Official Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, Efficacy, and Safety Study of Povorcitinib in Participants With Chronic Spontaneous Urticaria

NCT Number: NCT05936567

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Clinical Study Protocol

INCB 54707-207

A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, Efficacy, and Safety Study of Povorcitinib in Participants With Chronic Spontaneous Urticaria

Product:	**Povorcitinib (INCB054707)**
IND Number:	[redacted]
EU CT Number:	**2022-503062-72-00**
Phase of Study:	**2**
Brief Title:	**Study Evaluating the Efficacy and Safety of Povorcitinib in Adults With Chronic Spontaneous Urticaria**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**07 MAR 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54707-207 Protocol (dated 07 MAR 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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[redacted]

[redacted]

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AAS	angioedema activity score
AD	atopic dermatitis
AE	adverse event
[redacted]	[redacted]
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
CABG	coronary arterial revascularization with bypass graft
CAC	cardiovascular adjudication committee
CI	confidence interval
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CSR	Clinical Study Report
CSU	chronic spontaneous urticaria
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CXR	chest x-ray
DILI	drug-induced liver injury
[redacted]	[redacted]
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
ECG	electrocardiogram
ECI	event of clinical interest
eCOA	electronic clinical outcome assessment
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EOT1	end of treatment during the placebo-controlled period
EOT2	end of treatment during the extension period

Abbreviations and Special Terms	Definition
EQ	EuroQol
[redacted]	[redacted]
ET	early termination
EXT	extension
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
hsCRP	high-sensitivity C-reactive protein
HSS	hive severity score
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon
IgE	immunoglobulin E
IGRA	interferon-gamma release assay
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISS	itch severity score
[redacted]	[redacted]

Abbreviations and Special Terms	Definition
ITT	intent-to-treat
JAK	Janus kinase
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MCP-mod	multiple-comparison procedure and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MID	minimally important difference
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PC	placebo-controlled
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPD	purified protein derivative
PRO	patient-reported outcome
PT	prothrombin time
QD	once daily
QTF	QuantiFERON®-TB
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
STD	standard deviation
TB	tuberculosis
TEAE	treatment-emergent adverse event
UAS	urticaria activity score
UAS7	urticaria activity score over 7 days

Abbreviations and Special Terms	Definition
UCT	urticaria control test
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	women of nonchildbearing potential
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, Efficacy, and Safety Study of Povorcitinib in Participants With Chronic Spontaneous Urticaria

Brief Title: A Study Evaluating the Efficacy and Safety of Povorcitinib in Adults With Chronic Spontaneous Urticaria

Protocol Number: INCB 54707-207

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of povorcitinib in participants with CSU.	Change from baseline in the UAS7, defined as the 7-day sum of the individual, daily recorded scores for HSS and ISS, at Week 12.
Secondary	
To further evaluate the efficacy of povorcitinib in participants with CSU.	• Proportion of participants who achieve UAS7 ≤ 6 (controlled disease) at Week 12. • Time to first achievement of UAS7 ≤ 6 (controlled disease) during the PC period. • Proportion of participants with UAS7 = 0 at Week 12.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Treatment of patients with CSU that is inadequately controlled by second-generation H1 antihistamines.
Population	Participants aged 18 to 65 years who have had a diagnosis of CSU for ≥ 3 months that is inadequately controlled by second-generation H1 antihistamines. Inadequately controlled CSU is defined as UAS7 ≥ 16 during the 7 days prior to randomization.
Number of Participants	Approximately 136 participants will be randomized 1:1:1:1 to 1 of 4 treatment groups (≈ 34 participants per group). Participants will be stratified by previous treatment of CSU with an anti-IgE biologic agent (yes or no).
Study Design	Multicenter, parallel-group, double-blind, randomized, placebo-controlled, dose-ranging study.
Estimated Duration of Study Participation	It is estimated that an individual will participate for approximately 48 weeks (11 months) as follows: • Screening: up to 28 days • PC period (double-blinded): 12 weeks • EXT period (double-blinded): 24 weeks • Post-treatment follow-up: 60 days (± 7 days) after last dose of study drug
DSMB	Yes (internal)
CAC	Yes
Coordinating Principal Investigator	Prof. Dr. Marcus Maurer

Treatment Groups and Duration:

The study will enroll approximately 136 participants in a 1:1:1:1 randomization ratio, stratified by previous anti-IgE biologic use, into 1 of 4 treatment groups during the double-blind, PC period (12 weeks).

After completing the 12-week PC period, participants will enter the 24-week EXT period. During the EXT period, the participants initially randomized to povorcitinib will continue taking povorcitinib at the same dose regimen (ie, povorcitinib 15, 45, or 75 mg QD). The participants initially randomized to placebo at baseline will receive povorcitinib 15, 45, or 75 mg QD.

Participants will receive study drug until completion of the 36-week treatment period or until 1 of the criteria for study treatment discontinuation are met. Participants will return for a follow-up visit approximately 60 days after their last dose of study drug.

All participants are required to maintain a background therapy of a stable dose of second-generation H1 antihistamine (SOC) during the study (ie, from screening through follow-up). The SOC will be determined by the investigator. Further doses of second-generation H1 antihistamine may be used as rescue medication to treat worsening CSU symptoms at any time during the study. A 1-time, short course (maximum duration of 7 days) of glucocorticosteroids may be used as rescue medication after Week 4 in the case of severe exacerbation.

Figure 1 presents the study design schema, and Table 3 presents the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

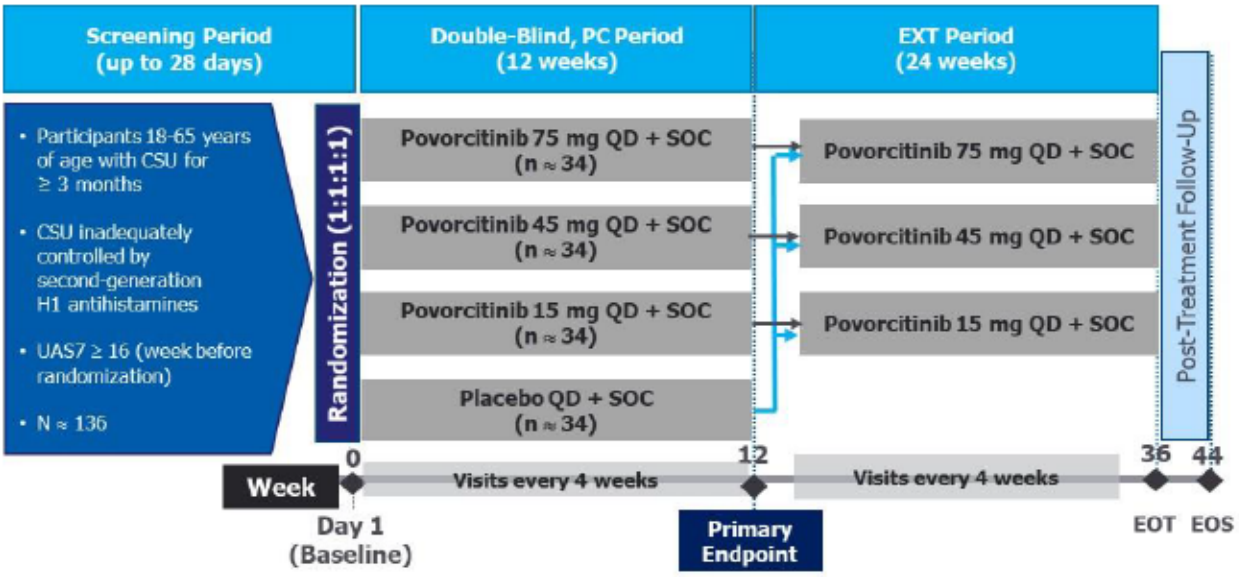


Table 3: Schedule of Activities

	Screening	PC Period (12 Weeks)				EXT Period (24 Weeks)						Post-Treatment Follow-Up	
Visit Day (Range)	Days −28 to −1	Baseline Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/ EOT1 (or ET1) (± 3 d)	Week 16 (± 3 d)	Week 20 (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36/ EOT2 (or ET2) (± 3 d)	Week 44/ EOS (± 7 d)	Notes and Protocol Section
Administrative procedures													
Informed consent	X												Section 8.1.1
Inclusion/exclusion criteria	X	X											Section 5
Demographic data, general medical history, and CSU medical and treatment history	X												Section 8.1.7
Previous use of anti-IgE biologic	X												
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.7
Rescue medication use		X	X	X	X	X	X	X	X	X	X	X	Section 6.7.3
Contact IRT	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.3
Dispense eDiary (handheld device) and instruct participant on use	X												Section 8.2.1.3
Randomization		X											Section 6.4
Dispense study drug		X	X	X	X	X	X	X	X	X			Section 6.1
Administer study drug at site		X	X	X	X	X	X	X	X	X	X		
Administer background therapy at site		X	X	X	X	X	X	X	X	X	X		
Distribute reminder card	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.4
Distribute participation card	X												Section 8.1.5

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	PC Period (12 Weeks)				EXT Period (24 Weeks)						Post-Treatment Follow-Up	Notes and Protocol Section
	Days −28 to −1	Baseline Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/ EOT1 (or ET1) (± 3 d)	Week 16 (± 3 d)	Week 20 (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36/ EOT2 (or ET2) (± 3 d)	Week 44/ EOS (± 7 d)	
Administrative procedures (continued)													
Collect study drug and review drug compliance			X	X	X	X	X	X	X	X	X		Section 6.5
Follow-up phone call for eDiary compliance	X*		X†		X*								Section 8.2.1.2.1 * 1 week before visit. † 2 weeks before visit.
Review eDiary compliance		X	X	X	X	X	X	X	X	X	X		Section 8.2.1.2.2
Safety assessments													
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.1
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	Section 5.3.1
Comprehensive physical examination	X				X						X		Section 8.3.2
Targeted physical examination		X	X	X		X	X	X	X	X		X	
Weight/height	X	X			X			X			X	X	Section 8.3.2 Height at screening only.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.3
12-lead ECG	X				X						X		Section 8.3.4

Table 3: Schedule of Activities (Continued)

	Screening	PC Period (12 Weeks)				EXT Period (24 Weeks)						Post-Treatment Follow-Up	
Visit Day (Range)	Days −28 to −1	Baseline Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/ EOT1 (or ET1) (± 3 d)	Week 16 (± 3 d)	Week 20 (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36/ EOT2 (or ET2) (± 3 d)	Week 44/ EOS (± 7 d)	Notes and Protocol Section
Efficacy assessments													
PROs													
eDiary (UAS/AAS)	Daily from screening through Week 44 (or ET, if applicable)												Sections 8.2.1.3, 8.2.1.4, and 8.2.1.5 Handheld device.
[redacted]													
Quality of life assessments													
[redacted]													
Laboratory assessments													
Serum FSH (WONCBP only)	X												Section 8.3.5
Pregnancy testing (WOCBP only)	X*	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†	X*	Section 8.3.5.1 * Serum test † Urine test (positive result to be confirmed by serum test)
TB screening	X												Section 8.3.5.2
HIV testing	X												Section 8.3.5.3

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Days −28 to −1	PC Period (12 Weeks) Baseline Day 1	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/ EOT1 (or ET1) (± 3 d)	EXT Period (24 Weeks) Week 16 (± 3 d)	Week 20 (± 3 d)	Week 24 (± 3 d)	Week 28 (± 3 d)	Week 32 (± 3 d)	Week 36/ EOT2 (or ET2) (± 3 d)	Post-Treatment Follow-Up Week 44/ EOS (± 7 d)	Notes and Protocol Section
Laboratory assessments (continued)													
Hepatitis testing	X												Section 8.3.5.4
HBV DNA (for required participants)	X				X			X			X		
Chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.5
Coagulation panel	X	X			X			X			X	X	
Urinalysis	X				X						X		
Nicotine metabolite screen (urine)		X			X						X		
Lipid panel		X			X			X			X	X	
hsCRP		X	X	X	X			X			X	X	
[redacted]													

Note: Unscheduled visits may occur at any time as medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

2. INTRODUCTION

2.1. Background

Urticaria is a heterogeneous group of diseases characterized by itchy hives and/or angioedema. Chronic spontaneous urticaria, formerly known as chronic idiopathic urticaria, is defined by the presence of wheals (hives), angioedema, or both for more than 6 weeks without an identifiable cause (Zuberbier et al 2022). The overall worldwide prevalence of CSU is approximately 1% with the potential for a high disease burden (Gonçalo et al 2021). Affected patients can experience an unpredictable disease course and duration with symptoms occurring in a spontaneous and recurrent manner and lasting over several years (Fok et al 2021). Furthermore, severe pruritus and the sudden and unpredictable appearance of wheals and angioedema can impact sleep and patients' well-being (Gonçalo et al 2021).

Treatment of CSU remains challenging with nonsedating, second-generation, H1 antihistamines being first-line therapy at up to 4 times the recommended daily dose if needed (Zuberbier et al 2022). While second-generation, H1 antihistamines are effective in relieving symptoms for some patients, approximately 50% of individuals show insufficient response to high-dose, second-generation antihistamines (Gonçalo et al 2021). Omalizumab, an anti-IgE monoclonal antibody (administered subcutaneously), is recommended in combination with second-generation, H1–antihistamine treatment as a second line in the treatment algorithm, with only approximately 35% of patients achieving a complete response after 12 weeks (Kaplan et al 2013). For those patients who continue to remain symptomatic with inadequate disease control, cyclosporin is recommended as a third-line treatment option in combination with second-generation, H1 antihistamines, although it is not licensed for urticaria and has a high incidence of adverse effects, limiting its use in many patients with CSU (Zuberbier et al 2022). Thus, there is a need for other second- and third-line treatment options that can be administered orally and potentially offer an improved efficacy and side-effect profile for the management of CSU.

The pathogenesis of CSU is not fully understood. Preliminary evidence suggests it is an autoimmune, mast cell–driven disease with at least 2 endotypes. In Type I autoimmune CSU, autoreactive IgE antibodies directed against autoantigens are thought to degranulate skin mast cells via the activation of the high-affinity IgE receptor FcεRIα. In Type IIb autoimmune CSU, degranulation of mast cells is thought to be caused by immunoglobulin G and/or immunoglobulin M autoantibodies directed against FcεRIα or FcεRIα-bound IgE (Altrichter et al 2021).

Histamine and other mediators, such as platelet-activating factor and cytokines released from activated skin mast cells, result in sensory nerve activation, vasodilation, and plasma extravasation as well as cell recruitment to urticarial lesions (Zuberbier et al 2022). Increased serum levels of Th1/Th2 and Th17 responses and related cytokines in CSU are correlated with the severity of the disease, which support the existence of an autoimmune basis and proinflammatory process in CSU (Chen et al 2018).

Increased expression of JAK-mediated inflammatory cytokines such as IL-9, IL-10, and STAT3 in the skin of patients with CSU (Feng et al 2020) as well as high serum levels of IFN-ɣ, IL-2,

and IL-21 (Chen et al 2018) suggest positive regulation of the JAK-STAT signaling pathway in CSU. IL-6 and IL-23, both activating the JAK/STAT3 signaling pathways, are increased in CSU, and their serum concentrations are related to the activity of the disease (Atwa et al 2014, Zhang et al 2021). Oncostatin M receptor, a member of the IL-6 receptor family, also participates in the pathogenesis of CSU through the JAK/STAT pathway (Zhang et al 2021).

Janus kinase signaling regulates several proinflammatory pathways and has been well-recognized as a key driver for numerous skin diseases. Small-molecule JAK inhibitors provide anti-inflammatory effects through disruption of the JAK-STAT signaling pathway used by multiple cytokine receptors, including those for IL-4, IL-6, IL-13, IL-31, and Th1/Th2/Th22-related cytokines. JAK1/2 inhibition can also modulate mast cell–activation, including degranulation and cytokine production (Hermans et al 2018) and reduces chemokine secretion, leading to less cellular infiltrate (ie, CXCL10; Fenwick et al 2015).

Janus kinase inhibitors also likely have itch-specific neuromodulatory effects. Janus kinase 1 is selectively expressed in itch-sensory neurons compared with JAK2 and JAK3, and in mouse models of AD-like disease, neuron-specific genetic deletion of JAK1 results in markedly reduced pruritus independent of the level of skin inflammation (Oetjen et al 2017). Janus kinase inhibitors have demonstrated substantial improvement in itch across diseases such as AD (Erikson et al 2021).

Chronic spontaneous urticaria case reports include a case study of a patient who was treated for myelofibrosis with oral ruxolitinib (a JAK1/2 inhibitor) and experienced complete control of their refractory CSU within 5 weeks (Fukunaga et al 2018). Another publication reports 4 cases of long-term refractory chronic urticaria and 1 case of urticarial vasculitis that were successfully managed with tofacitinib (a JAK1/3 inhibitor) and ultimately led to tapering and discontinuation of cyclosporine or antihistamines (Mansouri et al 2022).

Povorcitinib (INCB054707) is a novel, potent, oral, small-molecule, selective, JAK1 inhibitor under evaluation in HS, vitiligo, prurigo nodularis, and asthma clinical trials. Povorcitinib potently inhibits JAK1 ($IC_{50} \approx 9$ nM), with approximately 45- to greater than 1000-fold selectivity over the other JAK family members (ie, JAK2, JAK3, and TYK2).

[redacted]

2.2. Study Rationale

Despite the availability of several approved treatments and defined management guidelines for CSU, many patients with CSU have disease that remains uncontrolled by SOC therapies, indicating a significant unmet medical need for new treatment options.

Overall, JAK-mediated signaling has been implicated in the pathogenesis of CSU, and JAK inhibitors have the potential to target underlying pathophysiological mechanisms of disease. This study will evaluate the efficacy and safety of the JAK1 inhibitor povorcitinib in adults with CSU that is inadequately controlled using SOC treatment with second-generation H1 antihistamines.

2.2.1. Scientific Rationale for Study Design

In this proof-of-concept study, the clinical efficacy and safety of 3 dose regimens (15, 45, and 75 mg QD) of the oral JAK1 inhibitor povorcitinib will be evaluated in adult participants with CSU compared with placebo for 12 weeks followed by a 24-week EXT period. During the

EXT period, participants randomized to povorcitinib at baseline will remain on their randomized treatment dose regimen (povorcitinib 15, 45, or 75 mg QD) while participants receiving placebo will be assigned active treatment (povorcitinib 15, 45, or 75 mg) in a 1:1:1 ratio. All participants will remain on a background therapy of stable-dose, second-generation H1 antihistamine (SOC) throughout the study. The randomized, double-blind, placebo-controlled design supports the dose range-finding and assessment of efficacy as well as safety.

The use of placebo is considered appropriate since participants will continue with a stable dose of background therapy of second-generation H1 antihistamine (SOC). Participants will also be allowed rescue therapy with further doses of a second-generation H1 antihistamine throughout the study if needed. In addition, from Week 5, a 1-time, short course (maximum of 7 days) of glucocorticosteroids may be used as rescue medication in the case of severe symptom exacerbation. During the EXT period, participants in the placebo group will receive active treatment (povorcitinib 15, 45, or 75 mg QD).

During the post-treatment follow-up period all participants experiencing a worsening of symptoms may receive a rescue therapy deemed appropriate by the investigator (see Section 6.7.3).

The baseline stratification criterion selected for this study is previous treatment of CSU with an anti-IgE biologic. Participants with prior exposure to biologic therapies may have more severe disease and potentially distinct response to therapy, suggesting the importance of an adequate distribution of these participants across the different study treatment groups. The proposed stratification criterion may help balance the number of participants who have previously received anti-IgE biologics across the study treatment groups, potentially allowing a better understanding of the treatment effect of povorcitinib.

The time interval of 12 weeks for the PC period and the primary endpoint is sufficient to allow for assessment of both itch and angioedema resolution and is aligned with several other clinical trials in CSU, thereby imposing no increased time burden for participants entering this study versus others. Data of povorcitinib in HS demonstrate a treatment effect on itch at 2 weeks, with continued reduction of itch symptoms over 12 weeks (Kirby et al 2022c). Clinical studies of other JAK inhibitors for the treatment of AD reported reduction of itch early in treatment and continued improvements in disease severity at 16 weeks (Erikson et al 2021).

Findings from case studies reported on the use of tofacitinib in CSU (Mansouri et al 2022) suggest patients with the most severe symptoms may require a longer period of treatment and justifies a 24-week EXT period in the present study, which will include participants with CSU that is inadequately controlled on H1 antihistamines, who may have experienced treatment failure on or after monoclonal antibody therapy, or with CSU that is more difficult to treat.

After completion of the PC period, participants will continue the study in the 24-week EXT period, which allows participants initially randomized to placebo to receive active drug and further evaluation of the efficacy and safety of povorcitinib. The 60-day, post-treatment, follow-up period allows for assessment of persistence of the effect of povorcitinib in CSU without compromising participants who wish to enroll in other ongoing studies or need to receive alternative treatment for their CSU.

Details of the objectives and endpoints are included in Section 3. The primary efficacy endpoint of change from baseline in the UAS7 at Week 12 has been chosen because it is a validated

questionnaire and has been used in pivotal trials in CSU to measure reduction in CSU disease severity.

The secondary efficacy endpoints are commonly used in CSU clinical trials. The safety endpoints are typical for medicines in Phase 2 clinical development, and AESIs relevant to the JAK inhibitor class of compounds will also be monitored to enhance safety for participants. Safety will be assessed by evaluation of AE and laboratory data. Other endpoints in the study will assess health-related quality of life using validated PROs, which will provide insight into the participant's experience of their CSU and the impact of treatment on their disease. As this is the first use of povorcitinib in a CSU population, systemic drug concentration data and biomarkers will be assessed to characterize exposure and the PK/PD relationship of povorcitinib in participants with CSU.

2.2.2. Justification for Dose

This is the first clinical trial of povorcitinib in CSU, and thus, there are no povorcitinib data in patients with CSU to directly inform dose regimens. Therefore, dose selection for this study was based on the results of previous studies with povorcitinib in participants with HS, a dermatological indication associated with a systemic inflammatory burden, which displays some similarities with CSU regarding its immunological signature. The doses of povorcitinib (15, 45, and 75 mg) to be evaluated in the current study fall within the range of doses previously shown to have a favorable safety profile in completed and ongoing Phase 2 trials in HS.

Proof of concept was initially demonstrated for povorcitinib in 2 completed Phase 2, HS studies over 8 weeks of treatment with either a dose of 15 mg QD (Study INCB 54707-202 [NCT03569371]; n = 10 exposed to povorcitinib) or doses of 30, 60, and 90 mg QD (Study INCB 54707-203 [NCT03607487]; n = 26 exposed to povorcitinib). In both of these completed studies, all doses were generally well-tolerated with no SAEs (Alavi et al 2022). A third Phase 2, HS study is ongoing [redacted] and is evaluating povorcitinib 15, 45, and 75 mg QD administered up to 23 months. The doses selected for the current study are based on the primary analysis results from the 16-week, PC period of [redacted]. In that study, participants treated with povorcitinib 15 mg QD demonstrated clinical improvement across most of the clinician- and patient-reported outcomes, although generally not statistically different from placebo (Kirby et al 2022a, Kirby et al 2022b, Kirby et al 2022c); these results collectively suggest that povorcitinib 15 mg would be an adequate minimum effective dose. Participants treated with povorcitinib 45 and 75 mg QD experienced a significant improvement compared with placebo across all assessments. Further, participants with more severe disease demonstrated directionally better improvement when treated with povorcitinib 75 mg (data on file), suggesting that this would be an adequate upper dose level. Safety results demonstrated that povorcitinib was well-tolerated, with no increase in the incidence of TEAEs or other safety signs with increasing doses of povorcitinib. Overall, the findings from the Week 16 primary analysis of [redacted] suggest a trend toward dose-dependent efficacy between 15 mg and the 2 higher doses with no evidence for increased risk of serious toxicity at higher doses.

All participants will continue with a stable dose of background therapy of second-generation H1 antihistamine (SOC), and participants receiving placebo will be assigned active treatment (povorcitinib 15, 45, or 75 mg) in a 1:1:1 ratio in the EXT period.

In conclusion, it is expected that the doses selected in the current study are adequate and safe to explore the dose response of povorcitinib in participants with CSU.

2.3. Benefit/Risk Assessment

The potential risks to participants based on the available nonclinical and clinical data for povorcitinib and risks associated with other JAK inhibitors are summarized in Table 4.

Based on the expected mode of action of povorcitinib, participants randomly assigned to an active treatment group may experience clinically meaningful improvements in their CSU during the double-blind, PC period (12 weeks). Furthermore, all participants will be offered treatment with povorcitinib during the EXT period (24 weeks), which will provide the opportunity for symptom improvement in a disease with an unmet need that has a significant impact on participants' well-being and daily functioning.

The safety of participants will be monitored throughout the study, and based on individual response, the dose may be temporarily interrupted if there are AEs or laboratory abnormalities that may have an unclear relationship to study drug. Additionally, an internal DSMB will review safety data periodically throughout the study, and a CAC will assess potential cardiovascular and thromboembolic AEs.

Considering the cumulative safety information on povorcitinib, the potential risks identified are justifiable and appropriately balanced by the anticipated efficacy benefits expected to be afforded to participants. More detailed information about the known and expected benefits and risks and reasonably expected AEs of povorcitinib may be found in [redacted]

Table 4: Risk-Mitigation Assessment for Povorcitinib

Potential Risk of Clinical Significance	Summary of Data Available/Rationale for Risk	Mitigation Strategy
Grade 3 or higher ($< 50 \times 10^9$/L) decreases in platelet counts	Grade 3 or higher decreases in platelet counts have not yet been observed with povorcitinib. Transient and nonclinically significant events of Grade 1 (< 100 to 75×10^9/L) or Grade 2 (< 75 to 50×10^9/L) decreases in platelet counts have been observed in rare cases.	Potential participants with a history of thrombocytopenia, coagulopathy, or platelet dysfunction will be excluded. Randomized participants will be monitored for possible decreased platelet counts, and actions will be taken according to the study procedures (see Section 6.6.1)
Thromboembolic events	Increased incidence of MACE, pulmonary embolism, and venous and arterial thrombosis has been observed with other JAK inhibitors (FDA 2021). The association of thromboembolic events with povorcitinib has not been established. Pulmonary embolism has occurred in 2 participants with multiple independent risk factors.	Potential participants with a history of the following events will be excluded: venous and arterial thrombosis, deep vein thrombosis, pulmonary embolism, stroke, moderate to severe heart failure (NYHA Class III or IV), cerebrovascular accident, MI, coronary stenting, or CABG surgery. Randomized participants will be monitored for cardiovascular events and embolic and thrombotic events (see Sections 6.6.1 and 9.6.1). Additionally, a CAC will be implemented for this study (see Section 5.7).
Serious bacterial, fungal, viral, and opportunistic infections	Increased risk of serious bacterial, fungal, viral, and opportunistic infections has been observed with other JAK inhibitors (FDA 2021). The association of systemic infections with povorcitinib has not been established. Grade 1 and Grade 2 infections have been observed but did not require study drug interruption.	Participants will be screened for TB infection, chronic hepatitis, HIV, and chronic/recurrent infections. Randomized participants will be monitored for any signs and symptoms of infection throughout the study (eg, clinical laboratory tests, vital signs, and AE monitoring; see Sections 6.6.1, 6.6.1.3, and 9.6.1).
Malignancies	Increased risk of malignancies has been observed with other JAK inhibitors (FDA 2021). The association of malignancies with povorcitinib has not been established.	Participants will be screened for malignancies or history of malignancies, with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ. Randomized participants will be monitored for all types of malignancies (see Sections 6.6.1, 6.6.1.5, and 9.6.1).

Table 4: Risk-Mitigation Assessment for Povorcitinib (Continued)

Potential Risk of Clinical Significance	Summary of Data Available/Rationale for Risk	Mitigation Strategy
Retinal degeneration in individuals with albinism	Bilateral retinal degeneration has been observed in albino rats.	Individuals with albinism will not be enrolled in the study.
Reproductive and developmental toxicity	Preimplantation and postimplantation loss and decreased fetal weight have been observed in rat and rabbit studies.	Participants of reproductive potential will be required to use strict contraceptive measures (see Section 5.1 and Appendix A).
Aggravation of CSU	Worsening of CSU may occur either as a spontaneous event or due to insufficient efficacy of the study drug.	All participants will be taking background therapy (SOC) for the duration of the study. Participants will also be permitted to use rescue medication in the event of worsening CSU symptoms (see Section 6.7.3). Participants may withdraw from the study at any time for any reason, in which case they would be able to use alternative conventional treatments for their CSU.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of povorcitinib in participants with CSU.	Change from baseline in the UAS7, defined as the 7-day sum of the individual, daily recorded scores for HSS and ISS, at Week 12.
Secondary	
To further evaluate the efficacy of povorcitinib in participants with CSU.	• Proportion of participants who achieve UAS7 ≤ 6 (controlled disease) at Week 12. • Time to first achievement of UAS7 ≤ 6 (controlled disease) during the PC period. • Proportion of participants with UAS7 = 0 at Week 12.
Safety	
To evaluate the safety and tolerability of povorcitinib.	AEs, assessed by changes in vital signs and ECGs and through clinical laboratory sample evaluations and the results of physical examinations.
Exploratory	
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (continued)	
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (continued)	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, double-blind, placebo-controlled, multicenter study of povorcitinib in participants with CSU on stable SOC with second-generation H1 antihistamines. The study will enroll approximately 136 participants in a 1:1:1:1 randomization ratio, stratified at baseline by previous anti-IgE biologic use (yes or no), into 1 of 4 treatment groups during the PC period (12 weeks) as shown in Figure 1.

Treatment with study drug will start on Day 1 (baseline). After completing the 12-week PC period, participants will enter the 24-week EXT period. During the EXT period, the participants initially randomized to povorcitinib 15, 45, or 75 mg QD will continue taking povorcitinib at the same dose regimen. The participants initially randomized to placebo will be assigned to take 1 of these 3 dose regimens (ie, povorcitinib 15, 45, or 75 mg QD). Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment during the PC period. Participants and investigators will continue to remain blinded during the EXT period and post-treatment follow-up period.

Participants will receive study drug until completion of the 36-week treatment period or until 1 of the criteria for study treatment discontinuation are met. Participants will return for a follow-up visit approximately 60 days after their last dose of study drug.

All participants are required to maintain a stable dose of second-generation H1 antihistamine (SOC) during the study from the time of informed consent until the completion of the post-treatment follow-up visit. The SOC will be determined by the investigator. Further doses of second-generation H1 antihistamines may be used as rescue medication to treat worsening CSU symptoms at any time during the study. A 1-time, short course (maximum duration of 7 days) of glucocorticosteroids may be used as rescue medication after Week 4 in the case of severe exacerbation (see Section 6.7.3).

Efficacy will be evaluated using PROs, including the UAS7. Additional PRO outcomes are outlined in the SoA (see Table 3).

Safety and tolerability will be monitored throughout the study. The study will utilize an internal DSMB to monitor safety in addition to a CAC to adjudicate potential cardiovascular and thromboembolic AEs.

Serum samples will be collected for biomarker/translational analysis, and blood samples will be collected throughout the study for measurement of systemic concentrations of povorcitinib.

Final study analysis will be conducted after the last participant completes the last visit in the study.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit shown in Table 3 for the last participant in the study globally. A participant is considered to have completed the study if they have completed all periods/parts of the study, including the last visit. The study is considered complete when the last participant's last visit has occurred.

In European Union/European Economic Area, the results of the study will be based on the date of the last visit of the last participant in the study globally to ensure the results are robust, meaningful, and representative of all multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established. Not using the global date could potentially jeopardize the trial integrity and invalidate the trial conclusions due to potential bias and unblinding of study treatments, thus potentially violating the statistical analysis assumptions.

The study will include up to 28 days for screening, continuous treatment for 36 weeks (including the PC and EXT periods), and 60 (± 7) days for follow-up after the last dose of study drug. It is estimated that an individual will participate for approximately 11 months.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC of the study's completion or early termination in writing, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the DSMB (see Section 5.6). If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age 18 to 65 years inclusive at the time of signing the ICF.
3. CSU diagnosis for ≥ 3 months prior to screening.
4. CSU refractory to second-generation H1 antihistamines as defined by all of the following:
   a. The presence of persistent (almost daily) itch and hives for > 6 weeks at any time prior to screening despite current use of second-generation H1 antihistamines, consistent with SOC during this time period.
   b. UAS7 ≥ 16 during the 7 days prior to randomization (Day 1).
      – Note: Participants must have at least 5 nonmissing UAS daily scores out of the 7 days before Day 1 to calculate UAS7.
   c. Participants must have been on a stable dose of second-generation H1 antihistamine, consistent with SOC therapy for CSU, starting at least 3 consecutive days immediately prior to the screening visit through Day 1, and participants must agree to maintain the stable dose of second-generation H1 antihistamine throughout study and document its use in the eDiary.
5. Willingness and ability to comply with the study Protocol and procedures.
6. Willingness and ability to complete daily eDiary for the duration of the study.
7. Agreement to use contraception (see Appendix A), as follows:
   a. Female participants of childbearing potential (WOCBP) must agree to take appropriate precautions to avoid pregnancy with a highly effective method (ie, at least 99% certainty) from screening through 90 days after the last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed.
      – Note: This criterion does not apply to WONCBP, as defined in Appendix A.
   b. All women must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 90 days after receiving the last dose of study drug.

c. A male participant who is sexually active with a woman of childbearing potential (WOCBP) must agree to use a highly effective barrier method of birth control (as described in Appendix A) during the study and for at least 90 days after receiving the last dose of study drug.
d. All men must agree to not donate sperm during the study and for at least 90 days after receiving the last dose of study drug.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Treatment with an anti-IgE biologic (eg, omalizumab) within 8 weeks prior to screening.
2. Clearly defined predominant or sole trigger of chronic urticaria (chronic inducible urticaria) including urticaria factitial (symptomatic demographism), cold-, heat-, solar-, pressure-, delayed pressure–, aquagenic, cholinergic-, or contact-urticaria.
3. Other cutaneous or systemic diseases with symptoms of urticaria or angioedema.
4. Other skin or systemic diseases associated with chronic itching (eg, AD, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, or psoriasis) that, in the investigator's opinion, might influence the study evaluations and results.
5. Women who are pregnant (or who are considering pregnancy) or breastfeeding.
6. Concurrent conditions or history of other diseases, as follows:
    a. Thrombocytopenia, coagulopathy, or platelet dysfunction.
    b. Venous and arterial thrombosis, deep vein thrombosis, pulmonary embolism, stroke, moderate to severe heart failure (NYHA Class III or IV), cerebrovascular accident, MI, coronary stenting, or CABG surgery.
    c. Diagnosis of other significant cardiovascular diseases, including but not limited to angina, peripheral arterial disease, or uncontrolled arrhythmias such as atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and forms of carditis.
    d. Uncontrolled hypertension, as defined by a confirmed systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg.
    e. Participants who are permanently bedridden or wheelchair assisted.
    f. Recipient of an organ transplant that requires continued immunosuppression.
    g. Any malignancies or history of malignancies with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.
    h. Conditions that could interfere with drug absorption, including but not limited to short-bowel syndrome.
    i. Chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection, prior prosthetic joint infection at any time, or open, draining, or infected skin wounds or ulcers.
    j. Current or history of disseminated herpes zoster, or recurrent (more than 1 episode of) dermatomal herpes zoster.

k. Current or history of disseminated herpes simplex.
l. Active systemic infection or any active infection that, based on the investigator's clinical assessment, makes the participant an unsuitable candidate for the study.
m. Any other active skin disease or condition (eg, bacterial, fungal, or viral infection) that may interfere with the course, severity, or assessments of CSU.
n. Any clinically significant medical condition (other than CSU) or any other reason that the investigator determines would interfere with the participant's participation in this study or would make the participant an unsuitable candidate to receive study drug or would put the participant at risk by participating in the study.
o. Any clinically significant medical condition other than CSU, as determined by the investigator, that is not adequately controlled with appropriate treatment or may interfere with the course, severity, or assessments of CSU.
p. Albinism.

7. A screening 12-lead ECG that demonstrates clinically significant abnormalities requiring treatment (eg, acute MI, serious tachyarrhythmias or bradyarrhythmias) or that is indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome) or criteria associated with Q wave interval (QT)/Fridericia-corrected Q wave interval (QTcF) abnormalities.
8. Have undergone significant trauma or major surgery (per investigator's assessment) within 30 days preceding the screening visit.
9. History of clinically significant (per investigator's judgment) drug or alcohol abuse within 6 months preceding the screening visit.
10. History of treatment failure with any systemic or topical JAK inhibitor (eg, abrocitinib, baricitinib, brepocitinib, cerdulatinib, delgocitinib, deucravacitinib, filgotinib, ivarmacitinib, pacritinib, ritlecitinib, ropsacitinib, ruxolitinib, tofacitinib, upadacitinib) for CSU or any other inflammatory condition.
11. Receipt of medical treatment or investigational drugs within the following interval before the baseline visit (Day 1):
    a. < 12 weeks or 5 half-lives (if known), whichever is longer, for any investigational or experimental treatments.
    b. < 12 weeks or 5 half-lives (if known), whichever is longer, for immunomodulating biologic drugs (eg, adalimumab, anakinra, bermekimab, bimekizumab, brodalumab, certolizumab, dupilumab, etanercept, golimumab, guselkumab, infliximab, iscalimab, ixekizumab, risankizumab, rituximab, secukinumab, vilobelimab, ustekinumab) excluding anti-IgE biologics.
    c. < 8 weeks for live vaccine, or planning to receive live vaccine during the course of the study or within 8 weeks after the last dose of study drug.
    d. < 4 weeks for any topical or systemic JAK inhibitor (eg, abrocitinib, baricitinib, brepocitinib, cerdulatinib, delgocitinib, deucravacitinib, filgotinib, ivarmacitinib, pacritinib, ritlecitinib, ropsacitinib, ruxolitinib, tofacitinib, upadacitinib).

e. < 4 weeks for systemic immunosuppressive or immunomodulating small-molecule drugs (eg, corticosteroids [oral or intravenous], avacopan, IRAK4 inhibitors, methotrexate, cyclosporine, dapsone, azathioprine).

   – Note: Use of corticosteroid inhalers and intranasal sprays is allowed.

   – Note: Use of oral corticosteroids for nondermatologic conditions (eg, asthma exacerbation, bronchitis) is allowed for no longer than 7 days if deemed acceptable by the investigator and the sponsor (or designee).

f. < 1 week for any oral or topical PDE4 inhibitor (eg, apremilast, crisaborole).

g. < 1 week for strong systemic CYP3A4 inhibitors and strong and moderate systemic CYP3A4 inducers (see Appendix B). Examples include but are not limited to the following: rifampicin/rifampin, ketoconazole, itraconazole, carbamazepine, ritonavir, St John's wort, grapefruit/grapefruit juice, and Seville oranges.

12. Concurrent enrollment in another clinical study.

13. At the screening visit, any of the laboratory abnormalities defined in Table 6.

Table 6: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 100 \times 10^9$/L
b	Hemoglobin	< 10 g/dL
c	ANC	$< 1.5 \times 10^9$/L
d	Total WBC count (leukocyte count)	$< 3.0 \times 10^9$/L
e	Absolute lymphocyte count	$< 0.8 \times 10^9$/L
Hepatic		
f	ALT	> 2 × ULN
g	AST	> 2 × ULN
h	Total bilirubin	> 1.5 × ULN (Note: Participants with clinical diagnosis of Gilbert syndrome may have a direct bilirubin measured and would be eligible provided the direct bilirubin is < ULN)
Renal		
i	Estimated glomerular filtration rate	< 45 mL/min per 1.73 m^2 Note: Based on the simplified, 4-variable Modification of Diet in Renal Disease Formula

14. Evidence of infection with *Mycobacterium tuberculosis* (ie, TB) as defined in Section 8.3.5.2.
15. Active HIV or acquired immunodeficiency syndrome. Active HIV is defined as confirmed positive anti-HIV antibody test (see Section 8.3.5.3).
16. Evidence of HBV or HCV infection or risk of reactivation (see Section 8.3.5.4).
17. Known hypersensitivity or severe reaction to povorcitinib or excipients of povorcitinib (refer to the IB) and/or other products in the same class.
18. Any condition, laboratory result, or result of screening assessments that would, in the investigator's and sponsor's (or designee's) judgment, interfere with full participation in the study, including administration of study drug and attending required study visits, pose a significant risk to the participant, or interfere with interpretation of study data.

5.3. Lifestyle Considerations

5.3.1. Contraception

5.3.1.1. Female Participants

All female participants who are WOCBP must agree to use a highly effective method of contraception (ie, at least 99% certainty) consistently and correctly for the duration of the study and for at least 90 days after the last dose of investigational product.

5.3.1.2. Male Participants

All male participants must be willing to take appropriate precautions to avoid fathering children (with at least 99% certainty) consistently and correctly (as outlined in Appendix A) for the duration of the study and for at least 90 days after the last dose of investigational product. If the male participant has a partner who is of childbearing potential, the partner should also use contraception as outlined in Appendix A.

5.3.1.3. All Participants

The investigator or designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix A) and will confirm that the participant has been instructed in its consistent and correct use.

At timepoints indicated in the SoA (see Table 3), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception (see Appendix A). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

5.3.2. Meals and Dietary Restrictions

- Study drug will be taken orally, preferably in the morning and at about the same time each day, with a full glass of water. The study drug can be taken with or without food. On the day of study visits at Week 4, Week 12, and Week 16, participants will withhold study drug self-administration, as the dose will be administered at the clinic after collection of PD and/or PK samples as outlined in the SoA (see Table 3). Further instructions on study drug handling are outlined in Appendix C.
- On any of the study visit days, participants should not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements.
- Participants must abstain from consumption of grapefruit or grapefruit juice (pomelos, exotic citrus fruits, grapefruit hybrids) and Seville oranges from 7 days before the start of study drug until after the final dose of study drug.
- Participants must abstain from consumption of dietary supplements containing St John's wort (*Hypericum perforatum*) from 7 days before the start of study drug until after the final dose of study drug.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

All screening procedures with the possible exceptions noted below will be repeated during rescreening. The participant must meet all the eligibility criteria at the time of rescreening in order to qualify for the study. There is no minimum period of time a participant must wait to rescreen for the study. If the participant had a complete initial screening evaluation including the following assessments, these tests will not be required to be repeated for rescreening, provided the conditions noted in Sections 5.1 and 5.2 are met, there are no changes in the participant's medical history that would warrant retesting, and no more than 90 days have passed:

- HBV, HCV, and HIV serology
- IGRA (QTF Gold test [or IGRA equivalent such as T-SPOT® test] and/or local PPD skin test, if required)
- ECG

5.5. Replacement of Participants

No participants will be replaced at any time during this study. However, as noted in Appendix E, due to the evolving situation of the COVID-19 pandemic, the sponsor may decide to recruit additional participants in the study beyond the expected number (eg, if a substantial number of participants withdraw early from the study).

5.6. Data Safety Monitoring Board

This study will use an internal DSMB to monitor safety as detailed in the DSMB charter.

The voting members of the committee will be blinded to participants' treatment assignment for the initial safety review; however, the DSMB members may request unblinding at any time.

The members of the DSMB will not be involved with the study in any other way and will have no competing interests that could affect their roles with respect to the study.

The DSMB will make recommendations to the study team regarding steps to ensure both participant safety and the continued ethical integrity of the study. Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor, and requirements for the proper documentation of DSMB reports, meeting minutes, and recommendations will be described in the DSMB charter, which will be reviewed and approved by all DSMB members.

5.7. Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular and thromboembolic AEs. Details will be described in a separate CAC charter.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 7 presents the study treatment information. Participants will record study drug administration in an eDiary. Study drug administration and any interruptions and discontinuation of treatment will also be recorded in the eCRF. Further information regarding study drug administration is provided in Appendix C.

The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix E.

Table 7: Study Treatment Information

Study treatment name:	Povorcitinib	Povorcitinib matching placebo
Mechanism of action:	JAK inhibitor	Not applicable
Dose formulation:	Tablet oral	Matching tablet
Unit dose strength(s) / dose level(s):	15 mg = 1 povorcitinib 15-mg tablet and 4 placebo tablets 45 mg = 3 povorcitinib 15-mg tablets and 2 placebo tablets 75 mg = 5 povorcitinib 15-mg tablets	Matching placebo = 5 tablets
Administration instructions:	Povorcitinib or matching placebo will be taken orally QD with water at approximately the same time each day unless otherwise instructed by site personnel. The study drug can be taken with or without food. Note: Dose will be administered at the study site during visits. Participants will withhold self-administration on the days of those visits.	
Packaging and labeling:	Povorcitinib will be provided as 15 mg tablets; placebo tablets will match the povorcitinib tablets in smell, taste, and appearance. Tablets will be packaged in blister cards. Each blister card will be labeled as required per country requirement.	
Storage:	Ambient (15°C-30°C/59°F-86°F).	
Status of treatment in participating countries:	Investigational	

6.2. Background Therapy

All participants will be required to remain on a concurrent, stable dose of second-generation H1 antihistamine as background therapy (SOC), which will not be changed throughout the study.

6.3. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or designee is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Participant use of the study drug, including tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol (see Appendix C). The investigator or designee will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the study materials provided to the sites.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study.

All participants will be centrally assigned to study treatment using an IRT system. Study drug will be dispensed at the study visits summarized in the SoA (see Table 3). Returned study drug should not be redispensed to the participants. Full details will be provided in the IRT Study Reference Manual.

The sponsor will be blinded to the treatment throughout the PC period and will be unblinded at the time of primary analysis. Participants and investigators will remain blinded to each participant's treatment assignment throughout the study. This is implemented to minimize bias throughout the PC and EXT periods of the study.

Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.7 and refer to the Study Reference Manual).

6.5. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

6.5.1. Compliance With Povorcitinib/Placebo

Compliance with study drug will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability.

Compliance with study drug will be calculated for the PC and EXT periods based on the following:

Within the PC period:

- The first dose will occur on Day 1 (baseline).
- The last dose will occur on the day of the Week 12 visit or the day of the last study drug administration known to the investigator (or designee) as reported in the EDC for participants who prematurely discontinue study treatment or are lost to follow-up.

Within the EXT period:

- The first dose will occur the day after the Week 12 visit.
- The last dose will occur on the day of the Week 36 visit or the day of the last study drug administration known to the investigator (or designee) as reported in the EDC for participants who prematurely discontinue study treatment or are lost to follow-up.

Participants' compliance must be within 80% to 120% assessed at each study visit by the investigator (or designee). If outside of this range, it will be considered a Protocol deviation. Participants consistently noncompliant with the study drug may be withdrawn from the study. The decision on withdrawal will be made by the investigator after consultation with the sponsor, and relevant correspondence will be archived in the site study file.

6.5.2. Compliance With Background Therapy

Participants will be instructed to record background therapy administration in the eDiary from the screening visit until completion of the post-treatment follow-up visit (EOS). Compliance with background therapy will also be documented in the participant's study source documentation and monitored by the investigator (or designee).

6.6. Dose Modifications

No dose modifications will be allowed during the study. In some circumstances, it may be necessary to temporarily interrupt treatment with study drug as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug.

Decisions by the investigator (or designee) regarding dose interruption/discontinuation of study drug should be made using clinical judgment, taking into account relatedness of the AE to the study drug and the participant's underlying condition. The sponsor (or designee) may be consulted as needed. Instructions for dose interruption or discontinuation of study drug are outlined in Sections 6.6.1 and 6.6.2.

6.6.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Treatment with study drug may be interrupted for up to 28 days, unless otherwise specified in the Protocol or a longer period is approved by the sponsor (or designee), to allow for resolution of toxicity. The principal investigator (or designee) should contact the sponsor to discuss the case of any participant whose treatment has been interrupted for more than 21 days (but less than 28 days) before restarting treatment. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study.

Guidelines for interruption, restarting, and discontinuation of study drug are outlined in Table 8 as well as in Appendix E (for COVID-19) and Section 6.6.1.6 (for emergency and elective surgeries).

Table 8: Guidelines for Interruption, Restarting, and Discontinuation of Study Drug

Laboratory Value	Action Taken
Chemistry	
ALT and/or AST is > 3.0 × < 20 ULN	**Step 1:** Interrupt study drug. **Step 2:** Confirm whether potential Hy's law criteria have been met (see Appendix D), following applicable procedures. If potential Hy's law criteria are not met, proceed to Step 3. **Step 3:** Repeat ALT/AST assessments weekly for up to 3 weeks or until ALT and/or AST results are < 3.0 × ULN and then restart study drug at the same dose. If ALT and/or AST result(s) do not decrease to < 3.0 × ULN after 3 weeks of drug interruption, study drug will be permanently discontinued, and the participant will follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended. If the dose has been interrupted/restarted in 2 other instances due to ALT and/or AST results, and ALT and/or AST results are > 3.0 × ULN for a third time, study drug will be permanently discontinued, and the participant will follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended. In parallel to the participant starting the post-treatment follow-up period, the investigator, in collaboration with the medical monitor, will determine further steps.
ALT and/or AST is > 20.0 × ULN	**Step 1:** Discontinue study drug administration and have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended. **Step 2:** In parallel to the participant starting the post-treatment follow-up period, the investigator, in collaboration with the medical monitor, will determine further steps.
CPK is > 5.0 × ULN	**Step 1:** Evaluate if there are symptoms suggestive of myositis or rhabdomyolysis. Additionally, the investigator may repeat the test for confirmatory purposes. **Step 2:** If there are no symptoms suggestive of myositis or rhabdomyolysis, the participant may continue study drug at the investigator's discretion. Appropriate monitoring should be conducted. **Step 3:** If symptoms suggestive of myositis or rhabdomyolysis are identified, interrupt study drug and contact the medical monitor (or designee).

Table 8: Guidelines for Interruption, Restarting, and Discontinuation of Study Drug (Continued)

Laboratory Value	Action Taken
Hematology	
Platelet count is $< 50 \times 10^9$/L	**Step 1:** Interrupt study drug administration. **Step 2:** Repeat platelet count assessment promptly, **within 7 days**, to confirm value. **Step 3:** Repeat platelet count assessment weekly until platelet count reaches $\geq 100 \times 10^9$/L and then restart study drug at the same dose. **If platelet count does not increase to $\geq 100 \times 10^9$/L after 3 weeks of drug interruption, study drug will be permanently discontinued, and the participant will follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.**
ANC is $< 1.0 \times 10^9$/L	**Step 1:** Interrupt study drug administration until the toxicity has resolved to $\geq 1 \times 10^9$/L or the baseline value. **Step 2:** Restart study drug at the same dose and monitor as clinically indicated.
Hemoglobin is 8 to < 9 g/dL or > 2-g/dL decrease from baseline. Note: If the decrease results in a value < 8 g/dL, then follow the guidance below.	**Step 1:** Interrupt study drug administration until the toxicity has resolved, with hemoglobin meeting the criteria of ≤ 2-g/dL decrease from baseline. **Step 2**: Evaluate medical history to determine if the decrease in hemoglobin was likely related to underlying disease or investigational drug. **Step 3:** Restart study drug and monitor as clinically indicated.
Hemoglobin is < 8 g/dL	Discontinue study drug administration and have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.
Creatinine ≥ 2 mg/dL	**Step 1:** Repeat the test for serum creatinine (with the participant in a euvolemic state) within 7 days to confirm the result. **Step 2:** If the results of the repeat testing confirms creatinine ≥ 2 mg/dL, interrupt study drug. **Step 3:** Perform creatinine assessment weekly for up to 3 weeks, or until creatinine returns to less than or equal to the participant's baseline. Study drug may be restarted. **If creatinine does not decrease to less than or equal to the participant's baseline after 3 weeks of drug interruption, study drug will be permanently discontinued and the participant will follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.**

Table 8: Guidelines for Interruption, Restarting, and Discontinuation of Study Drug (Continued)

Laboratory Value	Action Taken
Other toxicities	
Serious infection/opportunistic infection (defined as any infection or opportunistic infection meeting SAE criteria [see Section 9.2])	**Step 1**: Interrupt study drug administration. **Step 2:** Initiate prompt diagnostic testing appropriate for an immunocompromised participant. As appropriate, antimicrobial therapy should be initiated, and the participant should be closely monitored. **Step 3:** Restart study drug once the infection has been successfully treated and closely monitor as clinically indicated.
New evidence of TB	Discontinue study drug administration and have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.
Herpes zoster	Consider interrupting study drug administration until the episode resolves.
Thrombosis events	**Step 1:** Promptly evaluate and treat appropriately if symptoms of thrombosis develop. **Step 2:** Discontinue study drug administration if any of the following diagnoses is confirmed: • Venous thrombosis (such as but not limited to deep vein thrombosis and pulmonary embolism) • Arterial thrombosis (such as but not limited to MI and stroke) • Any other thromboembolic event Have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.
Any malignancy except nonmelanoma skin cancer or carcinoma in situ of the cervix (see Section 6.6.1.5 for additional management guidance)	Discontinue study drug administration and have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.
Any Grade 1 or Grade 2 toxicity	Continue study drug administration and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity (except if specifically described in this table) if clinically significant and not manageable by supportive care	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug and monitor as clinically indicated.
Any other Grade 4 toxicity	Discontinue study drug administration and have the participant follow EOT visit procedures; a post-treatment follow-up visit (EOS) is also recommended.

6.6.1.1. Management of Serious Infections

Participants should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a participant develops a serious infection or a serious opportunistic infection. A participant who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised participant. As appropriate, antimicrobial therapy should be initiated, and the participant should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Participants with new evidence of TB must be permanently discontinued from study drug.

6.6.1.2. Management of Herpes Zoster

If a participant develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

6.6.1.3. Management of COVID-19

Participants who develop symptoms of COVID-19 may continue treatment with study drug.

In cases where treatment of COVID-19 with nirmatrelvir/ritonavir (or another strong CYP3A4 inhibitor or strong/moderate inducer for COVID-19 treatment) is required, study drug must be interrupted for up to 7 days to allow the antiviral treatment course to complete. Study drug may be restarted after a minimum of 7 days after the last dose of the antiviral therapy.

6.6.1.4. Management of Thrombosis Events

Participants who develop symptoms of thrombosis should be promptly evaluated and treated appropriately.

The participant must be discontinued from study drug if the diagnosis of the following is confirmed: venous thrombosis (such as but not limited to deep vein thrombosis and pulmonary embolism), arterial thrombosis (such as but not limited to MI and stroke), or any other thromboembolic event.

6.6.1.5. Management of Malignancy

Participants who develop malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix must be discontinued from study drug. Information including histopathological results should be queried for the confirmation of the diagnosis.

Periodic skin examination is recommended for participants who are at increased risk for skin cancer.

6.6.1.6. Emergency and Elective Surgeries

If a participant must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Elective surgery, and interruption of study drug for such a surgery, may be allowed during the EXT period. If the participant undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.6.2. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- A persistent AE requiring an interruption of study drug for more than 28 days unless a greater delay has been approved by the sponsor (or designee).
- Recurrence of an initial AE(s) that previously led to study drug interruption after restarting the study drug (unless otherwise specified in Table 8).
- Specific AEs requiring permanent discontinuation of study drug as described in Section 6.6.1.

See Section 7 for discontinuation procedures.

6.7. Prior and Concomitant Medications and Procedures

6.7.1. Prior Therapy for Chronic Spontaneous Urticaria

Any topical or systemic treatments for CSU since initial diagnosis will be recorded in the eCRF. Information associated with response to prior CSU therapy and reason for discontinuation will also be recorded in the eCRF. Examples of commonly used therapies for CSU include but are not limited to the following: second-generation H1 antihistamines, omalizumab, corticosteroids, and cyclosporin.

6.7.2. Background (Standard of Care) Therapy

All participants will be required to remain on a concurrent, stable dose of second-generation H1 antihistamine as background therapy (SOC), which will not be changed throughout the study. Choice of SOC regimen will be left to investigator discretion.

6.7.3. Rescue Medication

Initiation of non–study drug therapy to treat the worsening of pruritus, CSU, or flare of previously inactive skin disease is strongly discouraged throughout the PC period. If deemed to be medically necessary by the investigator, rescue treatments for CSU noted below may be added to study drug and background therapy.

All rescue medication must be entered into the EDC and classified as rescue medication with the following information:

- Name and dose regimen of the rescue medication.
- Date and time of administration.

From Week 1 to Week 4:

- Add another second-generation H1 antihistamine to treatment regimen.

From Week 5 to Week 36:

- Add another second-generation H1 antihistamine to treatment regimen.
- In the case of severe exacerbation of pruritus, a 1-time, short course (maximum 7 days) of glucocorticosteroids may be used as rescue medication from Day 1 of Week 5.
- If rescue medication is to be added, the efficacy and safety assessments for the visit should be completed before the start of rescue therapy.
- The participant may remain on study drug unless the rescue therapy is a prohibited medication or procedure.

From Week 36 to Week 44 (Post-Treatment Follow-Up Period):

- Any participant experiencing a worsening of symptoms can be treated with any rescue therapy deemed appropriate by the investigator.

6.7.4. Prohibited Medications and Procedures

The following medications and procedures are prohibited for all participants in the study:

- Conventional therapies with potential therapeutic impact on CSU, per discretion of the investigator or designee, with the exception of SOC and rescue medication.
- JAK inhibitors (systemic or topical) other than povorcitinib.
- Use of biologics with immunomodulatory effect.
- Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, dapsone, azathioprine).
- Apremilast, crisaborole, or any other systemic or topical PDE-4 inhibitor.

- Strong systemic CYP3A4 inhibitors and strong and moderate systemic CYP3A4 inducers (see Appendix B). Examples include but are not limited to the following medications: rifampicin/rifampin, ketoconazole, itraconazole, carbamazepine, ritonavir, St John's wort, and grapefruit/grapefruit juice.
  - In exceptional cases (eg, COVID-19 treatment with nirmatrelvir/ritonavir), and after study drug interruption, strong CYP3A4 inhibitors or strong/moderate inducers may be used for up to 7 days. The sponsor (or designee) must be informed of the investigator's (or designee's) decision and rationale within a reasonable timeframe. Study drug may be restarted after a minimum of 7 days of discontinuation of the strong CYP3A4 inhibitor or strong/moderate inducer.
  - If treatment with strong CYP3A4 inhibitors or strong/moderate CYP3A4 inducers is required for longer than 7 days after study drug interruption, the participant may be discontinued from the study and the ET visit performed.
- Live, attenuated vaccines (during the study and within 8 weeks after the last dose of study drug). Examples of live vaccines include but are not limited to the following:
  - BCG
  - herpes zoster
  - measles-mumps-rubella or measles-mumps-rubella-varicella
  - monovalent, live, attenuated influenza A (intranasal)
  - oral polio vaccine
  - rotavirus
  - seasonal, trivalent, live, attenuated influenza (intranasal)
  - smallpox
  - typhoid
  - varicella (chickenpox)
  - yellow fever
- Elective surgery
  - PC period: Will not be allowed
  - EXT period: May be allowed per determination of the investigator (or designee) after consultation with the sponsor (or designee). See Section 6.6.1.6 for details on study drug interruption.

  Note: If a participant must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. See Section 6.6.1.6 for details on study drug interruption.

6.8. Treatment After the End of the Study

Upon completion of the 36 weeks of treatment, participants will not be provided additional treatment within this study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in the public domain, may be solicited from or collected on the participant. Consent may also be partial. Participants may choose to discontinue study drug and remain in the study to complete the post-treatment follow-up visit.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Occurrence of unacceptable toxicity as noted in Section 6.6.
- Has received a prohibited medication or procedure as described in Section 6.7.4.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If a participant is consistently noncompliant with study procedures or with study drug or background therapy administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT/ET visit should be conducted (see Section 8.7). Reasonable efforts should be made to have the participant return for a post-treatment follow-up visit. These visits are described in Table 3. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT/ET visit should be performed and date recorded.

- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the post-treatment follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (post-treatment follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix E for COVID-19–related guidance.

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used by the sponsor and/or their designee(s) in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF and be assigned a new participant number (see Section 8.1.3).

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized in the study (Day 1/baseline). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. A signed ICF must be obtained as the first step and before IRT screening registration or any other study-specific assessments. The screening of a participant should be registered in the IRT, which will assign the study-specific ID. Each participant who has signed the ICF should be registered in the IRT contemporaneously and without undue delays.

Results from the screening visit evaluations will be reviewed to confirm eligibility before the randomization transaction is registered in the IRT and before the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT to obtain the participant ID number during screening.

Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at the study visits indicated in Table 3 to update the study drug supply. Additional details will be provided in the IRT manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit indicated in Table 3.

The reminder card will provide general information regarding study drug administration, including on which study visit days the participant should not self-administer their dose of study drug.

8.1.5. Distribution of Participant Cards

Participants will be provided with a participant card at screening.

Participants should be instructed to carry this card at all times and to present it to all healthcare professionals when either visiting any other medical facility or department other than the study site or hospitalized. The participant card will contain the name and contact details for the investigator.

8.1.6. Distribution of Electronic Diaries

Participants will be provided with an eDiary at screening.

Sites will be provided with training materials and instructions on the use of eCOA and will be responsible for training participants on eDiary use and eCOA completion. Further details on use

of the eDiaries and eCOA will be provided in respective study documentation. For PROs scheduled to be completed at study visits, questionnaires will be completed by the participant before site personnel perform any clinic assessments to avoid biasing the participant's response.

8.1.7. Demography and Medical History

8.1.7.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, family history of cardiovascular disease, family history of clotting disorders, risk factors associated with cardiovascular disease, history of nicotine and alcohol use, and current illnesses. Medical history will include relevant medical and surgical treatments that are considered to be clinically significant by the investigator.

History of clinical herpes zoster, herpes zoster vaccination, chickenpox vaccination, influenza vaccination, and hepatitis B vaccination status will be recorded as part of the medical history.

History of COVID-19 vaccination and COVID-19 infection (and/or hospitalization) will be recorded as part of the medical history.

A detailed medical history with respect to TB risk factors will be documented in the study source documentation. This information will include BCG vaccination; cohabitation with individuals who have had TB; and travel to, residence in, or work in TB endemic locations.

8.1.7.1.1. Justification for Collection of Race and Ethnicity

Epidemiologic estimates for CSU are sparse, and the impact of race and ethnicity on CSU is not yet understood. Demographic data, including race and ethnicity, will be collected during the screening period for this study and considered as part of assessments for treatment response heterogeneity.

8.1.7.2. Disease Characteristics and Treatment History

Complete CSU medical and treatment history, including date of diagnosis, relevant disease characteristics, and prior treatments, including systemic treatments, will be collected at screening. A medical history of other conditions related to CSU or relevant to the conduct of this study will also be collected at screening.

Additional information on the procedure for collection of prior CSU therapy and ongoing background therapy information is presented in Sections 6.7.1 and 6.7.2, respectively.

8.2. Efficacy Assessments

Efficacy will be evaluated using PRO measures in this study.

8.2.1. Patient-Reported Outcomes

All PROs will be collected via eCOA.

8.2.1.1. Daily Diary Patient-Reported Outcomes

8.2.1.2. Administrative Procedures

8.2.1.2.1. Follow-Up Phone Call

Study sites should contact participants 1 week prior to the baseline visit, 2 weeks prior to the Week 4 visit, and 1 week prior to the Week 12 visit to confirm compliance with the daily diary assessments.

8.2.1.2.2. Compliance With Daily Diary Patient-Reported Outcomes

Participants' compliance with daily diary PRO assessments (ie, ISS, HSS[redacted]) should be monitored by the investigator (or designee) throughout the study. Compliance will be evaluated as outlined below:

- Screening period:
  - A minimum of 5 daily diary assessments should be completed within the 7 days before the baseline visit.
- PC and EXT periods:
  - Participants' compliance with the daily diary assessments should be assessed at each study visit during the PC and EXT periods.
  - Participants who are consistently noncompliant with the daily diary assessments may be withdrawn from the study.

8.2.1.3. Daily eDiary

The daily eDiary includes the UAS, which will be used to calculate the UAS7, and the [redacted].

The daily eDiary is to be completed once per day by the participant for the duration of the study. The diary tablet will be given to the participant at the screening visit.

8.2.1.4. Urticaria Activity Score

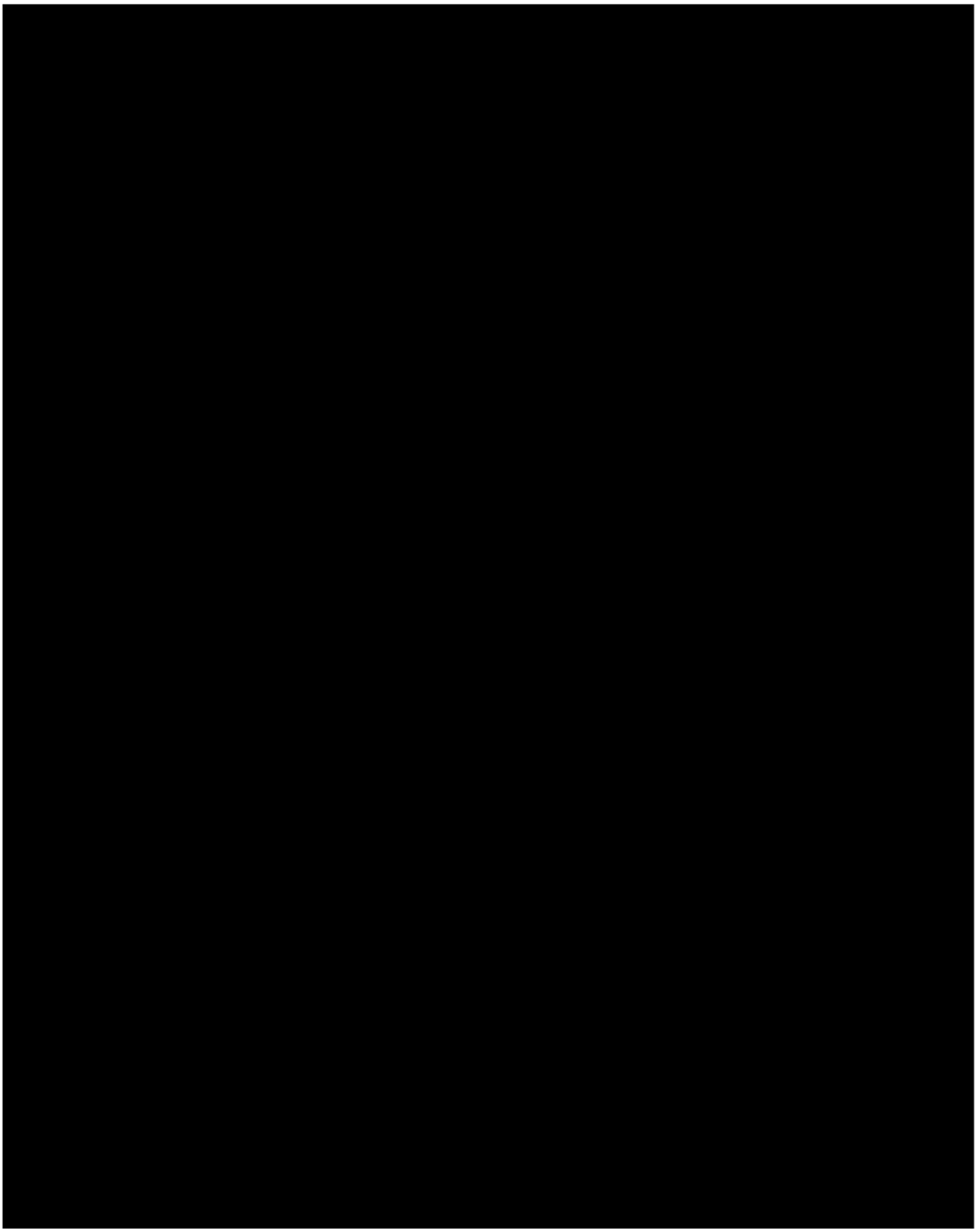
The UAS is a composite, eDiary-recorded score with numeric severity intensity ratings (0 = none to 3 = intense/severe) for a) the number of hives (ie, HSS) and b) the intensity of the pruritus (ie, ISS) over the past 24 hours.

8.2.1.4.1. Urticaria Activity Score Over 7 Days

The UAS7 is the 7-day sum of the daily UAS. The UAS7 (range 0 to 42) is equal to the ISS7 (range 0 to 21) plus the HSS7 (range 0 to 21).

If a participant has entered at least 5 daily UAS scores within the 7 days prior to the study visit, the UAS7 score is calculated as the sum of the available UAS scores, divided by the number of days that have a UAS score, multiplied by 7.

If there are more than 2 daily UAS scores missing within the prior 7 days, then the UAS7 score is missing for the week.



[redacted]

8.2.2. Medical Resource Utilization and Health Economics

Health economic parameters are included in the PROs, EQ-5D-5L questionnaire (see Section 8.2.1.10), and WPAI-CU questionnaire (see Section 8.2.1.9).

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in Table 3.

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 60 days after the last dose of study drug. Adverse events for randomized participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, that are considered related to the study drug procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs (as defined in Section 9.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A comprehensive physical examination, at visits specified in Table 3, will assess the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes. A brief neurologic examination will also be performed.

During the study, participants will have targeted physical examinations. Participants will be assessed by the investigator or medically qualified designee per institutional SOC. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the Adverse Events Form in the eCRF.

Height and body weight will be assessed as indicated in the SoA (see Table 3).

8.3.3. Vital Signs

Vital signs measurements include blood pressure, pulse, respiratory rate, and body temperature and will be obtained at each study visit. Participants should not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements (see Section 5.3.2 for details)

Vital signs should be collected before blood collection procedures. Alternatively, a minimum interval of 30 minutes between the completion of the blood collection procedures and the beginning of the vital signs collection is recommended. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.4. Electrocardiograms

Single, 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator or qualified designee for adequate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

See Table 9 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, serology, lipid panel, and urinalysis); urine pregnancy tests will be performed locally. Additional testing may be required by the investigator or sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3. Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before Day 1 (baseline). If performed more than 28 days before Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Day 1. See Section 5.4 for possible exceptions if a participant repeats the screening process.

Laboratory sample collection on Day 1 must be performed before study drug administration.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment) or are considered clinically significant by the investigator (eg, SAE, AE), then the result(s) of the **specific laboratory assessment(s)** must be recorded in the eCRF.

Table 9: Required Laboratory Analytes

Chemistry	Hematology	Urinalysis[a]	Serology	Pregnancy Testing
Albumin ALP ALT AST Amylase Bicarbonate or CO_2 Bilirubin: total, direct, and indirect Blood urea nitrogen or urea Calcium Chloride CPK Creatinine GGT Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total protein	Complete blood count, including: • Hemoglobin • Hemoglobin A_{1c} • Mean corpuscular volume • Hematocrit • Platelet count • Mean platelet volume[b] • Red blood cell count • Red blood cell distribution width • WBC count • Hepcidin • Ferritin • Bands Differential count (% and absolute values), including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocyte esterase Nitrite Occult blood Protein **Lipid Panel** Total cholesterol Triglycerides HDL LDL Non-HDL cholesterol **Other** hsCRP Nicotine metabolite screen (urine) IgE	HIV HBsAg[c] HBsAb HBcAb[c] HCV antibody[d] HBV DNA (reflex) HCV RNA (reflex) QTF Gold test. **Coagulation Panel** aPTT PT INR **Biomarker Samples** Chronic urticaria panel 2 (comprehensive) Basophil activation test	Pregnancy testing will be performed only for female participants. • **Serum FSH:** at screening for female participants to confirm WONCBP status (see guidance in Appendix A). • **Serum pregnancy test (WOCBP):** to be performed at visits indicated in the SoA (see Table 3). • **Urine pregnancy test (WOCBP):** to be performed locally at visits indicated in the SoA (see Table 3) Positive urine pregnancy test must be confirmed with serum pregnancy test. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
[a] Microscopic evaluation may be required in the case of abnormal urinalysis results.
[b] In samples with abnormalities in platelet count or size distribution (as indicated by an automated analyzer), a blood film should be examined.
[c] If either HBsAg or HBcAb is positive, a reflexive HBV DNA must be obtained (see Section 8.3.5.4).
[d] If HCV antibody is positive, a reflexive HCV RNA must be obtained (see Section 8.3.5.4).

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening and at the post-treatment follow-up visit. Urine pregnancy tests will be performed locally as outlined in Table 3, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

If the serum pregnancy test result is negative after a urine test result was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test result, see Section 9.8 for reporting requirements.

8.3.5.2. Tuberculosis Assessment

During the screening period, all participants will be screened for TB infection via central laboratory assessment (see Section 8.3.5.2.1). Confirmed negative status must be obtained before the participant is randomized in the study and receives study drug. The following outcomes may be considered:

- If QTF Gold (or IGRA equivalent) test (and PPD skin test, if applicable) is negative, the participant may be randomized.
- If QTF Gold (or IGRA equivalent) test (or PPD skin test, if applicable) is positive, the participant must be further evaluated via CXR (or alternative imaging method, such as MRI or CT) for confirmation of TB status (active or latent).
  - Participants with evidence of active TB must not be randomized.
  - Participants with evidence of latent TB must not be randomized, unless a course of at least 2 months of appropriate therapy has been completed prior to randomization.

During the study, if a participant is experiencing signs or symptoms suspicious for TB, an ad hoc TB test (including CXR or alternative imaging method, such as MRI or CT) may be performed ahead of the next scheduled assessment. The sponsor's medical monitor should be informed of such cases. Confirmed TB infection, after the participant has started the study, should be reported as an AE.

8.3.5.2.1. Tuberculosis Test

- QTF Gold test (or IGRA equivalent, such as T-SPOT TB test) is a default central laboratory assessment for TB. When required as per local standards, a PPD skin test (also known as tuberculin skin test or Mantoux) can be performed. The same TB testing method should be used throughout the study.

  Note: The PPD skin test should be read by a licensed health care professional between 48 and 72 hours after administration. A participant who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters of induration, and induration $\geq$ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm," not "negative." Participants who have had an ulcerating reaction to the PPD in the past should not be re-exposed, and the PPD test should be considered positive.

- For regions that require both PPD and QTF Gold testing (or IGRA equivalent, such as T-SPOT TB test), both will be performed. If either PPD or QTF Gold (or IGRA equivalent, such as T-SPOT TB test) is positive, the TB test is considered positive.

- If the first QTF Gold (or IGRA equivalent) test is indeterminate, then the investigator should perform a second QTF Gold (or IGRA equivalent) test to rule out a positive test result. The second QTF Gold (or IGRA equivalent) test should be performed centrally; if not possible to be performed centrally, a local laboratory result may be acceptable. If testing remains indeterminate after the second QTF Gold (or IGRA equivalent) test, then a PPD skin test will be performed.

8.3.5.2.2. Chest X-Ray

Participants can have a CXR (or alternative imaging method, such as MRI or CT) at any time during the study as warranted based on the opinion of the investigator (or designee). The CXR requires posterior-anterior and lateral views. A radiologist or pulmonologist must perform and document an assessment of the CXR. The investigator (or designee) will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the investigator (or designee) must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR demonstrates changes suggestive of previous TB (eg, calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the investigator (or designee) should contact the sponsor's medical monitor (or designee) before randomizing the participant. Participants who have already been randomized in the study but have a CXR after randomization that is clinically significant for TB must be discontinued from study drug.

8.3.5.2.3. Tuberculosis Prophylaxis

At screening, if a participant has evidence of latent TB infection, prophylactic treatment must be initiated at least 2 months prior to administration of the first dose of study drug (or per local guidelines, whichever is longer). Prophylaxis needs to be completed per local guidelines; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Note: Rifampicin and rifapentine are not allowed for concurrent TB prophylaxis. See Section 6.7.4 for a list of other prohibited medications.

Participants with a prior history of latent TB who have documented completion of a full course of anti-TB therapy may be allowed to be randomized in the study, provided nothing has changed in the participant's medical history to warrant repeat treatment. For participants with completion of a full course of anti-TB therapy but insufficient documentation, the investigator should consult with the sponsor's medical monitor (or designee) before randomizing the participant.

During the study, participants with new evidence of TB must be discontinued from study drug.

8.3.5.3. HIV Testing

All participants will be tested for the presence of HIV at screening. Participants will be screen failed if they test positive for HIV infection.

8.3.5.4. Hepatitis Testing

All participants will be tested for the presence of HBV and HCV at screening. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results.

8.3.5.4.1. Hepatitis B Virus

Participants must undergo screening for HBV at the study visits indicated in Table 3. At a minimum, this includes testing for HBsAg, HBcAb, and HBsAb.

Interpretation and management of HBV test results are shown in Table 10 with further explanation below.

Table 10: Interpretation and Management of Hepatitis B Virus Serologic Test Results

Scenario	HBsAg	HBcAb	HBsAb	Status
A	Positive	Negative or positive	Negative or positive	Not eligible
B	Negative	Negative	Negative	Eligible
C	Negative	Negative	Positive	**HBV DNA PCR required** Positive results: not eligible Negative results: eligible
D	Negative	Positive	Positive	
E	Negative	Positive	Negative	

The following applies to participants in Scenarios C, D, and E:

- If the HBV DNA test is negative, the participant is eligible and may be randomized.
  - For participants who test HBV DNA negative and are randomized in the study, an HBV DNA PCR test should be repeated approximately every 12 weeks (as outlined in Table 3). Note: HBV DNA PCR testing is not necessary for participants in Scenario C with a documented history of HBV vaccination.
- If the HBV DNA test is positive, the participant is not eligible and will be screen failed.
- In the event the HBV DNA test cannot be performed, the participant is not eligible and will be screen failed.

8.3.5.4.2. Hepatitis C Virus

Blood samples for HCV serology will be obtained at the screening visit and tested. A positive HCV antibody will trigger an HCV RNA test (reflex test). A participant will not be eligible and will be screen failed if test results indicate active hepatitis C (HCV RNA detectable in any participant with anti-HCV antibody). Participants who test positive for HCV but are successfully treated for HCV infection and have their screening visit at least 12 weeks after the last dose of HCV therapy may be eligible if HCV RNA is undetectable.

8.6. Unscheduled Visits

Unscheduled visits may occur as clinically indicated. Any assessments performed at those visits should be recorded in the eCRF and noted as an unscheduled visit.

8.7. End of Treatment and Early Termination

The EOT1 (PC period) coincides with the Week 12 visit, and the EOT2 (EXT period) coincides with the Week 36 visit. A participant who completes the Week 12/EOT1 visit will have completed the PC period and may continue into the EXT period. A participant who completes the Week 36/EOT2 visit will have completed the EXT period.

If a decision is made that the participant will permanently discontinue study drug prior to the Week 36/EOT2 visit, then the ET visit should be conducted and will be determined as ET1 (if during the PC period) or ET2 (if during the EXT period). If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET visit in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to complete the ET procedures. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Post-Treatment Follow-Up

The post-treatment follow-up period is the interval between the Week 36 visit and the scheduled follow-up visit, which should occur 60 (± 7) days after the Week 36 visit (or after the last dose of study drug if the Week 36 visit was not performed). Adverse events and SAEs must be reported up until 1) at least 60 days after the last dose of study drug or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the post-treatment follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the post-treatment follow-up visit, then the participant should be contacted by telephone for assessment of AEs and SAEs and sites should properly document this contact in the source.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition

- An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related.
- An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Additional Guidance for Events Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to disease progression) are to be reported as an AE.
- Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE.
- New conditions detected or diagnosed after the start of study drug administration are to be reported as an AE.
- New signs and/or symptoms due to the study disease that develop after the first dose of study drug are to be reported as an AE.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE.
- Signs and/or symptoms from dose administration errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE.
- "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. If judged by the investigator more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease can be reported as an AE or SAE. And if judged by the investigator more severe than expected for the participant's condition, the disease/disorder being studied or its expected progression, signs, or symptoms can be reported as an AE or SAE.
- A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history.
- Pre-existing diseases, pre-existing conditions, or new conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization or death due to disease progression).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers; intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for randomized participants, but only SAEs need to be reported for screen failure participants. For randomized participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Binder as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final post-treatment follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through at least 60 days after the last dose of study drug must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the post-treatment follow-up visit or more than 60 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 9.6.1) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study drug under clinical investigation are met.

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further

information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Events Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

See Appendix D for details on management of potential Hy's law cases/DILI.

Follow the SAE and follow-up reporting requirements per Section 9.2 as potential DILI AEs may be potential SAEs classified in the category of important medical event.

9.6. Events of Clinical Interest

An ECI is an AE (serious or nonserious) that Incyte wishes to document in an organized manner for monitoring or understanding. The ECIs will be captured in specific eCRFs.

An ECI does not require rapid communication by an investigator to Incyte unless it meets criteria for rapid communication as an SAE (see Section 9.2).

These ECIs include laboratory abnormalities and clinical AEs as follows:

- Increased serum creatinine (> 3 × ULN or > 3 × baseline) and renal dysfunction
- Hepatic events and increased hepatic transaminases (> 5 × ULN)
- Increased CPK (> 5 × ULN)
- Acne

9.6.1. Adverse Events of Special Interest

Incyte defines AESIs as a subset of ECIs that an investigator must rapidly communicate to Incyte for further evaluation.

If an AESI meets the SAE definition (see Section 9.2), it must be reported following the requirements for an SAE indicated in Section 9.4.

The AESIs are as follows:

- Serious infections
  - Defined as any infection meeting SAE criteria (see Section 9.2)
- Opportunistic infections
- Herpes zoster
- TB
- Malignancy (all types)
- MACE, defined as any of the following:
  - Nonfatal MI
  - Nonfatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage
  - Cardiovascular death defined as any of the following:
    - Death due to acute MI
    - Sudden cardiac death
    - Death due to heart failure
    - Death due to stroke
    - Death due to cardiovascular procedures
    - Death due to cardiovascular hemorrhage
    - Death due to other cardiovascular causes: peripheral artery disease
- Other embolic and thrombotic events (eg, pulmonary embolism, deep vein thrombosis, other thrombosis)

9.7. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. The investigator has the primary right to break the blind to treat a participant in emergency circumstances.

If a participant's treatment assignment is unblinded, the sponsor or its designee should be notified immediately by IRT for awareness.

If an investigator, the site personnel performing assessments, or a participant is unblinded, then the participant must discontinue study drug unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

9.8. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study treatment must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluations. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.9. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.10. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or their designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, they will return a copy of the product complaint communication with the product.

9.11. Treatment of Overdose

There has been no clinical experience with overdose of povorcitinib. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

Approximately 136 participants will be randomly assigned to 4 treatment groups (placebo or povorcitinib 15, 45, or 75 mg) in a 1:1:1:1 ratio.

The sample size is based on the primary efficacy endpoint, the change in weekly UAS7 score from baseline at Week 12. Based on a Phase 2b study (Maurer et al 2022), the mean change in UAS7 score at Week 12 is assumed to be −8 in the placebo group and −17 in the povorcitinib 75-mg group, with a common STD of 13. A sample size of 34 participants per group is sufficient to test for the presence of a dose-response relationship, based on the MCP-mod approach (Bretz et al 2005, Pinheiro et al 2013).

This sample size provides a minimum power of 0.85 to detect a dose effect at a 1-sided 2.5% significance level with the linear, log-linear, E_{max}, and quadratic models prespecified as candidates to characterize the underlying dose-response curve for povorcitinib on the mean change in weekly UAS7 score at Week 12. The set of candidate dose-response models and their corresponding dose-response curves are shown in Table 12 and Figure 2, respectively.

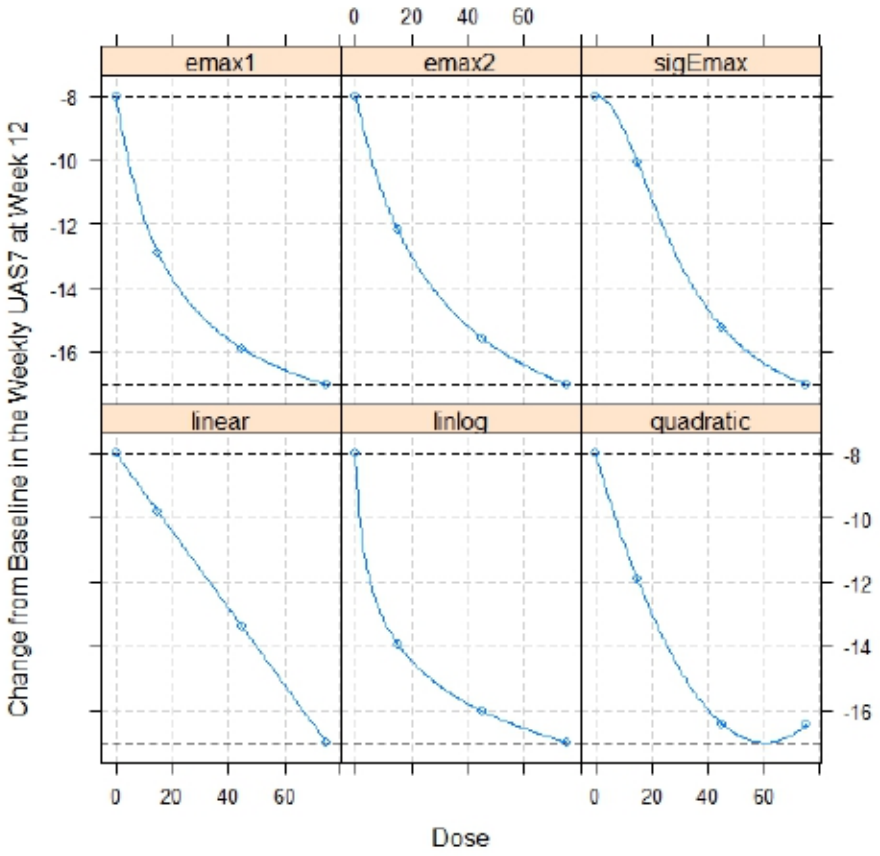
Table 12: Prespecified Candidate Models

Model	$f(d,\theta)$[a]	$f^0(d,\theta)$[b]	Initial Value(s) for Parameter(s)
Linear	$E_0 + \delta d$	d	Not applicable
Linear log-dose	$E_0 + \delta \log(d+1)$	$\log(d+1)$	Not applicable
$E_{max}1$	$E_0 + \frac{E_{max} d}{ED_{50} + d}$	$\frac{d}{ED_{50} + d}$	$ED_{50} = 20$
$E_{max}2$			$ED_{50} = 30$
Sigmoid-E_{max}	$E_0 + \frac{E_{max} d^h}{ED_{50}^h + d^h}$	$\frac{d^h}{ED_{50}^h + d^h}$	$ED_{50} = 30, h = 2$
Quadratic	$E_0 + \beta_1 d + \beta_2 d^2$	$d + \frac{\beta_2}{\lvert\beta_1\rvert} d^2$	$\delta = \frac{\beta_2}{\lvert\beta_1\rvert} = -0.0083$

[a] d is dose ($d = 0$ for placebo group), θ refers to the vector of model parameters, E_0 is the placebo effect for all candidate models (0.1), E_{max} is the maximum treatment effect over placebo, ED_{50} is the dose that gives 50% of the maximum effect for E_{max} model.

[b] Standardized model.

Figure 2: Prespecified Dose-Response Curves



For a reference of different assumptions of STD of the change in UAS7 score from baseline at Week 12, the sample sizes and the corresponding minimum power to detect a significant dose-response signal at a 1-sided 2.5% significance level are provided in Table 13.

Table 13: Samples Sizes and Minimum Power Across the 6 Prespecified Candidate Models Under Different Assumptions of Standard Deviation

Standard Deviation	Sample Size (Placebo:15 mg:45 mg:75 mg)	Minimum Power
11	100 (25:25:25:25)	0.85
12	116 (29:29:29:29)	0.84
13	136 (34:34:34:34)	0.85

10.2. Populations for Analysis

The populations for analysis are provided in Table 14.

Table 14: Populations for Analysis

Population	Description
FAS	The FAS includes all randomized participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the treatment they were assigned at the time of randomization. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition and for the analyses of all efficacy data.
Safety	The safety population includes all participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment. All safety analyses will be conducted using the safety population.
PK/PD-evaluable	The PK-evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 PK sample. The pharmacodynamic-evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 pharmacodynamic sample.

10.3. Level of Significance

The dose response will be tested at a 1-sided 0.025 level. No multiplicity adjustment will be applied for other statistical tests. Two-sided 95% CIs will be reported for all analyses when appropriate.

10.4. Statistical Analyses

The primary 12-week analysis will be performed after all participants have either completed the Week 12 visit or discontinued from the study.

The final analysis to summarize additional efficacy and safety (without statistical comparison to placebo) will be conducted once the last participant completes the last visit in the study.

Complete and specific details of the statistical analysis will be described and fully documented in the SAP. The SAP will be finalized prior to the database lock for the 12-week analysis. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Primary Analysis

The primary estimand and the strategies for addressing the defined intercurrent events are provided in Table 15 and Table 16, respectively.

Table 15: Estimand for Primary Endpoint

Primary Endpoint	Population	Treatment	Population-Level Summary
Change from baseline in the weekly UAS7 at Week 12.	Participants aged 18 to 65 years who have had a diagnosis of CSU for ≥ 3 months that is inadequately controlled by second-generation H1 antihistamines.	Each of the povorcitinib dose groups compared with placebo	The estimated mean change from baseline in UAS7 for each treatment group, as well as the difference in the estimated mean change from baseline in UAS7 score in each active treatment group as compared with the placebo group, at Week 12.

Table 16: Intercurrent Events and Strategies for the Primary Estimand

Intercurrent Event	Strategies for Addressing the Intercurrent Event
Treatment discontinuation due to any reason	The data collected for the variable are used regardless of whether or not the participant discontinues treatment due to any reason (treatment policy strategy)
Initiation of Protocol-allowed rescue medication	The data collected for the variable are used regardless of whether or not the participant starts the use of any Protocol-allowed rescue medication (treatment policy strategy)

The primary analysis will be performed in the FAS. The mean change from baseline at Week 12 in weekly UAS7 score will be assessed using an MMRM to include all available data at postbaseline visits in the PC period up to Week 12. Participants who have a baseline value and at least 1 postbaseline value in the PC period will be included in the analysis. The MMRM will include change from baseline to Week 12 as a response variable, and the fixed effect of treatment group, randomization stratification factor (previous use of an anti-IgE biologic [yes or no]), visit, treatment-by-visit interaction, and covariates of baseline value and baseline value by visit interaction. Unstructured covariance matrix will be assumed for the within-participant errors. Compound symmetry covariance matrix will be used if the model with unstructured variance covariance does not converge. The Kenward-Roger method will be used to estimate the degrees of freedom. Missing data will not be imputed. The least squares mean estimates for each treatment group and the associated covariance matrix obtained from the MMRM will be provided and further used in generalized MCP-mod framework.

At the MCP stage, a contrast test statistics and multiplicity adjusted p-value for the contrast test will be provided for each prespecified candidate model. A dose-response relationship will be declared if at least 1 model among the set of 6 prespecified candidate models is identified to be

statistically significant at the level $\alpha = 0.025$ 1-sided trend test. Once a significant dose-response is established, the best model will be selected using Akaike Information Criterion.

At the Mod stage, the selected model will be used to obtain the dose-response curve and the 95% CI. The estimated dose-response curve will be presented graphically.

10.4.2. Secondary Analysis

The secondary efficacy endpoints are listed in Table 5. The secondary efficacy analysis will be based on the FAS.

The odds ratios for the proportion of participants with UAS7 ≤ 6 at Week 12 in each of the povorcitinib groups and the placebo group and the corresponding 95% CIs will be assessed using logistic regression with treatment and stratification factor (previous use of an anti-IgE biologic [yes or no]). All participants who have not achieved UAS7≤ 6 in the PC period, as well as all participants who are missing postbaseline values, will be defined as nonresponders for the nonresponder imputation analysis.

The odds ratios for the proportion of participants with UAS7 = 0 at Week 12 in each of the povorcitinib groups and the placebo group and the corresponding 95% CIs will be assessed using logistic regression with treatment and stratification factor (previous use of an anti-IgE biologic [yes or no]). All participants who have not achieved UAS7 = 0 in the PC period, as well as all participants who are missing postbaseline values, will be defined as nonresponders for the nonresponder imputation analysis.

Time to first achievement of UAS7 ≤ 6 during the PC period is defined as the time from the date of randomization until the earliest date of achieving UAS7 ≤ 6 during the PC period. Participants who have not achieved UAS7 ≤ 6 during the PC period will be censored at the last available UAS7 measurement time. Summaries of time to first achievement of UAS7 ≤ 6 during the PC period will be assessed using the Kaplan-Meier method, and the estimated Kaplan-Meier curve will be displayed graphically.

All other secondary efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include the number and percentage of participants in each category. For continuous measurements, summary statistics will include the number of observations, mean, median, STD, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study drug and until 60 days after the last dose of study drug) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. The Protocol-defined ECIs and AESIs will be tabulated by preferred term and Protocol-defined categories for all events. Quantitative safety variables (eg, laboratory values, vital signs) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5.0 toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities. Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time.

10.4.4. Exploratory Analysis

All exploratory efficacy variables will be summarized using descriptive statistics, if applicable. For categorical measurements, summary statistics will include the number and percentage of participants in each category. For continuous measurements, summary statistics will include the number of observations, mean, median, STD, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable.

10.4.4.1. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be performed for the PK-evaluable population. The povorcitinib plasma concentration data will be analyzed by a population PK modeling approach. Such data may be combined with data from other studies in the clinical development program to develop or refine population PK models, in which populations of healthy participants, participants with moderate to severe asthma, and/or participants with other diseases will be evaluated and included into the model if significant as a covariate. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of povorcitinib and to determine measures of individual plasma exposures (such as steady-state peak, trough, and/or time-averaged concentrations). The population PK analysis will be reported separately.

Relationships between povorcitinib PK exposures and clinical responses (efficacy and safety) will be explored using an exposure-response analysis framework as deemed appropriate. For dichotomous endpoints, a generalized linear or nonlinear model with binomial link function will be used. For continuous endpoints, linear or nonlinear regressions will be used. Random effects on interindividual variability will be considered when supported by data. Clinical responses such as the primary and secondary efficacy responses and TEAEs with > 10% incidence rate will be analyzed. The exposure-response analysis will be reported separately.

10.5. Interim Analysis

No formal interim analysis is planned in this study. However, preplanned analyses of safety will be provided to an internal DSMB (see Section 5.6) as specified in the DSMB charter. The process by which the DSMB will review data and make recommendations and decisions will be documented in the DSMB charter.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

– All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the relevant study plans.

Quality tolerance limits will be predefined in the operational manual or equivalent to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure,

and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are considered WONCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
      - Lab alert will be defined in the study reference manual.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Permanently sterile (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method
- Male condom with cap, diaphragm, or sponge with spermicide
- Male and female condom used together

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Bilateral tubal ligation[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. LIST OF STRONG SYSTEMIC CYP3A4 INHIBITORS AND STRONG/MODERATE SYSTEMIC CYP3A4 INDUCERS

Strong Systemic CYP3A4 Inhibitors	Strong and Moderate Systemic CYP3A4 Inducers
• Ceritinib	• Apalutamide
• Clarithromycin	• Bosentan
• Cobicistat	• Carbamazepine
• Danoprevir	• Cenobamate
• Dasabuvir	• Dabrafenib
• Elvitegravir	• Efavirenz
• Idelalisib	• Enzalutamide
• Indinavir	• Etravirine
• Itraconazole	• Ivosidenib
• Ketoconazole	• Lorlatinib
• Lopinavir	• Lumacaftor
• Nefazodone	• Mitotane
• Nelfinavir	• Pexidartinib
• Ombitasvir	• Phenobarbital
• Paritaprevir	• Phenytoin
• Posaconazole	• Primidone
• Ritonavir[a]	• Rifampicin/rifampin
• Saquinavir	• Rifapentine
• Telithromycin	• Sotorasib
• Tipranavir	• St John's wort
• Troleandomycin	
• Voriconazole	
• Grapefruit/grapefruit juice	
• Seville oranges	

Note: Updated lists of CYP3A4 inhibitors/inducers can be found at the FDA's Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

[a] Paxlovid™ is a coadministration of nirmatrelvir and ritonavir.

APPENDIX C. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG

The participant must be instructed in the handling of study drug as follows:

- Store study drug at room temperature (15°C-30°C/59°F-86°F).
- Keep study drug in a safe place and out of reach of children.
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Take study drug once a day, at about the same time each day.
  - On site visit days, the dose will be taken at the study site.
- Make every effort to take doses on schedule.
- If a dose of study drug is missed by more than 12 hours, that dose should be skipped, and the next scheduled dose should be administered the next day at the usual time.
- Take study drug, preferably in the morning, with a full glass of water.
  - The study drug can be taken with or without food.
- Report any missed doses/lost tablets.
- Bring all used and unused study drug blister packs to the site at each visit.
- If vomiting occurs after taking study drug, do not take another dose. If vomiting is persistent, contact the study site.

APPENDIX D. MANAGEMENT OF POTENTIAL HY'S LAW CASES/POTENTIAL DILI

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's law criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and Pharmacovigilance representatives, in the review and assessment of cases fulfilling potential Hy's law criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than DILI caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to potential or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at the same time.

Hy's law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP/GGT indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN AND CONCURRENT TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and consequently determine whether the participant meets potential Hy's law criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN or total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets potential Hy's law criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has not had AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to the guidance provided in Evaluation of Alternative Causes (below).

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, irrespective of ALP, please follow the instruction below:

- Have the participant interrupt study drug.
- Notify the Incyte study team without delay.
  - The investigator or designee should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters, coagulation, and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the Laboratory eCRF as soon as possible.
- If at any time (in consultation with the medical monitor) the potential Hy's law case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for potential Hy's law are met, the medical monitor and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than DILI caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gallbladder and ductal imaging studies, especially if ALP/GGT is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to the outcome of the review and assessment, please follow the instructions below:

If there is an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have the participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have the participant permanently discontinue study drug and perform EOT procedures.
- Report an SAE (report term "Hy's law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related may be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's law is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of potential Hy's law was not chronic or progressing malignant disease, please follow the process for potential Hy's law review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of potential Hy's law was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for potential Hy's law review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty. Significant changes would include new onset or worsening jaundice, fatigue, pruritus, nausea, vomiting, pale-colored stools, and dark urine. Clinically relevant changes in liver function, that is, decrease in synthesis of albumin and clotting factors, would present with edema, hypercoagulability, bruising, and bleeding.

APPENDIX E. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic is an evolving situation and presents numerous challenges to the ongoing conduct of clinical trials. The sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added as needed to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Number of Study Participants

The evolving situation of the pandemic may result in a substantial number of participants' early withdrawal from the study, which could affect the data integrity of the study. Because of this risk and in order to mitigate it, the sponsor may decide to recruit additional participants in the study, beyond the expected number.

Study Visits

Remote Site Visit Guidelines

Note: Remote visits are not applicable in countries where remote visits are not permitted by local law.

The evolving situation of the pandemic may require further travel restrictions and isolation requirements, or the investigator's benefit/risk assessment may determine it to be unsafe for participants to attend study visits at the investigational site. In such cases, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (telephone or video calls). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed.
- No efficacy assessments can be performed via telemedicine (video call, phone call, or via photography).
- Laboratory sampling: in order to support investigator oversight of participant safety and disease management, off-site laboratory sampling (in accordance with the SoA; see Table 3) may be allowed as follows:
  - Instruct the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

On-site visits should be conducted whenever feasible, in addition to the mandatory on-site visits outlined below, even if the date that the participant eventually comes into the clinic deviates from the visit window.

Mandatory On-Site Visits

The visits outlined below **must be performed in person** in order to capture the investigator's efficacy assessments and the PROs, even if the date that the participant eventually comes into the clinic deviates from the visit window.

No efficacy assessments can be performed via telemedicine (video call, telephone call, or photography).

The visit window deviation must be documented, and the sponsor's representative must be informed of when it is believed that the participant can come into the clinic. Further instructions will be provided if needed.

The following visits must be performed in person:

- Screening
- Day 1 (baseline) visit
- Week 12 visit

During the EXT period, the following visits must be performed in person

- Week 24 visit
- Week 36 visit

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study drug via shipment to participants.

If the participant cannot attend a visit at the study site, adequate supplies of study drug determined by the investigator can be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant.

The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed due to documented COVID-19–related reasons; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, e-mails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. If allowed by local

regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Other Considerations

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the tests/procedures conducted outside of the SOC.

- In case of need, participants may refer to the local health care provider. Participants will be requested to obtain certified copies of the source data at the local health facility with the outcome of the contact and provide those to the investigator for appropriate oversight. The investigator/delegate will be requested to enter any relevant information into the EDC.
- Should COVID-19–related restrictions be localized and have an effect on a limited number of sites, the affected sites may utilize direct contracting of third parties to support continuous study conduct (eg, home nursing services, couriers, etc).

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse participants for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [nearby] laboratory tests).

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

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Approval Task	[redacted] Approver [redacted] Biostatistician 07-Mar-2023 18:28:19 GMT+0000
Approval Task	[redacted] [redacted] of Inflammation and AutoImmunity Group 07-Mar-2023 18:53:48 GMT+0000
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Approval Task	[redacted] [redacted] Clinical Operations 07-Mar-2023 21:43:40 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Research Scientist 08-Mar-2023 13:14:26 GMT+0000
Approval Task	[redacted] [redacted] Global Program Head 08-Mar-2023 15:39:04 GMT+0000

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