for the k_{irr} and k_{syn} of $500 1/\mu\text{M}^*\text{h}$ and $0.045 \mu\text{M}/\text{h}$, respectively, demonstrated good performance among other evaluated values (data not shown). Of note, parameter estimation or sensitivity analysis functions for the PD parameters were not feasible in the current version of the simulator (Simcyp v 21R1). Therefore, statistical analysis and visual predictive checks were employed to assess the PD model performance.

Further, the Applicant demonstrated the sensitivity of C_{max} and AUC to target abundance ($R_{max} = k_{syn}/k_{deg}$) and k_{irr} ($=k_{on}$) to support the manually optimized k_{irr} and k_{syn} values (Figure 58).

Figure 58. Parameter Sensitivity Analysis of R_{max} ($=K_{syn}/K_{deg}$, $K_{deg} = 0.01 \text{ h}^{-1}$) and K_{on} on C_{max} and AUC



Source: Response to FDA information request dated March 12, 2025, SDN 003, Module 1.11.3

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; K_{deg} , degradation constant; K_{on} , irreversible binding constant; K_{syn} , synthesis constant; R_{max} , target abundance

Drug Interactions

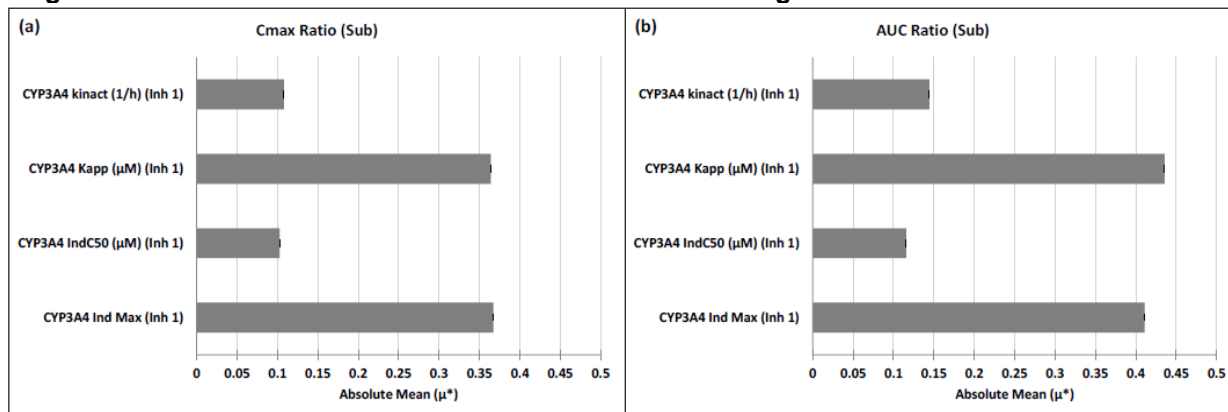
The in vitro parameters for CYP enzymes inhibition and induction and transporters inhibition are listed in [Table 90](#).

CYP3A4

Remibrutinib exhibits characteristics of both a reversible and time-dependent inhibitor and inducer of CYP3A4 in vitro. An initial PBPK model using the in vitro estimates of CYP3A4 interaction parameters did not accurately estimate the observed magnitude of the DDI between remibrutinib (100 mg BID) and midazolam (a CYP3A4 substrate) in Study X2102. Any of the induction parameters (i.e., maximal fold induction of an enzyme or gene expression [Ind_{max}], substrate concentration that induce enzyme by 50% [$IndC_{50}$]) or time-dependent inhibition (TDI) parameters (i.e., inhibition constant [K_I] and enzyme inactivation constant [k_{inact}]) could be adjusted accordingly to recover a clinical DDI data. Due to identifiability challenges associated with the optimization of TDI and induction parameters, local and global sensitivity analyses (GSA) were then performed to evaluate the impact of individual parameter variations on the predicted DDI and guide the rationale for parameter optimization. The GSA revealed that the most influential parameters affecting the AUC and C_{max} ratios were, in order of significance, K_I ($=K_{app}$), Ind_{max} , k_{inact} , and $IndC_{50}$ ([Figure 59](#)).

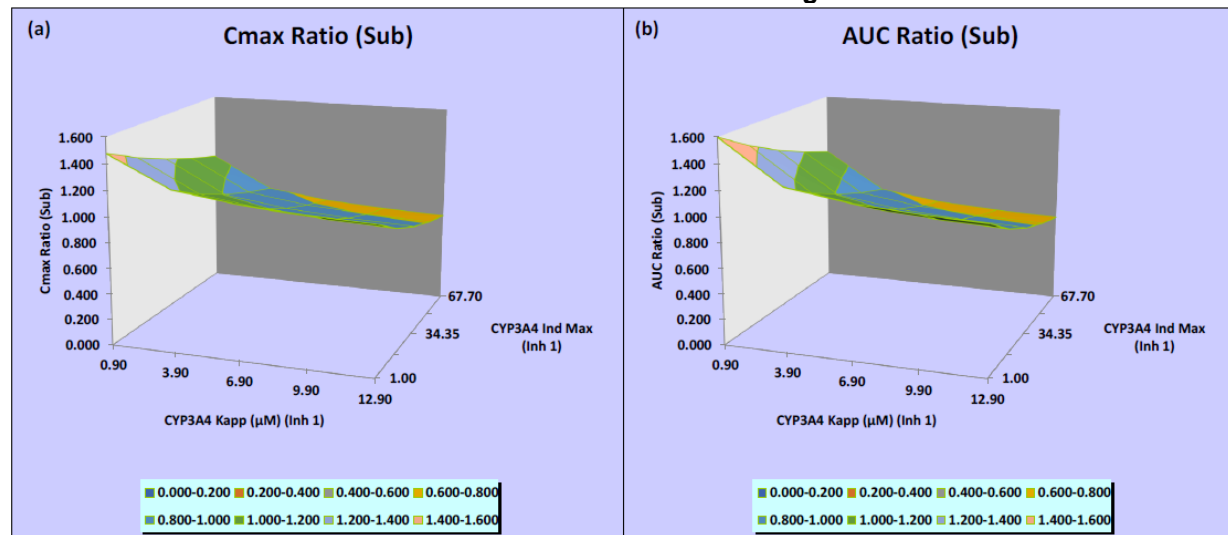
The local sensitivity analysis was subsequently conducted using a range that spanned three times the standard deviation of the in vitro values (0.9 to 12.90 μM for K_I and 1 to 67.7-fold for Ind_{max}), predicted AUC ratios ranging from 0.7 to 1.6 and C_{max} ratios from 0.7 to 1.48 ([Figure 60](#)). Based on these findings, the in vitro K_I value was reduced from 6.9 to 1.38 μM to best align with the observed AUC and C_{max} ratios of the DDI with midazolam. This optimization was achieved without altering the in vitro estimated values for the reversible inhibition, induction, or the TDI k_{inact} .

Figure 59. Global Sensitivity Analysis of Remibrutinib CYP3A4 In Vitro Interaction (Reversible and Time-Dependent Inhibition, Induction) Properties on the (a) C_{max} and (b) AUC Ratio of the Drug-Drug Interaction Between Midazolam and Remibrutinib 100 mg BID



Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Figure 8-2
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max} , maximum plasma concentration; CYP, cytochrome P450; Ind_{max}, maximal fold induction of an enzyme or gene expression; k_{app} , time-dependent inhibition constant; k_{inact} , enzyme inactivation constant

Figure 60. Local Parameter Sensitivity Analysis of Remibrutinib CYP3A4 Ind_{max} and K_i on C_{max} and AUC Ratios of DDI Between Midazolam and Remibrutinib 100 mg BID



Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Figure 8-3
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max} , maximum plasma concentration; CYP, cytochrome P450; DDI, drug-drug interaction; Ind_{max}, maximal fold induction of an enzyme or gene expression; K_i , time-dependent inhibition constant

Results and Discussion

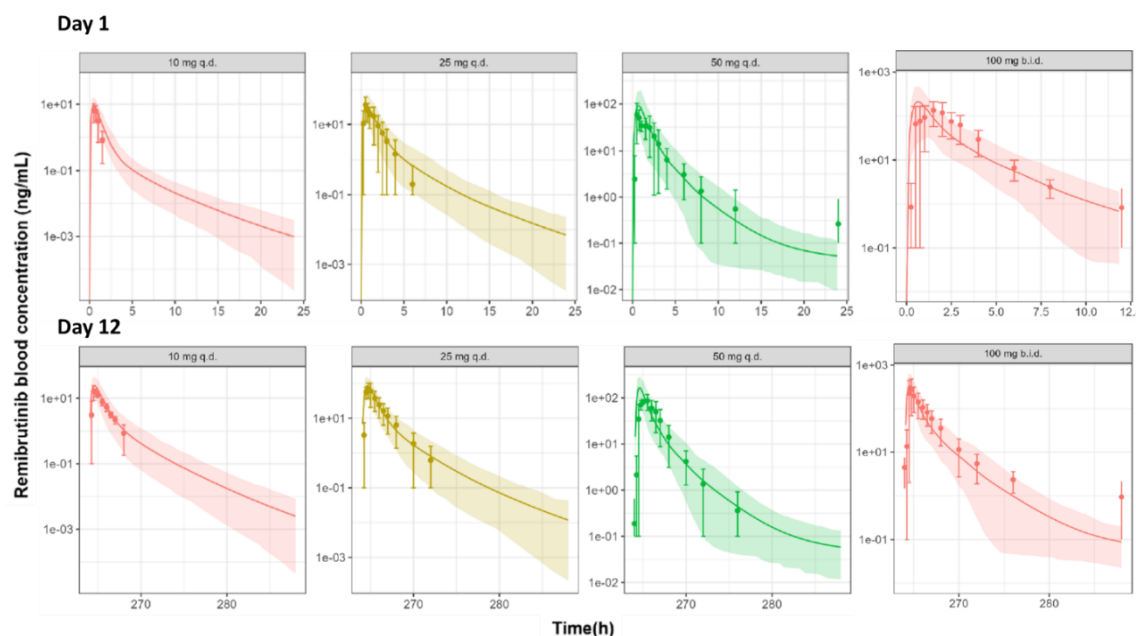
Remibrutinib PBPK Model Performance for Pharmacokinetics

The developed PBPK model for remibrutinib effectively captured the PK profiles in healthy subjects under various administration scenarios, including steady-state intravenous dosing (0.1 mg following a 50-mg oral dose), single oral doses (1.5 to 200 mg), and multiple oral doses (10 to 100 mg once daily or 25 to 200 mg twice daily for 12 days) (Figure 61 and Table 93).

Considering the high PK variability reported for remibrutinib, the predicted PK parameters demonstrated an adequate degree of accuracy, with 73% falling within 2-fold of the mean observed values and 50% within 0.7- to 1.4-fold. Additionally, the model accurately predicted the PK profile of remibrutinib at a dose of 25 mg twice daily in subjects with chronic spontaneous urticaria ([Figure 62](#) and [Table 93](#)).

The predicted CL/F of remibrutinib at 100 mg twice daily was 264 L/h, which is comparable to the observed CL_{ss}/F of 255 L/h from Study X2101. The model-predicted volume of distribution for remibrutinib at 100 mg twice daily for 12 days was 562 L (calculated from CL = 264 L/h and $\lambda\text{-Z} = 0.47 \text{ h}^{-1}$). This value is lower than the observed V_{ss}/F of 2040 L in Study X2101 but aligns closely with the observed volume of 576 L from the mass balance Study X2104 when remibrutinib was administered at 100 mg BID for 3 days. The estimated peripheral volume of distribution (V₂) from the population pharmacokinetic modeling was 1180 L. Clinical study results indicate that the volume of distribution increases with higher doses of remibrutinib, for example, following the administration of once daily doses of remibrutinib (10 to 600 mg) for 12 days in Study X2101, the V_{ss}/F increased from 554 L at 10-mg dose to 7130 L at 600-mg dose (see Section [14.2.1.1](#)).

Figure 61. Mean Simulated vs. Observed Blood Concentration-Time Profiles of Remibrutinib on Day 1 and Day 12 After Administration of Remibrutinib 10, 25, 50, and 100 mg Once Daily, Semilog Scale

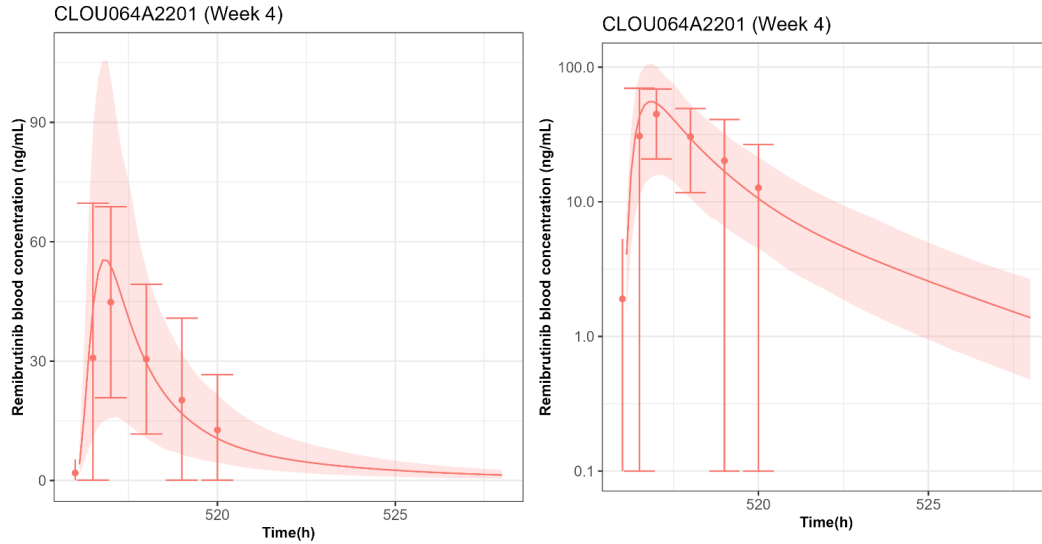


Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Figures 7-7 and 7-9

Colorful solid lines and filled circles with error bars represent the mean simulated population blood PK profile and the mean clinically observed PK profile of remibrutinib, respectively. The shaded areas illustrate the 5th to the 95th percentiles of the simulated remibrutinib pharmacokinetics.

Abbreviations: b.i.d., twice daily; h, hour; PK, pharmacokinetic; q.d., once daily

Figure 62. Mean Simulated vs. Observed Blood Concentration Time Profiles of Remibrutinib at Week 4 After Administration of 25 mg BID in Subjects With Chronic Spontaneous Urticaria (Left: Linear Scale; Right: Semilogarithmic Scale)



Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Figure 8-10
Colorful solid lines and filled circles with error bars represent the mean simulated population blood PK profile and the mean clinically observed PK profile of remibrutinib, respectively. The shaded areas illustrate the 5th to the 95th percentiles of the simulated remibrutinib pharmacokinetics.

Abbreviations: BID, twice daily; h, hour; PK, pharmacokinetic

Table 93. Summary of Observed and Simulated Remibrutinib Pharmacokinetics After Single and Multiple Oral Administration at Day 1, Day 12, and Day 22

Dose (mg)	C _{max} (ng/mL)			AUC _{last} (ng*h/mL)		
	Predicted	Observed	R _{Pred/Obs}	Predicted	Observed	R _{Pred/Obs}
Study X2101 single dose						
1.5	1.19±0.57	1.26±1.12	0.944	1.05±0.40	0.315±0.280	3.333
5	5.07±2.58	5.86±3.37	0.865	4.54±1.95	2.77±1.89	1.639
15	17.8±10.1	24.8±14.6	0.718	21.4±13	25.1±25.7	0.853
30	57.5±38.0	64.8±34.3	0.887	88.6±54.6	75.1±45.9	1.180
60	144±90.1	138±65.3	1.043	215±119	206±118	1.044
100	233±142	141±85.7	1.652	338±187	269±124	1.257
200	207±122	245±147	0.845	598±365	624±302	0.958
Study X2101 multiple doses						
10 QD Day 1	9.64±4.70	8.40±2.02	1.148	9.19±4.11	4.17±1.38	2.204
10 QD Day 12	25.3±13.2	18.2±5.90	1.390	33.4±17.9	22.9±3.50	1.459
25 QD Day 1	35.4±22.3	40.9±21.6	0.866	51.8±34.5	43.9±24.6	1.180
25 QD Day 12	87.1±41.7	85.9±31.5	1.014	129±60.2	114±59.7	1.132
50 QD Day 1	97.6±61.4	76.5±22.0	1.276	158±91.2	113±34.2	1.398
50 QD Day 12	173±77.8	102±22.0	1.696	254±115	207±80.4	1.227
100 QD Day 1	219±137	187±85.0	1.171	319±184	311±89.1	1.026
100 QD Day 12	307±156	233±84.1	1.318	440±225	488±172	0.902
25 BID Day 22*	102±51.1	55.5±34.7	1.854	157±66.2	183±97.5	0.858
100 BID Day 1	228±140	180±83.4	1.267	328±184	334±146	0.982
100 BID Day 12	342±171	306±202	1.118	496±252	518±334	0.958
200 BID Day 1	193±125	236±134	0.818	544±346	464±211	1.172
200 BID Day 12	282±164	347±112	0.813	810±500	963±439	0.841

Source: Reviewer-generated table based on Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Tables 6-4 and 6-5

Pharmacokinetic data are presented as arithmetic mean ± SD. Observed values were from Study X2101.

The AUC value of 1.5 mg was not included in the calculation as there was only one time point in the observed PK profile.

* Observed values were taken from the subject Study A2201 for Week 4. Pharmacokinetics was measured up to 4 hours postdose.

§ Only capsules of up to 50 mg were administered which may have an impact on the gastric emptying; therefore, the gastric emptying was increased from 0.27 to 1.18 hours, which is equal to the gastric emptying in the fed state.

Abbreviations: AUC_{last}, area under the concentration-time curve from time zero to the last measurable concentration sampling time; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; QD, once daily; R_{pred/obs}, ratio of predicted divided by observed value; SD, standard deviation

PBPK Model Performance for DDI

DDI simulations were conducted to evaluate the adequacy of the model to recover the clinical DDI data of remibrutinib with the strong CYP3A modulators ritonavir and carbamazepine, confirming the f_m CY3A4 value (43%) for remibrutinib included in the PBPK model.

Simulations were conducted for remibrutinib both oral (20 mg) and intravenous (0.1 mg) administration with ritonavir, as observed in the Study X2103. The predicted geometric mean ratios of C_{max} and AUC_{last} for oral remibrutinib 20 mg, when coadministered with ritonavir, were 3.03 and 4.09, respectively. For intravenous remibrutinib, the predicted geometric mean ratios of C_{max} and AUC_{last} were 1.84 and 1.07, respectively. The predicted DDI between ritonavir and remibrutinib was found to be comparable to the observed PK ratios, with a predicted/observed ratio range of 0.91 to 1.21 ([Figure 64](#) and [Table 94](#)).

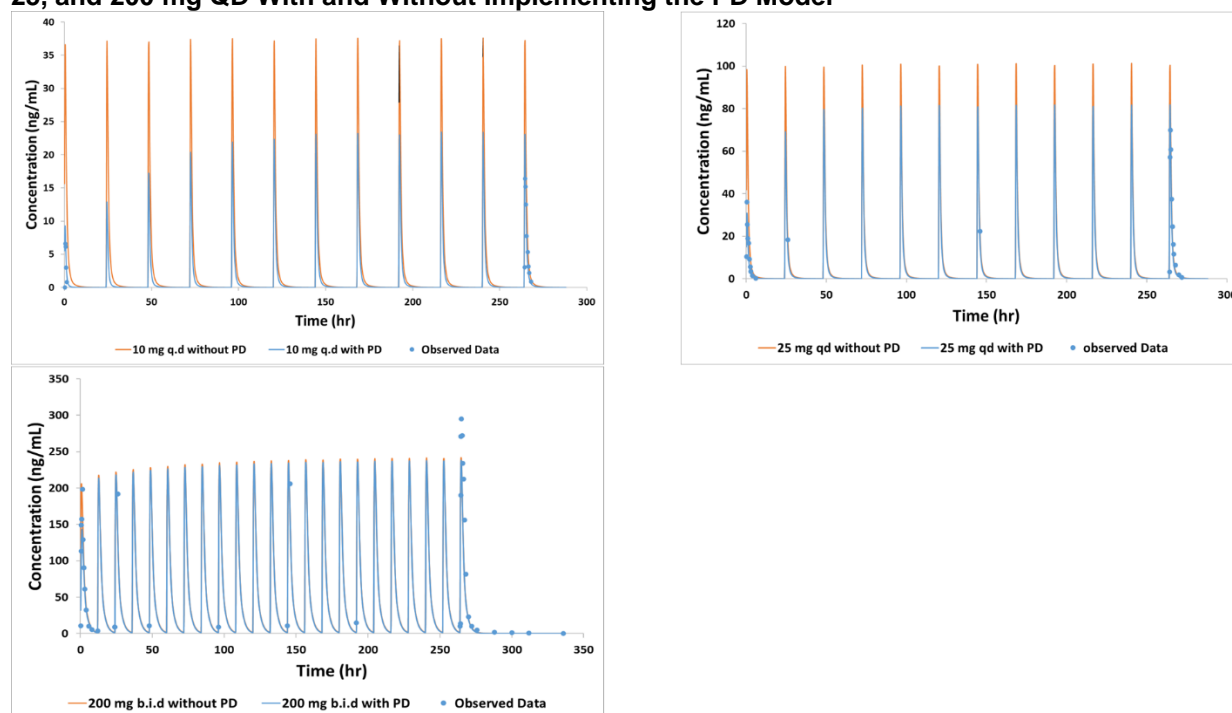
Similarly, simulations were conducted for remibrutinib 100 mg BID (five oral doses) with carbamazepine, as observed in the Study A02103. The predicted geometric mean ratios for C_{max} and AUC for remibrutinib, when coadministered with carbamazepine, were 0.369 and 0.312, respectively, which were slightly higher than the observed values of 0.26 and 0.23, respectively. The predicted/observed ratio were 1.42 for C_{max} and 1.36 for AUC ([Figure 64](#) and [Table 94](#)).

Overall, the PBPK model of remibrutinib adequately predicted the magnitude of the DDI between remibrutinib 20 mg steady state and ritonavir observed in Studies X2103, and slightly overpredicted the induction effect of carbamazepine on remibrutinib 100 mg steady state observed in Study A02103.

PBPK Model Performance Using PD Model

The reviewer conducted independent simulations for remibrutinib 10 mg QD, 25 mg QD, and 200 mg QD to assess the impact of integrating the PD model into the PBPK model. The PD model, which accounts for TMDD, demonstrated a notable advantage in accurately describing the observed PK data at lower doses (e.g., 10 mg and 25 mg) compared to the PBPK model without the PD component ([Figure 63](#)). However, at a higher dose of 200 mg, the PD model did not provide additional benefits in describing the observed PK data, as the simulated PK profiles were comparable with and without the PD model implementation.

Figure 63. Simulated Remibrutinib PK Profiles Following the Administration of Remibrutinib 10, 25, and 200 mg QD With and Without Implementing the PD Model



Source: Reviewer-generated figures using remibrutinib model submitted by the Applicant.
Abbreviations: b.i.d., twice daily; hr, hour; PD, pharmacodynamic; PK, pharmacokinetic; QD, once daily

To further assess the impact of incorporating the PD model into the PBPK model for remibrutinib, the reviewer conducted DDI simulations to predict the influence of the PD model on key model applications, namely the DDI magnitude between remibrutinib administered at 25 mg BID and a moderate CYP3A inhibitor (erythromycin) or inducer (efavirenz). PBPK simulations that included the PD model predicted C_{max} and AUC ratios for the interaction between remibrutinib 25 mg BID and erythromycin 500 mg to be 1.9 (90% CI: 1.84, 1.97) and 2.27 (90% CI: 2.18, 2.36), respectively. The PBPK simulations without the PD model predicted C_{max} and AUC ratios for the same interaction to be 1.83 (90% CI: 1.78, 1.89) and 2.20 (90% CI: 2.12, 2.29), respectively. Similarly, PBPK simulations that included the PD model predicted C_{max} and AUC ratios for the interaction between remibrutinib 25 mg BID and efavirenz 600 mg to be 0.405 (90% CI: 0.384, 0.428) and 0.361 (90% CI: 0.34, 0.384), respectively. PBPK simulations without the PD model predicted C_{max} and AUC ratios for the same interaction to be 0.44 (90% CI: 0.42, 0.46) and 0.39 (90% CI: 0.37, 0.41), respectively. The DDI magnitudes between remibrutinib 25 mg BID and either a moderate CYP3A inhibitor or inducer, with and without the inclusion of the PD model, were found to be comparable. Therefore, it can be concluded that the PD model does not significantly impact the prediction of drug-interaction magnitudes.

PBPK Model Applications

Remibrutinib PBPK model was used to predict drug interactions for scenarios that were not tested clinically at the proposed therapeutic dose of 25 mg BID.

Effects of CYP3A Inhibitors and Inducers on Remibrutinib

The net effects of induction, reversible inhibition, time-dependent inhibition, and saturation of CYP3A4 are expected to collectively influence the elimination of remibrutinib. The model predicted a net effect of 10 to 20% reduction in both hepatic and intestinal clearance when the dose is increased from 25 mg BID to 100 mg. Parameter sensitivity analysis has demonstrated that escalating the dose of remibrutinib from 20 mg to 200 mg results in a decrease in the f_m CYP3A4. This decrease leads to a reduction in the magnitude of drug interactions with strong CYP3A4 inhibitors and an increase in the magnitude of drug interactions with strong CYP3A4 inducers (data not shown). Time-dependent inhibition and CYP3A4 saturation were found to contribute to the reduction of both hepatic and intestinal intrinsic clearance by CYP3A4, particularly at doses ranging from 25 mg to 100 mg BID (data not shown). Notably, CYP3A4 saturation is more prevalent in the gut due to higher drug concentrations in this region. Additionally, auto-induction in the gut is more pronounced for remibrutinib at a dose of 100 mg BID compared to 25 mg BID.

Strong CYP3A Inhibitors

DDI simulations were conducted to extrapolate the outcome of the clinical DDI effect of ritonavir with remibrutinib at 20 mg to the proposed therapeutic dose of 25 mg BID, using ritonavir, itraconazole, and ketoconazole as strong CYP3A inhibitors. Following coadministration of ritonavir (100 mg BID for 7 days), itraconazole (200 mg QD for 7 days) or ketoconazole (200 mg BID for 7 days), the predicted geometric mean ratios for C_{max} and AUC_{tau} of remibrutinib 25 mg BID ranged from 2.47 to 2.67 and 3.21 to 3.65, respectively, in healthy subjects (Table 97). These data suggest that a strong CYP3A inhibitor is expected to cause a moderate inhibition effect on the exposure to remibrutinib 25 mg BID.

Moderate CYP3A Inhibitors

DDI simulations were conducted to predict the clinical DDI effect of the moderate CYP3A inhibitors fluconazole and erythromycin on remibrutinib 25 mg BID. The predicted geometric mean ratios for C_{max} and AUC_{tau} of remibrutinib 25 mg BID following oral administration of erythromycin (500 mg four times a day for 7 days) in healthy subjects, were 1.90 and 2.27, respectively (Table 97). Similarly, the predicted geometric mean ratios for C_{max} and AUC_{tau} of remibrutinib 25 mg BID following oral administration of fluconazole (200 mg QD for 7 days) in healthy subjects were 1.67 and 1.89, respectively (Table 97). These data suggest a moderate CYP3A inhibitor is expected to cause a weak to moderate effect on the exposure to remibrutinib 25 mg BID.

Weak CYP3A4 Inhibitor

Following coadministration of the weak CYP3A inhibitor fluvoxamine (50 mg QD for 7 days), the predicted geometric mean ratios for C_{max} and AUC_{tau} of remibrutinib 25 mg BID were 1.04 and 1.04, respectively (Table 97), in healthy subjects. These data suggest that a weak CYP3A inhibitor is not expected to impact the exposure to remibrutinib 25 mg BID.

Strong CYP3A Inducers

DDI simulations were conducted to predict the clinical DDI effect of the strong CYP3A inducers carbamazepine and rifampicin on remibrutinib 25 mg BID. The predicted geometric mean ratios

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for $C_{\max}$ and AUC_{τ} of remibrutinib 25 mg BID with carbamazepine (up to 300 mg BID for 22 days) were 0.358 and 0.257, respectively ([Table 97](#)). Similarly, the predicted geometric mean ratios for $C_{\max}$ and AUC_{τ} of remibrutinib 25 mg BID following oral administration of rifampicin (600 mg QD for 7 days) in healthy subjects were 0.122 and 0.095, respectively ([Table 97](#)). These data suggest that a strong CYP3A inducer is expected to cause a strong effect ($\geq 80\%$ decrease) on the exposure to remibrutinib 25 mg BID.

Moderate CYP3A4 Inducer

Following coadministration of the moderate CYP3A inducer efavirenz (600 mg QD for 7 days), the predicted geometric mean ratios for $C_{\max}$ and AUC_{τ} of remibrutinib 25 mg BID were 0.405 and 0.361, respectively ([Table 97](#)), in healthy subjects. These data suggest that a moderate CYP3A inducer is expected to cause a moderate effect (50 to 80% decrease) on the exposure to remibrutinib 25 mg BID.

Weak CYP3A4 Inducer

Following coadministration of the weak CYP3A4 inducer dexamethasone (8 mg BID for 7 days), the predicted geometric mean ratios for $C_{\max}$ and AUC_{τ} of remibrutinib 25 mg BID in healthy subjects were 0.672 and 0.626, respectively ([Table 97](#)). These data suggest that a weak CYP3A inducer is expected to cause a weak effect (20 to 50% decrease) on the exposure to remibrutinib 25 mg BID. Moreover, the model predicted no impact of remibrutinib 25 mg BID on the pharmacokinetics of dexamethasone, as a CYP3A4 substrate ([Table 96](#)).

Effect of Remibrutinib on P-gp Substrates (Digoxin)

Previously, the Applicant has used PBPK modeling and clinical DDI studies of different P-gp precipitants with digoxin aiming to establish a scaling factor (SF) for the in vitro P-gp inhibition constant (IC_{50}/K_i). Based on this analysis results, the Applicant proposed a scaling factor in the range of (b) (4) for P-gp inhibition constant. The SF P-gp is implemented in the simulations by dividing the fraction unbound in incubation ($f_{u,inc}$) with the scaling factor as $f_{u,inc,scalded} = f_{u,inc} / SF \text{ P-gp}$.

In remibrutinib PBPK modeling analysis, simulations were conducted to evaluate the ability of the model to recover the clinical DDI effect of remibrutinib 100 mg BID with digoxin (0.25-mg single oral dose) from Study A02103. While using SF P-gp of (b) (4), the predicted geometric mean ratios of $C_{\max}$ and AUC for digoxin following coadministration of remibrutinib in healthy subjects were (b) (4), respectively. However, the model underpredicted the observed $C_{\max}$ and AUC ratios of 2.08 and 1.45, respectively ([Figure 64](#) and [Table 95](#)). The prediction errors of the interaction on both the geometric mean $C_{\max}$ and AUC ratios were (b) (4)%. Subsequently, simulations were conducted using the higher SF P-gp of (b) (4), which did not improve the underprediction of the clinical DDI magnitude (the predicted geometric mean $C_{\max}$ and AUC ratios were (b) (4), respectively). In addition, the reviewer conducted simulations without using SF P-gp and the predicted $C_{\max}$ and AUC ratios for digoxin 0.25-mg single oral dose following oral administration of remibrutinib 100 mg BID were (b) (4), respectively, with prediction errors of (b) (4)% for $C_{\max}$ and (b) (4)% for AUC.

DDI simulations were conducted to interpolate the outcome of the clinical DDI effect of remibrutinib 100 mg BID to 25 mg BID, using SF P-gp of (b) (4). The predicted geometric mean ratios for $C_{\max}$ and AUC_{τ} of digoxin 0.25-mg single oral dose following oral administration of

remibrutinib 25 mg BID in healthy subjects, were (b) (4), respectively (Table 96). Since the PBPK simulations using remibrutinib 100 mg underpredicted the clinical DDI effect, the PBPK simulations of the interaction magnitude at 25 mg BID is possibly under predicted as well.

Effect of Remibrutinib on Midazolam (Sensitive CYP3A4 Substrate)

To simulate the results from Study X2102, the predicted geometric mean ratios of C_{max} and AUC for midazolam 2-mg single oral dose on Day 3 and Day 11 following oral administration of remibrutinib 100 mg BID in healthy subjects were 1.29 and 1.35 on Day 3 and 1.35 and 1.46 on Day 11, respectively. These predicted interaction magnitudes were comparable to the observed ratios in Study X2102 with a predicted/observed ratios range of 0.93 to 1.06 (Figure 64 and Table 95). The assessment of DDI between remibrutinib and midazolam on Day 3 and 11 takes in consideration the net effect of remibrutinib on CYP3A4 function which may exhibit a time-dependent characteristics. The predicted reversible inhibition effect is likely more pronounced at the initiation of treatment (Day 3), while the induction effect may be most evident after the cessation of treatment (Day 11).

The geometric mean ratios for C_{max} and AUC_{tau} of midazolam 2-mg single oral dose on Day 3 and Day 11 following oral administration of remibrutinib 25 mg BID in healthy subjects were predicted to be 1.18 and 1.20 on Day 3 and 1.22 and 1.25 on Day 11, respectively (Table 96). Based on the predicted effects of remibrutinib 25 mg BID on midazolam exposure on Days 3 and 11, it can be inferred that remibrutinib has a low potential to inhibit or induce CYP3A4.

Effect of Remibrutinib on Ethinylestradiol (Oral Contraceptive, CYP3A4 Substrate)

To simulate the results from Study X2102, the predicted geometric mean ratios of C_{max} and AUC for ethinylestradiol 0.03-mg single oral dose on Day 11 following oral administration of remibrutinib 100 mg BID in healthy subjects were 1.09 and 1.12, respectively. These predicted interaction magnitudes were comparable to the observed ratios in Study X2102 with a predicted/observed ratio of 0.852 for C_{max} and 0.966 for AUC (Figure 64 and Table 95).

The predicted geometric mean ratios for C_{max} and AUC_{tau} of ethinylestradiol 0.03-mg single oral dose on Day 11 following oral administration of remibrutinib 25 mg BID in healthy subjects, were predicted to be 1.07 and 1.08, respectively (Table 96). Therefore, remibrutinib lacks the potential to induce or inhibit CYP3A4.

Effect of Remibrutinib on Rosuvastatin (OATP1B and BCRP Substrate)

The in vitro inhibition constants for OATP1B and BCRP were not directly applied in the PBPK model of remibrutinib. Instead, the Applicant aimed to establish scaling factors based on their analysis of available clinical drug interactions of various OATP1B/BCRP perpetrators with the biomarker coproporphyrin I and several statins, including rosuvastatin. Based on the analysis results, the Applicant proposed scaling factors of (b) (4) (SF OATP1B = (b) (4)) and (b) (4) (SF BCRP = (b) (4)) for OATP and BCRP, respectively. These scaling factors are implemented in the modeling analysis by dividing the unbound fraction in the inlet ($f_{u,inc}$) of the precipitant by the respective scaling factor (e.g., $f_{u,inc,scaled} = f_{u,inc}/SF$).

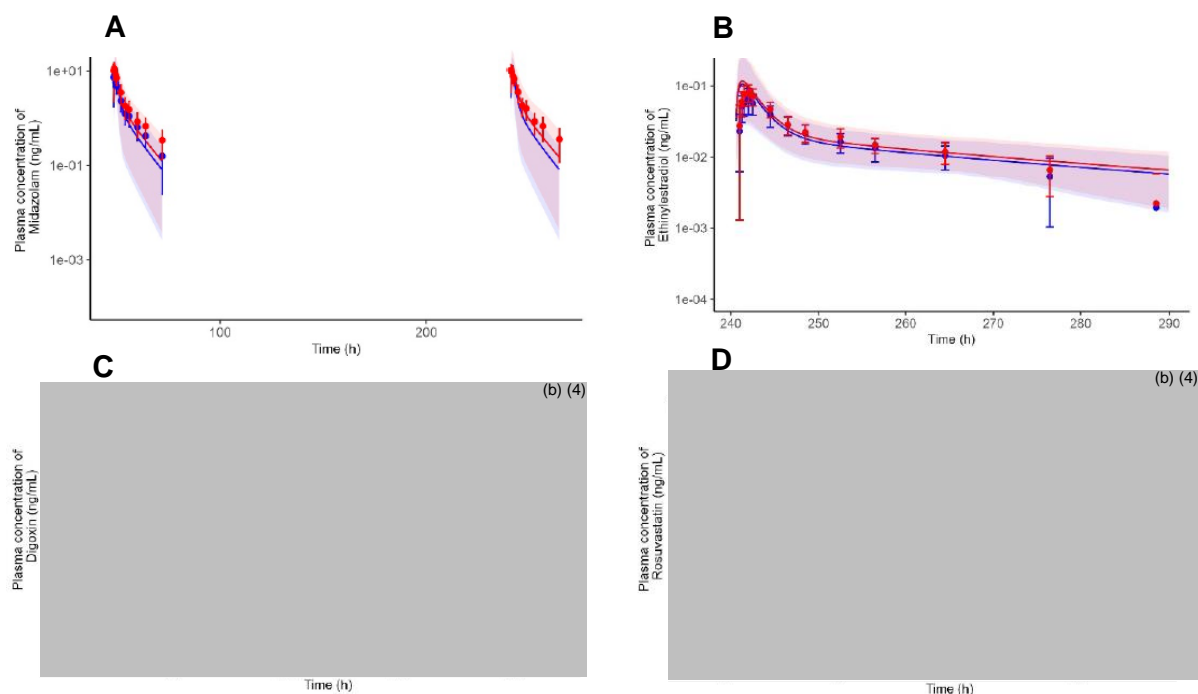
In the simulations of remibrutinib, the scaling factor for OATP1B was not utilized because remibrutinib 100 mg BID did not affect the exposure to coproporphyrin I (an endogenous

OATP1B substrate) in Study A02103 (the observed geometric mean C_{max} and AUC ratios were 1.02 and 0.98, respectively).

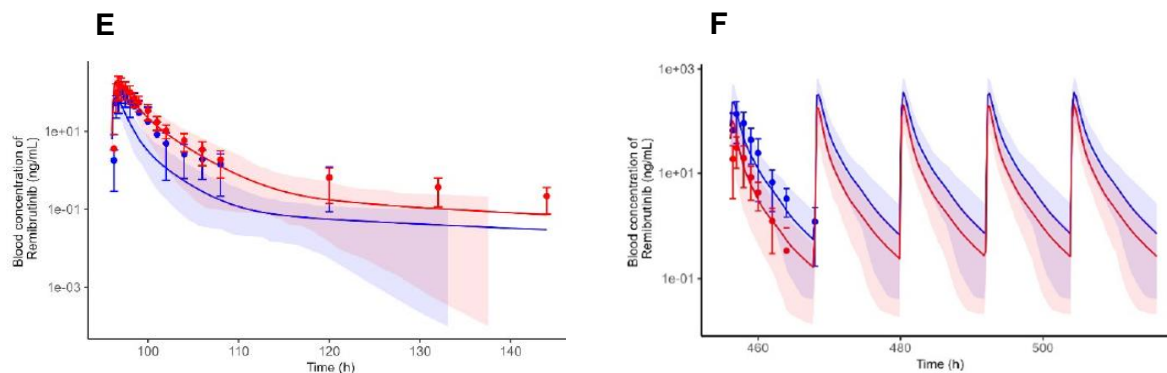
DDI simulations were conducted to evaluate the model performance to recover the clinical DDI effect of remibrutinib 100 mg with rosuvastatin from Study A02103. Using a SF of (b) (4) or OATP1B and an SF of (b) (4) for BCRP, the geometric mean ratios of C_{max} and AUC for rosuvastatin 10-mg single oral dose, following the oral administration of remibrutinib 100 mg BID, were predicted to be (b) (4), respectively. In the clinical setting, the observed geometric mean ratios of C_{max} and AUC for rosuvastatin 10-mg single oral dose, following the oral administration of remibrutinib 100 mg BID, in healthy subjects were 1.56 and 1.65, respectively. Consequently, the model prediction errors for this drug interaction were (b) (4)% and (b) (4)% for the C_{max} and AUC ratios, respectively (Figure 64 and Table 95).

DDI simulations were conducted to interpolate the outcome of the clinical DDI effect of remibrutinib 100 mg to 25 mg BID. The predicted geometric mean ratios for C_{max} and AUC_{tau} of rosuvastatin 10-mg single oral dose following the oral administration of remibrutinib 25 mg BID, while using the same scaling factors (SF OATP1B of (b) (4) and SF BCRP of (b) (4)), were (b) (4), respectively (Table 96). Since the simulations for remibrutinib 100 mg tended to mis-predict the clinical effect on rosuvastatin, simulation results of the interaction magnitude at 25 mg BID may possibly be mis-predicted as well.

Figure 64. Mean Simulated and Observed Blood Concentration-Time Profiles of Remibrutinib (With and Without Coadministration of Ritonavir or Carbamazepine) and Midazolam, Digoxin, Ethinylestradiol (With and Without Coadministration of Remibrutinib)



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Source: PBPK Report DMPK R2301014, Figures 7-12, 7-14, 7-17, 7-18, 7-19, 7-20.

^A Blue and red solid lines represent mean simulated population plasma PK profile of midazolam 2-mg p.o. single dose on Day 3 and Day 11 without and with concomitant administration of remibrutinib 100 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed plasma PK profile of midazolam without and with concomitant administration of remibrutinib, respectively.

^B Blue and red solid lines represent mean simulated population plasma PK profile of ethinylestradiol 0.03-mg p.o. single dose on Day 11 without and with concomitant administration of remibrutinib 100 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed plasma PK profile of ethinylestradiol without and with concomitant administration of remibrutinib, respectively.

^C Blue and red solid lines represent mean simulated population plasma PK profile of digoxin 0.25-mg p.o. single dose on Day 4 without and with concomitant administration of remibrutinib 100 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed plasma PK profile of digoxin without and with concomitant administration of remibrutinib, respectively.

^D Blue and red solid lines represent mean simulated population plasma PK profile of rosuvastatin 10-mg p.o. single dose on Day 4 without and with concomitant administration of remibrutinib 100 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed plasma PK profile of rosuvastatin without and with concomitant administration of remibrutinib, respectively.

^E Blue and red solid lines represent mean simulated population blood PK profile of remibrutinib 20-mg p.o. without and with concomitant administration of ritonavir 100 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed PK profile of remibrutinib without and with concomitant administration of ritonavir 100 mg BID, respectively.

^F Blue and red solid lines represent mean simulated population blood PK profile of remibrutinib 100 mg BID without and with concomitant administration of carbamazepine up titrated from 100 to 200 and then to 300 mg BID, respectively. Filled blue and red circles with error bars represent the mean clinically observed PK profile of remibrutinib without and with concomitant administration of carbamazepine, respectively.

The light blue and light red shaded areas illustrate the 5th to the 95th percentiles of the substrate pharmacokinetics without and with concomitant administration of the perpetrator.

Abbreviations: BID, twice daily; DMPK, drug metabolism and pharmacokinetics; h, hour; PBPK, physiologically based pharmacokinetics; PK, pharmacokinetic; p.o., oral administration

Table 94. Summary of Observed and Simulated Remibrutinib Pharmacokinetics Following Oral Administration With Ritonavir 100 mg BID or Carbamazepine Up-Titrated to 300 mg BID

Substrate	Ritonavir	Geometric Mean C _{max} * (ng/mL)		Geometric Mean AUC _{last} # (ng*h/mL)		Geometric Mean C _{max} Ratio (90% CI)		Geometric Mean AUC Ratio (90% CI)	
		Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Remibrutinib 0.1 mg IV	No	2.72	3.26	1.23	1.39	1.07	0.887	1.84	1.67
	Yes	2.92	2.89	2.27	2.33	(1.07, 1.08)		(1.80, 1.90)	
R _{pred/obs}						1.21		1.1	
Remibrutinib 20 mg oral	No	87.0	123	146	219	3.03	3.32	4.09	4.27
	Yes	193	159	404	389	(2.86-3.21)	(2.81-3.93)	(3.83-4.37)	(3.84-4.74)
R _{pred/obs}						0.913		0.958	
Substrate	Carbamazepine	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Remibrutinib 100 mg BID	No	177	125	270	276	0.369	0.26	0.312	0.23
	Yes	65.1	33.7	84.4	64.8	(0.346-0.392)	(0.21-0.33)	(0.289-0.337)	(0.19-0.28)
R _{pred/obs}						1.42		1.36	

Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Tables 6-7 and 6-8

* C_{max,ss} for the drug interaction with carbamazepine

AUC_{tau} for the drug interaction with carbamazepine

Study design for DDI between remibrutinib 0.1 mg IV and ritonavir: remibrutinib 0.1 mg on Day 1 at 11:00 a.m for total of five single doses + ritonavir 100 mg on Day 1 at 12:00 a.m., 8:00 a.m., and 8:00 p.m.; ritonavir 100 mg on Day 2 at 8:00 a.m. and 8:00 p.m.

Study design for DDI between remibrutinib 20 mg oral and ritonavir: remibrutinib 50 mg p.o. on Day 1 to 4 at 9:00 a.m., remibrutinib 20 mg p.o on Day 5 at 9:00 a.m. for a total of five doses + ritonavir 100 mg on Day 5 at 12:00 a.m., 8:00 a.m., and 8:00 p.m.; ritonavir 100 mg on Day 6 at 8:00 a.m. and 8:00 p.m.

Study design for DDI between remibrutinib 100 mg oral and carbamazepine: remibrutinib 100 mg BID for a total of five doses starting on Day 20 + carbamazepine 100 mg BID for Day 1 to 3; 200 mg BID for Day 4 to 6; 300 mg BID Day 7 to 22

Abbreviations: AUC_{last}, area under the concentration-time profile to the last measured timepoint; AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum blood concentration; DDI, drug-drug interaction; IV, intravenous; R_{pred/obs}, ratio of predicted divided by observed value

Table 95. Summary of Observed and Simulated Pharmacokinetics Midazolam, Ethynyl Estradiol, Digoxin, Coproporphyrin-1 and Rosuvastatin Following Oral Administration With 100-mg BID Remibrutinib

Substrate	Remibrutinib	Geometric Mean C _{max} (90% CI) (ng/mL)		Geometric Mean AUC (90% CI) (ng*h/mL)		Geometric Mean C _{max} Ratio (90% CI)		Geometric Mean AUC Ratio (90% CI)	
		Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Midazolam, Day 3 [†]	No	8.47 (7.63, 9.40)	8.56 (7.86, 9.33)	23.8 (21.2, 26.7)	32.4 (29.3-35.8)				
	Yes	10.9 (9.90, 12.1)	11.6 (10.7, 12.7)	32.1 (28.7, 35.9)	46.9 (42.4-52.0)	1.29 (1.26, 1.32)	1.36 (1.26-1.47)	1.35 (1.32,1.39)	1.45 (1.36-1.54)
R _{pred/obs}						0.949		0.931	
Midazolam, Day 11	Yes	11.4 (10.3,12.7)	10.9 (9.99,11.9)	34.8 (31,39)	46.5 (42,51.5)	1.35 (1.32, 1.39)	1.27 (1.18,1.38)	1.46 (1.42, 1.5)	1.43 (1.35, 1.52)
R _{pred/obs}						1.06		1.02	

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Substrate	Remibrutinib	Geometric Mean C _{max} (90% CI) (ng/mL)		Geometric Mean AUC (90% CI) (ng*h/mL)		Geometric Mean C _{max} Ratio (90% CI)		Geometric Mean AUC Ratio (90% CI)	
		Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Ethinyl estradiol [§]	No	0.0832 (0.073, 0.093)	0.0636 (0.057, 0.070)	0.906 (0.857, 0.958)	0.509 (0.468-0.553)	1.09 (1.08, 1.10)	1.28 (1.19, 1.39)	1.12 (1.11, 1.13)	1.16 (1.10, 1.22)
	Yes	0.0907 (0.080, 0.102)	0.0816 (0.0735, 0.0906)	1.01 (0.957, 1.07)	0.591 (0.543, 0.643)				
R _{pred/obs}						0.852		0.966	
Digoxin #	No	(b) (4)	0.92 (0.83, 1.02)	(b) (4)	13.77 (12.49, 15.17)	(b) (4)		(b) (4)	
	Yes		1.92 (1.72, 2.14)		19.90 (18.05, 21.94)		2.08 (1.81, 2.40)		1.45 (1.36, 1.54)
R _{pred/obs}									
Rosuvastatin ®	No		3.60 (2.98, 4.33)		38.57 (30.90, 48.14)				
	Yes		5.63 (4.67, 6.78)		63.54 (50.90, 79.31)		1.56 (1.35, 1.81)		1.65 (1.47, 1.84)
R _{pred/obs}									

Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Tables 6-11 and 6-12

Study design for DDI between remibrutinib and victim drugs: remibrutinib 100 mg BID starting on Day 1 for a total of 28 doses + two single doses of midazolam 2 mg, caffeine 200 mg, or tolbutamide 500 mg on Day 3 and Day 11; + ethinylestradiol 0.03 mg single dose on Day 11. Remibrutinib 100 mg BID starting on Day 1 for a total of 26 doses + digoxin 0.25 single dose or rosuvastatin 10-mg single dose on Day 4; + coproporphyrin I sampling for 12 hours pre-remibrutinib dosing and at Day 4.

Pharmacokinetic data are presented as geometric means with 90% confidence interval (CI) in parentheses. Observed values were from Studies X2102 and A02103.

R_{pred/obs}, ratio of predicted divided by observed value.

* PBPK predicted values for midazolam correspond to AUC_{0-24h} as AUC_{inf} was not output for the specific day, whereas AUC_{inf} values are for the observed.

§ PBPK predicted values for ethinyl estradiol correspond to AUC_{0-96h} whereas AUC_{0-24h} values are for the observed.

PBPK simulated values are using a scaling factor of (b) (4) for P-gp K_{i,u} i.e., K_{i,u,scaled} = K_{i,u}* (b) (4).

® PBPK simulated values are using a scaling factor of (b) (4) for Coproporphyrin-1 and a scaling factor of (b) (4) for BCRP K_{i,u} i.e., K_{i,u,scaled} = K_{i,u}* (b) (4)

β Observed C6h ratios calculated from geometric values; caffeine DDI in CLOU064X2102 is reported as ratio of paraxanthine/caffeine at 6h plasma concentration

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BID, twice daily; C6h, plasma concentration measured at 6 hours postdose;

C_{max}, maximum blood concentration; DDI, drug-drug interaction; IV, intravenous; K_{i,u}, unbound inhibition constant (reversible inhibition); P-gp, P-glycoprotein; R_{pred/obs}, ratio of predicted divided by observed value

Table 96. Summary of PBPK-Simulated PK Parameters and DDI Magnitude of CYP Sensitive Substrates After Multiple Oral Administration of Remibrutinib 25 BID

Substrate	Remibrutinib	Geometric Mean C _{max} (ng/mL) [#]	Geometric Mean AUC (ng*h/mL) [@]	C _{max} Ratio	AUC Ratio
Midazolam 2 mg, Day 3	No	8.47 (7.63, 9.40)	23.8 (21.2, 26.7)		
	Yes	10.0 (9.06, 11.1)	28.6 (25.6, 32.0)	1.18 (1.17-1.20)	1.20 (1.19-1.22)
Midazolam 2 mg, Day 11	Yes	10.3 (9.30, 11.4)	29.8 (26.6, 33.3)	1.22 (1.20-1.23)	1.25 (1.23-1.27)
Ethinyl estradiol	No	0.0832 (0.0739, 0.937)	0.906 (0.857, 0.958)		
	Yes	0.0889 (0.0789, 0.100)	0.977 (0.924, 1.03)	1.07 (1.06-1.07)	1.08 (1.07-1.08) ^{(b) (4)}
Digoxin	No				
	Yes				
Rosuvastatin	No				
	Yes				
Dexamethasone 8 mg BID oral	No	49.4 (47.0, 51.8)	265 (249, 281)		
	Yes	50.7 (48.2, 53.2)	274 (258, 292)	1.03 (1.02, 1.03)	1.04 (1.03, 1.04)

Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Tables 6-14, 6-15, and 6-16

Study design for DDI between remibrutinib and victim drugs: remibrutinib 25 mg BID starting on Day 1 for a total of 28 doses + two single doses of midazolam 2 mg, caffeine 200 mg, or tolbutamide 500 mg on Day 3 and Day 11; + ethinylestradiol 0.03-mg single dose on Day 11. Remibrutinib 25 mg BID starting on Day 1 for a total of 26 doses + digoxin 0.25 single dose or rosuvastatin 10-mg single dose on Day 4; + coproporphyrin I sampling for 12 hours pre-remibrutinib dosing and at Day 4; + dexamethasone 8 mg QD starting on Day 1 for a total of 14 doses.

[#] For caffeine and tolbutamide, the geometric mean concentration and ratio after 6h (C_{6h}) and 24h (C_{24h}) is reported, respectively.

[@] For caffeine and tolbutamide, AUC ratio is not reported. For midazolam AUC ratio corresponds to 24h AUC ratio, whereas for ethinyl estradiol corresponds to AUC_{last} ratio

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; CI, confidence interval; C_{max}, maximum blood concentration; CYP, cytochrome P450; DDI, drug-drug interaction; PK, pharmacokinetic

Table 97. Summary of PBPK Model-Simulated PK Parameters and DDI Magnitude After Multiple Oral Administration of Remibrutinib 25 Twice Daily With CYP3A4 Inhibitors or Inducers

Perpetrator	Perpetrator Present	Geometric Mean C _{max,ss} (ng/mL)	Geometric Mean AUC _{tau} (ng*h/mL)	C _{max,ss} Ratio	AUC _{tau} Ratio
Ketoconazole 200 mg BID	No	100 (92.7, 108)	149 (139, 161)	2.53 (2.41, 2.65)	3.38 (3.20, 3.58)
	Yes	254 (243, 265)	505 (481, 531)		
Itraconazole solution, 200 mg QD	No	97.1 (90.2, 105)	142 (133, 152)	2.47 (2.37, 2.57)	3.21 (3.06, 3.36)
	Yes	240 (228, 252)	455 (432, 480)		
Ritonavir 100 mg BID	No	100 (92.5, 109)	149 (139, 161)	2.67 (2.53, 2.81)	3.65 (3.43, 3.88)
	Yes	267 (256, 279)	546 (520, 573)		
Fluconazole 200 mg QD	No	99.2 (92.1, 107)	146 (137, 157)	1.67 (1.63, 1.71)	1.89 (1.85, 1.94)
	Yes	166 (157, 176)	277 (262, 293)		
Erythromycin 500 mg QID	No	98.0 (90.6, 106)	145 (134, 156)	1.90 (1.84, 1.97)	2.27 (2.18, 2.36)
	Yes	187 (175, 199)	328 (304, 353)		

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Perpetrator	Perpetrator Present	Geometric Mean	Geometric Mean	C _{max,ss} Ratio	AUC _{tau} Ratio
		C _{max,ss} (ng/mL)	AUC _{tau} (ng*h/mL)		
Fluvoxamine 50 mg QD	No	101 (93.0, 109)	150 (139, 161)	1.04 (1.03, 1.04)	1.04 (1.04, 1.05)
	Yes	104 (96.3, 112)	156 (145, 168)		
Carbamazepine 300 mg BID (up-titration)*	No	30.7 (27.7, 33.9)	46.2 (41.5, 51.3)	0.358 (0.336, 0.380)	0.257 (0.239, 0.278)
	Yes	11.0 (9.75, 12.3)	11.9 (10.7, 13.2)		
Rifampicin, 600 mg QD	No	100 (92.8, 108)	149 (139, 161)	0.122 (0.105, 0.141)	0.095 (0.081, 0.11)
	Yes	12.2 (10.1, 14.8)	14.2 (11.8, 17.1)		
Efavirenz 600 mg QD	No	100 (92.7, 109)	149 (139, 161)	0.405 (0.384, 0.428)	0.361 (0.340, 0.384)
	Yes	40.6 (36.7, 45.0)	53.9 (48.8, 59.6)		
Dexamethasone 8 mg BID	No	98.3 (91.0, 106)	145 (134, 165)	0.672 (0.659, 0.686)	0.626 (0.611, 0.642)
	Yes	66.1 (61.3, 71.3)	90.7 (84.8, 97.1)		

Source: Study 2301014: Final physiologically based pharmacokinetic (PBPK) model and simulations for remibrutinib, Tables 6-13 and 6-14

Study design for remibrutinib as a victim: remibrutinib 25/100 mg BID on Day 1 for a total of 14 doses + ritonavir 100 mg BID starting Day 1 for a total of 14 doses; ketoconazole 200 mg BID starting Day 1 for a total of 14 doses; itraconazole solution 200 mg QD starting Day 1 for a total of 7 doses; erythromycin 500 mg QID starting Day 1 for a total of 28 doses; fluconazole 200 mg QD starting Day 1 for a total of 7 doses; fluvoxamine 50 mg QD starting Day 1 for a total of 7 doses; rifampicin 600 mg QD starting Day 1 for a total of 14 doses; efavirenz 600 mg QD starting Day 1 for a total of 14 doses; or dexamethasone 8 mg QD starting on Day 1 for a total of 14 doses.

Pharmacokinetic data are presented as geometric means with 90% confidence interval (CI) range in parentheses. All simulations, except for the remibrutinib carbamazepine interaction, were run with remibrutinib coadministered with CYP3A4 perpetrators for 7 days starting at Day 1. The geometric mean C_{max} and AUC ratio at steady state (i.e., of the last dose) with 90% confidence interval (CI) range in parentheses is presented.

*Custom study design to replicate the clinical study design of Study A02103 is used. Pharmacokinetic parameters as well as the drug-drug interaction magnitude (AUC and C_{max} ratio) are presented as geometric means with 90% confident interval (CI) range in parentheses for the first dose of remibrutinib

Abbreviations: AUC_{tau}, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max,ss}, maximum blood concentration at steady state; QID, four time a day; QD, once daily

Conclusion

The pharmacokinetics of remibrutinib are significantly influenced by drugs that modulate CYP3A activity. PBPK simulation studies have predicted clinically significant changes in remibrutinib's $C_{max,ss}$ and AUC_{tau} when coadministered with strong or moderate inhibitors or inducers of CYP3A, which agreed with the observed clinical DDI results of remibrutinib with strong CYP3A modulators.

When remibrutinib 25 mg BID is coadministered with multiple doses of strong CYP3A inhibitors such as ritonavir, itraconazole, or ketoconazole, the $C_{max,ss}$ and AUC_{tau} are predicted to increase by approximately 2.47- to 2.67-fold and 3.21- to 3.65-fold, respectively. Similarly, moderate CYP3A inhibitors like erythromycin and fluconazole are predicted to elevate the $C_{max,ss}$ and AUC_{tau} by around 1.67- to 1.9-fold and 1.89- to 2.27-fold, respectively. In contrast, weak CYP3A4 inhibitors such as fluvoxamine do not significantly affect the PK parameters of remibrutinib 25 mg BID.

Conversely, strong CYP3A inducers like carbamazepine and rifampicin can markedly decrease the $C_{max,ss}$ and AUC_{tau} of remibrutinib by approximately 62.4% to 87.8% and 74.3% to 90.5%, respectively. Moderate CYP3A inducers such as efavirenz reduce these PK parameters by about 59.5% and 64%, respectively.

In clinical Study A02103, remibrutinib 100 mg BID increased the C_{max} and AUC of the P-gp substrate digoxin by 2.08-fold and 1.45-fold, respectively, and the C_{max} and AUC of the BCRP substrate rosuvastatin by 1.56-fold and 1.65-fold, respectively. PBPK simulations tended to mispredict the observed magnitude of the interaction between remibrutinib 100 mg BID and these transporter substrates. Therefore, due to the inherent limitations of model predictions and confidence in the predicted results, the clinical findings from Study A02103, conducted with the 100-mg BID dosage of remibrutinib, should be applicable to subjects receiving the lower dosage of 25 mg BID.

PBPK simulations and clinical DDI studies have demonstrated the absence of an impact of remibrutinib coadministration on the exposure to CYP3A4 substrates, such as midazolam and oral contraceptives.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Trials A2301 and A2302

Additional details for Trials A2301 and A2302 not included in Section [6.2.2](#) are described below.

15.1.1. Schedule of Assessments, Trials A2301 and A2302

The study visits and procedures are presented in [Table 98](#), which lists all of the assessments and indicates with an “X” the visits at which they were performed.

Table 98. Schedule of Assessments, Trials A2301 and A2302

Visit Name	Period	Screening	Treatment										Follow-up	Unscheduled visit		
	Screening	Screening	Baseline/ Randomization ¹	week 2 ¹	week 4	week 8	week 12 ¹	week 16	week 20	week 24	week 32	week 40	Early treatment discontinuation	week 52/Study discontinuation ¹	week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-	
Informed consent	X															
Pharmacogenetic Informed Consent	X															
IRT transaction	X	X		X	X	X	X	X	X	X	X	X	X	X		
Inclusion / Exclusion criteria	X	X														
Randomization		X														
Demography	X															
Pregnancy and assessments of fertility ²	XS	S		S	S	S	S	S	S	S	S	S	S	S	S	S
Evidence of urticaria	S	S														
Hepatitis screen	X															

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Period	Screening	Treatment										Follow-up	Unscheduled visit		
Visit Name	Screening	Baseline/ Randomization ¹	week 2 ²	week 4	week 8	week 12 ¹	week 16	week 20	week 24	week 32	week 40	Early treatment discontinuation	week 52/Study discontinuation ¹	week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Relevant medical history	X														
Dispense patients' eDiary ³	S											S	S		
CSU History and prior urticaria treatment	X														
Cardiovascular history	X														
Physical Examination ⁴	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height and Weight ⁵	X	X				X			X			X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X	X ⁶			X ⁶			X			X	X ⁶	X	X
Patient's eDiary review ⁷		S	S	S	S	S	S	S	S	S	S	S	S		S
DLQI ⁸		X		X		X			X			X	X		X
PGI severity ⁹		X	X	X		X			X			X	X		X
PGI Change ⁹			X	X		X			X			X	X		X
UCT ⁹		X	X	X		X			X			X	X		X
EQ-5D-5L ⁹		X				X			X			X	X		X
WPAI ⁹		X				X			X			X	X		X
Fric Test ⁹		X				X			X			X	X		

Period	Screening	Treatment										Follow-up	Unscheduled visit		
Visit Name	Screening	Baseline/ Randomization ¹	week 2 ²	week 4	week 8	week 12 ¹	week 16	week 20	week 24	week 32	week 40	Early treatment discontinuation	week 52/Study discontinuation ¹	week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Study drug dispensation		X		X	X	X	X	X	X	X	X				
Background medication dispensation and compliance assessment ¹⁷	X	X		X	X	X	X	X	X	X	X	X	X	X	
Rescue medication dispensation and usage ¹⁰	X	X		X	X	X	X	X	X	X	X	X	X		
PK blood collection ¹¹			X			X							X ¹²		X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X		X		X			X			X	X	X	X
IgG (total IgA, IgE, IgG, IgM)		X		X		X			X			X	X	X	
Serum for autoantibodies and other exploratory biomarkers (optional) ¹³		X		X		X			X			X	X	X	
B cell count and B cell subset ¹⁴		X		X		X			X			X	X		

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Period	Screening	Treatment											Follow-up	Unscheduled visit	
Visit Name	Screening	Baseline/ Randomization ¹	week 2 ²	week 4	week 8	week 12 ¹	week 16	week 20	week 24	week 32	week 40	Early treatment discontinuation	week 52/Study discontinuation ¹	week 56/Safety FU/Study completion	Unscheduled visit
Days	-28 to -1	1	15	29	57	85	113	141	169	225	281	-	365	394	-
Hepatitis B re-activation monitoring ¹⁵				X	X	X	X	X	X	X	X	X	X	X	X
CU Index		X												X	
Exploratory DNA Sampling (optional) ¹⁶		X													
Eligibility assessment for extension study ¹⁵													X		
Prior and concomitant medication												X			
Adverse events												X			
Study completion information												X			

¹ Patient to come fasting for ≥ 8 h (Ideally overnight) to visits: baseline/randomization, week 2, week 12 and week 52
² Serum pregnancy test and fertility assessment will be done at Screening. Urine pregnancy test to be completed every 4 weeks by WoCBP from Randomization through Study completion visit. At Weeks 28, 36, 44 and 48 test might have been performed at home - sites must have contacted patients to obtain test results. Any positive or undetermined test result had to be confirmed by a serum pregnancy test done by central lab and results obtained electronically. Urine pregnancy results were reported as source. If patients were unable to perform a home urine pregnancy test (e.g., prohibited by local regulations), a urine or serum test could have been performed at the local laboratory
³ Patients eDiary was returned to site at either week 52/study discontinuation.
⁴ Complete physical exam at screening, short physical exam at all subsequent visits including body temperature monitoring (per local practice)
⁵ Height collected at screening visit only
⁶ pre and post dose
⁷ eDiary included UPDD (Urticaria Patient Daily Diary) with UAS (Urticaria Activity Score, part of UPDD) and AAS (Angioedema Activity Score), eDiary had to be completed from screening to week 52/study discontinuation
⁸ Completed in the patient's eDiary during site visit. Order of completion: DLQI - PGIS - PGIC - UCT - EQ5D-5L - WPAI. All questionnaires had to be completed prior to any other physician assessment.
⁹ Only for patients with a history of symptomatic dermographism. Post-baseline assessments only performed in patients with positive test at baseline
¹⁰ Rescue medication usage was assessed by reviewing the patient's eDiary answer to UPDD question 5.
¹¹ At PK sampling visits, IMP had to be taken on site (fasting). PK sampling was to be performed 45 min and 90 min after IMP intake, respectively.
¹² PK sample not collected at study discontinuation visit if patient early discontinues
¹³ Additional biomarker ICF was obtained before optional biomarker sampling.
¹⁴ At selected sites only
¹⁵ Hepatitis B re-activation monitoring only for patients who were HBsAg negative and HBcAb (anti-HBc) positive with a negative HBV DNA test at Screening.
¹⁶ Genetic ICF was obtained before the optional DNA sampling. This optional sample could be collected anytime during Day 1 or thereafter
¹⁷ Dispensation for background medication covers prescription, dispensation and/or instruction of the patient on dosing and use of background medication and protocol requirements, considering different procedures for the provision of background medication at Investigational sites. At Week 56/Safety FU/Study completion visit only compliance was to be checked
¹⁸ Only for patients who have completed Week 52 visit, not applicable at Study discontinuation visit
Source: Appendix 16.1.1-Protocol-Table 8-1

Abbreviations: CSU, chronic spontaneous urticaria; CU, chronic urticaria; DLQI, dermatology life quality index; EQ5D-5L, EuroQol 5 Dimension 5 Level (test); FU, follow-up; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICF, informed consent form; Ig, immunoglobulin; IMP, investigational medicinal product; PGI, Patient Global Impression; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; UCT, Urticaria Control Test; WoCBP, women of childbearing potential; WPAI, Work Productivity and Activity Impairment (questionnaire)

15.1.2. Prohibited Medications, Trials A2301 and A2302

A list of the medications prohibited during Trials A2301 and A2302 is outlined below in [Table 99](#).

Table 99. Prohibited Medications, Trials A2301 and A2302

Medication Category	Prohibition Period
Biologics for treatment of CSU (including omalizumab and ligelizumab)	4 months prior to randomization until end of treatment
Routine oral corticosteroids (more than three doses over 5 days)	30 days prior to screening until end of treatment
IV/IM/IA corticosteroids	30 days prior to screening until end of treatment
Leukotriene antagonists (including montelukast and zafirlukast)	From screening until end of treatment
H2-antihistamines	From screening until end of treatment
First generation antihistamines	From screening until end of treatment
Second generation antihistamines (other than defined background and rescue medication)	From 7 days prior to randomization until end of treatment
Immunosuppressive/immunomodulating medications	30 days or five half-lives (whichever is longer) prior to screening until end of treatment
Intravenous immunoglobulins or plasmapheresis	30 days prior to screening until end of treatment
Ultraviolet (UV) therapy	From screening until end of treatment
Other urticaria therapies (including herbal therapies)	From 2 weeks prior to randomization until end of treatment
Live attenuated vaccines	6 weeks prior to randomization until at least 4 weeks after last dose of study treatment
Strong inhibitors of CYP3A4	From 2 weeks prior to randomization until end of treatment
Moderate and strong inducers of CYP3A4	From 2 weeks prior to randomization until end of treatment
Anticoagulant medications	From screening until end of treatment
Antiplatelet medications (except acetylsalicylic acid ≤ 100 mg/d or clopidogrel ≤ 75 mg/d)	From screening until end of treatment

Source: Clinical Reviewer-generated from Applicant CSR

Abbreviations: IA, intra-articular; CSU, chronic spontaneous urticaria; CYP, cytochrome P450; IM, intramuscular; IV, intravenous

15.1.3. PRO Instruments, Trials A2301 and A2302

PROs collected through electronic diary assessments included the UPDD and AAS. The UPDD assessed the UAS7, range 0 to 42, which comprised the ISS7, range 0 to 21 and HSS7, range 0 to 21. Screenshots of the instruments as seen by trial subjects are shown below in the following figures.

Figure 65. Patient Diary: Urticaria Patient Daily Diary

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

For each question, please choose the response that describes your experience.

Please pay close attention to the timeframe of interest. Some questions ask about the past 12 hours, while others ask about the past 24 hours.

Instructions for Counting the Number of Hives

Count each hive separately even if you have more than one hive grouped together with other hives.

Today's Date

day			month				year		

Please complete this section every morning throughout the duration of the study.
(Please circle only one response.)

1. Thinking about the past 12 hours, please record the severity of itch and the number of hives you may have had associated with your skin condition. Please count each hive separately even if you have more than one hive grouped together with other hives.

Itch (severity)

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

Hives (number)

- 0 = none
- 1 = between 1 and 6 hives
- 2 = between 7 and 12 hives
- 3 = greater than 12 hives

Today's Date

day			month				year		

Please complete this section every evening throughout the duration of the study.
(Please circle only one response.)

2. Thinking about the past 12 hours, please record the severity of itch and the number of hives you may have had associated with your skin condition. Please count each hive separately even if you have more than one hive grouped together with other hives.

Itch (severity)

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

Hives (number)

- 0 = none
- 1 = between 1 and 6 hives
- 2 = between 7 and 12 hives
- 3 = greater than 12 hives

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Today's Date

day	month	year

Please complete this section once each day throughout the duration of the study (preferably at the same time each day).

(Please circle only one response.)

3. Please rate how much your hives or itch interfered with your sleep during the past 24 hours.

- 0 = No interference
- 1 = Mild, little interference with sleep
- 2 = Moderate, awoke occasionally, some interference with sleep
- 3 = Substantial, woke up often, severe interference with sleep

4. Please rate how much your hives or itch interfered with your daily activities during the past 24 hours. This could include work, school, sports, hobbies, and activities with friends and family.

- 0 = No interference
- 1 = Mild, little interference with daily activities
- 2 = Moderate, some interference with daily activities
- 3 = Substantial, severe interference with daily activities

These next questions are about your symptoms and how you managed them during the past 24 hours.

5. During the past 24 hours, how many tablets of rescue medication did you use in order to control symptoms of your skin condition such as itch or hives?

The maximum number of tablets per day should be according to your doctor's recommendation.

6a. During the past 24 hours, did you have any rapid swelling on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called angioedema, is at a deeper level under your skin than hives.

- 0 = No (GO TO Question 7)
- 1 = Yes

6b. If Yes, how did you treat this rapid swelling? (Circle all that apply.)

- 0 = Did nothing (GO TO Question 7)
- 1 = Took some prescription or non-prescription medication
- 2 = Called my doctor, nurse or nurse practitioner
- 3 = Went to see my doctor, nurse or nurse practitioner
- 4 = Went to the emergency room at the hospital
- 5 = Was hospitalized

7. During the past 24 hours, did you or someone else call your doctor, nurse or nurse practitioner because of your skin condition?

- 0 = No
- 1 = Yes

Source: SDN 1, Module 5, Trials A2301 and A2302 CSRs, Appendix16.4 PRO Tools

Figure 66. Angioedema Activity Score

Instructions: Please document your symptoms retrospectively once a day. Refer to the last 24 hours in each case. Please answer all questions as fully as possible

		Day						
		1	2	3	4	5	6	7
Have you had a swelling episode in the last 24 hours?	no							
	yes							
 Please answer the questions below about this swelling episode during the last 24 hours. If you did not have a swelling episode, leave them blank.								
At what time(s) of day was this swelling episode(s) present? (please select all applicable times)	midnight – 8 a.m.							
	8 a.m. – 4 p.m.							
	4 p.m. - midnight							
How severe is / was the physical discomfort caused by this swelling episode(s) (e.g., pain, burning, itching?)	no discomfort							
	slight discomfort							
	moderate discomfort							
	severe discomfort							
Are / were you able to perform your daily activities during this swelling episode(s)?	no restriction							
	slight restriction							
	severe restriction							
	no activities possible							
Do / did you feel your appearance is / was adversely affected by this swelling episode(s)?	no							
	slightly							
	moderately							
	severely							
How would you rate the overall severity of this swelling episode?	negligible							
	mild							
	moderate							
	severe							

Source: SDN 1, Module 5, Trials A2301 and A2302 CSRs, Appendix16.4 PRO Tools

15.1.4. Statistical Analysis Plan, Trials A2301 and A2302

Additional details regarding the statistical analysis plan for the individual trials and prespecified pooling of data from the two trials are provided below.

15.1.4.1. Sample Size Determination, Trials A2301 and A2302

Based on the primary endpoints analysis of phase 2b Study CLOU064A2201, the Applicant assumed a common standard deviation of 6 and treatment difference between remibrutinib and placebo of 4 in the mean change from baseline of ISS7 at Week 12. A t-test with type I error of one-sided 0.025 had more than 99% power to detect a treatment difference of 4 with a sample size of 270 subjects in the remibrutinib arm and 135 subjects in the placebo arm. Assuming approximately 10% dropout by Week 12, a sample size of 300 subjects in the remibrutinib arm and 150 subjects in the placebo arm was targeted.

15.1.4.2. Supplementary Analysis at Week 24, Trials A2301 and A2302

An analysis of the change from baseline in HSS7 and ISS7 at Week 24 was conducted by the Applicant as an exploratory analysis. The analysis used the same methods as the primary analysis at Week 12, with intercurrent events handled similarly. However, the intercurrent event of intake of strongly confounding prohibited medication was defined as biologics treatment at any time before Week 24, cyclosporin after Week 8 to Week 24, or systemic corticosteroids after Week 8 to Week 12. As with the analyses at Week 12, the treatment policy strategy was recommended to the Applicant during the planning and is of primary regulatory interest. The results presented in this review correspond to the Applicant's prespecified intercurrent event handling strategy and comparisons of the analyses of the two estimands are discussed where relevant. Further, oral corticosteroids were allowed as an additional rescue therapy for CSU only after Week 12 on an as-needed basis for unbearable symptoms.

15.1.4.3. Sensitivity and Supplementary Analyses, Trials A2301 and A2302

A prespecified supplementary analysis varied the intercurrent event handling strategies of the primary estimand. The change from baseline in ISS7 and HSS7 score up to Week 12 was replaced with zero (i.e., no clinical improvement from baseline) for the intercurrent event of "Intake of strongly confounding prohibited medication (e.g., biologics treatment at any time before Week 12, cyclosporin after Week 8 to Week 12, systemic corticosteroids after Week 8 to Week 12)" handled with composite strategy.

Subjects who did not meet the inclusion criteria of baseline ISS7 ≥ 6 and HSS7 ≥ 6 were noted by the review team. A sensitivity analysis was performed for the coprimary endpoints which excluded such subjects and methods were the same as for the primary analysis.

At the IND stage, the Agency recommended that the Applicant conduct sensitivity analyses to investigate the robustness of the assumption in the primary analysis that data were MAR. Although no such analysis was prespecified by the Applicant prior to submission, the Agency requested a tipping-point analysis be performed in line with the prespecified Agency recommendation. Assumptions were varied on the missing outcomes handled through treatment policy strategy for discontinuations of study treatment prior to Week 12 due to any reasons and

the missing outcomes handled under jump-to-reference or MAR assumption. The steps were as follows.

- Step 1: As per the primary analysis, all missing ISS7/HSS7 scores at Week 12 were imputed following the same imputation method specified for primary estimand.
- Step 2: In each imputed dataset i ($i = 1, \dots, 100$), in the remibrutinib arm, positive shift δ_j was added to the imputed missing scores and in the placebo arm, negative shift δ_k was added to the imputed missing scores. This imputed a worse outcome in the remibrutinib arm and a better outcome in the placebo arm. This was done so that the resulting values cannot exceed possible range of variables (minimum 0 and maximum 21). Observed data and the worst scores used under the composite strategy remained. Then the same MMRM as for primary analysis was fitted.
- Step 3: The shift values δ_j and δ_k were varied over a plausible range for both arms. For ISS7 and HSS7, δ_j varied between 0 to 21 (0, 5, 10, 15, 21) for the remibrutinib arm and δ_k varied between 0 to -21 (0, -5, -10, -15, -21) for the placebo arm.

15.1.4.4. Subgroup Analyses, Trials A2301 and A2302

Subgroup analyses performed within study using an MMRM with the same covariates as the primary analysis, as well the subgroup and interaction of subgroup with treatment.

15.1.4.5. Secondary Analyses, Trials A2301 and A2302

For the secondary endpoints of proportion of subjects with UAS7 ≤ 6 at Week 2, proportion of subjects with UAS7 ≤ 6 at Week 12, and proportion of subjects with UAS7 =0 at Week 12, the prescribing information presents the risk difference and its 95% confidence interval, rather than the conditional odds ratio as specified in the primary analyses of these endpoints. The Applicant specified the methodology for calculating the risk difference and its confidence interval as follows.

1. A logistic model was fit with maximum likelihood that regresses the outcome on treatment assignments and prespecified baseline covariates, including an intercept term.
2. For each subject, the model-based prediction of the probability of response under treatment was computed in both the treatment group and placebo group using each subject's specific baseline covariates.
3. The average response under treatment was estimated by averaging (across all subjects in the trial) the probabilities estimated in Step 2.
4. For each subject, the model-based prediction of the probability of response under placebo was computed in both the treatment group and placebo group using each subject's specific baseline covariates.
5. The average response under placebo was estimated by averaging (across all subjects in the trial) the probabilities estimated in Step 4.
6. The estimates of average responses rates in the two treatment groups from Steps 3 and 5 were used to estimate the risk difference.

The delta method was applied to calculate the standard error of the risk difference. The steps above were done for each imputed data set separately and the results were combined using Rubin's rules, leading to a pooled estimate of the marginal difference and of the standard error. Based on these estimates, a 95% confidence interval for the marginal difference was calculated.

15.1.4.6. Pooled Subgroup Analyses, Trials A2301 and A2302

Pooled analyses were prespecified by combining data from Trials A2301 and A2302. For the coprimary endpoints, LS means for within-treatment and treatment-comparison (within subgroups) were evaluated using an MMRM including treatment group, baseline score (respectively HSS7/ISS7) score, study, geographical region, previous exposure to anti-IgE biologics for CSU, week, the interaction of treatment by week, and the interaction of baseline score (respectively HSS7/ISS7) by week as fixed effects, in addition to the respective subgroup variable and interaction between the respective subgroup, treatment and week, with estimand related multiple imputation data.

For the cases where the computation of the MMRM took extreme amount of time, the `ddfm = bw` option was considered in the corresponding SAS procedure. When the MMRM with an unstructured covariance matrix did not converge, the compound-symmetry structure was used. When this also failed, the analysis of covariance model was used including treatment group, baseline score (respectively HSS7/ISS7) score, study, geographical region, previous exposure to anti-IgE biologics for CSU, the respective subgroup variable, and interaction of treatment with the respective subgroup variable.

Rubin's rule was applied to combine the multiple imputed datasets of estimates to produce the overall estimates, standard errors, and confidence intervals. If no data were missing, there was no imputation; the imputed datasets were all identical, and calculations were based on the first imputed dataset only.

The following subgroups were prespecified:

- Randomization strata:
  - Previous exposure to anti-IgE biologics (yes/no)
  - Geographic region (Latin America, The Caribbean, and Canada; Region Europe; Japan; United States; Asia, Middle East and Africa)
- Age (18-<65, 65-<85, 85+)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Other)
- Ethnicity (Hispanic or Latino, Non-Hispanic or Latino)
- Baseline UAS7 score (16-<28 moderate, 28+ severe)
- Previous experience of angioedema (defined based on prior urticaria history with angioedema occurrence; yes/no)
- Baseline chronic urticaria index status (10+ positive, <10 negative)

- Duration of CSU defined as time since diagnosis of urticaria (defined as informed consent date—diagnosis date +1; ≤ 1 year, $1 < \leq 3$ years, $3 < \leq 5$ years, > 5 years)
- Baseline total IgE level (≤ 43 IU/mL low, > 43 IU/mL normal/high)
- Prior use of second-generation antihistamines
- Diagnosis of concomitant chronic inducible urticaria (yes/no)

As a post hoc exploratory analysis, the review team investigated a subgroup of subjects with previous exposure to omalizumab with a treatment duration of at least 3 months and discontinued for reasons documented as lack of efficacy, adverse event, or physician decision. Results were generated for the coprimary endpoints following the same methods as the Applicant's prespecified subgroup analyses.

15.2. Study A2201

15.2.1. Study Design, Study A2201

The primary objective was to characterize the remibrutinib dose-response on the presence of hives and itch. Study A2201 was a phase 2 multicenter, randomized, double-blind, placebo-controlled, dose-finding study in adults with CSU inadequately controlled by H1-antihistamines (see Sections [6.2](#) and [14.2.7](#) for additional details on design and conduct). The study employed a 1:1:1:1:1:1 randomization scheme across seven treatment arms, including six different remibrutinib dosing regimens and placebo. Conducted across 82 centers in 17 countries from June 2019 to April 2021, the study enrolled 311 subjects who underwent a 12-week treatment period followed by a 4-week treatment-free follow-up period.

15.2.2. Eligibility Criteria, Study A2201

The study population consisted of male and female adults aged ≥ 18 years with a confirmed CSU diagnosis for ≥ 6 months prior to screening and disease inadequately controlled by second-generation H1-antihistamines, as evidenced by the presence of itch and hives for ≥ 6 consecutive weeks despite appropriate antihistamine treatment according to local guidelines. Key inclusion criteria required subjects to have a UAS7 score ≥ 16 and HSS7 score ≥ 8 during the 7 days prior to randomization, with documented presence of hives within 3 months before randomization. The study excluded subjects with chronic inducible urticaria (having clearly defined triggers), other diseases with urticaria or angioedema symptoms (such as urticaria vasculitis or mastocytosis), other chronic itching skin diseases that could confound study evaluations, significant ECG abnormalities, bleeding disorders, or ongoing chronic/recurrent infectious diseases.

15.2.3. Study Treatment and Concomitant Medications, Study A2201

The investigational medical product was formulated as hard gelatin capsules for oral administration in three dosage strengths: 10 mg, 25 mg, and 50 mg. Placebo was provided as matching hard gelatin capsules. Subjects were randomized equally to one of the following treatment groups:

- Remibrutinib 10 mg once daily
- Remibrutinib 35 mg once daily
- Remibrutinib 100 mg once daily
- Remibrutinib 10 mg twice daily
- Remibrutinib 25 mg twice daily
- Remibrutinib 100 mg twice daily
- Placebo

Permitted Therapies

Second-generation H1-antihistamines with renal elimination pathways were permitted for subjects experiencing flare-ups of unbearable disease symptoms.

Prohibited Therapies

- CSU-specific biologics
- Systemic corticosteroids
- Leukotriene antagonists
- Antihistamines (except defined background and rescue medications)

15.2.4. Study Endpoints, Study A2201

All subjects were provided with an eDiary that contained the UPDD, AAS, and DLQI. The UAS7 was recorded twice daily, while the AAS was recorded once daily. All PRO instruments were the same as those used in the phase 3 trials (Section [15.1.3](#)).

Safety Assessments

The primary safety variables were AE, SAEs, study discontinuations, laboratory test results, vital signs, EKG, and physical exams.

Primary Efficacy Endpoint

- Change from baseline in UAS7 at Week 4

Secondary Efficacy Endpoints

- Change from baseline in UAS7 at Week 12
- Change from baseline in UAS7 throughout the study period
- Complete clinical response (UAS7 =0) throughout the study period
- Disease control (UAS7 $\leq$ 6)
- Cumulative number of weeks with an AAS7 =0 response (absence of angioedema) from baseline through Week 12
- Achievement of DLQI score of 0 or 1 at Week 4 and Week 12, and change from baseline in DLQI scores at these time points
- Concentrations of remibrutinib in blood and calculation of respective PK parameters at Week 4 and Week 12

15.3. Study A2201E1

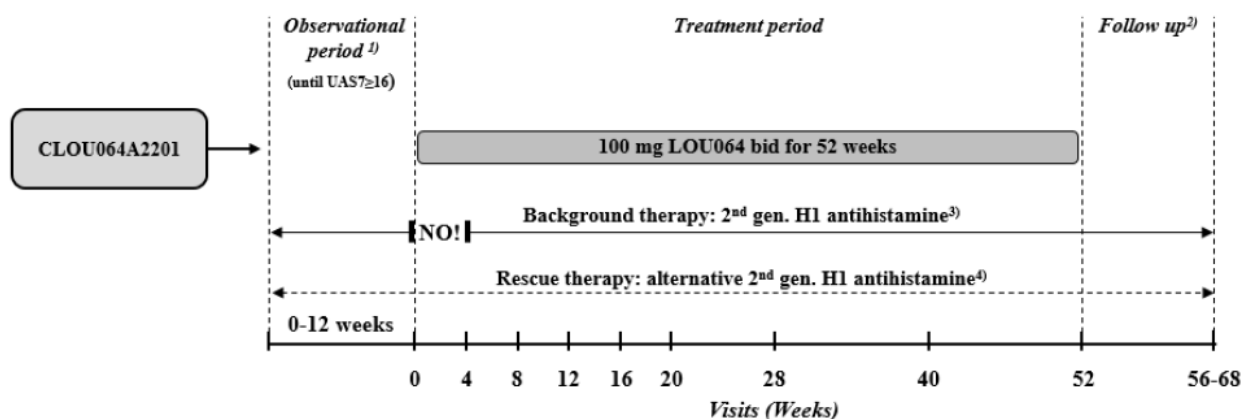
15.3.1. Study Design, Study A2201E1

The primary objective of Study A2201E1 was to assess the long-term safety and tolerability of remibrutinib in subjects with CSU who had participated in Study A2201. Study A2201E1 was an open-label, single-arm, multicenter, long-term safety, and tolerability extension study designed to evaluate the extended use of remibrutinib in subjects with CSU who had previously participated in the core Study A2201. The study was conducted across 72 sites in 15 countries and enrolled 230 subjects between October 2019 and September 2022.

The study consisted of three distinct periods. First, an observational period where subjects rolling over from the core study with controlled disease (defined as UAS7 <16) were monitored without receiving remibrutinib for up to 12 weeks to assess disease stability. If subjects experienced a relapse (defined as UAS7 $\geq$ 16), they would transition to the treatment period. Second, a treatment period where subjects with UAS7 $\geq$ 16 either from the core study rollover or from relapse during the observational period received open-label remibrutinib 100 mg twice daily for 52 weeks. Notably, background H1-antihistamine therapy was prohibited for the first 4 weeks of treatment to assess the drug's efficacy as monotherapy. Finally, a treatment-free follow-up period provided post-treatment monitoring for a minimum of 4 weeks, with extended follow-up up to 16 weeks for subjects who achieved disease control (defined as UAS7 $\leq$ 6) at the end of treatment to monitor for relapse.

The study allocation was based on disease activity scores at specific timepoints from the preceding core study, with subjects having UAS7 $\geq$ 16 at Week 12 or 16 entering the treatment period directly, while those with UAS7 <16 at Week 16 entering the observational period first. This design allowed for evaluation of both the long-term safety profile and the durability of treatment response in subjects with CSU as depicted in [Figure 67](#).

Figure 67. Study Design Schema, Study A2201E1



Source: Applicant provided CSR for CLOU0642201A1, p. 25
Abbreviation: bid, twice daily; LOU064, remibrutinib; UAS7, weekly urticaria activity score

15.3.2. Eligibility Criteria, Study A2201E1

Key inclusion criteria consisted of male and female adult subjects with CSU who had received various doses of remibrutinib or placebo in the core study (Study A2201) and who had completed either the Week 12 visit (end of treatment period) OR the Week 16 visit (end of follow-up period) of Study A2201.

15.3.3. Study Treatment and Concomitant Medications, Study A2201E1

IMP consisted of open-label 100 mg remibrutinib twice daily. Permitted and prohibited concomitant medications were the same as in Study A2201 (see Section [15.3.3](#)).

15.3.4. Study Variables and Assessments, Study A2201E1

The primary study variables focused on safety parameters, specifically the occurrence of TEAEs during the extension study period. Although efficacy assessments included various outcomes based on UAS7 (e.g., change from baseline, proportion achieving $UAS7 \leq 6$ and $UAS7 = 0$), these results are not presented or discussed in this review because the interpretability of uncontrolled, unblinded efficacy results for a PRO in a condition with relatively high spontaneous remission rate is extremely limited.

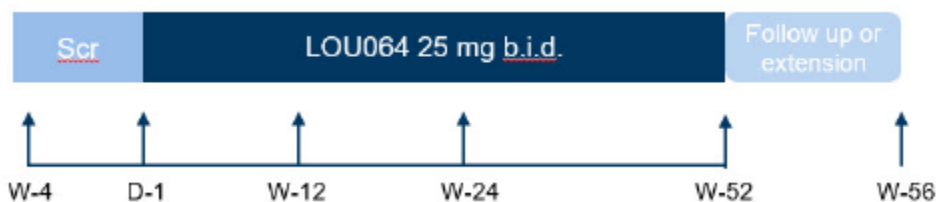
15.4. Study A1301

15.4.1. Study Design, Study A1301

The primary objective was to evaluate safety through assessment of TEAEs during the 52-week treatment period. Study A1301 was a multicenter, open-label phase 3 clinical study conducted across 13 centers in Japan from January 2022 to December 2023. The study investigated the safety, tolerability, and efficacy of remibrutinib at a dose of 25 mg twice daily in 71 adult Japanese subjects with CSU who remained inadequately controlled despite treatment with H1-antihistamines at locally approved doses.

The study design consisted of three periods totaling up to 60 weeks: a screening period of up to 4 weeks, an open-label treatment period of 52 weeks with remibrutinib, and a treatment-free follow-up period of 4 weeks.

Figure 68. Study Design Schema, Study A1301



Source: Applicant provided CSR for Study A1301, p. 28
Abbreviations: b.i.d., twice daily; Scr, Screening; W, Week

15.4.2. Eligibility Criteria, Study A1301

Eligible subjects were adults aged 18 years or older with CSU for at least 6 months prior to screening. Key eligibility criteria included inadequately controlled disease despite treatment with second-generation H1-antihistamines at locally approved doses defined as having persistent itch and hives for at least 6 consecutive weeks prior to screening despite ongoing antihistamine therapy, a UAS7 score of at least 16, an ISS7 score of at least 6, and an HSS7 score of at least 6. Additionally, subjects were required to have documented evidence of hives within 3 months before baseline and be on a stable, locally approved dose of second-generation H1-antihistamines at the time of study entry.

15.4.3. Study Treatment and Concomitant Medications, Study A1301

The IMP consisted of remibrutinib 25-mg film-coated tablets. Subjects were instructed to administer one tablet in the morning and one tablet in the evening.

Permitted Medications

- All subjects were required to remain on a stable, locally approved dose of a second-generation H1-antihistamine throughout the entire study duration.
- Oral corticosteroids were allowed as rescue therapy after Week 12.

Prohibited Medications

- Biologics for CSU treatment, including omalizumab and ligelizumab.
- Routine oral corticosteroids (defined as more than three doses over 5 days).
- Injectable corticosteroids.
- Leukotriene antagonists.
- H2-antihistamines, first-generation antihistamines, alternative second-generation antihistamines beyond the designated background medication.
- Immunosuppressive or immunomodulating agents.
- Intravenous immunoglobulins or plasmapheresis.
- Ultraviolet therapy, and any other urticaria-specific treatments including herbal therapies.
- Live attenuated vaccines.
- Strong inhibitors of CYP3A4, moderate and strong inducers of CYP3A4.
- Anticoagulant medications, and antiplatelet medications with the exception of low-dose acetylsalicylic acid (up to 100 mg daily) or clopidogrel (up to 75 mg daily) as monotherapy; dual antiplatelet therapy combinations were not allowed.

15.4.4. Study Variables and Assessments, Study A1301

Safety Assessments

The primary safety variables were TEAEs during the 52-week treatment period including number and proportion of subjects with at least one TEAE. Although efficacy assessments included various outcomes based on UAS7 (e.g., change from baseline, proportion achieving UAS7 ≤ 6 and UAS7 =0), AAS7 (cumulative weeks with AAS7 =0), and DLQI (proportion with DLQI =0 to 1), these results are not presented or discussed in this review because the interpretability of uncontrolled, unblinded efficacy results for a PRO in a condition with relatively high spontaneous remission rate is extremely limited.

15.5. Study A2305

15.5.1. Study Design, Study A2305

The primary objective focused on cardiovascular safety assessed by ABPM. Study A2305 was a global, multicenter, open-label phase 3 study evaluating remibrutinib 25 mg twice daily in adult subjects with CSU inadequately controlled by second-generation H1-antihistamines. The study was conducted across 45 centers in 10 countries including Argentina, Canada, France, Germany, South Korea, Singapore, Slovakia, Spain, Turkey, and the United States.

The study design consisted of three distinct periods: a screening period of up to 4 weeks, a 12-week open-label treatment period where all subjects received remibrutinib 25-mg film-coated tablets administered orally twice daily, and a treatment-free follow-up period of 4 weeks, resulting in a total study duration of up to 20 weeks. The planned sample size was approximately 136 subjects, with 144 subjects ultimately completing the screening and enrollment process.

The primary outcome evaluated whether the 24-hour weighted average systolic blood pressure as measured by ABPM increased by more than 3 mm Hg at steady state (Week 4) compared to baseline. Secondary outcomes included change in both systolic and diastolic blood pressure during daytime and nighttime periods, as well as overall safety and tolerability. Exploratory outcomes encompassed various efficacy measures related to urticaria disease activity, including changes in urticaria activity scores, quality of life assessments, and pharmacokinetic parameters. Refer to the cardiac safety integrated review team consult memo dated June 13, 2025 (DARRTS Reference ID 5608166) for additional details on the design and results.

15.6. Study F12101

15.6.1. Study Design, Study F12101

The primary objective was to evaluate if immune responses following influenza and PPV-23 vaccinations in healthy subjects with interrupted remibrutinib treatment are noninferior to placebo. Study F12101 was a phase 1, randomized, double-blind, placebo-controlled, parallel-group study that evaluated the effect of remibrutinib 100 mg twice daily on immune responses to three different types of vaccines in healthy subjects aged 18 to 55 years. Approximately 90 subjects were randomized 1:1:1 into three treatment arms over a 43-day treatment period: Arm A received concomitant remibrutinib treatment (placebo for Days 1 to 7, then remibrutinib Days 8 to 42), Arm B received interrupted remibrutinib treatment (remibrutinib Days 1 to 7, placebo Days 8 to 28, then remibrutinib Days 29 to 42), and Arm C received placebo throughout Days 1 to 42. All subjects received three vaccines simultaneously on Day 15: quadrivalent seasonal influenza vaccine (intramuscular, dominant arm), PPV-23 pneumococcal vaccine (intramuscular, nondominant arm), and KLH neoantigen vaccine (subcutaneous, nondominant lower arm). The vaccines were administered 3 hours after study drug dosing, with subjects domiciled at the clinical site from Days -1 to 1 and Days 14 to 17. The study included a 28-day screening period, followed by the 43-day treatment period, an end-of-study visit on Day 57, and a safety follow-up call on Day 72, for a total study duration of approximately 85 days per subject. The intent of this design was to determine whether temporarily interrupting remibrutinib treatment around

vaccination could preserve immune responses compared to continuous treatment or placebo control. The primary endpoints were the proportion of ‘responders’ to T-cell-dependent influenza quadrivalent vaccine and T-cell-independent PPV-23 vaccine in the interrupted remibrutinib group compared to placebo. Response was defined as ≥ 4 -fold increase in hemagglutinin antibody titers (or $\geq 1:40$ if baseline $< 1:10$) for influenza, and ≥ 2 -fold increase in IgG titers for at least 50% of PPV-23 serotypes (≥ 12 out of 23) at 28 days postvaccination. Noninferiority to placebo was tested applying a noninferiority margin of 0.30. The primary analysis was performed on the PD analysis set, which included all randomized subjects who had no relevant protocol deviations and had completed the planned study treatment. Secondary endpoints assessed immune responses with concomitant remibrutinib treatment, KLH vaccine responses with interrupted treatment, and antibody titers/concentrations in the concomitant and interrupted remibrutinib groups relative to placebo over time. For additional details regarding the design of Study F12101, refer to the CBER consult memo (Inter-Center Consult #: 01066955) dated June 2, 2025, in DARRTS (Reference ID 5601342).

16. Efficacy

Results of supplementary analyses performed on data from the individual pivotal trials as well as pooled data from the pivotal trials are presented in the sections below.

16.1. Trials A2301 and A2302

16.1.1. Results of Analyses at Week 24, Trials A2301 and A2302

[Table 100](#) and [Table 101](#) summarize the results for Trials A2301 and A2302 for efficacy endpoints of change from baseline to Week 24 in HSS7 and ISS7, respectively. After adjusting for baseline HSS7 score, geographical region, prior exposure to anti-IgE biologics, visit week, treatment by visit interaction, and baseline HSS7 score by visit interaction, the estimated least-squares mean change from baseline in HSS7 score at Week 24 was greater in magnitude in the remibrutinib group (LS means = -10.88 [SE 0.40] and -10.92 [SE 0.41]) compared to placebo (LS means = -7.97 [SE 0.55] and -7.31 [SE 0.56]) in Trials A2301 and A2302, respectively. For HSS7, the estimated difference in LS means relative to placebo was -2.91 (95% CI: -4.16, -1.66) and -3.61 (95% CI: -4.92, -2.29) in Trials A2301 and A2302, respectively. Similarly, after adjusting for similar covariates, the estimated least-squares mean change from baseline in ISS7 score at Week 24 was greater in magnitude in the remibrutinib group (LS means = -9.81 [SE 0.34] and -9.49 [SE 0.35]) compared to placebo (LS means = -8.00 [SE 0.47] and -6.46 [SE 0.48]) in Trials A2301 and A2302, respectively. For ISS7, the estimated difference in LS means relative to placebo was -1.81 (95% CI: -2.88, -0.73) and -3.03 (95% CI: -4.16, -1.90) in Trials A2301 and A2302, respectively. Both endpoints were nominally significant in both trials.

Up to Week 24, one subject in the remibrutinib 25-mg group experienced the intercurrent event of intake of strongly confounding medication in Trial A2301. In Trial A2302, one subject in the remibrutinib 25-mg group and two subjects in the placebo group experienced the intercurrent event of intake of strongly confounding medication. Results of analyses which correspond to the

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estimand with treatment policy strategy for all intercurrent events were substantially similar, with $p\text{-value} < 0.001$ and small differences in point estimates and confidence intervals which do not impact the interpretation of the results.

Table 100. Efficacy Analysis: Change From Baseline in HSS7 at Week 24 in FAS, Trials A2301 and A2302

Parameter	Trial A2301		Trial A2302	
	Remibrutinib 25 mg N=309	Placebo N=153	Remibrutinib 25 mg N=297	Placebo N=153
LS mean (SE)	-10.88 (0.40)	-7.97 (0.55)	- 10.92 (0.41)	- 7.31 (0.56)
Treatment difference LS mean (95% CI)	-2.91 (-4.16, -1.66)	-	- 3.61 (- 4.92, - 2.29)	-
Nominal p-value	<0.001	-	<.0001	-

Source: Statistical Analyst-reproduced results using Applicant-submitted datasets adsl and admiup24

MMRM adjusted for treatment arm, geographical region, baseline HSS7 score, prior exposure to anti-IgE biologics, visit week, treatment by visit, and baseline score by visit with ddfm = bw option.

Abbreviations: CI, confidence interval; ddfm = bw, denominator degrees of freedom = betweenwithin; FAS, full analysis set; HSS7, weekly hives severity score; IgE, immunoglobulin E; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; SE, standard error

Table 101. Efficacy Analysis: Change From Baseline in ISS7 at Week 24 in FAS, Trials A2301 and A2302

Parameter	Trial A2301		Trial A2302	
	Remibrutinib 25 mg N=309	Placebo N=153	Remibrutinib 25 mg N=297	Placebo N=153
LS mean (SE)	- 9.81 (0.34)	- 8.00 (0.47)	- 9.49 (0.35)	- 6.46 (0.48)
Treatment difference LS mean (95% CI)	- 1.81 (- 2.88, - 0.73)	-	- 3.03 (- 4.16, - 1.90)	-
Nominal p-value	0.001	-	<.0001	-

Source: Statistical Analyst reproduced results using Applicant-submitted datasets adsl and admiup24

MMRM adjusted for treatment arm, geographical region, baseline ISS7 score, prior exposure to anti-IgE biologics, visit week, treatment by visit, and baseline score by visit with ddfm = bw option.

Abbreviations: CI, confidence interval; ddfm = bw, denominator degrees of freedom = betweenwithin; FAS, full analysis set; ISS7, weekly itch severity score; IgE, immunoglobulin E; LS, least squares; MMRM, mixed model for repeated measures; N, number of subjects; SE, standard error

16.1.2. Change From Baseline in HSS7 and ISS7 Over Time, Trials A2301 and A2302

To supplement [Figure 4](#) and [Figure 6](#) in Section 6.2.2.8.3, [Table 102](#) summarizes the observed change from baseline in HSS7 and ISS7 at 4-week increments through Week 52 in Trial A2301. Similarly, [Table 103](#) supplements [Figure 5](#) and [Figure 7](#) in Section 6.2.2.8.3 for Trial A2302.

Table 102. Change From Baseline in HSS7 and ISS7 at 4-Week Increments Through Week 52, Observed Data in FAS Population, Trial A2301

Week	Remibrutinib 25 mg			Placebo		
	n	HSS7 Mean (SE)	ISS7 Mean (SE)	n	HSS7 Mean (SE)	ISS7 Mean (SE)
4	295	- 10.58 (0.39)	- 9.17 (0.35)	144	- 5.17 (0.51)	- 5.42 (0.42)
8	285	- 11.21 (0.41)	- 10.16 (0.35)	138	- 6.55 (0.60)	- 6.50 (0.52)
12	284	- 11.26 (0.42)	- 10.16 (0.35)	139	- 7.04 (0.60)	- 7.04 (0.50)
16	279	- 11.50 (0.43)	- 10.39 (0.36)	134	- 7.75 (0.62)	- 7.46 (0.53)
20	269	- 11.47 (0.45)	- 10.54 (0.37)	126	- 8.17 (0.65)	- 8.03 (0.57)
24	262	- 11.88 (0.43)	- 10.74 (0.36)	131	- 8.26 (0.65)	- 8.26 (0.57)
28	256	- 12.41 (0.41)	- 11.17 (0.34)	125	- 11.78 (0.58)	- 10.66 (0.55)
32	253	- 12.67 (0.42)	- 11.44 (0.35)	120	- 11.66 (0.62)	- 10.46 (0.58)
36	242	- 12.67 (0.42)	- 11.52 (0.35)	119	- 11.28 (0.66)	- 10.32 (0.62)
40	245	- 12.64 (0.43)	- 11.54 (0.35)	119	- 11.81 (0.63)	- 10.87 (0.60)
44	246	- 12.74 (0.43)	- 11.64 (0.36)	118	- 11.68 (0.62)	- 10.83 (0.60)
48	242	- 12.61 (0.44)	- 11.52 (0.36)	119	- 11.67 (0.62)	- 10.99 (0.57)
52	248	- 12.16 (0.46)	- 11.06 (0.38)	117	- 11.81 (0.64)	- 11.20 (0.56)

Source: Statistical Reviewer-produced results using Applicant-submitted dataset adqsupd
Abbreviations: FAS, full analysis set; HSS7, weekly hives severity score; ISS7, weekly itch severity score; n, number of subjects; SE, standard error

Table 103. Change From Baseline in HSS7 and ISS7 at 4-Week Increments Through Week 52, Observed Data in FAS Population, Trial A2302

Week	Remibrutinib 25 mg			Placebo		
	n	HSS7 Mean (SE)	ISS7 Mean (SE)	n	HSS7 Mean (SE)	ISS7 Mean (SE)
4	287	- 9.95 (0.40)	- 8.12 (0.34)	147	- 3.37 (0.44)	- 3.50 (0.40)
8	274	- 10.94 (0.41)	- 9.12 (0.35)	136	- 5.29 (0.56)	- 4.98 (0.48)
12	264	- 11.41 (0.41)	- 9.67 (0.35)	134	- 6.28 (0.59)	- 5.82 (0.50)
16	257	- 11.79 (0.42)	- 9.91 (0.36)	131	- 6.90 (0.60)	- 6.20 (0.51)
20	255	- 11.77 (0.41)	- 9.93 (0.36)	130	- 7.37 (0.62)	- 6.62 (0.56)
24	246	- 11.92 (0.43)	- 10.22 (0.38)	125	- 7.72 (0.67)	- 6.59 (0.57)
28	245	- 12.52 (0.42)	- 10.84 (0.37)	122	- 11.96 (0.61)	- 9.72 (0.53)
32	243	- 12.77 (0.40)	- 11.11 (0.36)	119	- 11.62 (0.62)	- 9.49 (0.54)
36	241	- 12.87 (0.40)	- 11.20 (0.35)	118	- 12.03 (0.63)	- 9.78 (0.55)

Week	Remibrutinib 25 mg			Placebo		
	n	HSS7 Mean (SE)	ISS7 Mean (SE)	n	HSS7 Mean (SE)	ISS7 Mean (SE)
40	238	- 12.80 (0.41)	- 11.17 (0.36)	114	- 11.92 (0.65)	- 9.87 (0.57)
44	223	- 12.92 (0.42)	- 11.23 (0.37)	110	- 12.12 (0.63)	- 10.04 (0.57)
48	224	- 12.79 (0.41)	- 11.21 (0.37)	109	- 12.14 (0.62)	- 9.82 (0.56)
52	222	- 12.33 (0.44)	- 10.65 (0.40)	109	- 12.26 (0.62)	- 10.09 (0.56)

Source: Statistical Reviewer-produced results using Applicant-submitted dataset adqsupd
Abbreviations: FAS, full analysis set; HSS7, weekly hives severity score; ISS7, weekly itch severity score; n, number of subjects; SE, standard error

16.1.3. Results of Sensitivity and Supplementary Analyses, Trials A2301 and A2302

Results for the prespecified supplementary analysis which varied the intercurrent event handling strategies of the primary estimand were similar to and supportive of the primary analysis.

One subject in the placebo group did not meet inclusion criteria of baseline ISS7 ≥ 6 and HSS7 ≥ 6 in Trial A2301. Three subjects in the FAS (two remibrutinib, one placebo) did not meet this inclusion criteria in Trial A2302. Results from the sensitivity analyses which excluded these subjects were consistent with the primary analysis.

In both Trials A2301 and A2302, the tipping-point analysis for HSS7 did not identify a tipping point across the explored plausible delta values, supporting the robustness of the primary analysis to violations of its missing data assumptions. Tipping points were identified for ISS7 for both trials, as shown in [Table 104](#) and [Table 105](#). The assumptions at which one-sided p-value > 0.025 vary from the most extreme assumptions (all subjects with missing data in the placebo group experiencing the best possible score and simultaneously all subjects with missing data in the remibrutinib group experiencing the worst possible score), to somewhat less extreme assumptions. These analyses reasonably support the robustness of the primary analysis with respect to missing data assumptions in both trials.

Table 104. Sensitivity Analysis: Tipping-Point Analysis of Change From Baseline in ISS7 at Week 12 in FAS, One-Sided p-Values, Trial A2301

Drug	Delta	Placebo				
		0	- 5	- 10	- 15	- 21
Remibrutinib 25 mg	0	<0.001	<0.001	<0.001	<0.001	<0.001
	5	<0.001	<0.001	0.002	0.004	0.004
	10	<0.001	0.006	0.017	0.024	0.026*
	15	0.003	0.019	0.047*	0.064*	0.068*
	21	0.008	0.037*	0.080*	0.105*	0.110*

Source: Applicant's results, Table 2-4 (Page 7) of Response to Information Request with stamp date February 24, 2025

Delta is the value added to the predictions of missing scores.

P-value: one-sided p-value of the treatment comparison in LS mean from a mixed effect model with repeated measures adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score, the interaction of treatment by visit week, and the interaction of baseline score by visit week.

* P-value > 0.025

Abbreviations: FAS, full analysis set; IgE, immunoglobulin E; ISS7, weekly itch severity score; LS, least squares

Table 105. Sensitivity Analysis: Tipping-Point Analysis of Change From Baseline in ISS7 at Week 12 in FAS, One-Sided p-Values, Trial A2302

Drug	Delta	Placebo				
		0	- 5	- 10	- 15	- 21
Remibrutinib 25 mg	0	<0.001	<0.001	<0.001	<0.001	<0.001
	5	<0.001	<0.001	0.001	0.005	0.007
	10	<0.001	0.002	0.013	0.036*	0.048*
	15	<0.001	0.008	0.044*	0.095*	0.119*
	21	0.002	0.018	0.079*	0.152*	0.184*

Source: Applicant's results, Table 2-5 (Page 7) of Response to Information Request with stamp date February 24, 2025

Delta is the value added to the predictions of missing scores.

P-value: one-sided p-value of the treatment comparison in LS mean from a mixed effect model with repeated measures adjusting for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, baseline score, the interaction of treatment by visit week, and the interaction of baseline score by visit week.

* p>0.025

Abbreviations: FAS, full analysis set; IgE, immunoglobulin E; ISS7, weekly itch severity score; LS, least squares

16.1.4. Results of Subgroup Analyses, Trials A2301 and A2302

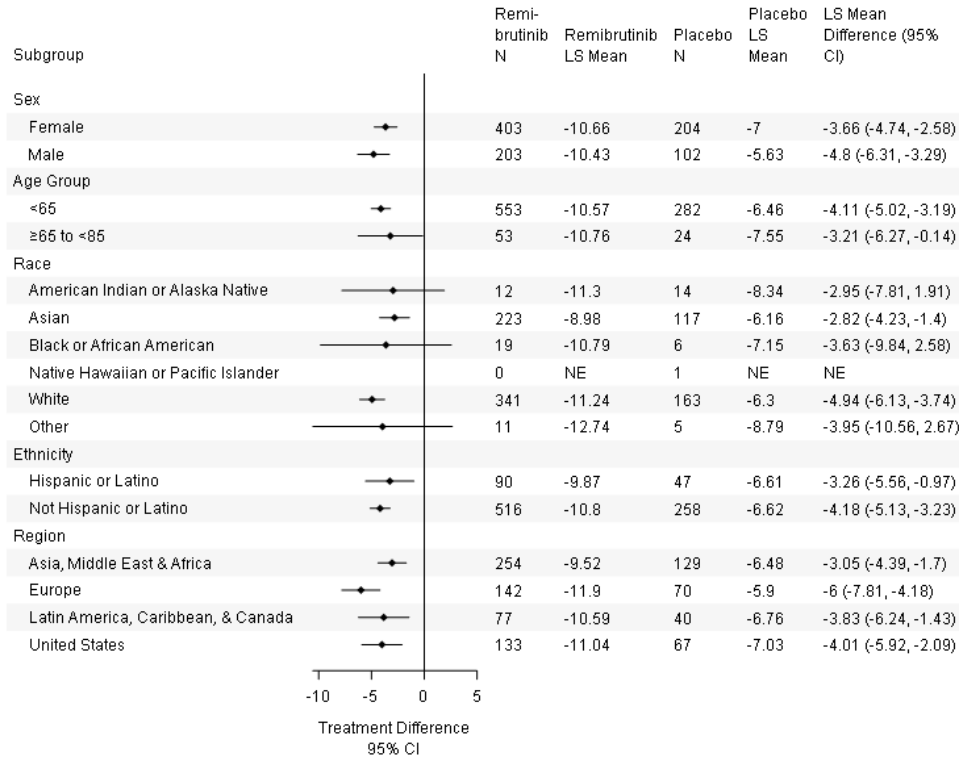
Subgroup analyses within Trial A2301 and A2302 were generally consistent with the primary analyses results, as well as the results of the pooled analyses. The results of the pooled subgroup analyses provide more precise estimates than estimates within each trial, and pooled results are presented in Section [16.2.1](#).

16.2. Pooled Analyses, Trials A2301 and A2302

16.2.1. Results of Subgroup Analyses, Pooled Analyses, Trials A2301 and A2302

Results for subgroups for HSS7 (respectively, ISS7) are summarized in [Figure 69](#) and [Figure 71](#) for demographic characteristics and in [Figure 70](#) and [Figure 72](#) for baseline disease characteristics. Results are consistent with the primary analysis and treatment-effect estimates favor remibrutinib for all prespecified subgroups.

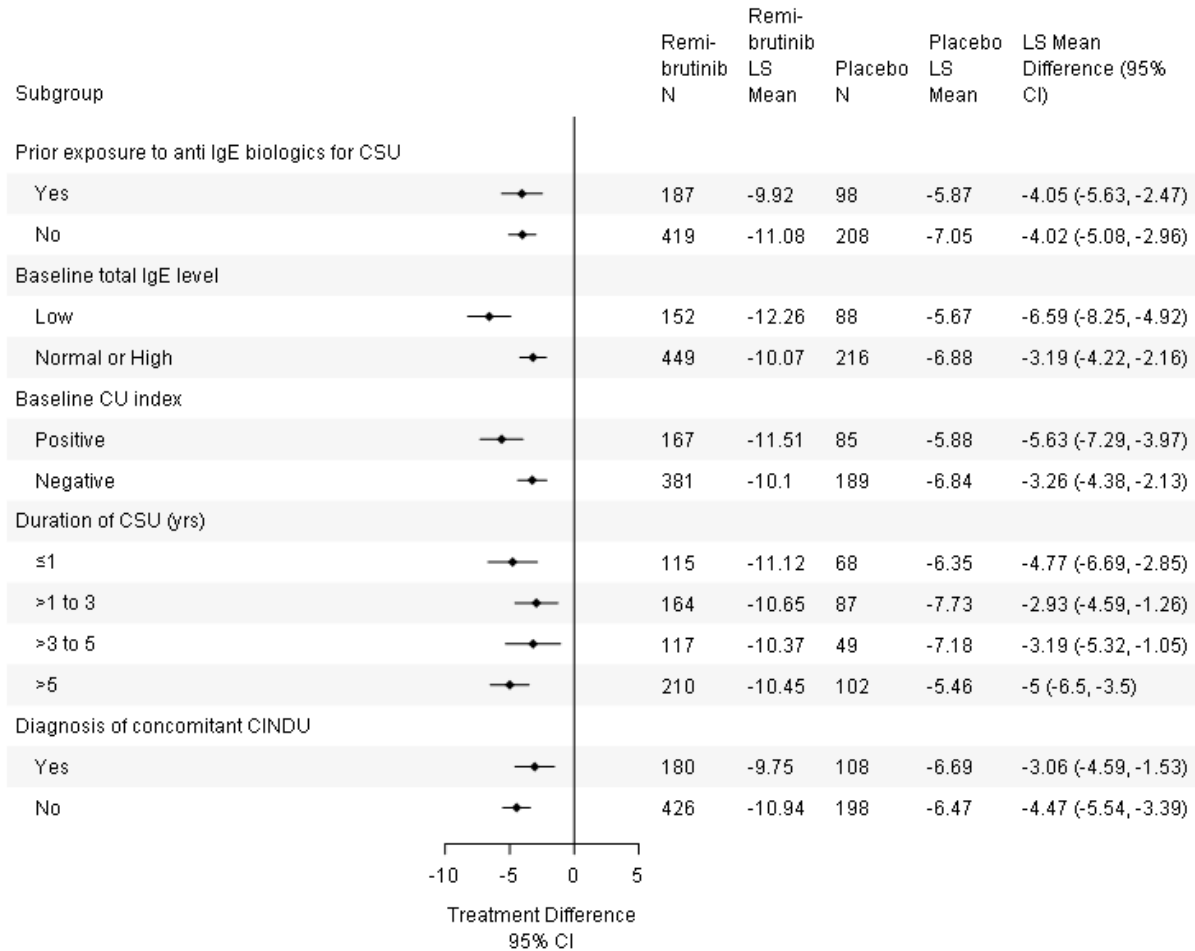
Figure 69. Subgroup Analysis: Forest Plot of Change From Baseline in HSS7 at Week 12 by Demographic Characteristics, FAS, Pooled Analysis, Trials A2301 and A2302



Abbreviations: HSS7=hives severity score, FAS=full analysis set, LS=least squares, CI=confidence interval
MMRM model adjusted for treatment group, geographical region (excluded in corresponding subgroup analysis), prior exposure to anti-IgE biologics(excluded in corresponding subgroup analysis), visit week, study, baseline score, subgroup variable, interaction of treatment by visit week, interaction of baseline score by visit week, interaction of respective subgroup by treatment and interaction of respective subgroup, treatment and visit week as fixed effects.

Source: Statistical Analyst reproduced results using applicant submitted datasets adsl and admiup12

Figure 70. Subgroup Analysis: Forest Plot of Change From Baseline in HSS7 at Week 12 by Baseline Disease Characteristics, FAS, Pooled Analysis, Trials A2301 and A2302

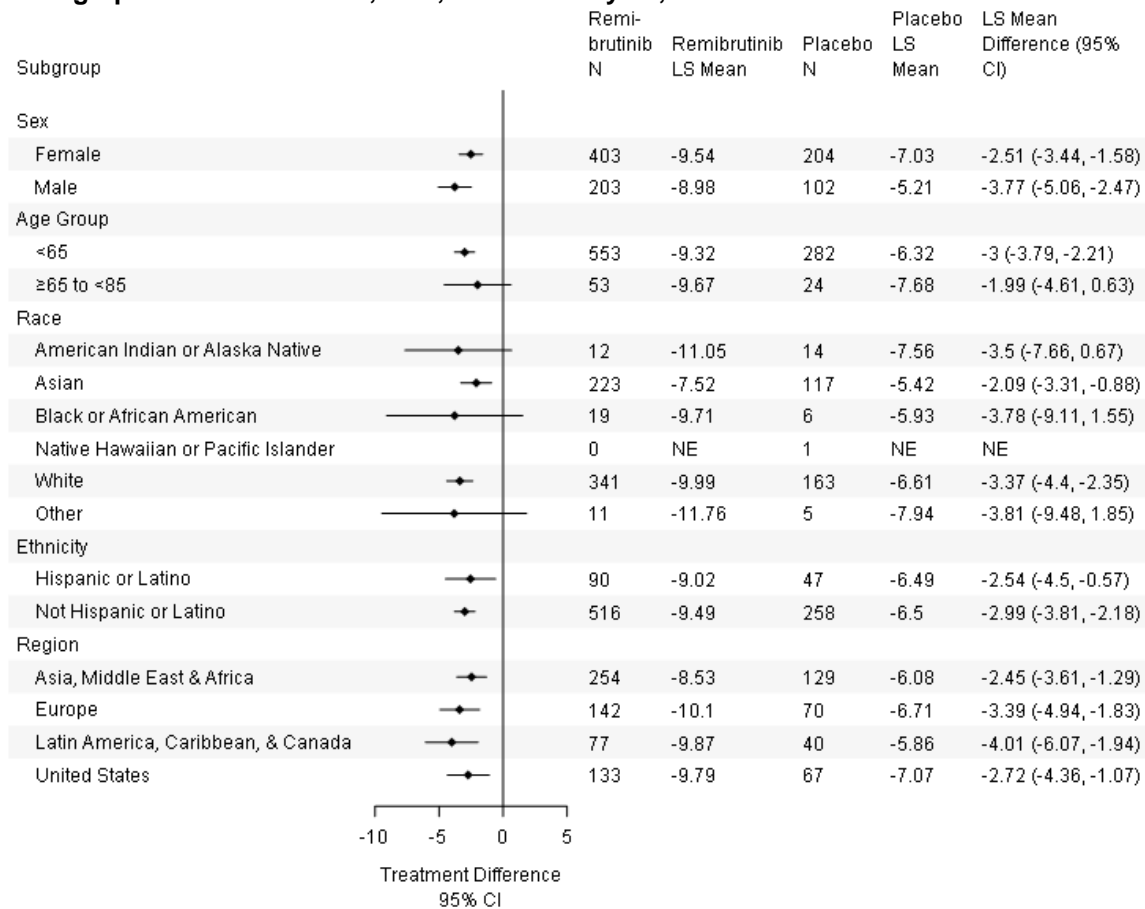


Abbreviations: HSS7=hives severity score, FAS=full analysis set, LS=least squares, CI=confidence interval, IgE=immunoglobulin E, CSU=chronic spontaneous urticaria, CU=chronic urticaria, CINDU=chronic inducible urticaria

MMRM model adjusted for treatment group, geographical region (excluded in corresponding subgroup analysis), prior exposure to anti-IgE biologics(excluded in corresponding subgroup analysis), visit week, study, baseline score, subgroup variable, interaction of treatment by visit week, interaction of baseline score by visit week, interaction of respective subgroup by treatment and interaction of respective subgroup, treatment and visit week as fixed effects.

Source: Statistical Analyst reproduced results using applicant submitted datasets adsl and admiup12

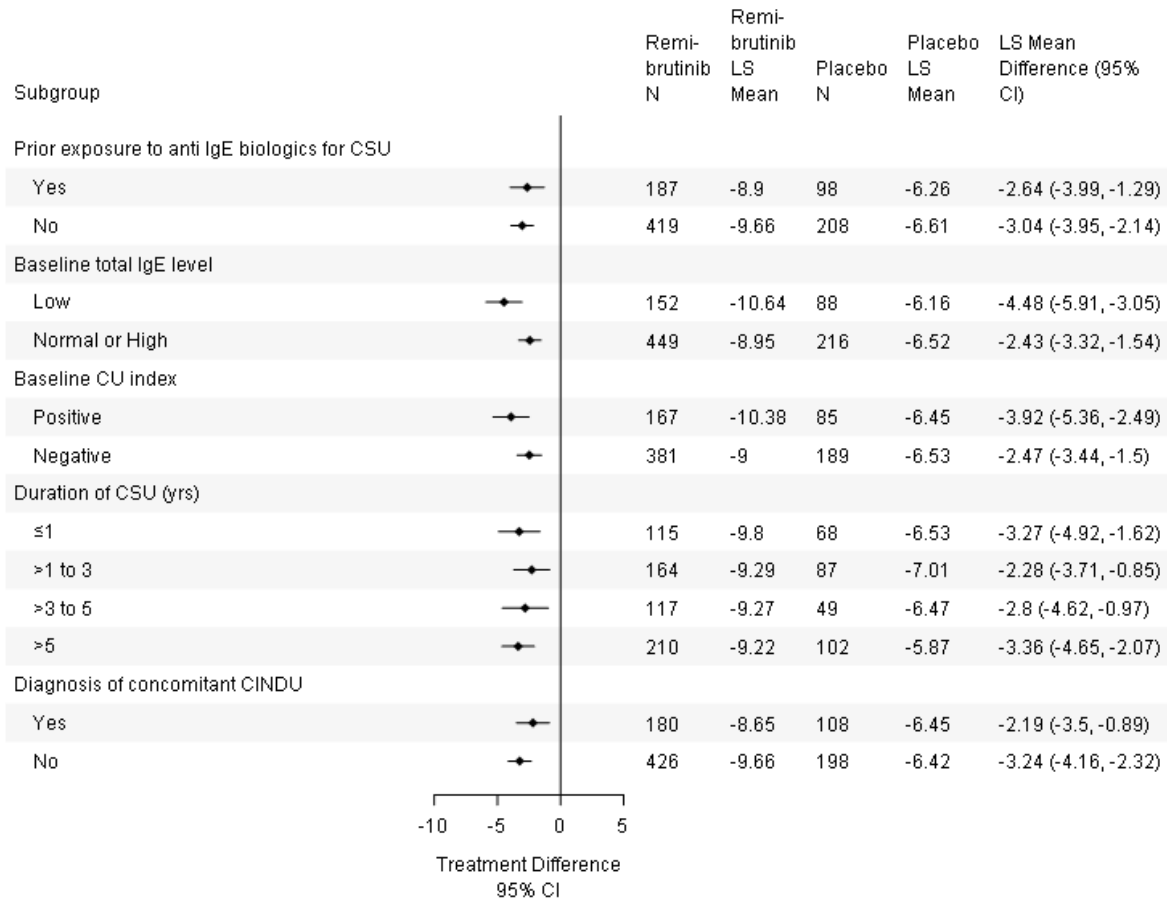
Figure 71. Subgroup Analysis: Forest Plot of Change From Baseline in ISS7 at Week 12 by Demographic Characteristics, FAS, Pooled Analysis, Trials A2301 and A2302



Abbreviations: ISS7=itch severity score, FAS=full analysis set, LS=least squares, CI=confidence interval
MMRM model adjusted for treatment group, geographical region (excluded in corresponding subgroup analysis), prior exposure to anti-IgE biologics(excluded in corresponding subgroup analysis), visit week, study, baseline score, subgroup variable, interaction of treatment by visit week, interaction of baseline score by visit week, interaction of respective subgroup by treatment and interaction of respective subgroup, treatment and visit week as fixed effects.

Source: Statistical Analyst reproduced results using applicant submitted datasets adsl and admiup12

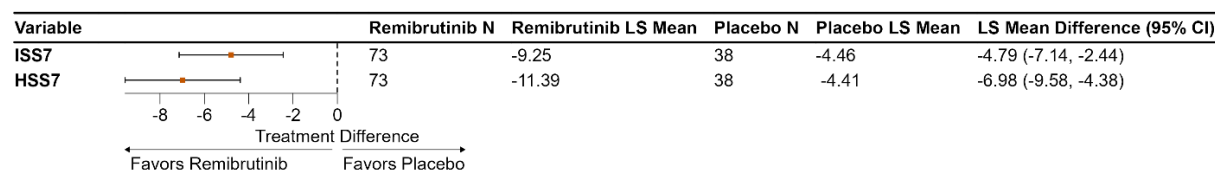
Figure 72. Subgroup Analysis: Forest Plot of Change From Baseline in ISS7 at Week 12 by Baseline Disease Characteristics, FAS, Pooled Analysis, Trials A2301 and A2302



Abbreviations: ISS7=itch severity score, FAS=full analysis set, LS=least squares, CI=confidence interval, IgE=immunoglobulin E, CSU=chronic spontaneous urticaria, CU=chronic urticaria, CINDU=chronic inducible urticaria
MMRM model adjusted for treatment group, geographical region (excluded in corresponding subgroup analysis), prior exposure to anti-IgE biologics(excluded in corresponding subgroup analysis), visit week, study, baseline score, subgroup variable, interaction of treatment by visit week, interaction of baseline score by visit week, interaction of respective subgroup by treatment and interaction of respective subgroup, treatment and visit week as fixed effects.
Source: Statistical Analyst reproduced results using applicant submitted datasets adsl and admiup12

Figure 73 summarizes the results of the post hoc exploratory subgroup analysis of the group of subjects with previous exposure to omalizumab with a treatment duration of at least 3 months and discontinued for reasons documented as lack of efficacy, adverse event, or physician decision. Results are consistent with the primary analysis and the treatment-effect estimates favor remibrutinib.

Figure 73. Exploratory Subgroup Analysis: Forest Plot of Change From Baseline in ISS7 and HSS7 at Week 12 Subjects With Previous Exposure to Omalizumab of at Least 3 Months and Discontinued for Reasons of Lack of Efficacy, Adverse Event, or Physician Decision, FAS, Pooled Analysis, Trials A2301 and A2302



Source: Statistical Review Analysis using Applicant's-submitted datasets adsl and admiup12
MMRM adjusted for treatment group, geographical region, prior exposure to anti-IgE biologics, visit week, study, baseline score, subgroup variable, interaction of treatment by visit week, interaction of baseline score by visit week, interaction of subgroup by treatment, and interaction of respective subgroup, treatment, and visit week as fixed effects
Abbreviations: CI, confidence interval; FAS, full analysis set; HSS7, weekly hives severity score; IgE, immunoglobulin E; ISS7, weekly itch severity score; LS, least squares; MMRM, mixed model for repeated measures; N, sample size

17. Clinical Safety

This section includes additional information and analyses that supported the primary safety assessment of data from the 24-week controlled treatment period of Trials A2301 and A2302.

17.1. Subgroup Analyses, Trials A2301 and A2302

The clinical review team conducted a subgroup analysis of AEs by sex, age, race, ethnicity, and country as shown in [Table 106](#). Refer to Section [7.6.1.6](#) for additional details.

Table 106. Overview of Adverse Events by Demographic Subgroup, SAF, Trials A2301 and A2302 (Pooled)

Characteristic	Remibrutinib N=606 n/N _s (%)	Placebo N=306 n/N _s (%)	Risk Difference % (95% CI)
Sex			
Female	271/403 (67)	136/204 (67)	0.6 (-7.2, 8.6)
Male	122/203 (60)	62/102 (61)	-0.7 (-12.0, 11.1)
Age group, years			
<65	355/553 (64)	182/282 (65)	-0.3 (-7.1, 6.6)
65 to <85	38/53 (72)	16/24 (67)	5.0 (-15.8, 28.1)
Age group ≥65, years			
≥65	38/53 (72)	16/24 (67)	5.0 (-15.8, 28.1)
Age group ≥75, years			
≥75	7/10 (70)	1/2 (50)	20.0 (-36.7, 71.3)

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	7/12 (58)	7/14 (50)	8.3 (– 29.3, 43.5)
Asian	142/223 (64)	71/117 (61)	3.0 (– 7.7, 14.0)
Black or African American	15/19 (79)	4/6 (67)	12.3 (– 22.4, 53.6)
Multiple	6/9 (67)	2/3 (67)	– 0.0 (– 48.0, 56.8)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	2/2 (100)	2/2 (100)	0.0 (– 71.9, 71.9)
White	221/341 (65)	112/163 (69)	– 3.9 (– 12.4, 5.0)
Ethnicity			
Hispanic or Latino	54/90 (60)	26/47 (55)	4.7 (– 12.4, 22.0)
Non-Hispanic or Latino	339/516 (66)	171/258 (66)	– 0.6 (– 7.5, 6.6)
Not reported	0/0 (NA)	1/1 (100)	NA
Is in United States			
United States	91/133 (68)	36/67 (54)	14.7 (0.5, 28.8)*
Non-United States	302/473 (63)	162/239 (68)	– 3.9 (– 11.1, 3.5)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SAF, safety analysis set

Notably, there were more AEs reported in the remibrutinib versus placebo treatment arms in the United States compared to non-US countries. While definitive conclusions cannot be drawn from the limited number of AEs within each subgroup, the primary driver of this difference was COVID-19 infections that occurred during Trial A2301.

A breakdown of the most common TEAEs (nasopharyngitis, hemorrhage, headache, nausea, and abdominal pain) by demographic subgroup is shown in [Table 107](#), [Table 108](#), [Table 109](#), [Table 110](#), and [Table 111](#).

Table 107. Demographic Subgroup Analysis of Nasopharyngitis TEAEs, Safety Population, Pooled Analysis, Trials A2301 and A2302

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	52/403 (12.9)	15/204 (7.4)	5.6 (0.3, 10.2)*
Male	15/203 (7.4)	12/102 (11.8)	– 4.4 (– 12.6, 2.3)
Age group, years			
<65	61/553 (11.0)	25/282 (8.9)	2.2 (– 2.4, 6.2)
65 to <85	6/53 (11.3)	2/24 (8.3)	3.0 (– 15.8, 16.3)
Age group ≥65, years			
≥65	6/53 (11.3)	2/24 (8.3)	3.0 (– 15.8, 16.3)
Age group ≥75, years			
≥75	0/10 (0)	0/2 (0)	0.0 (– 67.7, 29.5)

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	3/12 (25.0)	0/14 (0)	25.0 (– 0.2, 53.8)
Asian	14/223 (6.3)	9/117 (7.7)	– 1.4 (– 8.2, 4.0)
Black or African American	1/19 (5.3)	0/6 (0)	5.3 (– 35.4, 25.2)
Multiple	1/9 (11.1)	0/3 (0)	11.1 (– 49.9, 45.1)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	1/2 (50.0)	0/2 (0)	50.0 (– 46.8, 92.4)
White	47/341 (13.8)	18/163 (11.0)	2.7 (– 3.8, 8.5)
Ethnicity			
Hispanic or Latino	13/90 (14.4)	1/47 (2.1)	12.3 (2.2, 21.5)*
Non-Hispanic or Latino	54/516 (10.5)	26/258 (10.1)	0.4 (– 4.5, 4.7)
Not reported	0/0 (NA)	0/1 (0)	NA
Is in United States			
United States	10/133 (7.5)	1/67 (1.5)	6.0 (– 1.0, 12.1)
Non-United States	57/473 (12.1)	26/239 (10.9)	1.2 (– 4.1, 5.9)

Source: adae.xpt; Software: R

OCMQ Nasopharyngitis contains: Upper respiratory tract infection, Nasopharyngitis, Acute sinusitis, Chronic sinusitis, Pharyngitis, Rhinitis, Rhinitis allergic, and Pharyngitis streptococcal.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; OCMQ, OND custom medical query; OND, Office of New Drugs; TEAE, treatment-emergent adverse event

Table 108. Demographic Subgroup Analysis of Hemorrhage TEAEs, Safety Population, Pooled Analysis, Trials A2301 and A2302

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	46/403 (11.4)	6/204 (2.9)	8.5 (4.3, 12.4)*
Male	9/203 (4.4)	1/102 (1.0)	3.5 (– 1.2, 7.4)
Age group, years			
<65	50/553 (9.0)	7/282 (2.5)	6.6 (3.3, 9.6)*
65 to <85	5/53 (9.4)	0/24 (0)	9.4 (– 4.9, 20.3)
Age group ≥65, years			
≥65	5/53 (9.4)	0/24 (0)	9.4 (– 4.9, 20.3)
Age group ≥75, years			
≥75	2/10 (20.0)	0/2 (0)	20.0 (– 52.2, 52.3)

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	0/12 (0)	0/14 (0)	0.0 (– 22.2, 25.0)
Asian	18/223 (8.1)	1/117 (0.9)	7.2 (2.8, 11.7)*
Black or African American	2/19 (10.5)	0/6 (0)	10.5 (– 30.8, 31.9)
Multiple	1/9 (11.1)	0/3 (0)	11.1 (– 49.9, 45.1)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	0/2 (0)	0/2 (0)	0.0 (– 71.9, 71.9)
White	34/341 (10.0)	6/163 (3.7)	6.3 (1.5, 10.6)*
Ethnicity			
Hispanic or Latino	5/90 (5.6)	0/47 (0)	5.6 (– 2.2, 12.4)
Non-Hispanic or Latino	50/516 (9.7)	7/258 (2.7)	7.0 (3.5, 10.2)*
Not reported	0/0 (NA)	0/1 (0)	NA
Is in United States			
United States	13/133 (9.8)	3/67 (4.5)	5.3 (– 3.4, 12.4)
Non-United States	42/473 (8.9)	4/239 (1.7)	7.2 (4.0, 10.4)*

Source: adae.xpt; Software: R

OMCQ Hemorrhage contains: Contusion, Epistaxis, Petechiae, Haematuria, Conjunctival haemorrhage, Ecchymosis, Haemorrhagic ovarian cyst, Purpura, Intermenstrual bleeding, Gingival bleeding, Haematoma, Urinary occult blood positive, and Menometrorrhagia.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; OCMQ, OND custom medical query; OND, Office of New Drugs; TEAE, treatment-emergent adverse event

Table 109. Demographic Subgroup Analysis of Headache TEAEs, Safety Population, Pooled Analysis, Trials A2301 and A2302

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	32/403 (7.9)	16/204 (7.8)	0.1 (– 5.0, 4.4)
Male	9/203 (4.4)	3/102 (2.9)	1.5 (– 4.2, 5.8)
Age group, years			
<65	38/553 (6.9)	19/282 (6.7)	0.1 (– 3.8, 3.6)
65 to <85	3/53 (5.7)	0/24 (0)	5.7 (– 8.6, 15.5)
Age group ≥65, years			
≥65	3/53 (5.7)	0/24 (0)	5.7 (– 8.6, 15.5)
Age group ≥75, years			
≥75	0/10 (0)	0/2 (0)	0.0 (– 67.7, 29.5)

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	0/12 (0)	0/14 (0)	0.0 (– 22.2, 25.0)
Asian	8/223 (3.6)	6/117 (5.1)	– 1.5 (– 7.5, 2.8)
Black or African American	4/19 (21.1)	2/6 (33.3)	– 12.3 (– 53.6, 22.4)
Multiple	0/9 (0)	0/3 (0)	0.0 (– 58.3, 31.8)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	1/2 (50.0)	1/2 (50.0)	– 0.0 (– 74.9, 74.9)
White	28/341 (8.2)	10/163 (6.1)	2.1 (– 3.3, 6.5)
Ethnicity			
Hispanic or Latino	9/90 (10.0)	3/47 (6.4)	3.6 (– 8.1, 12.9)
Non-Hispanic or Latino	32/516 (6.2)	16/258 (6.2)	– 0.0 (– 4.0, 3.4)
Not reported	0/0 (NA)	0/1 (0)	NA
Is in United States			
United States	18/133 (13.5)	3/67 (4.5)	9.1 (0.0, 16.8)*
Non-United States	23/473 (4.9)	16/239 (6.7)	– 1.8 (– 6.1, 1.6)

Source: adae.xpt; Software: R

OCMQ Headache contains: Headache and Migraine

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; OCMQ, OND custom medical query; OND, Office of New Drugs; TEAE, treatment-emergent adverse event

Table 110. Demographic Subgroup Analysis of Nausea TEAEs, Safety Population, Pooled Analysis, Trials A2301 and A2302

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	13/403 (3.2)	4/204 (2.0)	1.3 (– 2.0, 3.8)
Male	5/203 (2.5)	1/102 (1.0)	1.5 (– 3.0, 4.8)
Age group, years			
<65	18/553 (3.3)	5/282 (1.8)	1.5 (– 1.1, 3.6)
65 to <85	0/53 (0)	0/24 (0)	0.0 (– 14.0, 6.8)
Age group ≥65, years			
≥65	0/53 (0)	0/24 (0)	0.0 (– 14.0, 6.8)
Age group ≥75, years			
≥75	0/10 (0)	0/2 (0)	0.0 (– 67.7, 29.5)

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	0/12 (0)	0/14 (0)	0.0 (– 22.2, 25.0)
Asian	5/223 (2.2)	0/117 (0)	2.2 (– 1.0, 5.1)
Black or African American	1/19 (5.3)	1/6 (16.7)	– 11.4 (– 52.8, 13.2)
Multiple	0/9 (0)	0/3 (0)	0.0 (– 58.3, 31.8)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	0/2 (0)	0/2 (0)	0.0 (– 71.9, 71.9)
White	12/341 (3.5)	4/163 (2.5)	1.1 (– 2.9, 4.1)
Ethnicity			
Hispanic or Latino	2/90 (2.2)	2/47 (4.3)	– 2.0 (– 12.3, 4.3)
Non-Hispanic or Latino	16/516 (3.1)	3/258 (1.2)	1.9 (– 0.5, 4.0)
Not reported	0/0 (NA)	0/1 (0)	NA
Is in United States			
United States	5/133 (3.8)	1/67 (1.5)	2.3 (– 4.5, 7.3)
Non-United States	13/473 (2.7)	4/239 (1.7)	1.1 (– 1.7, 3.3)

Source: adae.xpt; Software: R

OCMQ Nausea contains: Nausea.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; OCMQ, OND custom medical query; OND, Office of New Drugs; TEAE, treatment-emergent adverse event

Table 111. Demographic Subgroup Analysis of Abdominal Pain TEAEs, Safety Population, Pooled Analysis, Trials A2301 and A2302

Characteristic	Remibrutinib N=606 n/N_s (%)	Placebo N=306 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	12/403 (3.0)	4/204 (2.0)	1.0 (– 2.2, 3.5)
Male	6/203 (3.0)	2/102 (2.0)	1.0 (– 4.1, 4.7)
Age group, years			
<65	16/553 (2.9)	6/282 (2.1)	0.8 (– 1.9, 2.9)
65 to <85	2/53 (3.8)	0/24 (0)	3.8 (– 10.4, 12.8)
Age group ≥65, years			
≥65	2/53 (3.8)	0/24 (0)	3.8 (– 10.4, 12.8)
Age group ≥75, years			
≥75	0/10 (0)	0/2 (0)	0.0 (– 67.7, 29.5)

Characteristic	Remibrutinib N=606 n/N _s (%)	Placebo N=306 n/N _s (%)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	0/12 (0)	1/14 (7.1)	- 7.1 (- 32.1, 18.8)
Asian	8/223 (3.6)	3/117 (2.6)	1.0 (-4.0, 4.8)
Black or African American	1/19 (5.3)	0/6 (0)	5.3 (- 35.4, 25.2)
Multiple	0/9 (0)	0/3 (0)	0.0 (- 58.3, 31.8)
Native Hawaiian or Other Pacific Islander	0/0 (NA)	0/1 (0)	NA
Unknown	0/2 (0)	0/2 (0)	0.0 (- 71.9, 71.9)
White	9/341 (2.6)	2/163 (1.2)	1.4 (- 1.9, 3.9)
Ethnicity			
Hispanic or Latino	2/90 (2.2)	2/47 (4.3)	- 2.0 (- 12.3, 4.3)
Non-Hispanic or Latino	16/516 (3.1)	4/258 (1.6)	1.6 (- 1.0, 3.7)
Not reported	0/0 (NA)	0/1 (0)	NA
Is in United States			
United States	3/133 (2.3)	0/67 (0)	2.3 (- 3.2, 6.4)
Non-United States	15/473 (3.2)	6/239 (2.5)	0.7 (- 2.4, 3.1)

Source: adae.xpt; Software: R

OCMQ Abdominal Pain contains: Abdominal pain, Abdominal pain upper, Epigastric discomfort, and Abdominal discomfort
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; OCMQ, OND custom medical query; OND, Office of New Drugs; TEAE, treatment-emergent adverse event

Although the incidence of common TEAEs generally appears similar across demographic subgroups, there are some imbalances, such as an apparent increased risk for bleeding-related TEAEs in females (versus males), geriatric subjects ≥ 65 or 75 years of age (versus < 65 or 75 years), and subjects of non-White race or Non-Hispanic ethnicity (versus Asian/Black/Multiple or Hispanic ethnicity) who were treated with remibrutinib. Some of the differences are likely artifacts caused by the small number of subjects within particular subgroups; however, the reason for an imbalance between females and males is unclear.

17.2. Open-Label Period, Trials A2301 and A2302

The open-label (OL) periods for Trials A2301 and A2302 provided an additional 28 weeks of exposure to subjects who had participated in the double-blind period (see Section 7.5 for additional exposure details).

During the OL period of Trial A2301, 43.7% of subjects in the remibrutinib-to-remibrutinib group and 46.6% of subjects in the placebo-to-remibrutinib group experienced at least one TEAE. The majority of TEAEs were mild-to-moderate in severity. SAEs occurred in 1.5% and 0.8% of subjects in the respective groups during the OL period.

The overall TEAE incidence in the OL period of Trial A2302 was 52.9% in the remibrutinib-to-remibrutinib group and 55.0% in the placebo-to-remibrutinib group. The most frequently reported TEAEs ($\geq 2\%$ frequency) included COVID-19 (7.3% and 10.1%, respectively), upper respiratory tract infection (5.0% and 6.2%), nasopharyngitis (3.9% and 2.3%), and suspected

COVID-19 (2.7% and 3.1%). These findings are consistent with common respiratory infections and may reflect the study conduct period during the COVID-19 pandemic and do not raise any new or unexpected safety signals.

Bleeding

During the OL period of Trials A2301 and A2302, the bleeding risk profile demonstrated specific patterns when analyzed through EAOR. In the remibrutinib group during the entire study period, 11.7% of subjects experienced bleeding AESIs compared to 10.6% during the placebo-controlled period. The EAOR analysis showed a decrease from 43.4 events per 100 patient-years during the placebo-controlled period to 25.4 events per 100 patient-years during the entire study period. For subjects who transitioned from placebo to remibrutinib during the OL phase, 6.9% experienced bleeding AESIs. The median time-to-event onset was 47.5 days with a median event duration of 43.0 days. All events in this population were mild or moderate in severity, with no severe or serious bleeding events reported. The temporal analysis revealed that bleeding AESIs occurred predominantly within the first 4 to 12 weeks of treatment initiation. During the OL extension period, no additional serious bleeding AESIs were reported beyond those occurring in the placebo-controlled phase. The types of bleeding events remained consistent throughout the study duration, consisting primarily of cutaneous bleeding manifestations including petechiae, contusion, and ecchymosis. Most bleeding events resolved during the study period, and most did not require treatment modifications. See Section [7.7.1](#) for details on the bleeding risk during the placebo-controlled period.

Infection

During the entire study period, 45.7% of subjects in the remibrutinib 25-mg BID group experienced infection AESIs, with the EAOR decreasing to 82.7 events per 100 patient-years compared to the placebo-controlled period, suggesting no increase in infection risk with longer treatment duration. For subjects who transitioned from placebo to remibrutinib, 26.3% experienced infection AESIs with an EAOR of 66.9 per 100 patient-years. The most frequently reported infections were respiratory tract infections, including COVID-19 (10.7% versus 11.4% in remibrutinib versus placebo groups), nasopharyngitis (6.6% versus 4.6%), and upper respiratory tract infections, similar to the placebo-controlled period. No opportunistic infections were reported using the standardized MedDRA query, and bacterial encapsulated infections were not observed. See Section [7.7.2](#) for details on the infection risk during the placebo-controlled period.

Cytopenia

During the entire study period, 5.9% of subjects in the remibrutinib 25-mg BID group experienced cytopenia AESIs, with the EAOR decreasing from 12.1 per 100 patient-years during the placebo-controlled period to 8.9 per 100 patient-years during the entire study period, suggesting no increase in cytopenia risk with longer treatment duration. For subjects who transitioned from placebo to remibrutinib, 1.5% experienced cytopenia AESIs and the majority did not require treatment modifications. No serious cytopenia AESIs were reported, and none were associated with increased infections or bleeding events. See Section [7.7.3](#) for details on the cytopenia risk during the placebo-controlled period.

DILI

Liver enzyme elevations continued to occur at low frequencies with patterns similar to those observed during the placebo-controlled period. In the remibrutinib group during the entire study period, ALT or AST elevations greater than three times the ULN occurred in 1.5% of subjects compared to 1.3% during the placebo-controlled period alone. One additional subject in the remibrutinib group developed an asymptomatic AST elevation between 3x and 5x ULN after completion of the placebo-controlled period ([Table 112](#)). For subjects who transitioned from placebo to remibrutinib during the OL phase, liver enzyme elevations occurred in 1.2% of subjects for ALT or AST greater than 3x ULN. This population experienced two asymptomatic ALT elevations between 3x and 5x ULN and one ALT elevation between 10x and 20x ULN combined with AST elevation between 5x and 8x ULN. Notably, the latter case occurred 14 days after the last dose of remibrutinib and was attributed to excess antihistamine use in a subject with underlying fatty liver disease who had previously experienced spontaneous ALT/AST elevation during placebo treatment. Throughout the entire study period, no potential Hy's Law cases were identified. See Section [7.6.1.8](#) for details on the risk of elevated liver enzymes during the placebo-controlled period.

Table 112. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, SAF, Pooled Analysis, Trials A2301 and A2302

Laboratory Parameter	OL Data Only		DB + OL Data
	Remibrutinib (DB) to Remibrutinib (OL) N=529 n/N _w (%)	Placebo (DB) to Remibrutinib (OL) N=262 n/N _w (%)	Remibrutinib (DB) to Remibrutinib (OL) N=529 n/N _w (%)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5x ULN)	3/523 (0.6)	5/253 (2.0)	8/529 (1.5)
Level 2 (>2x ULN)	0/523 (0)	2/253 (0.8)	1/529 (0.2)
Level 3 (>3x ULN)	0/523 (0)	0/253 (0)	0/529 (0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3x ULN)	1/523 (0.2)	3/252 (1.2)	6/529 (1.1)
Level 2 (>5x ULN)	0/523 (0)	1/252 (0.4)	1/529 (0.2)
Level 3 (>10x ULN)	0/523 (0)	1/252 (0.4)	1/529 (0.2)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3x ULN)	1/523 (0.2)	2/252 (0.8)	5/529 (0.9)
Level 2 (>5x ULN)	0/523 (0)	1/252 (0.4)	0/529 (0)
Level 3 (>10x ULN)	0/523 (0)	0/252 (0)	0/529 (0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5x ULN)	3/523 (0.6)	1/252 (0.4)	7/529 (1.3)
Level 2 (>2x ULN)	0/523 (0)	0/252 (0)	0/529 (0)
Level 3 (>3x ULN)	0/523 (0)	0/252 (0)	0/529 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks for the double-blind period and 28 weeks for the open-label period.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot..."

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal

In conclusion, the safety data obtained during the OL periods of Trials A2301 and A2302 were similar to the safety data from the initial 24-week controlled periods. The safety profile remained

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consistent over time with no new signals identified and no significant change in the frequency or severity of TEAEs with longer term exposure.

17.3. Study A2201

The results from Study A2201 provide a limited assessment of the dose-response for safety across remibrutinib dosages of 10 mg QD up to 100 mg BID. Similar to the efficacy results from this study, there were no apparent dose-related patterns observed in TEAEs, SAEs, TEAEs leading to treatment discontinuations, laboratory abnormalities, vital signs, or ECG parameters. The overall incidence of TEAEs was higher in the combined remibrutinib groups (58.1%) compared to placebo (42.9%) as shown in [Table 113](#).

Table 113. Adverse Events, SAF, Study A2201

Adverse Events	REMI 10 mg QD N=44 n (%)	REMI 35 mg QD N=44 n (%)	REMI 100 mg QD N=47 n (%)	REMI 10 mg BID N=44 n (%)	REMI 25 mg BID N=43 n (%)	REMI 100 mg BID N=45 n (%)	Any REMI N=267 n (%)	Placebo N=42 n (%)
Subjects with any TEAE(s)	29 (66)	23 (52)	27 (57)	21 (48)	26 (61)	29 (64)	155 (58)	18 (43)
Subjects with any SAE(s)								
Death	0	0	0	0	0	0	0	0
Nonfatal SAE(s)	1 (2)	0	0	2 (5)	2 (5)	0	5 (2)	0
Discontinued study treatment due to any TEAE(s)	0	0	0	3 (7)	1 (2)	3 (7)	7 (3)	0
Discontinued study treatment due to any SAE(s)	0	0	0	1 (2)	1 (2)	0	2 (1)	0
Treatment interruption due to TEAE(s)	2 (5)	1 (2)	2 (4)	0	0	0	5 (2)	1 (2)
Treatment interruption due to SAE(s)	0	0	0	0	0	0	0	0

Source: Applicant-provided CSR for Study A2201, p.110

Abbreviations: BID, twice daily; N, number of subjects; n, number of subjects with specific adverse event; QD, once daily; REMI, remibrutinib; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event

Of the five remibrutinib-treated subjects who experienced SAEs, two reported CSU (remibrutinib 25-mg and 10-mg BID arms), and the remaining SAEs were reported in one subject each: lymphadenopathy (remibrutinib 10 mg QD), renal abscess (remibrutinib 25 mg BID) and ureterolithiasis (remibrutinib 10 mg BID). TEAEs leading to study drug discontinuation revealed no particular pattern or dose-response relationship for the events: 10 mg BID (CSU, COVID-19 and renal pain), 25 mg BID (urinary tract infection/renal abscess), and 100 mg BID (bradycardia, hematuria, and petechiae).

The most commonly reported adverse events were headache, nasopharyngitis, and CSU, the majority of which were mild-to-moderate in severity.

Table 114. Common TEAEs by Preferred Term, SAF, Study A2201

Preferred Term	REMI 10 mg QD N=44 n (%)	REMI 35 mg QD N=44 n (%)	REMI 100 mg QD N=47 n (%)	REMI 10 mg BID N=44 n (%)	REMI 25 mg BID N=43 n (%)	REMI 100 mg BID N=45 n (%)	Any REMI N=267 n (%)	Placebo N=42 n (%)
Any preferred term	29 (66)	23 (52.3)	27 (57.4)	21 (47.7)	26 (60.5)	29 (64.4)	155 (58.1)	18 (42.9)
Headache	1 (2)	7 (15.9)	4 (8.5)	3 (6.8)	6 (14.0)	5 (11.1)	26 (9.7)	6 (14.3)
Nasopharyngitis	7 (16)	2 (4.5)	2 (4.3)	4 (9.1)	4 (9.3)	4 (8.9)	23 (8.6)	3 (7.1)
Chronic spontaneous urticaria	3 (7)	2 (4.5)	3 (6.4)	4 (9.1)	2 (4.7)	2 (4.4)	16 (6.0)	1 (2.4)
Nausea	2 (5)	3 (6.8)	1 (2.1)	1 (2.3)	1 (2.3)	2 (4.4)	10 (3.7)	0
Upper respiratory tract infection	1 (2)	2 (4.5)	2 (4.3)	0	3 (7.0)	0	8 (3.0)	1 (2.4)
Diarrhea	2 (5)	0	0	4 (9.1)	0	1 (2.2)	7 (2.6)	2 (4.8)
Pyrexia	3 (7)	0	0	2 (4.5)	1 (2.3)	0	6 (2.2)	0

Source: Applicant-provided CSR for Study A2201, p. 107-108

Abbreviations: BID, twice daily; N, number of subjects; n, number of subjects with specific treatment-emergent adverse event; QD, once daily; REMI, remibrutinib; SAF, safety analysis set; TEAE, treatment-emergent adverse event

Regarding adverse events of special interest, infection rates were comparable between remibrutinib (25.1%) and placebo (21.4%) groups, as were cytopenias (3.0% versus 2.4%). Bleeding events were slightly more frequent in remibrutinib groups (6.7% versus 2.4%) but were mostly mild, with only two moderate cases of gingival bleeding and hematuria, and two bleeding events leading to discontinuation. Overall, there did not appear to be a dose-response pattern for AESIs suggesting the safety profile of remibrutinib was consistent across the tested dose range. Laboratory assessments revealed notable liver enzyme abnormalities in three subjects (all in once-daily arms), but these were isolated elevations that did not meet Hy's Law criteria and did not require treatment discontinuation. Hematology, clinical chemistry, and vital signs showed no significant drug-related safety concerns. During the placebo-controlled period, four female subjects experienced isolated QTcF values in the 10 mg BID, 25 mg BID, and 100 mg BID groups. Notably, no subject exceeded the critical 500 ms threshold, and one case occurred during the extension period, suggesting no treatment relationship. The observed QTcF elevations were transient and were not associated with clinical adverse events nor was there a dose-response relationship.

17.4. Study A2202E1

The safety profile of chronic treatment with remibrutinib 100 mg BID was consistent with the preceding 12-week core study and did not reveal any new safety concerns. TEAEs were reported in 139 out of 194 subjects (71.6%), with the majority being mild (35.1%) or moderate (32.5%) in severity. The most commonly reported TEAEs included chronic spontaneous urticaria (11.3%, primarily occurring during the treatment-free follow-up period), COVID-19 (8.2%), headache (6.7%), and eczema (5.2%). Only 23 subjects (11.9%) experienced TEAEs suspected to be related to study treatment, with all individual treatment-related events occurring in two or fewer subjects each.

Serious adverse events were infrequent, occurring in only six subjects (3.1%) with seven total SAEs reported, and none were considered related to study treatment. COVID-19 pneumonia was the only SAE reported in more than one subject (two subjects, 1.0%). No deaths occurred during the study. Treatment discontinuation due to adverse events was relatively uncommon, affecting 11 subjects (5.7%), with diarrhea being the only AE leading to discontinuation in more than one subject (two subjects, 1.0%).

Regarding adverse events of special interest, infections were reported in 61 subjects (31.4%), with COVID-19 and nasopharyngitis being the most frequent. Bleeding events occurred in 12 subjects (6.2%), and cytopenias were rare, affecting only 2 subjects (1.0%). Notable changes in vital signs included sitting diastolic blood pressure abnormalities in 20.6% of subjects and sitting systolic blood pressure abnormalities in 19.1%, though subjects with hypertension history were permitted in the study. Laboratory abnormalities and ECG changes, including QTcF prolongation, were infrequent and did not indicate new safety concerns. One pregnancy occurred during the study with a normal course and healthy delivery, with the infant showing normal development at 12-month follow-up.

17.5. Study A1301

The safety results from Study A1301 were similar to the findings in Trials A2301 and A2302, revealing no additional safety concerns with remibrutinib 25 mg BID over 52 weeks of treatment. No deaths occurred during the study, and the overall completion rate was high with 68 of 71 subjects (95.8%) completing the full 52-week treatment period.

Adverse events were reported in 62 subjects (87.3%), but all were either mild (52.1% of subjects) or moderate (35.2% of subjects) in severity, with no severe adverse events reported. The most commonly affected system organ classes were infections and infestations (57.7% of subjects) and skin and subcutaneous tissue disorders (53.5% of subjects), with COVID-19 (19.7%) and headache (12.7%) being the most frequent individual adverse events. Treatment-related adverse events occurred in 19 subjects (26.8%), primarily consisting of diarrhea, petechiae, and purpura, each reported in 3 subjects (4.2%).

Three SAEs were reported (Meniere's disease, worsening epiretinal membrane, and rhegmatogenous retinal detachment), none of which were considered related to study treatment. Treatment discontinuation due to adverse events occurred in one subject (1.4%) due to worsening atopic dermatitis, which was assessed as unrelated to study treatment. AESIs included infections in 42 subjects (59.2%), bleeding events in 13 subjects (18.3%), and cytopenia in 5 subjects (7.0%), all of which were nonserious and predominantly mild in severity. Laboratory evaluations, vital signs, and ECG parameters showed no clinically relevant abnormalities or drug-related safety concerns, with the majority of laboratory abnormalities being CTCAE Grade 1 or 2 with no clinical consequences.

17.6. Study A2305

The safety profile of remibrutinib in this study was based on 33.51 subject-years of cumulative exposure across 144 subjects and demonstrated consistency with the known safety profile for remibrutinib, with no new or unexpected safety signals identified and no deaths reported during the study period. Overall, 86 subjects (59.7%) experienced at least one AE, with the majority being mild (41.7% of subjects) or moderate (16.0% of subjects) in severity, while only three subjects (2.1%) reported severe AEs. The most commonly reported system organ classes were infections and infestations (22.2% of subjects) and skin and subcutaneous tissue disorders (15.3%), with the most frequent individual AEs being headache (9.0%), nasopharyngitis (8.3%), and chronic spontaneous urticaria (6.3%). Treatment-related AEs were reported in 21 subjects (14.6%), with purpura, nausea, headache, and heavy menstrual bleeding being the most common (2.1% each).

SAEs occurred in four subjects (2.8%), including one case each of acute cholecystitis, dizziness, chronic spontaneous urticaria, and aortic dissection. Two subjects (1.4%) discontinued treatment due to AEs (increased blood pressure and aortic dissection). Infection AESIs were reported in 22.9% of subjects, with all 51 events being nonserious and mild-to-moderate in severity; bleeding AESIs occurred in 8.3% of subjects with all 21 events being nonserious and mild; and cytopenia AESIs were reported in 4.2% of subjects with all 6 events being mild-to-moderate and nonserious. Laboratory analyses, vital signs, and ECG monitoring revealed no clinically relevant abnormalities or drug-related safety concerns, with all newly occurring laboratory abnormalities

being CTCAE Grade 1 or 2 except for a single Grade 3 triglyceride increase in a subject with preexisting elevated triglycerides at baseline. There were no liver enzyme abnormalities exceeding three times the upper limit of normal and no cases meeting potential Hy's Law criteria.

The clinical pharmacologist within the Division of Cardiology and Nephrology reviewed the study with regard to hypertension-related adverse events and concluded that the study supported that 25-mg remibrutinib is not associated with clinically significant changes in blood pressure (see review dated June 13, 2025).

17.7. Study F12101

The safety profile of remibrutinib 100 mg BID administered to healthy subjects was consistent with prior remibrutinib clinical studies and comparable to placebo, with no new safety signals identified. The overall incidence of adverse events was similar across treatment groups, with 84.2% in the concomitant remibrutinib group, 88.6% in the interrupted remibrutinib group, and 82.4% in the placebo group. The majority of adverse events were mild-to-moderate in severity, with 83.2% classified as Grade 1 and 14.0% as Grade 2.

No deaths or serious adverse events were reported during the study. Adverse events leading to study treatment discontinuation were more frequent in the concomitant remibrutinib group (13.2%) compared to the interrupted remibrutinib group (2.9%) and placebo group (5.9%), with COVID-19 being the most common reason for discontinuation.

The overall incidence of infections was numerically higher in the concomitant remibrutinib group (23.7%) compared to the interrupted remibrutinib (14.3%) and placebo (17.6%) groups, though no specific infectious condition drove this difference. Bleeding events were reported in the concomitant remibrutinib group (7.9%) and placebo group (8.8%) but not in the interrupted remibrutinib group; all bleeding events were Grade 1 in severity, and none led to treatment discontinuation. No cytopenia adverse events were reported in any treatment group. Laboratory parameters, vital signs, and ECG remained generally comparable between treatment groups with no clinically meaningful changes observed throughout the study. For additional details regarding the significance of this study, refer to Section [7.7.5](#).

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Refer to Section [5](#) for discussion of pharmacologic activity and mechanism of action. Drug resistance is not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to Section [10](#).

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the PI as compared to the Applicant’s draft PI ([Table 115](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 115. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to PI ² Compared to Applicant’s Draft PI
1 INDICATIONS AND USAGE	Revised the EPC (b) (4) to kinase inhibitor. The rationale for the EPC is included in Section 5.1 . No changes made to the proposed indication statement, but a limitation of use was added consistent with other products for CSU. <u>Limitations of Use:</u> RHAPSIDO is not indicated for other forms of urticaria.
2 DOSAGE AND ADMINISTRATION	Recommendations for (b) (4).
5 WARNINGS AND PRECAUTIONS	- Risk of Bleeding was added in Section 5 because of RHAPSIDO’s mechanism of action, increased frequency of bleeding/bruising adverse reactions in clinical trials, mitigation for bleeding, and benefit-risk considerations for CSU. - Vaccine information was relocated to Section 5 from Section 7 as proposed by the Applicant because the reduction of immunological response to a vaccine from an immunosuppressive drug is not considered a drug interaction.
6 ADVERSE REACTIONS	- Common adverse reactions table revised (Table 1 in the PI) to present adverse drug reactions according to OCMQ grouped terms for ‘hemorrhage’. - Description of bleeding events revised to reflect OCMQ for ‘hemorrhage’ and remove (b) (4).
7 DRUG INTERACTIONS	Revised to provide actionable recommendations for drug-drug interactions. Drug-drug interaction information that (b) (4). (b) (4). Lastly, vaccine information was relocated to Section 5.

Full PI Sections ¹	Rationale for Major Changes to PI ² Compared to Applicant's Draft PI
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Subsections 8.1 and 8.2 was revised consistent with PLLR and in consultation with DPMH. Please refer to DPMH review dated August 28, 2025. There was no evidence to support safety and effectiveness of a drug for an indication in pediatric patients and the appropriate pediatric statement was included in the Pediatric Use subsection. The Geriatric Use subsection included the appropriate language consistent with the Geriatric Information in Human Prescription Drug and Biological Product Labeling. A Hepatic Impairment (HI) subsection was included because the hepatic impairment study showed an increase in AUC of remibrutinib in patients with mild, moderate, and severe HI. Therefore, the subsection was revised to convey avoid use in patients with any degree of HI.
10 OVERDOSAGE	This section was revised to remove (b) (4) and included a statement to contact the Poison Help line for overdose management recommendation.
12 CLINICAL PHARMACOLOGY	12.1 Mechanism of Action: summarized the established mechanism of action in humans. 12.2 Pharmacodynamic: revisions included language for Exposure-Response, Cardiac Electrophysiology, and Effects on Blood Pressure. 12.3 Pharmacokinetics: revisions were provided to align with the clinical pharmacology recommended format.
13 NONCLINICAL TOXICOLOGY	Included results that did not show evidence of carcinogenic potential from a 6-month rasH2 mouse study. Remibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay and was not clastogenic in an in vitro micronucleus assay in human peripheral lymphocytes or in an in vivo blood reticulocyte micronucleus assay in rats. Lastly, remibrutinib did not impact fertility in female or male rats.
14 CLINICAL STUDIES	- Demographics table added to reflect the FAS population (b) (4) - Figures revised to remove (b) (4) and to combine into a single representative figure for ISS7 and HSS7 through Week 24. - Statement regarding subgroup analyses limited to relevant information for providers (baseline IgE only).
17 PATIENT COUNSELING INFORMATION	Revised to incorporate W&P in Section 5 and updates to other relevant sections (e.g., pregnancy registry)

Full PI Sections¹	Rationale for Major Changes to PI² Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	These sections are consistent with product labeling considerations.

Source: Labeling Discussion Comments dated August 28, September 15, and xx 2025

Abbreviations: (b) (4) AUC, area under the concentration-time curve; (b) (4) (b) (4) DPMH, Division of Pediatrics and Maternal Health; EPC, established pharmacologic class; FAS, full analysis set; HSS7, weekly hives severity score; IgE, immunoglobulin E; ISS7, weekly itch severity score; OCMQ, OND custom medical query; OL, open-label; OND, Office of New Drugs; PI, Prescribing Information; PLLR, Pregnancy and Lactation Labeling Rule; UAS7, weekly urticaria activity score; W&P, Warnings and Precautions

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Package Insert
- Carton and Container

24. Postmarketing Requirements and Commitments

PMR 1 (4896-1)

Conduct a 24-week randomized, double-blind, placebo-controlled, parallel-group study in pediatric patients aged 12 to less than 18 years with chronic spontaneous urticaria who remain symptomatic despite H1-antihistamine treatment to assess the efficacy, safety, and pharmacokinetic responses to remibrutinib.

- Final Protocol Submission: September 2022 (complete)
- Study Completion: September 2027
- Final Report Submission: February 2028

PMR 2 (4896-2)

Conduct a 24-week, open-label, pharmacokinetic study in pediatric patients aged 6 to less than 12 years with chronic spontaneous urticaria who remain symptomatic despite H1-antihistamine treatment.

- Final Protocol Submission: December 2027
- Study Completion: October 2030
- Final Report Submission: March 2031

PMR 3 (4896-3)

Conduct an additional oral (gavage) juvenile toxicity study in the rat. The age of rats at study start should be equivalent to pediatric patients approximately 6 years old. The study should include ophthalmic examinations performed prestudy, at the end of the dosing period, and at the end of the recovery period. Potential neurobehavioral effects should also be evaluated in animals at the end of the dosing and recovery periods.

- Draft Protocol Submission: September 2026
- Final Protocol Submission: February 2027
- Study Completion: May 2027
- Final Report Submission: August 2027

PMR-4 (4896-4)

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 United States 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.

- Draft Protocol Submission: June 2026
- Final Protocol Submission: June 2027
- Interim Reports:
  - June 2028
  - June 2029
  - June 2030
  - June 2031
  - June 2032
  - June 2033
  - June 2034
  - June 2035
  - June 2036
  - June 2037
- Study Completion: June 2038
- Final Report Submission: December 2038

PMR-5 (4896-5)

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).

- Draft Protocol Submission: June 2026
- Final Protocol Submission: June 2027
- Interim reports:
  - June 2029
  - June 2030
  - June 2031
  - June 2032
- Study Completion: June 2033
- Final Report Submission: December 2033

PMR-6 (4896-6)

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

- Draft Protocol Submission: March 2026
- Final Protocol Submission: July 2026
- Study Completion: July 2028
- Final Report Submission: September 2028

25. Financial Disclosure

Table 116. Covered Clinical Studies: Trial A2301, Trial A2302, Study A2201, Study A2201E1, Study A1301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study LOU064A2201 U.S. investigators: 12 centers with multiple investigators per center non-U.S. investigators: 72 centers across multiple countries including Argentina, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Japan, Netherlands, Poland, Russia, Slovakia, Spain, Turkey, and United Kingdom Study LOU064A2201E1 U.S. investigators: 11 centers non-U.S. investigators: 64 centers across similar international locations Study LOU064A1301 U.S. investigators: Not applicable (no U.S. sites) non-U.S. investigators: 13 centers (primarily in Japan) Trial LOU064A2301 U.S. investigators: 32 centers Non-U.S. investigators: 94 centers across multiple countries including Argentina, Australia, Bulgaria, Colombia, Czech Republic, France, Hungary, India, Italy, Japan, Korea, Mexico, Russia, Singapore, Spain, Taiwan, and Turkey Trial LOU064A2302 U.S. investigators: 31 centers Non-U.S. investigators: 94 centers across multiple countries including Austria, Brazil, Canada, China, Denmark, Germany, India, Malaysia, Poland, Russia, Slovakia, South Africa, Switzerland, Taiwan, Thailand, United Kingdom, and Vietnam		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Investigator received €120,000 from the Applicant during the time period of March 2018 to April 2020 for a scientific research project Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature

- Bailey, DG, G Dresser, and JM Arnold, 2013, Grapefruit-Medication Interactions: Forbidden Fruit or Avoidable Consequences?, *Cmaj*, 185(4):309-316.
- Erickson, RI, LK Schutt, JM Tarrant, M McDowell, L Liu, AR Johnson, SC Lewin-Koh, M Hedehus, J Ross, RA Carano, K Staflin, F Zhong, JJ Crawford, S Zhong, K Reif, A Katewa, H Wong, WB Young, DM Dambach, and DL Misner, 2017, Bruton's Tyrosine Kinase Small Molecule Inhibitors Induce a Distinct Pancreatic Toxicity in Rats, *J Pharmacol Exp Ther*, 360(1):226-238.
- Fuhr, U, KL Rost, R Engelhardt, M Sachs, D Liermann, C Belloc, P Beaune, S Janezic, D Grant, UA Meyer, and AH Staib, 1996, Evaluation of Caffeine as a Test Drug for CYP1A2, NAT2 and CYP2E1 Phenotyping in Man By In Vivo Versus In Vitro Correlations, *Pharmacogenetics*, 6(2):159-176.
- Gurley, B, MA Hubbard, DK Williams, J Thaden, Y Tong, WB Gentry, P Breen, DJ Carrier, and S Cheboyina, 2006, Assessing the Clinical Significance of Botanical Supplementation on Human Cytochrome P450 3A Activity: Comparison of a Milk Thistle and Black Cohosh Product to Rifampin and Clarithromycin, *J Clin Pharmacol*, 46(2):201-213.
- Hawro, T, T Ohanian, N Schoepke, M Metz, A Peveling-Oberhag, P Staubach, M Maurer, and K Weller, 2018, The Urticaria Activity Score-Validity, Reliability, and Responsiveness, *J Allergy Clin Immunol Pract*, 6(4):1185-1190.e1181.
- Jetter, A, M Kinzig-Schippers, A Skott, A Lazar, D Tomalik-Scharte, J Kirchheiner, M Walchner-Bonjean, U Hering, V Jakob, M Rodamer, W Jabrane, D Kasel, J Brockmüller, U Fuhr, and F Sörgel, 2004, Cytochrome P450 2C9 Phenotyping Using Low-Dose Tolbutamide, *European Journal of Clinical Pharmacology*, 60(3):165-171.
- Kawaguchi-Suzuki, M, RF Frye, HJ Zhu, BJ Brinda, KD Chavin, HJ Bernstein, and JS Markowitz, 2014, The Effects of Milk Thistle (*Silybum Marianum*) on Human Cytochrome P450 Activity, *Drug Metab Dispos*, 42(10):1611-1616.
- Kulthanan, K, L Chularojanamontri, C Rujitharanawong, P Weerasubpong, K Weller, and M Maurer, 2019, Angioedema Activity Score (AAS): a Valid and Reliable Tool to Use in Asian Patients, *Biomed Res Int*, 2019:9157895.
- Lang, DM, 2022, Chronic Urticaria, *N Engl J Med*, 387(9):824-831.
- Loos, NHC, JH Beijnen, and AH Schinkel, 2022, The Mechanism-Based Inactivation of CYP3A4 by Ritonavir: What Mechanism?, *Int J Mol Sci*, 23(17).
- Venkataramanan, R, V Ramachandran, BJ Komoroski, S Zhang, PL Schiff, and SC Strom, 2000, Milk Thistle, a Herbal Supplement, Decreases the Activity of CYP3A4 and Uridine Diphosphoglucuronosyl Transferase in Human Hepatocyte Cultures, *Drug Metab Dispos*, 28(11):1270-1273.

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Weller, K, A Groffik, M Magerl, N Tohme, P Martus, K Krause, M Metz, P Staubach, and M Maurer, 2013, Development, Validation, and Initial Results of the Angioedema Activity Score, *Allergy*, 68(9):1185-1192.

Zuberbier, T, W Aberer, R Asero, AH Abdul Latiff, D Baker, B Ballmer-Weber, JA Bernstein, C Bindslev-Jensen, Z Brzoza, R Buense Bedrikow, GW Canonica, MK Church, T Craig, IV Danilycheva, C Dressler, LF Ensina, A Giménez-Arnau, K Godse, M Gonçalo, C Grattan, J Hebert, M Hide, A Kaplan, A Kapp, CH Katelaris, E Kocatürk, K Kulthanan, D Larenas-Linnemann, TA Leslie, M Magerl, P Mathelier-Fusade, RY Meshkova, M Metz, A Nast, E Nettis, H Oude-Elberink, S Rosumeck, SS Saini, M Sánchez-Borges, P Schmid-Grendelmeier, P Staubach, G Sussman, E Toubi, GA Vena, C Vestergaard, B Wedi, RN Werner, Z Zhao, and M Maurer, 2018, The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria, *Allergy*, 73(7):1393-1414.

Guidances and Guidelines

ICH harmonised guideline *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (April 2023)

(b) (4)

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

FDA guidance for industry *Financial Disclosure by Clinical Investigators: Guidance for Clinical Investigators, Industry, and FDA Staff* (February 2013)

FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998)

FDA guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022)

FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Uncategorized References

ICH harmonised (b) (4) guideline *Impurities in New Drug Products Q3B(R2)* (June 2006)

27. Review Team

Table 117. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Nina Ton, Ji LaRose (CPMS)
Nonclinical reviewer	Edward Dougherty
Nonclinical team leader	Carol Galvis
OCP reviewer(s)	Youssef Mousa
OCP team leader(s)	Amer Al-Khouja
Clinical reviewer	Kat Clarridge
Clinical team leader	Stacy Chin
Biometrics reviewer	Emily Shives
Biometrics team leader	Yongman Kim
Cross-discipline team leader	Stacy Chin
Division director (pharm/tox)	Carmen Booker
Tertiary reviewer (OCP)	Yunzhao Ren
Division director (OB)	Weiya Zhang
Division director (clinical)	Kelly Stone
Office director (or designated signatory authority)	Kathleen Donohue

Abbreviations: OB, Office of Biostatistics; CPMS, Clinical Pharmacology Modeling and Simulation; OCP, Office of Clinical Pharmacology

Table 118. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Craig Bertha (ATL)
OPQ Drug Product	Afsana Tajmim
OPQ Drug Substance	Zhixing Shan, Donna Christner (TL)
OPMA Facility	Jing Fang, Jean Tang (TL)
Established Conditions (ECs)	Eric Twum, Geok Yan Loo, Marcus Yambot
Biopharmaceutics	Swapna Pamu, Tapash Ghosh (TL)
Environmental	Xiaoqin Wu
Labeling	Afsana Tajmim, Julia Pinto (TL)
OPRO Regulatory Business Process Manager	Emma Gimose
Pharmacometrics	Huali Wu, Jerry Jingyu Yu (TL)
Pharmacogenomics	Hobart Rogers, Sarah Dorff (TL)
PBPK	Youssef Mousa, Manuela Grimstein (TL)
Division of Analytics and Informatics	Johanna Copeland, Liping Sun (TL)
OPDP	Quynh-Nhu Capasso
Patient Labeling Team	Lonice Carter, Mary Carroll, Marcia Williams (TL)
OSI	Suyoung Tina Chang, Phillip Kronstein (TL)
CBER	Anne Miranowski, Katie Hise (TL)
DNH	Saleh Ayache, Margaret Thompson (TL)
OSE/DEPI	Huei-Ting Tsai, Natasha Pratt (TL)
OSE/DMEPA	Susan Shermock, Damon Birkemeier (TL)
OSE/DRISK	Lindsey Crist, Jackie Sheppard (TL)
OSE Safety RPM	Cristina Attinello, Ameet Joshi (TL)
DPMH	Abby Melake, Miriam Dinatale (TL), Tamara Johnson (TL)
QT-IRT	Mario Sampson, Lars Johannesen (TL)
ABPM Review Team	Lars Johannesen

Abbreviations: ABPM; Ambulatory Blood Pressure Monitoring; CBER, Center for Biologics Evaluation and Research; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatrics and Maternal Health; DRISK, Division of Risk Management; DNH, Division of Nonmalignant Hematology; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OPRO, Office of Program and Regulatory Operations; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; PBPK, physiologically based pharmacokinetic; QT-IRT, QT Interdisciplinary Review Team; RPM, regulatory project manager; TL, team lead

27.1. Reviewer Signatures

Table 27-119 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Ji Hyun Larose ORO DROII	Sections: Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ji Hyun Larose		Digitally signed by Ji Hyun Larose Date: 9/29/2025 3:10 PM EDT GUID: 2025929191031		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Huali Wu OCP DPM	Sections: 14.5.1, 14.5.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Huali Wu		Digitally signed by Huali Wu Date: 9/29/2025 3:10 PM EDT GUID: 2025929191023		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Youssef Mousa OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 8.3, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Youssef Mousa		Digitally signed by Youssef Mousa Date: 9/29/2025 3:10 PM EDT GUID: 2025929191047		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Youssef Mousa OCP DIIP	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Youssef Mousa		Digitally signed by Youssef Mousa Date: 9/29/2025 3:11 PM EDT GUID: 2025929191142		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Kelly Stone OII DPACC	Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kelly Stone		Digitally signed by Kelly Stone Date: 9/29/2025 3:12 PM EDT GUID: 2025929191222		

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Non-Clinical Reviewer Discipline Secondary Reviewer	Carol Galvis OII DPTII	Sections: 5, 7.1, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Carol Galvis		Digitally signed by Carol Galvis Date: 9/29/2025 3:15 PM EDT GUID: 202592919154		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Yunzhao Ren OCP DIIP	Sections: 5.2, 6.1, 7.7, 8.1, 8.2, and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yunzhao Ren		Digitally signed by Yunzhao Ren Date: 9/29/2025 3:15 PM EDT GUID: 2025929191554		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Jessica Lee OII DPACC	Sections: Labeling	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Jessica Lee		Digitally signed by Jessica Lee Date: 9/29/2025 3:27 PM EDT GUID: 2025929192712		

NDA 218436
RHAPSIDO (remibrutinib, LOU064)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Phuong Ton ORO DROII	Sections: 5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Phuong Ton		Digitally signed by Phuong Ton Date: 9/29/2025 3:30 PM EDT GUID: 2025929193014		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Manuela Grimstein OCP DPM	Sections: 14.5.3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Manuela Grimstein		Digitally signed by Manuela Grimstein Date: 9/29/2025 3:39 PM EDT GUID: 202592919390		

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Other Discipline Primary Reviewer	Liping Sun OB DAI	Sections: 6.2.2, 16.1, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Liping Sun		Digitally signed by Liping Sun		
		Date: 9/29/2025 3:41 PM EDT GUID: 2025929194155		

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Biostatistics Discipline Primary Reviewer	Emily Shives OB DBIII	Sections: 6.2.2, 15.1.4, 16.1, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Emily Shives		Digitally signed by Emily Shives		
		Date: 9/29/2025 3:42 PM EDT GUID: 2025929194256		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Secondary Reviewer	Liping Sun OB DAI	Sections: 6.2.2, 16.1, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Liping Sun		Digitally signed by Liping Sun Date: 9/29/2025 3:43 PM EDT GUID: 202592919435		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Weiya Zhang OB DBIII	Sections: Sections 6, 15, and 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Weiya Zhang		Digitally signed by Weiya Zhang Date: 9/29/2025 3:50 PM EDT GUID: 2025929195016		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Stacy Chin OII DPACC	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 15, 16, 17, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Stacy Chin Digitally signed by Stacy Chin Date: 9/29/2025 4:28 PM EDT GUID: 202592920289				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Katherine Clarridge OII DPACC	Sections: 1,2,3,4,6,7,8.3,10,11, 15,16,17,22,24,25,26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Approval
Signature: Katherine Clarridge Digitally signed by Katherine Clarridge Date: 9/29/2025 4:30 PM EDT GUID: 2025929203038				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yongman Kim OB DBIII	Sections: 6.2, 6.3, 15.1.4, 16.1, 16.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yongman Kim		Digitally signed by Yongman Kim Date: 9/29/2025 5:48 PM EDT GUID: 2025929214844		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Stacy Chin OII DPACC	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Stacy Chin		Digitally signed by Stacy Chin Date: 9/29/2025 9:12 PM EDT GUID: 20259301124		

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CMC (OPQ/ONDP) Discipline Secondary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Craig Bertha		Digitally signed by Craig Bertha Date: 9/30/2025 5:07 AM EDT GUID: 2025930979		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Tertiary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Craig Bertha		Digitally signed by Craig Bertha Date: 9/30/2025 5:07 AM EDT GUID: 20259309744		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Craig Bertha		Digitally signed by Craig Bertha Date: 9/30/2025 5:08 AM EDT GUID: 20259309816		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Amer Al-Khouja OCP DIIP	Sections: 5.2, 6.1, 7.7, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amer Al-Khouja		Digitally signed by Amer Al-Khouja Date: 9/30/2025 7:42 AM EDT GUID: 202593011423		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Jingyu Yu OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jingyu Yu		Digitally signed by Jingyu Yu Date: 9/30/2025 10:07 AM EDT GUID: 202593014716		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Primary Reviewer	Edward Dougherty OII DPTII	Sections: 5.1, 7.1, 8.4, 13, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Edward Dougherty		Digitally signed by Edward Dougherty Date: 9/30/2025 10:14 AM EDT GUID: 2025930141441		

NDA 218436
 RHAPSIDO (remibrutinib, LOU064)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Non-Clinical Reviewer Discipline Tertiary Reviewer	Carmen Booker OII DPTII	Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Carmen Booker		Digitally signed by Carmen Booker Date: 9/30/2025 11:27 AM EDT GUID: 2025930152711		

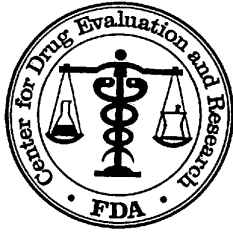
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/s/

STACY J CHIN
09/30/2025 11:34:04 AM

KELLY D STONE
09/30/2025 11:38:23 AM

KATHLEEN M DONOHUE
09/30/2025 11:43:17 AM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number: NDA218436

Drug Name: Remibrutinib (LOU064)

Indication: Treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1-antihistamine treatment

Applicant: Novartis Pharmaceuticals Corporation,
Incorporated
One Health Plaza, East Hanover, NJ 07936

Test Facility for Rats Study: (b) (4)

(b) (4)

Documents Reviewed: Study reports (Rat Study 1870308) and electronic data submitted via NDA218436/0000

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Zhuang Miao, Ph.D.

Concurring Reviewer: Rahman, Atiar Mohammad, Ph.D.

Reviewing Pharmacologist: Dougherty, Edward, Ph.D.

Keywords: Carcinogenicity, Dose response

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Summary

In this submission the sponsor included the report of one animal carcinogenicity study in Crl:WI (Han)rats. This study was intended to assess the carcinogenic potential of LOU064, when administered by oral gavage once daily for 104 weeks.

Rats Study:

Survival analysis:

1. For either male or female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the water control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and any of the treated groups.
2. For either male or female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups.

Tumor analysis:

1. For male rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the water control groups and the treated groups. The pairwise comparisons did not show any statistically significant increases in tumor incidence between the water control groups and any of the treated groups.
2. For male rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the vehicle control groups and the treated groups. The pairwise comparisons did not show any statistically significant differences in tumor incidence between the vehicle control groups and any of the treated groups.
3. For female rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the water control groups and the treated groups. The pairwise comparisons did not show any statistically significant differences in tumor incidence between the water control groups and any of the

- treated groups.
4. For female mice, the trend test showed a statistically significant positive dose response relationships in incidence of endometri adenocarcinoma in uterus (p -value=0.0021<0.005). The pairwise comparisons did not show any statistically significant differences in tumor incidence between the vehicle control groups and any of the treated groups.

1. Background

In this submission the sponsor included the report of one animal carcinogenicity study in Crl:WI (Han) rats. This study was intended to assess the carcinogenic potential of LOU064, when administered by oral gavage once daily for 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control, and one vehicle control group. Two hundred and fifty rats of each sex were randomly assigned to the treated groups, water control group, and vehicle control group in equal size of 50 rats per group. The study was designed to continue for up to 104 weeks for both sexes. Rats in water control group received purified water. Rats in vehicle control group received 2% w/w Kollidon VA64, 0.1% w/w Sodium Lauryl Sulfate in water.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day) Male/Female	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Water	50	50
2	0	Vehicle	50	50
3	30	Low	50	50
4	100	Mid	50	50
5	300	High	50	50

1.1. Sponsor's analyses

1.1.1. Survival analysis

Tests to compare survival were performed using two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for pairwise comparisons of the water control and each dosed group against

vehicle control using Kaplan-Meier product-limit estimation curves, along with Log-Rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS (SAS 2002-2008). The time to death or euthanasia (in weeks, calculation detailed in the following) was the dependent variable. The groups were included as the strata. Animals with a death or euthanasia status recorded as a scheduled euthanasia (interim or terminal) or accidental death were censored in the analysis.

Sponsor's findings: The sponsor's analysis showed that the numbers (percents) of survival were 26 (52%), 27 (54%), 25 (50%), 25 (50%) and 23 (46%) male rats, and 28 (56%), 29 (58%), 24 (48%), 26 (52%) and 25 (50%) in female rats in water control, vehicle control, low, mid and high dose groups, respectively.

The sponsor concluded that oral (gavage) administration of 30, 100, or 300 mg/kg/day LOU064 to CrI:WI (Han) rats for up to 104 weeks resulted in no LOU064-related effects on mortality in males or females.

1.1.2. Tumor data analysis

Tests to compare tumor incidence were performed using a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and dosed groups only) and for pairwise comparisons of the water control and each dosed group against the vehicle control group. The water and vehicle control groups were compared using a two sided tests.

For tumors occurring in animals dying spontaneously or euthanized in a moribund condition during the study, the pathologist classified the context of observation as one of the following.

Fatal: The tumor was a factor in the demise of the animal.

Nonfatal: The tumor was not a factor in the demise of the animal.

Uncertain: Not clear if the tumor was a factor in the demise of the animal.

Non-palpable non-fatal and fatal tumors were analyzed by the IARC asymptotic fixed interval-based prevalence and death rate tests respectively (Peto et al 1980).

The cut-off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to 92, 93 to before terminal euthanasia, and the terminal euthanasia. Fatal and non-fatal tumors were analyzed together, with separate stratum for each. No tumors of uncertain context were noted. The test was implemented using PROC MULTTEST in the SAS system (SAS 2002-2008). In the case of sparse tables (<10 total in a stratum), the exact form of the test was used for that stratum. Otherwise, the asymptotic version of the test was used.

Sponsor's findings: Sponsor concluded that oral (gavage) administration of 30, 100, or 300 mg/kg/day LOU064 to CrI:WI (Han) rats for up to 104 weeks resulted in no LOU064-related neoplastic findings in males or females.

1.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

1.2.1. Survival analysis

The survival distributions of three treated groups, vehical control group, and water control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1 and 2 in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 6 and 7 in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the water control and the treated groups, and among the vehicle control and three treated groups are given in Tables 8 to 11 in the appendix for male and female rats, respectively.

Reviewer's findings: The reviewer's analysis showed that the numbers (percents) of survival were 26 (52%), 27 (54%), 25 (50%), 25 (50%) and 23 (46%) male rats, and 28 (56%), 29 (58%), 24 (48%), 26 (52%) and 25 (50%) in female rats in water control, vehicle control, low, mid and high dose groups, respectively.

For either male or female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the water control group and treated groups. The pairwise comparisons also did not show any statistically significant differences in mortality between the water control group and any of the treated groups in either sex.

For either male or female rats, the survival analyses did not show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups. The pairwise comparisons also did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups in either sex.

1.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes were then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104

week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between the water control and the treated group, and between the vehicle control and three treated groups are listed in Tables 12 to 15 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 2 to 5 below showed p-values less than or equal to 0.05 in the tests between water control or vehicle control and the treated groups for males and females.

Based on the criteria of adjustment for multiple testing discussed in the rats data analysis section, we make the following statistical conclusions:

1. For male rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the water control groups and the treated groups. The pairwise comparisons did not show any statistically significant

- differences in tumor incidence between the water control groups and any of the treated groups.
2. For male rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the vehicle control groups and the treated groups. The pairwise comparisons did not show any statistically significant differences in tumor incidence between the vehicle control groups and any of the treated groups.
  3. For female rats, the tumor analyses did not show any statistically significant dose response relationship in tumor incidence across the water control groups and the treated groups. The pairwise comparisons did not show any statistically significant differences in tumor incidence between the water control groups and any of the treated groups.
  4. For female mice, the trend test showed a statistically significant positive dose response relationships in incidence of endometri adenocarcinoma in uterus (p -value=0.0021<0.005). The pairwise comparisons did not show any statistically significant differences in tumor incidence between the vehicle control groups and any of the treated groups.

Table 2: Tumor Types with P-Values $\leq$ 0.05 for Comparisons between Water Control and Treated Groups -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
THYROID	B-ADENOMA, FOLLICULAR CELL	4/50 (41) 0.0170	4/50 (40) 0.6298	5/50 (37) 0.4336	10/50 (40) 0.0634
Thyroid	C_C cell adenoma+carcinoma	3/50 (41) 0.4474	10/50 (40) 0.0298	5/50 (37) 0.2991	6/50 (39) 0.2162
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 3: Tumor Types with P-Values $\leq$ 0.05 for Comparisons between Vehicle

Control and Treated Groups -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
LYMPH NODE, MESENT	B-HEMANGIOMA	2/50 (42) 0.0137	5/49 (39) 0.1864	4/50 (37) 0.2788	9/50 (39) 0.0174
SKIN/SUBCUTIS	B-TUMOR, HAIR FOLLICLE, BEN*	2/50 (41) 0.0121	4/50 (39) 0.3139	6/50 (37) 0.1010	9/50 (39) 0.0192
THYROID	B-ADENOMA, FOLLICULAR CELL	6/50 (42) 0.0430	4/50 (40) 0.8233	5/50 (37) 0.6620	10/50 (40) 0.1725
Whold Body	C_Hemangiosarcoma+Hemangioma	6/50 (42) 0.0281	10/50 (41) 0.1874	7/50 (37) 0.4001	14/50 (41) 0.0308

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water
Control and Treated Groups -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
MAMMARY GLAND	B-FIBROADENOMA	9/50 (43) 0.0827	14/50 (42) 0.1485	17/50 (43) 0.0497	16/50 (41) 0.0574

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 5: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle
Control and Treated Groups -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
UTERUS	M-ADENOCARCINOMA, ENDOMETRI*	1/50 (42) 0.0021	0/50 (41) 1.0000	2/50 (41) 0.4909	6/50 (39) 0.0438

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

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Ph.D.

Zhuang Miao,

Statistician

Mathematical

Concur:

Rahman, Atiar Mohammad, Ph.D.

Mathematical Statistician, Deputy Director, Biometrics-6

cc:

Yi Tsong, Ph.D.

Appendix

Table 6: Intercurrent Mortality Rate -Male Rats

Week	0 mg/kg/day Water		0 mg/kg/day Vehicle		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	2.00	.	.	2	4.00	2	4.00	1	2.00
53 - 78	4	10.00	8	16.00	8	20.00	11	26.00	9	20.00
79 - 99	7	24.00	7	30.00	4	28.00	7	40.00	10	40.00
92 - 104	12	48.00	8	46.00	11	50.00	5	50.00	7	54.00
Ter. Sac.	26	52.00	27	54.00	25	50.00	25	50.00	23	46.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 7: Intercurrent Mortality Rate -Female Rats

Week	0 mg/kg/day Water		0 mg/kg/day Vehicle		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	2.00	.	.	2	4.00	2	4.00	4	8.00
53 - 78	6	14.00	8	16.00	1	6.00	4	12.00	5	18.00
79 - 99	2	18.00	3	22.00	8	22.00	10	32.00	5	28.00
92 - 104	13	44.00	10	42.00	15	52.00	8	48.00	11	50.00
Ter. Sac.	28	56.00	29	58.00	24	48.00	26	52.00	25	50.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Comparison between Treated Groups and Water Control -Male Rats

Test	Statistic	P_Value	P_Value	P_Value	P_Value
		Water vs Treated Groups Dose Response	Water vs. Low	Water vs. Med	Water vs. High
Dose-Response	Likelihood Ratio	0.4697	0.7409	0.5328	0.4167
Homogeneity	Log-Rank	0.8714	0.7395	0.5296	0.4116

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.4154	0.6188	0.4592	0.3384
Homogeneity	Log-Rank	0.8068	0.6162	0.4546	0.3343

Table 10: Intercurrent Mortality Comparison between Treated Groups and Water Control -Female Rats

Test	Statistic	P_Value Water vs Treated Groups Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High
Dose-Response	Likelihood Ratio	0.6266	0.4326	0.6307	0.4505
Homogeneity	Log-Rank	0.8529	0.4263	0.6289	0.4469

Table 11: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.5690	0.3876	0.5273	0.3681
Homogeneity	Log-Rank	0.7918	0.3823	0.5243	0.3643

Table 12: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
ADIPOSE, WHITE	B-FIBROMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
ADRENAL	B-ADENOMA, CORTEX	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	B-GANGLIONEUROMA, BENIGN	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	B-PHEOCHROMOCYTOMA, BENIGN	1/50 (41) 0.6665	0/50 (39) 1.0000	2/50 (37) 0.4611	0/50 (37) 1.0000
	M-PHEOCHROMOCYTOMA, MALIGNA*	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
BRAIN	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.0565	0/50 (39) NC	0/50 (37) NC	2/50 (37) 0.2218
	M-EPENDYMOMA, MALIGNANT	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-TUMOR, GRANULAR CELL, MAL*	2/50 (41) 0.9361	2/50 (39) 0.6731	1/50 (37) 0.8599	0/50 (37) 1.0000
CECUM	B-LEIOMYOMA	0/50 (41) 0.0573	0/50 (39) NC	0/49 (36) NC	2/49 (37) 0.2218
CONNECTIVE TISSUE	B-FIBROMA	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
	M-LIPOSARCOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-SCHWANNOMA, MALIGNANT	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
EAR	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4744
	B-TUMOR, BASAL CELL, BENIGN	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
	M-TUMOR, BASAL CELL, MALIGN*	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
EPIDIDYMIS	B-SCHWANNOMA, BENIGN	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-MESOTHELIOMA, MALIGNANT	1/50 (41) 0.4314	0/50 (39) 1.0000	0/50 (37) 1.0000	1/50 (38) 0.7339
EYE	B-LEIOMYOMA, UVEA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
FOOT	M-CARCINOMA, BASAL CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
HEMOLYMPHO- RETICU	M-HISTIOCYTIC SARCOMA	1/50 (41) 0.8115	1/50 (39) 0.7405	1/50 (37) 0.7269	0/50 (37) 1.0000
	M-MALIGNANT LYMPHOMA- LYMPHO*	1/50 (41) 0.6677	0/50 (39) 1.0000	2/50 (38) 0.4712	0/50 (37) 1.0000
JEJUNUM	M-HEMANGIOSARCOMA	1/50 (41) 1.0000	0/48 (37) 1.0000	0/48 (36) 1.0000	0/49 (36) 1.0000
KIDNEY	M-NEPHROBLASTOMA	0/50 (41) 0.7355	1/50 (40) 0.4938	0/50 (37) NC	0/50 (37) NC
LIVER	B-ADENOMA, HEPATOCYTE	0/50 (41) 0.2743	1/50 (39) 0.4875	1/50 (37) 0.4744	1/50 (37) 0.4744
	B-CHOLANGIOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-CARCINOMA, HEPATOCYTE	0/50 (41) 0.2452	0/50 (39) NC	0/50 (37) NC	1/50 (38) 0.4810
LYMPH NODE, MANDIB	M-HEMANGIOSARCOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
LYMPH NODE, MEDIAS	B-HEMANGIOMA	1/48 (39) 1.0000	0/49 (38) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-HEMANGIOSARCOMA	0/48 (39) 0.4901	0/49 (38) NC	1/50 (37) 0.4868	0/50 (37) NC
LYMPH NODE, MESENT	B-HEMANGIOMA	2/50 (42) 0.0137	5/49 (39) 0.1864	4/50 (37) 0.2788	9/50 (39) 0.0174
	M-HEMANGIOSARCOMA	1/50 (41) 0.2008	4/49 (38) 0.1566	3/50 (37) 0.2696	4/50 (39) 0.1642
Liver	C_Hepatocyte adenoma+carcinoma	0/50 (41) 0.1100	1/50 (39) 0.4875	1/50 (37) 0.4744	2/50 (38) 0.2282
MUSCLE, BICEPS FEM	M-HEMANGIOSARCOMA	0/50 (41) 0.2452	0/50 (39) NC	0/50 (37) NC	1/50 (38) 0.4810
	M-RHABDOMYOSARCOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
MUSCLE, OTHER	M-RHABDOMYOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-SCHWANNOMA, MALIGNANT	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
NASAL CAVITY	M-SARCOMA	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
PANCREAS	B-ADENOMA, ACINAR CELL	0/50 (41) 0.2952	1/50 (39) 0.4875	0/50 (37) NC	1/50 (37) 0.4744
	B-ADENOMA, ISLET CELL	3/50 (41) 0.6524	3/50 (39) 0.6381	4/50 (37) 0.4418	2/50 (37) 0.7870

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
	M-CARCINOMA, ISLET CELL	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
PARATHYROID	B-ADENOMA	0/50 (41) 0.1959	0/46 (35) NC	2/48 (35) 0.2088	1/50 (37) 0.4744
PAROTID SALIVARY G	M-ADENOCARCINOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
PITUITARY	B-ADENOMA, PARS DISTALIS	20/50 (45) 0.9863	20/50 (43) 0.5077	14/48 (39) 0.8458	10/50 (40) 0.9828
	M-CARCINOMA, PARS DISTALIS	0/50 (41) 0.1758	0/50 (39) NC	1/48 (36) 0.4675	1/50 (38) 0.4810
PREPUTIAL GLAND	M-CARCINOMA, SQUAMOUS CELL	0/49 (41) 0.7320	1/50 (39) 0.4875	0/50 (37) NC	0/48 (36) NC
PROSTATE	B-ADENOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-ADENOCARCINOMA	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
Pancreas	C_Acinar cell adenoma+islet cell adenoma	3/50 (41) 0.5283	4/50 (39) 0.4716	4/50 (37) 0.4418	3/50 (37) 0.6120
SKIN/SUBCUTIS	B-DERMAL FIBROMA	4/50 (41) 0.1315	1/50 (39) 0.9688	3/50 (37) 0.7396	5/50 (38) 0.4508
	B-FIBROMA	1/50 (41) 0.7318	0/50 (39) 1.0000	1/50 (37) 0.7269	0/50 (37) 1.0000
	B-KERATOACANTHOMA	1/50 (41) 0.4863	1/50 (39) 0.7405	1/50 (37) 0.7269	1/50 (37) 0.7269
	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.1848	0/50 (39) NC	2/50 (37) 0.2218	1/50 (37) 0.4744
	B-TUMOR, BASAL CELL, BENIGN	1/50 (41) 0.3683	0/50 (39) 1.0000	1/50 (37) 0.7269	1/50 (37) 0.7269
	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	B-TUMOR, HAIR FOLLICLE, BEN*	2/50 (41) 0.0121	4/50 (39) 0.3139	6/50 (37) 0.1010	9/50 (39) 0.0192
	M-CARCINOMA, BASAL CELL	0/50 (41) 0.6030	1/50 (39) 0.4875	1/50 (37) 0.4744	0/50 (37) NC
	M-CARCINOMA, SEBACEOUS CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-FIBROSARCOMA	2/50 (42) 0.9811	1/50 (39) 0.8654	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-HISTIOCYTIC SARCOMA	1/50 (41) 0.9304	1/50 (39) 0.7405	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-OSTEOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
	M-SARCOMA NOS	0/50 (41) 0.1767	0/50 (39) NC	1/50 (37) 0.4744	1/50 (38) 0.4810
SPLEEN	M-HEMANGIOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
STOMACH	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
	M-ADENOCARCINOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-CARCINOMA, SQUAMOUS CELL	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-SCHWANNOMA, MALIGNANT	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
Skin subcutis	C_Keratoacanthoma+squamous cell papilloma+carcinoma	1/50 (41) 0.2625	1/50 (39) 0.7405	3/50 (37) 0.2696	2/50 (37) 0.4611
TAIL	B-KERATOACANTHOMA	1/49 (40) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
	B-PAPILLOMA, SQUAMOUS CELL	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4805
	M-FIBROSARCOMA	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4805
TESTIS	B-ADENOMA, LEYDIG CELL	2/50 (42) 0.4676	2/50 (39) 0.6636	1/50 (37) 0.8548	2/50 (38) 0.6534
	M-CARCINOMA, RETE TESTIS	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-MESOTHELIOMA, MALIGNANT	1/50 (41) 0.5042	1/50 (39) 0.7405	3/50 (37) 0.2696	1/50 (38) 0.7339
THYMUS	B-THYMOMA, BENIGN	2/48 (39) 0.8800	1/43 (33) 0.8468	3/47 (36) 0.4615	0/49 (37) 1.0000
THYROID	B-ADENOMA, C-CELL	6/50 (41) 0.7553	9/50 (40) 0.2664	3/50 (37) 0.8966	5/50 (39) 0.7109
	B-ADENOMA, FOLLICULAR CELL	6/50 (42) 0.0430	4/50 (40) 0.8233	5/50 (37) 0.6620	10/50 (40) 0.1725
	M-CARCINOMA, C-CELL	1/50 (41) 0.4693	1/50 (39) 0.7405	2/50 (37) 0.4611	1/50 (37) 0.7269
	M-CARCINOMA, FOLLICULAR CELL	3/50 (41) 0.5834	2/50 (39) 0.8045	2/50 (37) 0.7870	2/50 (37) 0.7870
TONGUE	B-PAPILLOMA, SQUAMOUS CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
Thyroid	C_C cell adenoma+carcinoma	6/50 (41) 0.6741	10/50 (40) 0.1863	5/50 (37) 0.6779	6/50 (39) 0.5856
	C_Follicular cell adenoma+carcinoma	8/50 (42) 0.1010	6/50 (40) 0.7817	7/50 (37) 0.6169	11/50 (40) 0.2596

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
URINARY BLADDER	M-CARCINOMA, UROTHELIAL	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4805
Whold Body	C_Hemangiosarcoma+Hemangioma	6/50 (42) 0.0281	10/50 (41) 0.1874	7/50 (37) 0.4001	14/50 (41) 0.0308

Table 13: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
ADIPOSE, WHITE	B-FIBROMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
ADRENAL	B-ADENOMA, CORTEX	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	B-GANGLIONEUROMA, BENIGN	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	B-PHEOCHROMOCYTOMA, BENIGN	1/50 (41) 0.6665	0/50 (39) 1.0000	2/50 (37) 0.4611	0/50 (37) 1.0000
	M-PHEOCHROMOCYTOMA, MALIGNA*	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
BRAIN	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.0565	0/50 (39) NC	0/50 (37) NC	2/50 (37) 0.2218
	M-EPENDYMOMA, MALIGNANT	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-TUMOR, GRANULAR CELL, MAL*	2/50 (41) 0.9361	2/50 (39) 0.6731	1/50 (37) 0.8599	0/50 (37) 1.0000
CECUM	B-LEIOMYOMA	0/50 (41) 0.0573	0/50 (39) NC	0/49 (36) NC	2/49 (37) 0.2218
CONNECTIVE TISSUE	B-FIBROMA	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
	M-LIPOSARCOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-SCHWANNOMA, MALIGNANT	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
EAR	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4744
	B-TUMOR, BASAL CELL, BENIGN	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
	M-TUMOR, BASAL CELL, MALIGN*	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
EPIDIDYMIS	B-SCHWANNOMA, BENIGN	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-MESOTHELIOMA, MALIGNANT	1/50 (41) 0.4314	0/50 (39) 1.0000	0/50 (37) 1.0000	1/50 (38) 0.7339
EYE	B-LEIOMYOMA, UVEA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
FOOT	M-CARCINOMA, BASAL CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
HEMOLYMPHO- RETICU	M-HISTIOCYTIC SARCOMA	1/50 (41) 0.8115	1/50 (39) 0.7405	1/50 (37) 0.7269	0/50 (37) 1.0000
	M-MALIGNANT LYMPHOMA- LYMPHO*	1/50 (41) 0.6677	0/50 (39) 1.0000	2/50 (38) 0.4712	0/50 (37) 1.0000
JEJUNUM	M-HEMANGIOSARCOMA	1/50 (41) 1.0000	0/48 (37) 1.0000	0/48 (36) 1.0000	0/49 (36) 1.0000
KIDNEY	M-NEPHROBLASTOMA	0/50 (41) 0.7355	1/50 (40) 0.4938	0/50 (37) NC	0/50 (37) NC
LIVER	B-ADENOMA, HEPATOCYTE	0/50 (41) 0.2743	1/50 (39) 0.4875	1/50 (37) 0.4744	1/50 (37) 0.4744
	B-CHOLANGIOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-CARCINOMA, HEPATOCYTE	0/50 (41) 0.2452	0/50 (39) NC	0/50 (37) NC	1/50 (38) 0.4810
LYMPH NODE, MANDIB	M-HEMANGIOSARCOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
LYMPH NODE, MEDIAS	B-HEMANGIOMA	1/48 (39) 1.0000	0/49 (38) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-HEMANGIOSARCOMA	0/48 (39) 0.4901	0/49 (38) NC	1/50 (37) 0.4868	0/50 (37) NC
LYMPH NODE, MESENT	B-HEMANGIOMA	2/50 (42) 0.0137	5/49 (39) 0.1864	4/50 (37) 0.2788	9/50 (39) 0.0174
	M-HEMANGIOSARCOMA	1/50 (41) 0.2008	4/49 (38) 0.1566	3/50 (37) 0.2696	4/50 (39) 0.1642
Liver	C_Hepatocyte adenoma+carcinoma	0/50 (41) 0.1100	1/50 (39) 0.4875	1/50 (37) 0.4744	2/50 (38) 0.2282
MUSCLE, BICEPS FEM	M-HEMANGIOSARCOMA	0/50 (41) 0.2452	0/50 (39) NC	0/50 (37) NC	1/50 (38) 0.4810
	M-RHABDOMYOSARCOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
MUSCLE, OTHER	M-RHABDOMYOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-SCHWANNOMA, MALIGNANT	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
NASAL CAVITY	M-SARCOMA	1/50 (42) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
PANCREAS	B-ADENOMA, ACINAR CELL	0/50 (41) 0.2952	1/50 (39) 0.4875	0/50 (37) NC	1/50 (37) 0.4744
	B-ADENOMA, ISLET CELL	3/50 (41) 0.6524	3/50 (39) 0.6381	4/50 (37) 0.4418	2/50 (37) 0.7870

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
	M-CARCINOMA, ISLET CELL	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
PARATHYROID	B-ADENOMA	0/50 (41) 0.1959	0/46 (35) NC	2/48 (35) 0.2088	1/50 (37) 0.4744
PAROTID SALIVARY G	M-ADENOCARCINOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
PITUITARY	B-ADENOMA, PARS DISTALIS	20/50 (45) 0.9863	20/50 (43) 0.5077	14/48 (39) 0.8458	10/50 (40) 0.9828
	M-CARCINOMA, PARS DISTALIS	0/50 (41) 0.1758	0/50 (39) NC	1/48 (36) 0.4675	1/50 (38) 0.4810
PREPUTIAL GLAND	M-CARCINOMA, SQUAMOUS CELL	0/49 (41) 0.7320	1/50 (39) 0.4875	0/50 (37) NC	0/48 (36) NC
PROSTATE	B-ADENOMA	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-ADENOCARCINOMA	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
Pancreas	C_Acinar cell adenoma+islet cell adenoma	3/50 (41) 0.5283	4/50 (39) 0.4716	4/50 (37) 0.4418	3/50 (37) 0.6120
SKIN/SUBCUTIS	B-DERMAL FIBROMA	4/50 (41) 0.1315	1/50 (39) 0.9688	3/50 (37) 0.7396	5/50 (38) 0.4508
	B-FIBROMA	1/50 (41) 0.7318	0/50 (39) 1.0000	1/50 (37) 0.7269	0/50 (37) 1.0000
	B-KERATOACANTHOMA	1/50 (41) 0.4863	1/50 (39) 0.7405	1/50 (37) 0.7269	1/50 (37) 0.7269
	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.1848	0/50 (39) NC	2/50 (37) 0.2218	1/50 (37) 0.4744
	B-TUMOR, BASAL CELL, BENIGN	1/50 (41) 0.3683	0/50 (39) 1.0000	1/50 (37) 0.7269	1/50 (37) 0.7269
	B-TUMOR, GRANULAR CELL, BEN*	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	B-TUMOR, HAIR FOLLICLE, BEN*	2/50 (41) 0.0121	4/50 (39) 0.3139	6/50 (37) 0.1010	9/50 (39) 0.0192
	M-CARCINOMA, BASAL CELL	0/50 (41) 0.6030	1/50 (39) 0.4875	1/50 (37) 0.4744	0/50 (37) NC
	M-CARCINOMA, SEBACEOUS CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-FIBROSARCOMA	2/50 (42) 0.9811	1/50 (39) 0.8654	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-HISTIOCYTIC SARCOMA	1/50 (41) 0.9304	1/50 (39) 0.7405	0/50 (37) 1.0000	0/50 (37) 1.0000
	M-OSTEOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
	M-SARCOMA NOS	0/50 (41) 0.1767	0/50 (39) NC	1/50 (37) 0.4744	1/50 (38) 0.4810
SPLEEN	M-HEMANGIOSARCOMA	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
STOMACH	B-PAPILLOMA, SQUAMOUS CELL	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
	M-ADENOCARCINOMA	0/50 (41) 0.2403	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4744
	M-CARCINOMA, SQUAMOUS CELL	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-SCHWANNOMA, MALIGNANT	0/50 (41) 0.4805	0/50 (39) NC	1/50 (37) 0.4744	0/50 (37) NC
Skin subcutis	C_Keratoacanthoma+squamous cell papilloma+carcinoma	1/50 (41) 0.2625	1/50 (39) 0.7405	3/50 (37) 0.2696	2/50 (37) 0.4611
TAIL	B-KERATOACANTHOMA	1/49 (40) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/49 (36) 1.0000
	B-PAPILLOMA, SQUAMOUS CELL	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4805
	M-FIBROSARCOMA	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/49 (37) 0.4805
TESTIS	B-ADENOMA, LEYDIG CELL	2/50 (42) 0.4676	2/50 (39) 0.6636	1/50 (37) 0.8548	2/50 (38) 0.6534
	M-CARCINOMA, RETE TESTIS	0/50 (41) 0.7338	1/50 (39) 0.4875	0/50 (37) NC	0/50 (37) NC
	M-MESOTHELIOMA, MALIGNANT	1/50 (41) 0.5042	1/50 (39) 0.7405	3/50 (37) 0.2696	1/50 (38) 0.7339
THYMUS	B-THYMOMA, BENIGN	2/48 (39) 0.8800	1/43 (33) 0.8468	3/47 (36) 0.4615	0/49 (37) 1.0000
THYROID	B-ADENOMA, C-CELL	6/50 (41) 0.7553	9/50 (40) 0.2664	3/50 (37) 0.8966	5/50 (39) 0.7109
	B-ADENOMA, FOLLICULAR CELL	6/50 (42) 0.0430	4/50 (40) 0.8233	5/50 (37) 0.6620	10/50 (40) 0.1725
	M-CARCINOMA, C-CELL	1/50 (41) 0.4693	1/50 (39) 0.7405	2/50 (37) 0.4611	1/50 (37) 0.7269
	M-CARCINOMA, FOLLICULAR CELL	3/50 (41) 0.5834	2/50 (39) 0.8045	2/50 (37) 0.7870	2/50 (37) 0.7870
TONGUE	B-PAPILLOMA, SQUAMOUS CELL	1/50 (41) 1.0000	0/50 (39) 1.0000	0/50 (37) 1.0000	0/50 (37) 1.0000
Thyroid	C_C cell adenoma+carcinoma	6/50 (41) 0.6741	10/50 (40) 0.1863	5/50 (37) 0.6779	6/50 (39) 0.5856
	C_Follicular cell adenoma+carcinoma	8/50 (42) 0.1010	6/50 (40) 0.7817	7/50 (37) 0.6169	11/50 (40) 0.2596

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
URINARY BLADDER	M-CARCINOMA, UROTHELIAL	0/49 (40) 0.2418	0/50 (39) NC	0/50 (37) NC	1/50 (37) 0.4805
Whold Body	C_Hemangiosarcoma+Hemangioma	6/50 (42) 0.0281	10/50 (41) 0.1874	7/50 (37) 0.4001	14/50 (41) 0.0308

Table 14: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
ADRENAL	B-ADENOMA, CORTEX	0/50 (42) 0.4845	0/50 (41) NC	2/50 (41) 0.2410	0/50 (39) NC
	B-PHEOCHROMOCYTOMA, BENIGN	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-PHEOCHROMOCYTOMA, COMPLEX*	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-PHEOCHROMOCYTOMA, MALIGNA*	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
BRAIN	M-ASTROCYTOMA, MALIGNANT	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-OLIGODENDROGLIOMA, MALIGN*	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
CONNECTIVE TISSUE	M-CARCINOMA, UNDIFFERENTIAT*	0/50 (42) 0.4938	0/49 (40) NC	1/50 (41) 0.4940	0/50 (39) NC
DUODENUM	B-LEIOMYOMA	0/49 (41) 0.7469	1/50 (41) 0.5000	0/50 (41) NC	0/50 (39) NC
FEMUR + MARROW	M-OSTEOSARCOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
HEART	M-SCHWANNOMA, ENDOCARDIAL	1/50 (42) 0.7423	0/50 (41) 1.0000	1/50 (41) 0.7470	0/50 (39) 1.0000
HEMOLYMPHO- RETICU	M-LYMPHOCYTIC LEUKAEMIA	0/50 (42) 0.2439	0/50 (41) NC	0/50 (41) NC	1/50 (40) 0.4878
JEJUNUM	B-LEIOMYOMA	0/49 (41) 0.2407	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4875
KIDNEY	M-NEPHROBLASTOMA	0/50 (42) 0.2439	0/50 (41) NC	0/50 (41) NC	1/50 (40) 0.4878
LIVER	B-ADENOMA, HEPATOCYTE	3/50 (42) 0.2782	3/50 (41) 0.6505	1/50 (41) 0.9391	4/50 (40) 0.4723
	M-CARCINOMA, HEPATOCYTE	0/50 (42) 0.1877	0/50 (41) NC	2/50 (41) 0.2410	1/50 (39) 0.4815
LYMPH NODE, MESENT	B-HEMANGIOMA	0/50 (42) 0.1816	2/50 (41) 0.2410	1/50 (41) 0.4940	2/50 (39) 0.2287
	M-HEMANGIOSARCOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
MAMMARY GLAND	B-ADENOMA	1/50 (42) 0.7857	5/50 (41) 0.0953	5/50 (42) 0.1008	1/50 (39) 0.7343
	B-FIBROADENOMA	9/50 (43) 0.0827	14/50 (42) 0.1485	17/50 (43) 0.0497	16/50 (41) 0.0574

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
	M-ADENOCARCINOMA	7/50 (44) 0.6478	3/50 (42) 0.9478	1/50 (41) 0.9963	4/50 (40) 0.8702
	M-ADENOCARCINOMA ARISING IN*	0/50 (42) 0.6118	1/50 (41) 0.4940	1/50 (41) 0.4940	0/50 (39) NC
MESENTERY	M-SARCOMA NOS	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
MUSCLE, BICEPS FEM	B-TUMOR, GRANULAR CELL, BEN*	0/50 (42) 0.6133	1/49 (40) 0.4878	1/50 (41) 0.4940	0/50 (39) NC
MUSCLE, OTHER	B-HEMANGIOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
OVARY	B-ADENOMA, RETE OVARIII	2/50 (42) 0.5461	0/50 (41) 1.0000	1/50 (41) 0.8751	1/50 (39) 0.8654
	B-TUMOR, GRANULOSA CELL, BE*	1/50 (42) 0.4224	0/50 (41) 1.0000	0/50 (41) 1.0000	1/50 (39) 0.7343
	B-TUMOR, SERTOLI CELL, BENI*	0/50 (42) 0.1772	0/50 (41) NC	1/50 (41) 0.4940	1/50 (39) 0.4815
	M-THECOMA, MALIGNANT	0/50 (42) 0.1788	2/50 (42) 0.2470	0/50 (41) NC	2/50 (40) 0.2349
PANCREAS	B-ADENOMA, ISLET CELL	1/49 (41) 0.6804	0/49 (40) 1.0000	2/50 (41) 0.5000	0/50 (39) 1.0000
PARATHYROID	B-ADENOMA	0/49 (41) 0.4906	0/49 (40) NC	1/48 (39) 0.4875	0/50 (39) NC
PITUITARY	B-ADENOMA, PARS DISTALIS	26/50 (46) 0.7625	29/50 (45) 0.2885	28/50 (44) 0.3182	23/50 (43) 0.6916
	B-ADENOMA, PARS INTERMEDIA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
	M-CARCINOMA, PARS DISTALIS	4/50 (42) 0.9893	2/50 (42) 0.8992	1/50 (41) 0.9707	0/50 (39) 1.0000
SKIN/SUBCUTIS	B-DERMAL FIBROMA	1/50 (42) 0.6082	2/50 (41) 0.4909	0/50 (41) 1.0000	1/50 (39) 0.7343
	B-FIBROMA	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
	B-HEMANGIOMA	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	B-KERATOACANTHOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-PAPILLOMA, SQUAMOUS CELL	1/50 (42) 0.5149	1/50 (41) 0.7470	0/50 (41) 1.0000	1/50 (39) 0.7343
	B-TUMOR, BASAL CELL, BENIGN	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-TUMOR, HAIR FOLLICLE, BEN*	1/50 (42) 0.3750	0/50 (41) 1.0000	1/50 (41) 0.7470	1/50 (39) 0.7343

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
	M-CARCINOMA, BASAL CELL	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	M-CARCINOMA, SQUAMOUS CELL	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
	M-FIBROSARCOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
Skin Subcutis	C_Keratoacanthoma+Papilloma+Carci noma	1/50 (42) 0.3102	2/50 (41) 0.4909	0/50 (41) 1.0000	2/50 (39) 0.4719
THORACIC CAVITY	M-LIPOSARCOMA	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
THYMUS	B-THYMOMA, BENIGN	5/50 (43) 0.8485	4/49 (40) 0.7209	5/47 (39) 0.5665	2/49 (39) 0.9290
THYROID	B-ADENOMA, C-CELL	2/50 (42) 0.4297	4/50 (41) 0.3263	3/50 (41) 0.4884	3/50 (39) 0.4644
	B-ADENOMA, FOLLICULAR CELL	2/50 (42) 0.2304	1/50 (41) 0.8751	5/50 (41) 0.2063	3/50 (39) 0.4644
	M-CARCINOMA, C-CELL	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-CARCINOMA, FOLLICULAR CELL	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
TONGUE	B-TUMOR, GRANULAR CELL, BEN*	0/50 (42) 0.6118	1/50 (41) 0.4940	1/50 (41) 0.4940	0/50 (39) NC
Thyroid	C_C cell adenoma+carcinoma	2/50 (42) 0.5034	5/50 (41) 0.2063	3/50 (41) 0.4884	3/50 (39) 0.4644
	C_Follicular cell adenoma+carcinoma	2/50 (42) 0.2384	1/50 (41) 0.8751	6/50 (41) 0.1245	3/50 (39) 0.4644
UTERUS	B-LEIOMYOMA	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
	B-POLYP, ENDOMETRIAL STROMAL	7/50 (42) 0.1994	8/50 (42) 0.5000	6/50 (42) 0.7261	10/50 (42) 0.2940
	M-ADENOCARCINOMA, ENDOMETRI*	6/50 (43) 0.0971	0/50 (41) 1.0000	2/50 (41) 0.9664	6/50 (39) 0.5498
	M-CARCINOMA, ADENOSQUAMOUS	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-HISTIOCYTIC SARCOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
	M-SARCOMA, ENDOMETRIAL STRO*	0/50 (42) 0.4845	0/50 (41) NC	2/50 (41) 0.2410	0/50 (39) NC
	M-SCHWANNOMA, MALIGNANT	0/50 (42) 0.1816	2/50 (41) 0.2410	1/50 (41) 0.4940	2/50 (39) 0.2287

Organ Name	Tumor Name	0 mg/kg/day Water (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Water vs. Low	100 mg/kg/day Mid (N=50) P-value - Water vs. Med	300 mg/kg/day High (N=50) P-value - Water vs. High
Uterus	C_endometrial stromal polyp+sarcoma	7/50 (42) 0.2045	8/50 (42) 0.5000	7/50 (43) 0.6330	10/50 (42) 0.2940
Whold Body	C_Hemangiosarcoma+Hemangioma	1/50 (42) 0.3513	2/50 (41) 0.4909	3/50 (41) 0.2988	2/50 (39) 0.4719

Table 15: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups- Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
ADRENAL	B-ADENOMA, CORTEX	1/50 (42) 0.6734	0/50 (41) 1.0000	2/50 (41) 0.4909	0/50 (39) 1.0000
	B-PHEOCHROMOCYTOMA, BENIGN	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-PHEOCHROMOCYTOMA, COMPLEX*	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-PHEOCHROMOCYTOMA, MALIGNA*	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
BRAIN	B-TUMOR, GRANULAR CELL, BEN*	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	M-ASTROCYTOMA, MALIGNANT	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-OLIGODENDROGLIOMA, MALIGN*	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
CONNECTIVE TISSUE	M-CARCINOMA, UNDIFFERENTIAT*	0/50 (42) 0.4938	0/49 (40) NC	1/50 (41) 0.4940	0/50 (39) NC
DUODENUM	B-LEIOMYOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
EAR	B-TUMOR, GRANULAR CELL, BEN*	1/50 (42) 1.0000	0/49 (40) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
FEMUR + MARROW	M-OSTEOSARCOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
FOOT	B-TUMOR, HAIR FOLLICLE, BEN*	1/48 (40) 1.0000	0/49 (40) 1.0000	0/49 (40) 1.0000	0/50 (39) 1.0000
HEART	M-SCHWANNOMA, ENDOCARDIAL	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
HEMOLYMPHO- RETICU	M-LYMPHOCYTIC LEUKAEMIA	0/50 (42) 0.2439	0/50 (41) NC	0/50 (41) NC	1/50 (40) 0.4878
	M-MALIGNANT LYMPHOMA- LYMPHO*	1/50 (43) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
JEJUNUM	B-LEIOMYOMA	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
KIDNEY	M-NEPHROBLASTOMA	0/50 (42) 0.2439	0/50 (41) NC	0/50 (41) NC	1/50 (40) 0.4878
LIVER	B-ADENOMA, HEPATOCYTE	1/50 (42) 0.1124	3/50 (41) 0.2988	1/50 (41) 0.7470	4/50 (40) 0.1648
	M-CARCINOMA, HEPATOCYTE	1/50 (42) 0.3506	0/50 (41) 1.0000	2/50 (41) 0.4909	1/50 (39) 0.7343

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
LYMPH NODE, MESENT	B-HEMANGIOMA	2/50 (42) 0.4687	2/50 (41) 0.6830	1/50 (41) 0.8751	2/50 (39) 0.6636
	M-HEMANGIOSARCOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
MAMMARY GLAND	B-ADENOMA	1/49 (41) 0.7919	5/50 (41) 0.1006	5/50 (42) 0.1063	1/50 (39) 0.7405
	B-FIBROADENOMA	12/49 (43) 0.1743	14/50 (42) 0.3793	17/50 (43) 0.1809	16/50 (41) 0.1980
	M-ADENOCARCINOMA	6/49 (42) 0.5744	3/50 (42) 0.9222	1/50 (41) 0.9935	4/50 (40) 0.8233
	M-ADENOCARCINOMA ARISING IN*	1/49 (41) 0.8243	1/50 (41) 0.7531	1/50 (41) 0.7531	0/50 (39) 1.0000
MESENTERY	M-SARCOMA NOS	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
MUSCLE, BICEPS FEM	B-TUMOR, GRANULAR CELL, BEN*	0/50 (42) 0.6133	1/49 (40) 0.4878	1/50 (41) 0.4940	0/50 (39) NC
MUSCLE, OTHER	B-HEMANGIOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
OVARY	B-ADENOMA, RETE OVARIII	2/50 (42) 0.5461	0/50 (41) 1.0000	1/50 (41) 0.8751	1/50 (39) 0.8654
	B-TUMOR, GRANULOSA CELL, BE*	1/50 (42) 0.4224	0/50 (41) 1.0000	0/50 (41) 1.0000	1/50 (39) 0.7343
	B-TUMOR, SERTOLI CELL, BENI*	0/50 (42) 0.1772	0/50 (41) NC	1/50 (41) 0.4940	1/50 (39) 0.4815
	B-TUMOR, SEX CORD STROMAL, *	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	M-THECOMA, MALIGNANT	0/50 (42) 0.1788	2/50 (42) 0.2470	0/50 (41) NC	2/50 (40) 0.2349
PANCREAS	B-ADENOMA, ISLET CELL	0/49 (41) 0.4906	0/49 (40) NC	2/50 (41) 0.2469	0/50 (39) NC
PARATHYROID	B-ADENOMA	1/49 (41) 0.7421	0/49 (40) 1.0000	1/48 (39) 0.7405	0/50 (39) 1.0000
PITUITARY	B-ADENOMA, PARS DISTALIS	27/50 (47) 0.7789	29/50 (45) 0.3181	28/50 (44) 0.3490	23/50 (43) 0.7223
	B-ADENOMA, PARS INTERMEDIA	2/50 (42) 0.8703	0/50 (41) 1.0000	1/50 (41) 0.8751	0/50 (39) 1.0000
	M-CARCINOMA, PARS DISTALIS	0/50 (42) 0.7189	2/50 (42) 0.2470	1/50 (41) 0.4940	0/50 (39) NC
SKIN/SUBCUTIS	B-DERMAL FIBROMA	2/50 (42) 0.7448	2/50 (41) 0.6830	0/50 (41) 1.0000	1/50 (39) 0.8654
	B-FIBROMA	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
	B-KERATOACANTHOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-LIPOMA	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	B-PAPILLOMA, SQUAMOUS CELL	1/50 (42) 0.5149	1/50 (41) 0.7470	0/50 (41) 1.0000	1/50 (39) 0.7343
	B-TUMOR, BASAL CELL, BENIGN	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	B-TUMOR, HAIR FOLLICLE, BEN*	0/50 (42) 0.1772	0/50 (41) NC	1/50 (41) 0.4940	1/50 (39) 0.4815
	M-CARCINOMA, SQUAMOUS CELL	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
	M-FIBROSARCOMA	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
Skin Subcutis	C_Keratoacanthoma+Papilloma+Carci noma	1/50 (42) 0.3102	2/50 (41) 0.4909	0/50 (41) 1.0000	2/50 (39) 0.4719
THORACIC CAVITY	M-SCHWANNOMA, MALIGNANT	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
THYMUS	B-THYMOMA, BENIGN	6/50 (43) 0.8930	4/49 (40) 0.8125	5/47 (39) 0.6805	2/49 (39) 0.9607
THYROID	B-ADENOMA, C-CELL	4/50 (42) 0.6328	4/50 (41) 0.6300	3/50 (41) 0.7737	3/50 (39) 0.7521
	B-ADENOMA, FOLLICULAR CELL	3/50 (42) 0.3198	1/50 (41) 0.9391	5/50 (41) 0.3426	3/50 (39) 0.6260
	M-CARCINOMA, C-CELL	1/50 (42) 0.9348	1/50 (41) 0.7470	0/50 (41) 1.0000	0/50 (39) 1.0000
	M-CARCINOMA, FOLLICULAR CELL	1/50 (42) 0.7423	0/50 (41) 1.0000	1/50 (41) 0.7470	0/50 (39) 1.0000
TONGUE	B-TUMOR, GRANULAR CELL, BEN*	0/50 (42) 0.6118	1/50 (41) 0.4940	1/50 (41) 0.4940	0/50 (39) NC
Thyroid	C_C cell adenoma+carcinoma	5/50 (42) 0.7691	5/50 (41) 0.6154	3/50 (41) 0.8599	3/50 (39) 0.8428
	C_Follicular cell adenoma+carcinoma	4/50 (42) 0.4225	1/50 (41) 0.9707	6/50 (41) 0.3534	3/50 (39) 0.7521
UTERUS	B-LEIOMYOMA	0/50 (42) 0.2393	0/50 (41) NC	0/50 (41) NC	1/50 (39) 0.4815
	B-POLYP, ENDOMETRIAL STROMAL	7/50 (43) 0.1905	8/50 (42) 0.4798	6/50 (42) 0.7102	10/50 (42) 0.2757
	B-POLYP, GLANDULAR	1/50 (42) 1.0000	0/50 (41) 1.0000	0/50 (41) 1.0000	0/50 (39) 1.0000
	M-ADENOCARCINOMA, ENDOMETRI*	1/50 (42) 0.0021	0/50 (41) 1.0000	2/50 (41) 0.4909	6/50 (39) 0.0438

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=50) P-value - Trend	30 mg/kg/day Low (N=50) P-value - Vehicle vs. Low	100 mg/kg/day Mid (N=50) P-value - Vehicle vs. Med	300 mg/kg/day High (N=50) P-value - Vehicle vs. High
	M-CARCINOMA, ADENOSQUAMOUS	0/50 (42) 0.7423	1/50 (41) 0.4940	0/50 (41) NC	0/50 (39) NC
	M-HISTIOCYTIC SARCOMA	0/50 (42) 0.4908	0/50 (41) NC	1/50 (41) 0.4940	0/50 (39) NC
	M-SARCOMA, ENDOMETRIAL STRO*	0/50 (42) 0.4845	0/50 (41) NC	2/50 (41) 0.2410	0/50 (39) NC
	M-SCHWANNOMA, MALIGNANT	0/50 (42) 0.1816	2/50 (41) 0.2410	1/50 (41) 0.4940	2/50 (39) 0.2287
Uterus	C_endometrial stromal polyp+sarcoma	7/50 (43) 0.1953	8/50 (42) 0.4798	7/50 (43) 0.6144	10/50 (42) 0.2757
Whold Body	C_Hemangiosarcoma+Hemangioma	2/50 (42) 0.4739	2/50 (41) 0.6830	3/50 (41) 0.4884	2/50 (39) 0.6636

Figure 1: Kaplan-Meier Survival Functions for Male Rats

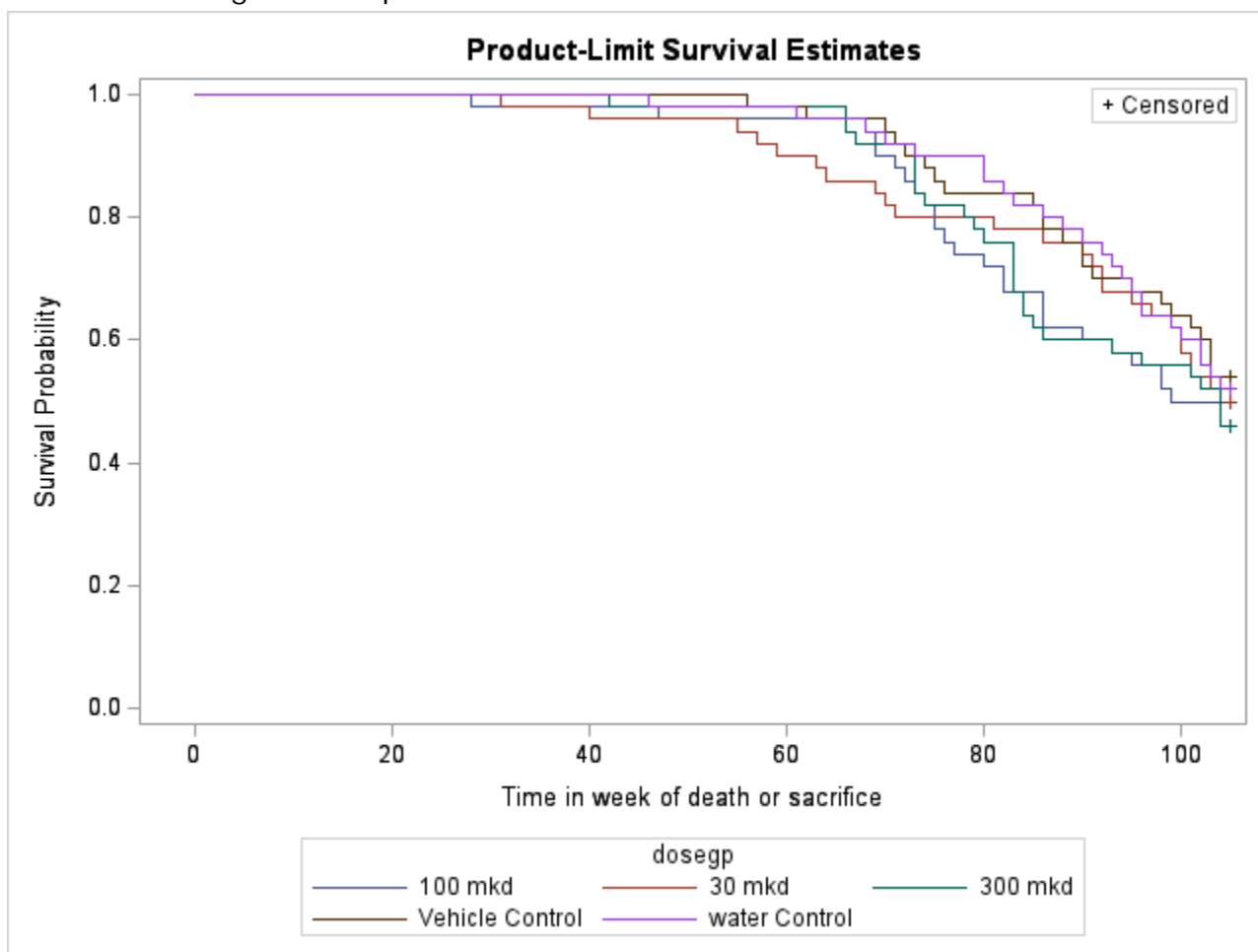
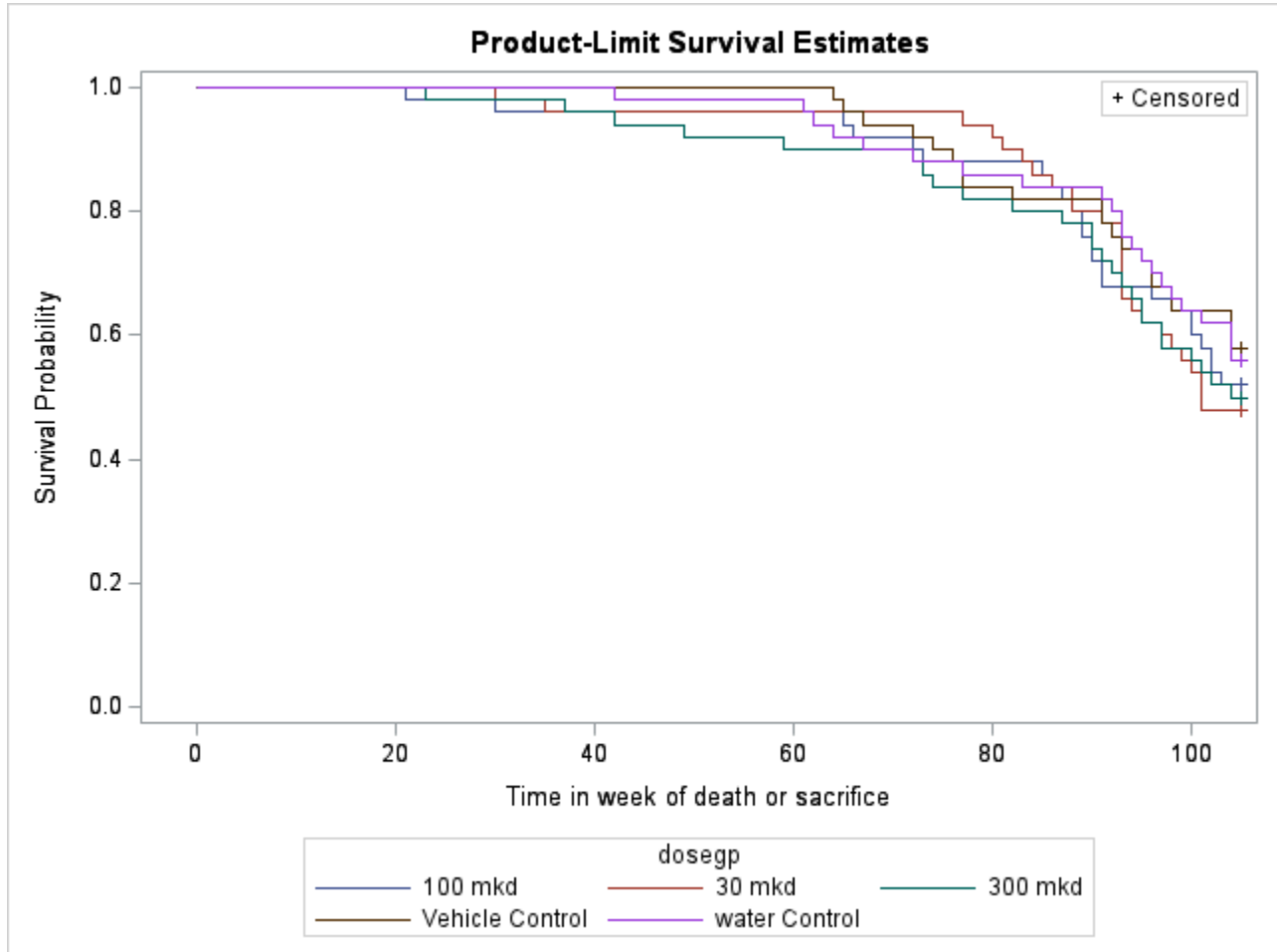


Figure 2: Kaplan-Meier Survival Functions for Female Rats



References

- Kaplan EL and Meier P (1958) Nonparametric estimation from incomplete observations. *J. Am. Statist. Assoc.*, 53, 457-481.
- Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*, 50, 163-170.
- Peto R (1974) Guidelines on the analysis of tumour rates and death rates in experimental animals. *British J. Cancer*, 29, 101-105.
- Lin KK (2000) Carcinogenicity Studies of Pharmaceuticals. In: *Encyclopedia of Biopharmaceutical Statistics*, ed. Shein-Chung Chow, Marcel Dekker, New York.
- Peto R et al. (1980) Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: *Long term and Short term Screen Assays for Carcinogens: A Critical Appraisal*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 2, pp.311-426. WHO International Agency for Research on Cancer, Lyon.
- SAS Institute (2002) SAS OnlineDoc® Version Nine. SAS Institute Inc., Cary, NC, USA.
- Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J.Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426, 1980.
- Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
- Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
- Tarone RE, "Test for trend in life table analysis", *Biometrika* 1975, 62: 679-82
- Lin K.K. and Rahman M.A., " Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15, 1998.

- Rahman, A.M., and K.K. Lin (2008), "A Comparison of False Positive Rates of Peto and Poly-3 methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
- Haseman, J, "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339, 1983.
- Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 2001.
- Lin, KK, and MA Rahman (2019), Comparisons of False Negative Rates from a Trend Test Alone and from a Trend Test Jointly with a Control-High Groups Pairwise Test in the Determination of the Carcinogenicity of New Drugs, *Journal of Biopharmaceutical Statistics*, 29(1):128-142.
- Lin, K.K., M.A. Rahman (2018), "Chapter 8: Expanded Statistical Decision Rules for Interpretations of Results of Rodent Carcinogenicity Studies of Pharmaceuticals", IN *Biopharmaceutical Applied Statistics Symposium, Volume 3: Pharmaceutical Applications*, Editors: Peace, Karl E., Chen, Ding-Geng, Menon, Sandeep (Eds.), recently published by Springer in August 2018, Pages 151-183.

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ZHUANG MIAO
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MOHAMMAD A RAHMAN
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