Protocol VTX958-201 v3.0

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VTX958 in Participants With Moderate to Severe Psoriasis

NCT05655299

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A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF VTX958 IN PARTICIPANTS WITH MODERATE TO SEVERE PSORIASIS

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PROTOCOL VTX958-201

FINAL

VERSION 3.0

05-MAY-2023

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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 07-OCT-2022	Initial version	N/A
2.0 (NA) / 09-FEB-2023	To update the protocol with an additional 16-week LTE period.	Throughout the protocol, the study design was updated to include an additional 16-week LTE treatment period. A possible 2-week study product interruption before entering in the LTE was also added, resulting in a total study duration of up to 42 weeks.
	To correct the erroneously marked procedures and to add a footnote detailing blood sampling for genetic testing in the Schedule of Events.	Section 1.3 (Table 1): 'X's were removed from the Follow-up/Week 20 visit for dosing diary distribution/collection/review and study product accountability. An 'X' was removed from the Week 16 visit for study product dispensing/redispensing. A footnote was added for the item "Blood sampling for genetic testing (optional)" to indicate that the sample could be collected at a later study visit, if applicable.
	To clarify that presence of induration for participants with an sPGA score of 1 should not be collected because an sPGA score of 1 is described as "no thickening", and to correct a typographical error.	Section 8.1.2: Collecting data on presence (yes/no) of induration for participants with an sPGA score of 1 was removed.
	To update the AE severity grading to CTCAE criteria and to clarify discontinuation/interruption criteria based on CTCAE grading.	Sections 4.5, 8.4.4, and 8.4.9: Clarified discontinuation/interruption criteria based on CTCAE event and removed bulleted items on cardiovascular events, thrombosis events, and ECG abnormalities. Updated current severity grading system to CTCAE severity grades.
	To clarify the study product discontinuation and interruption procedures.	Section 4.5: Included details on study product interruption procedures in case of AEs or laboratory abnormalities.
	To include additional details for exclusion criterion #18.	Synopsis and Section 5.2: Added clarification that participants having a negative HBsAg and positive anti-HBc may enroll if they have positive anti-HBs, demonstrating natural immunity.
	To detail the window periods for PK blood draws.	Section 8.3.7: Added window periods to post morning dose PK blood draws at Week 4.
	To update the protocol with data from the updated IB.	Sections 2.1.2.2 and 4.3: Updated clinical studies and toxicology data to align with v4.0 of the IB.

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Version	Rationale for amendment	Main changes to the protocol
	To update the populations and include additional statistical considerations in the protocol.	Synopsis, Section 9.2, and Section 9.3.3: Added FAS population for analysis of efficacy outcomes and included additional details for efficacy analyses.
	To update the regulatory number on the cover page.	Cover page: Removed EudraCT number and replaced with IND number.
2.0 (POL) / 01-MAR-2023	To correct the erroneously marked procedures and to add a footnote detailing blood sampling for genetic testing in the Schedule of Events.	Section 1.3 (Table 1): 'X's were removed from the Follow-up/Week 20 visit for dosing diary distribution/collection/review and study product accountability. An 'X' was removed from the Week 16 visit for study product dispensing/redispensing. Section 1.3 (Table 2): Footnote regarding study product dispensing was removed from LTE Day 1 visit. A footnote was added for the item "Blood sampling for genetic testing (optional)" to indicate that the sample could be collected at a later study visit, if applicable.
	To clarify that presence of induration for participants with an sPGA score of 1 should not be collected because an sPGA score of 1 is described as "no thickening", and to correct a typographical error.	Section 8.1.2: Collecting data on presence (yes/no) of induration for participants with an sPGA score of 1 was removed.
	To update the AE severity grading to CTCAE criteria and to clarify discontinuation/interruption criteria based on CTCAE grading.	Sections 4.5, 8.4.4, and 8.4.9: Clarified discontinuation/interruption criteria based on CTCAE event and removed bulleted items on cardiovascular events, thrombosis events, and ECG abnormalities. Updated current severity grading system to CTCAE severity grades.
	To clarify the study product discontinuation and interruption procedures.	Section 4.5: Included details on study product interruption procedures in case of AEs or laboratory abnormalities.
	To include additional details for exclusion criterion #18.	Synopsis and Section 5.2: Added clarification that participants having a negative HBsAg and positive anti-HBc may enroll if they have positive anti-HBs, demonstrating natural immunity.
	To detail the window periods for PK blood draws.	Section 8.3.7: Added window periods to post morning dose PK blood draws at Week 4.
	To update the protocol with data from the updated IB.	Sections 2.1.2.2 and 4.3: Updated clinical studies and toxicology data to align with v4.0 of the IB.

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Version	Rationale for amendment	Main changes to the protocol
		Updated throughout to remove language on pending toxicology data.
	To update the populations and include additional statistical considerations in the protocol.	Synopsis, Section 9.2, and Section 9.3.3: Added FAS population for analysis of efficacy outcomes and included additional details for efficacy analyses.
	To clarify that administration of placebo tablets will not occur only in the placebo-controlled period, but also for the VTX958 300 mg QD and 50 mg BID groups in the LTE period.	Section 6.1 (Table 3): Removed "during the placebo-controlled period only" from placebo dosing instructions.
3.0 / 05-MAY-2023	To merge protocol versions 2.0 for North America and Poland into one global protocol.	Aligned protocol language throughout.
	To update the protocol with an additional 36-week OLE period.	Throughout the protocol, the study design was updated to include an additional 36-week OLE treatment period. A possible 28-day study product interruption was also added.
	To correct minor discrepancies and update/optimize statistical analyses.	Throughout the protocol, minor corrections were applied, and updates were made for statistical methods.

Abbreviation: AE, adverse event; anti-HBc, hepatitis B antibodies to core antigens; anti-HBs, hepatitis B surface antibody; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; FAS, full analysis set; HBsAg, hepatitis B surface antigens; IB, Investigator's Brochure; IND, investigational new drug; LTE, long term extension; NA, North America; N/A, not applicable; OLE, open-label extension; PK, pharmacokinetic; POL, Poland; QD, once daily; sPGA, static Physician's Global Assessment.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form (ICF), recruitment materials, and all participant materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the study. All changes to the consent form will be IRB/REB approved.

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SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and date (DD-MMM-YYYY)
PPD		

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PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I confirm that I have read the protocol and that I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AUC	area under the curve
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminase
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CI	confidence interval
CK	creatine kinase
C_{max}	maximal plasma concentrations
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease-2019
CPK	creatine phosphokinase
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
FCIR	film coated immediate release
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit

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HCV	hepatitis C virus
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose, throat
Hgb	hemoglobin
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
IFNα	interferon alpha
IFNγ	interferon gamma
IL	interleukin
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IWRS	Interactive Web Response System
JAK	Janus kinase
JH2	pseudokinase domain of tyrosine kinase 2
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LMW	low molecular weight
LOCF	last observation carried forward
LTE	long-term extension
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model of repeated measures
MPV	mean platelet volume
NA	North America
N/A	not applicable
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NR	non-responder
NRI	non-response imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug

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OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
PASI-75	at least 75% improvement from baseline in Psoriasis Area and Severity Index
PASI-90	at least 90% improvement from baseline in Psoriasis Area and Severity Index
PASI-100	100% improvement from baseline in Psoriasis Area and Severity Index
PD	pharmacodynamic
PK	pharmacokinetic
PLT	platelets
POL	Poland
PP	per-protocol
PSSD	Psoriasis Symptoms and Signs Diary
PT	Preferred Term
PUVA	psoralen-UV-A
QC	quality control
QD	once daily
RBC	red blood cell (count)
REB	research ethics board
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
sPGA	static Physician's Global Assessment
STAT	signal transducer and activator of transcription
TB	tuberculosis
TBNK	T- and B-lymphocytes and natural killer cells
TEAE	treatment-emergent adverse event
Th	T helper
TNF	Tumor Necrosis Factor
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UVB	ultraviolet B
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of childbearing potential

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1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Ventyx Biosciences, Inc.	**Name of Study Product:** VTX958	**Name of Active Ingredient:** VTX958.adipate

Title of Study:

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VTX958 in Participants With Moderate to Severe Psoriasis

Phase of Development:

Phase 2

Study Centers:

Approximately 70 study centers located in the United States, Canada, and Poland will participate in this study. During the conduct of the study, additional countries and/or sites may be added if necessary.

Number of Participants (planned):

Approximately 200 participants with moderate to severe psoriasis are planned to be randomized into this study (approximately 40 participants/arm for the placebo-controlled period).

Duration of Study:

The study duration for each participant is up to 76 weeks, from screening to the end of study (EOS) visit (including a screening period of up to 30 days, a 16-week placebo-controlled period, a 16-week long-term extension (LTE) period, a 36-week open label extension (OLE) period, and a 4-week safety follow-up period). Study product may be interrupted between the placebo-controlled and LTE periods, and between the LTE and OLE periods.

Investigational Products, Dosage, and Mode of Administration:

VTX958 300 mg twice daily (BID), 225 mg BID, 300 mg once daily (QD), or 50 mg BID, or placebo tablets BID will be orally administered for 16 weeks during the placebo-controlled period. VTX958 will be available in 125 mg and 50 mg strength tablets. Matching placebo will be identical to VTX958 but will not contain the active ingredient.

Participants will be randomized in a 1:1:1:1:1 ratio on Day 1. During the LTE period, all participants will receive VTX958 orally administered for 16 weeks. The dose of VTX958 to be administered during the LTE will depend on their initial treatment in the placebo-controlled period and/or the participant's response status (based on PASI-75) at Week 16. During the OLE period, all participants will receive VTX958 300 mg BID orally administered for 36 weeks.

Objectives and Endpoints for Placebo-Controlled Period:

OBJECTIVES	ENDPOINTS
Primary objectives	
To determine the efficacy of VTX958 after treatment for 16 weeks in participants with moderate to severe psoriasis.	Primary efficacy endpoint:
	• Proportion of participants achieving PASI-75 at Week 16
	Primary safety endpoints:

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Name of Sponsor/Company: Ventyx Biosciences, Inc.	**Name of Study Product:** VTX958	**Name of Active Ingredient:** VTX958.adipate

To evaluate the safety and tolerability of VTX958 during the placebo-controlled treatment period in participants with moderate to severe psoriasis.	• Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
Secondary objective	
To evaluate the efficacy of VTX958 on improvement of various measures of psoriasis after treatment for 16 weeks in participants with moderate to severe psoriasis.	Secondary efficacy endpoints: • Proportion of participants achieving an sPGA score of 0 (clear) or 1 (almost clear) at Week 16 • Change and percent change from baseline in PASI at Week 16 • Proportion of participants achieving PASI-90 at Week 16 • Proportion of participants achieving PASI-100 at Week 16 • Change from baseline in DLQI scores at Week 16 • Change from baseline in BSA at Week 16
Exploratory objectives	
To examine the efficacy of VTX958 at various timepoints during the first 16 weeks of treatment in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Proportion of participants achieving PASI-75 at Weeks 1, 2, 4, 8, and 12 • Proportion of participants achieving PASI-90 at Weeks 1, 2, 4, 8, and 12 • Proportion of participants achieving PASI-100 at Weeks 1, 2, 4, 8, and 12 • Change and percent change from baseline in PASI at Weeks 1, 2, 4, 8, and 12 • Change from baseline in sPGA at Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving an sPGA score of 0 (clear) or 1 (almost clear) at Weeks 1, 2, 4, 8, and 12 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in BSA at Weeks 1, 2, 4, 8, and 12 • Change from baseline in pruritus NRS at Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at Weeks 1, 2, 4, 8, 12, and 16 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at Weeks 4, 8, and 12 • Change from baseline in PSSD at Weeks 1, 2, 4, 8, 12, and 16
To evaluate the plasma concentration of VTX958 during the placebo-controlled period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: • Measurement of plasma concentrations of VTX958 in participants receiving active treatment
To evaluate the effects of VTX958 on blood and skin biomarkers.	Exploratory PD endpoint: • Change in blood and skin biomarker levels

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PASI-75, at least 75% improvement from baseline in

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Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PD, pharmacodynamic; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

Objectives and Endpoints for Long-Term Extension Period:

OBJECTIVES	ENDPOINTS
Exploratory objectives	
To examine the efficacy of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Change and percent change from baseline in PASI at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-75 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-90 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-100 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in sPGA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in BSA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in pruritus NRS at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at LTE Weeks 1, 2, 4, 8, 12, and 16 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at LTE Weeks 4, 8, 12, and 16 • Change from baseline in PSSD at LTE Weeks 1, 2, 4, 8, 12, and 16
To evaluate the safety and tolerability of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the plasma concentration of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: Measurement of plasma concentrations of VTX958

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; LTE, long-term extension; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PASI-75, at least 75% improvement from baseline in Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

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Objectives and Endpoints for Open-Label Extension Period:

OBJECTIVES	ENDPOINTS
Exploratory objectives	
To examine the efficacy of VTX958 during the OLE period in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Change and percent change from baseline in PASI at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-75 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-90 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-100 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in sPGA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in BSA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in pruritus NRS at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in PSSD at OLE Weeks 4, 8, 16, 24, 32, 36, and 40
To evaluate the safety and tolerability of VTX958 during the OLE period in participants with moderate to severe psoriasis.	Exploratory safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the plasma concentration of VTX958 during the OLE period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: Measurement of plasma concentrations of VTX958

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; NRS, Numeric Rating Scale; OLE, open-label extension; PASI, Psoriasis Area Severity Index; PASI-75, at least 75% improvement from baseline in Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

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Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of VTX958 in participants with moderate to severe psoriasis. This study will also evaluate the plasma concentrations of VTX958 and explore the immune response to VTX958 in participants with moderate to severe psoriasis.

Approximately 200 male and female participants, aged 18 years or older, with moderate to severe plaque psoriasis will be randomized in this study. To be eligible for the study, participants will need to have a history of plaque psoriasis for at least 6 months prior to the screening visit. In addition, participants will need to have the following characteristics at screening and on Day 1: Psoriasis Area Severity Index (PASI) score ≥ 12, static Physician's Global Assessment (sPGA) score ≥ 3, and plaque psoriasis covering ≥ 10% of body surface area (BSA).

All participants will read and sign an informed consent form (ICF) prior to any screening procedures being performed. Participants who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible participants will be randomized (1:1:1:1:1) on Day 1 to receive VTX958 at 300 mg BID, 225 mg BID, 300 mg QD, or 50 mg BID, or placebo BID orally administered for 16 weeks during the placebo-controlled period. Randomization will be stratified based on prior treatment with biologics for psoriasis (yes/no). The number of participants with prior treatment with biologics targeting IL-12/-23 or IL-23 to be randomized into this study will be capped at 20% of the total number of participants.

Participants who complete the placebo-controlled period will continue into the LTE period. At the conclusion of the placebo-controlled period, participants may have a study product interruption of up to 14 days if needed to allow for flexibility in starting the LTE period. In such cases, rescreening would not be necessary, but any change in the participants' condition should be reported in the eCRF. If study product interruption is longer than 14 days, the participant may be discontinued from the study and will be asked to come back for a follow-up visit. Participants who decide to withdraw or are withdrawn after completing the placebo-controlled period will undergo a 4-week follow-up period. Participants who were assigned to placebo during the placebo-controlled period will receive the highest dose of VTX958 (300 mg BID) during the LTE period. Participants who were assigned to VTX958 225 mg BID, 300 mg QD, or 50 mg BID in the placebo-controlled period and were assessed as being responders to treatment will continue on the same assigned treatment dose during the LTE period. Participants who were assigned to VTX958 225 mg BID, 300 mg QD, or 50 mg BID in the placebo-controlled period and were non-responders to treatment will receive the highest dose of VTX958 (300 mg BID) during the LTE period. Participants who were assigned to the highest dose of VTX958 (300 mg BID) in the placebo-controlled period will continue on the same assigned treatment dose during the LTE period. A responder is defined as a participant who achieves PASI-75 at Week 16.

Participants who complete the LTE period will continue into the OLE period. Participants who continue into the OLE period will receive VTX958 at 300 mg BID and continue study treatment (ie, LTE Week 16 will occur on the same visit as OLE Day 1). However, a study product interruption of up to 28 days is permitted between LTE and OLE periods if needed to allow for flexibility in starting the OLE period. In such cases, rescreening would not be necessary, but any change in the participants' condition should be reported in the eCRF. If study product interruption is longer than 28 days, the participant will be discontinued from the study and will be asked to come back for a follow-up visit. Participants who decide to withdraw or are withdrawn after completing the LTE period will also be asked to come back for a follow-up visit as described in the Schedule of Events for the LTE period.

The OLE period will be followed by a 4-week follow-up period. For scheduled study visits, participants will come to the study centers on up to 23 occasions, as described in the Schedules of Events.

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Efficacy will be assessed using PASI, BSA, sPGA, pruritus Numeric Rating Scale (NRS), and Psoriasis Symptoms and Signs Diary (PSSD). Quality of life will be evaluated using the Dermatology Life Quality Index (DLQI).

Safety will be assessed by collecting adverse events (AEs), recording vital signs, performing complete and targeted physical examinations, and evaluating clinical laboratory and electrocardiogram (ECG) results.

During the placebo-controlled period, blood samples will be collected from all participants predose (if applicable) to evaluate plasma concentrations of VTX958, and the effect of VTX958 on inflammatory biomarkers and lymphocyte subsets (T- and B-lymphocytes and natural killer cells [TBNK]). Optional blood samples for genetic testing (analysis of deoxynucleic acid [DNA]) will be collected before administration of the study treatment. In addition, optional blood samples for PK analysis will be collected in a subset of participants who consent to the additional blood collection at the Week 4 visit at 1, 2, 4, 6, and 24-hours post-morning dose.

During the LTE and OLE period, blood samples will be collected from all participants predose (if applicable) to evaluate plasma concentrations of VTX958.

During the placebo-controlled period, the effect of VTX958 on skin biomarkers will be evaluated by collecting tape strips from all participants. At selected study centers, in a subset of participants who consent to the procedure, the effect of VTX958 on skin biomarkers will be evaluated by collecting six or eight optional skin biopsies. The target for this study is to reach approximately 100 participants who consent to collection of biopsies.

During the placebo-controlled period, at selected study centers, in a subset of participants who consent, optional medical photographs (full body, front and back) will be taken to illustrate the outcome of the trial.

During the placebo-controlled period, at selected study centers, in a subset of participants who consent, optional SkinCam photographs (one lesional and one nonlesional area) will be taken at various timepoints to illustrate the progress throughout the trial.

Inclusion/Exclusion Criteria:

Inclusion criteria:

In order to be eligible to participate in this study, a participant must meet all of the following criteria, at both the screening visit and Day 1, unless it is noted in the criterion at only one of the specified visits (screening or Day 1):

1. Male or female participant aged 18 or older at the time of consent.
2. Participant has a history of primarily plaque psoriasis for at least 6 months prior to the screening visit.

   Note: Participants with concomitant guttate or inverse psoriasis may be included in the study; however, it should not be a predominant form.
3. Participant has had stable psoriasis conditions for at least 3 months before screening (information obtained from medical chart or participant's physician, or directly from the participant).
4. Participant has moderate to severe plaque psoriasis as defined by a PASI score of ≥ 12 and an sPGA score of ≥ 3 at screening and Day 1.
5. Participant has plaque psoriasis covering ≥ 10% of the total BSA at screening and Day 1.
6. Participant is deemed by the investigator to be eligible for phototherapy or systemic therapy.
7. For female participant of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use a highly effective contraceptive method from at least

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4 weeks prior to Day 1 until at least 4 weeks after the last dose of study product. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥ 4 months prior to screening, with surgical success confirmed by the participant), tubal ligation, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

Note: Participants using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.

Note: The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

Note: A female participant of nonchildbearing potential is defined as follows:

- Female participant who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
- Female participant who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels)

Note: Female participants must agree to not have egg retrieval from Day 1 until at least 4 weeks after the last dose of study product.

8. For male participant involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 7 from Day 1 until at least 90 days after the last dose of study product. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 90 days after the last dose of study product.

   Note: Male participants must refrain from donating sperm from Day 1 until at least 90 days after the last dose of product.
9. Female participant of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
10. Participant has a negative tuberculosis (TB) infection test result at screening. Participant will be evaluated for active or latent TB infection with a purified protein derivative test or a QuantiFERON-TB Gold test. Participants who demonstrate evidence of latent TB infection (either purified protein derivative ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study, unless documentation of prior and complete anti-TB treatment, appropriate in duration and type according to current local country guidelines, can be provided.
11. Participant has a body mass index (BMI) within the range of 18 to 40 kg/m^2, inclusive, and a total body weight >50 kg (110 lbs).
12. Participant is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.

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13. Participants must be willing to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A participant who meets any of the following criteria at the screening visit and/or Day 1, as applicable, will be excluded from participation in this study:

1. Participant is a female who is breastfeeding, pregnant, lactating, or who is planning to become pregnant during the study.
2. Participant has evidence of erythrodermic, pustular, predominantly inverse or guttate psoriasis, or drug-induced psoriasis.
3. Participant has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Participant is known to have immune deficiency or is immunocompromised.
5. Participant has immune-mediated conditions commonly associated with psoriasis, such as psoriatic arthritis, active uveitis, inflammatory bowel disease, that currently require systemic treatment (including corticosteroids, immunosuppressants, or biologics).

   Note: Participants with immune-mediated conditions commonly associated with psoriasis that do not require systemic treatment may be included in the study.
6. Participant has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, or local active infection/infectious illness, or thromboembolic disease), psychiatric condition, or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with interpretation of study results.
7. Participant has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months prior to screening.
8. Participant had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
9. Participant has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
10. Participant has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg at screening, confirmed by 3 measurements.
11. Participant has been hospitalized in the past 3 months for asthma, has ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or has required more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within 6 months prior to Day 1.
12. Participant has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Participants with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
13. Participant has a history or evidence of an active systemic infection and/or febrile illness within 7 days prior to Day 1.
14. Participant has a history of serious infections that led to hospitalization and/or intravenous antibiotic treatment within 12 weeks prior to Day 1, or requiring oral antibiotic treatment within 4 weeks prior to Day 1.
15. Participant has a history of chronic or recurrent infectious disease, including but not limited to

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chronic renal infection, chronic chest infection, recurrent urinary tract infection, fungal infection (with the exception of superficial fungal infection of the nailbed), or infected skin wounds or ulcers.

16. Participant has a history of infected prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
17. Participant has an active herpes simplex infection that occurs more frequently than monthly or that requires suppressive therapy, or active herpes zoster infection identified on examination and/or medical history within 8 weeks prior to Day 1.
18. Participant has a positive result for hepatitis B virus (HBV; positive for hepatitis B surface antigens [HBsAg] or positive for hepatitis B antibodies to core antigens [anti-HBc]; participants having a negative HBsAg and a positive anti-HBc may enroll if they have a positive hepatitis B surface antibody [anti-HBs] demonstrating natural immunity), hepatitis C virus (HCV; positive for HCV antibodies; however, a participant with documented proof of cure from HCV may be enrolled), or human immunodeficiency virus (HIV) at screening.
19. Participant has any of the following laboratory values at the screening visit:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 2.0 times the upper limit of normal (ULN);
    - Hemoglobin (Hgb) < 9.0 g/dL (< 90.0 g/L);
    - White blood cell count (WBC) < 3.0 x 10^9/L (< 3000/mm^3);
    - Absolute neutrophil count of < 1.0 x 10^9/L (< 1000/mm^3);
    - Absolute lymphocyte count of < 0.5 x 10^9/L (< 500/mm^3);
    - Platelet count < 100 x 10^9/L (< 100,000/mm^3);
    - Total bilirubin ≥ 1.5 times the ULN.
20. Participant has thyroid-stimulating hormone (TSH) levels outside the normal range that is deemed clinically significant by the investigator at the screening visit.
21. Participants who have given > 50 ml of blood or plasma within 4 weeks of screening or > 499 mL of blood or plasma within 8 weeks prior to screening (during a clinical trial or at a blood bank donation).
22. Participant has used any topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], Janus kinase [JAK] inhibitors, or tar) within 2 weeks prior to Day 1.
23. Participant has used any systemic treatment that could affect psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, anakinra, methotrexate, cyclosporine, oral JAK inhibitors, or apremilast) within 4 weeks prior to Day 1.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
24. Participant has received any ultraviolet B (UVB) phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
25. Participant has had psoralen and ultraviolet A (PUVA) treatment within 4 weeks prior to Day 1.
26. Participant has received any live or live-attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last dose of study product.

    Note: Nonlive-attenuated vaccines (eg, ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive-attenuated vaccines or

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boosters for coronavirus disease-2019 (COVID-19), are allowed during the study. The study site should follow local guidelines related to COVID-19.

27. Participant is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
28. Participant has received any marketed or investigational biologic agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criterion 32 that are to be excluded as specified).
29. Participant is currently receiving sensitive substrates of cytochrome P450 (CYP)1A2, 2C9 and 2B6, or strong inducers of CYP3A4 (as listed in Table 9) that would, in the opinion of the investigator in consultation with the sponsor and medical monitor, put the participant at undue risk or interfere with interpretation of study results.
30. Participant has received treatment with an investigational or marketed tyrosine kinase 2 (TYK2) inhibitor.
31. Participant has a history of loss of response to > 2 marketed biologic agents for psoriasis of any mechanism of action, when administered after at least 12 weeks of therapy.
32. Participant has received rituximab or other immune-cell depleting therapy within 6 months prior to Day 1.
33. Participant is currently receiving terbinafine, lithium, antimalarials, leflunomide, or intramuscular (IM) gold, or have received terbinafine, lithium, antimalarials, or IM gold within 4 weeks or leflunomide within 12 weeks prior to Day 1.
34. Participant has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study. Note: Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
35. Participant has a known or suspected allergy to VTX958 or any component of the investigational product.
36. Participant has a known history of clinically significant drug or alcohol abuse in the last year prior to screening.
37. For participants consenting to biopsy collection only:
    - Participant has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    - Participant has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    - Participant has taken anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin ≤81 mg which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

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Sample Size Consideration:

Using published data from 2 Phase III studies (POETYK-PSO-1 and POETYK-PSO-2 – Deucravacitinib 6 mg QD)[1,2], a two group χ^2 test with a 5% two-sided significance level will have 87% power to detect the difference between a placebo PASI-75 responder rate of 0.15 and a PASI-75 responder rate of at least 0.48 (odds ratio of 5.231) in each active treatment group at Week 16 when the sample size in each group is 36. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group (VTX958 300 mg BID), and ending with the lowest dose group (ie, VTX958 50 mg BID). To allow for a post-randomization dropout rate of approximately 10%, 200 participants will be randomized (40 participants/treatment group).

Statistical Methods:

Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in a separate statistical analysis plan (SAP) that will be finalized and signed off before the database is locked and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final clinical study report, as appropriate.

All statistical tests will be two-sided and will be performed with a significance (alpha) level of 0.05, unless otherwise specified in the SAP. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group (VTX958 300 mg BID), and ending with the lowest dose group (ie, VTX958 50 mg BID). No adjustment to alpha level will be made to account for multiple testing between treatment groups for the secondary and exploratory efficacy endpoints.

Efficacy Analyses:

Placebo-Controlled Period:

The primary endpoint can be translated as a responder analysis, where a participant will be classified as responder if he or she achieves PASI-75 at Week 16. The pairwise comparisons between groups for the primary endpoint will be done using an adjusted Cochran-Mantel-Haenszel (CMH) test, with adjusted for the prior treatment with biologics for psoriasis included as a stratification factor (yes/no). The comparison between the highest dose of VTX958 (300 mg BID) versus placebo will be performed first and will be followed with the comparisons involving the lower doses (as per hierarchical testing procedure). The primary efficacy analysis will be performed on the Full Analysis Set (FAS), while the Per-Protocol Set will be used to perform a supportive analysis. For the primary analysis of primary efficacy using FAS, missing data will be handled through the non-response imputation (NRI). For the supportive analysis on the Per-Protocol Set, participants with missing observation will be excluded from the analysis. Additional supportive and sensitivity analyses will be performed and will be described in the SAP.

The primary analysis of secondary and exploratory endpoints involving proportions of participants will be analyzed using the same approach (adjusted CMH test) as described for the primary analysis of the primary efficacy analysis, at each time point based on the FAS. Missing data imputation for the primary analysis of these endpoints will be handled through the NRI. Additional supportive and sensitivity analyses may be performed and will be described in the SAP.

The continuous secondary and exploratory endpoints involving change from baseline will be analyzed using the mixed model for repeated measures (MMRM). The model will include treatment group, analysis visit, treatment-by-visit interaction, and prior treatment with biologics for psoriasis (yes/no) as fixed effects and baseline value as a covariate. An unstructured covariance matrix will be specified for

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the MMRM model. LS means at visits and LS mean differences between treatment groups will p-values and corresponding 95% CIs will be reported. Supportive and sensitivity analyses related to missing data imputation for these endpoints will be described in the SAP.

Long-Term Extension Period:

For the efficacy variables collected during the LTE period, descriptive summaries by treatment sequence (treatment received during the placebo-controlled period – treatment received during the LTE period), by dose, and by visit, when applicable, will be provided based on the LTE analysis set. No inferential statistical testing will be done on the efficacy variables for the LTE period. A sensitivity analysis excluding participants who experienced a study product interruption between the placebo-controlled period and the LTE period may be performed. More details on this will be provided in the SAP.

Open-Label Extension Period:

For the efficacy variables collected during the OLE period, descriptive summaries by treatment sequence, all combined, and by visit, when applicable, will be provided based on the OLE Set. No inferential statistical testing will be done on the efficacy variables for the OLE period. A sensitivity analysis excluding participants who had a study product interruption between the LTE period and the OLE period may be performed. More details on this will be provided in the SAP.

Safety Analyses:

Safety analyses will be performed by study period using the study population related to the analysis time period (Safety Set for the placebo-controlled period, LTE Set for the LTE period, and OLE Set for the OLE period). All safety data, including AEs and serious adverse events (SAEs) will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification by treatment group and study period. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, action taken with respect to the study product, and the outcome. The focus in this protocol will be the prevalence of treatment-emergent adverse events (TEAEs).

Reported TEAEs will be summarized by the number of participants reporting the events, as well as by System Organ Class (SOC), Preferred Term (PT), severity, seriousness, and relationship to study product.

Results from laboratory analyses, vital signs, and ECGs will be tabulated by treatment group and visit using descriptive statistics for each study period separately. The observed value at each visit as well as the change from baseline will be presented descriptively.

Clinically significant changes in laboratory analyses, vital signs, ECGs, and new findings on physical examination will be recorded as AEs.

Shift tables describing shifts to out-of-normal range may be provided for clinical laboratory results, and normal-abnormal shift tables may be provided for vital signs.

Concomitant medications will be coded with the WHO-Drug Dictionary and listed by participant. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

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Pharmacokinetic Analyses:

Analyses of pharmacokinetic data will be described in a separate analysis plan.

Pharmacodynamic Analyses:

Analyses of blood and skin biomarkers will be described in a separate analysis plan.

Other Analyses:

Descriptive summaries of baseline characteristics, including demographic data and prior concomitant therapy, and of participant disposition will be presented by treatment group for each study period. In addition, a list of participants who discontinued from the study along with discontinuation reason will be provided.

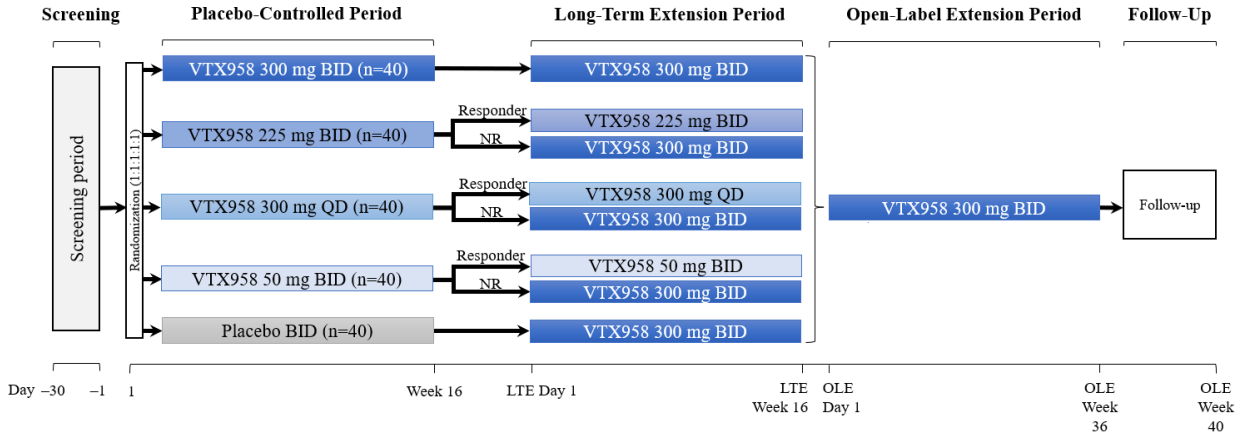
Protocol deviations will be summarized by treatment, category, and study period.

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1.2 Study Diagram

Figure 1: Study Diagram



Abbreviation: BID, twice daily; LTE, long-term extension; NR, non-responder; OLE, open-label extension; PASI-75, 75% improvement from baseline in PASI; QD; once daily.
Notes: Responder is defined as a participant who achieves PASI-75 at Week 16.
To maintain the blind, participants randomized to VTX958 300 mg QD will receive VTX958 300 mg for the morning dose and placebo for the evening dose.

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1.3 Schedule of Events

The screening evaluation will only be performed after the participant has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the participant fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1, Table 2, and Table 3 provide a description of the procedures to be performed at each visit for the placebo-controlled period, the LTE period, and the OLE period, respectively.

Unless specified otherwise, the study assessments scheduled during the study visits must be performed before the study product administration (not applicable at visits without study product administration).

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

- Vital signs
- 12-lead ECG
- Blood draw

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Table 1: Schedule of Events – Placebo-Controlled Period

Study Visits	Screening	Placebo-Controlled Period							Follow-up[a]	ET
		Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	
		Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	
Window (days)	-30 to -1	–	(±2)	(±2)	(±2)	(±3)	(±3)	(+3)	(±4)	
Informed consent	X									
Demographics	X									
Medical and surgical history	X	X								
Prior use of biologics for psoriasis	X	X								
Inclusion-exclusion	X	X								
Pregnancy test[b]	X	X		X	X	X	X	X	X	X
Serum chemistry[c] and hematology	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X						X	X	X
Serology (HBV, HCV, HIV)	X									
Urinalysis	X	X						X		X
hsCRP		X			X	X	X	X		X
TSH	X							X		
Fasting lipid panel		X						X		X
Serum IgM, IgG, IgA, IgE		X			X	X	X	X		X
Physical examination[d]	X	X	X	X	X	X	X	X	X	X
Physical measurements[e]	X	X			X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X		X	X	X	X	X		X
TB evaluation[f]	X									
PASI	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X	X
Pruritus NRS		X	X	X	X	X	X	X	X	X
PSSD		X	X	X	X	X	X	X	X	X
DLQI		X			X	X	X	X	X	X
Randomization		X								
Study product administration[g,h]		X ———						X[i]		
Study product dispensing/ redispensing		X	X[j]	X[j]	X	X	X			
Study product accountability			X	X	X	X	X	X		X
Dosing diary distribution/collection/review		X	X	X	X	X	X	X		X

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Study Visits	Screening	Placebo-Controlled Period							Follow-up[a]	ET
		Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	
		Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	
Window (days)	-30 to -1	–	(±2)	(±2)	(±2)	(±3)	(±3)	(+3)	(±4)	
Blood sampling for VTX958 concentration[k]		X	X	X	X	X	X	X	X	X
Blood sampling for PK (optional)[l]					X					
Blood sampling for biomarker analysis		X			X			X		
Blood sampling for TBNK		X			X			X		
Blood sampling for genetic testing (optional)[m]		X								
Tape strips[n]		X						X		
Medical photographs (optional)[o]		X			X			X		
SkinCam photographs (optional)[p]		X————		——X————		X	X	X		
Skin biopsies collection (optional)[q]		X			X[r]			X		
Concomitant medication, procedures, and non-drug therapies	X	X	X	X	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; LTE, long-term extension; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment; TB, tuberculosis; TBNK, T- and B-lymphocytes and natural killer cells; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] A follow-up visit after the placebo-controlled period is only applicable to participants who withdraw or are withdrawn from the study prior to continuation into the LTE period (eg, possible study product interruption between both periods greater than the allowed 14 days or participant who withdraw consent during the possible study product interruption).

[b] For WOCBP only, serum β-hCG test at screening and urine pregnancy test at the other visits.

[c] Levels of FSH will be measured at screening only for females who have had a cessation of menses for ≥ 12 months without an alternative medical cause.

[d] Complete physical examination at screening and Week 16 (end of placebo-controlled treatment). Targeted physical examination at all other visits.

[e] Includes height and weight at screening, and BMI at screening and Day 1. Only weight will be measured at all other visits.

[f] If purified protein derivative is used, a second visit will be necessary for purified protein derivative reading only.

[g] On study visit days within the placebo-controlled period, the morning dose of the study product will be administered at the clinic, under the supervision of the study staff, after completion of all assessments on the day of visit (if applicable).

[h] If a study visit must occur in the afternoon, participants may take their morning dose at the regular scheduled time at home, and do not have to wait to take the dose at the clinic; during the afternoon visit, all assessments will be performed accordingly, except study product will not be administered in the clinic if the last dose occurred less than 8 hours prior. This is not applicable at Week 4 visit for participants who consent to the optional blood sampling for PK.

[i] Study product administration for the placebo-controlled period will not be given during the Week 16 visit. After all Week 16 visit assessments are completed, the first dose of study product of the LTE will be given, and this will be considered Day 1 of the LTE period.

[j] Participants may be redispensed their returned study product after compliance is reviewed if there are adequate amounts of study product returned to last until the next study visit.

[k] Blood samples will be collected prior to the morning dose (as applicable). If needed, a blood sample may also be obtained at unscheduled visits to assess VTX958 plasma levels.

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Study Visits	**Screening**	**Placebo-Controlled Period**							**Follow-up[a]**	**ET**
		Day 1	**Day 8**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	
		Week 0	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	
Window (days)	-30 to -1	–	(±2)	(±2)	(±2)	(±3)	(±3)	(+3)	(±4)	

[l] Optional, at selected study sites, in a subset of participants who consent to the procedure, additional blood samples for PK analysis will be collected at 1, 2, 4, 6, and 24-hours after the morning dose. Participants will have to remain on site for at least 6 hours after the morning dose and come back for an additional visit the next day for their 24-hour post-morning dose sample collection.

[m] If required, another blood sample can be collected at any other visit for the genetic testing (eg, in case it was missed or collected incorrectly at Day 1).

[n] Skin tape strips (from lesional skin and from nonlesional skin in the vicinity of the lesional skin) for all participants will be collected on Day 1, and from the same lesional skin at Week 16 (even if the lesion has cleared).

[o] Optional, at selected study sites, in a subset of participants who consent to the procedure, medical photographs (full body, front and back) will be taken.

[p] Optional, at selected study sites, in a subset of participants who consent to the procedure, SkinCam photographs (one lesional and one nonlesional area) will be taken. Participants will have their photos taken on site at each visit for a total of approximately 12 photos. Participants will take SkinCam photographs at home, daily from Day 2 to Day 14 and weekly from Day 16 to Day 28 for a total of approximately 30 photos. Participants will be trained on how to use the SkinCam photo at Day 1.

[q] Optional, only for participants who consent to the procedure: four 4-mm skin biopsies on Day 1 (two from lesional skin and two from nonlesional skin in the vicinity of the lesional skin) and two 4-mm punch biopsies at Week 16 (from same lesional skin; outside the scar of the previous biopsies, at least 1 cm away from the previous scars, even if the lesions have cleared).

[r] Two additional 4-mm skin biopsies (from same lesional skin; outside the scars of the previous biopsies, at least 1 cm away from the previous scars) will be collected at Week 4 for participants who consent to eight biopsies.

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Table 2: Schedule of Events – Long-Term Extension Period

Study Visits	Long-Term Extension Period							Follow-up[i]	ET
	LTE Day 1[a]	LTE Day 8	LTE Day 15	LTE Day 29	LTE Day 57	LTE Day 85	LTE Day 113	LTE Day 141	
	LTE Week 0[a]	LTE Week 1	LTE Week 2	LTE Week 4	LTE Week 8	LTE Week 12	LTE Week 16	LTE Week 20	
Window (days)	–	(±2)	(±2)	(±2)	(±3)	(±3)	(±3)	(±4)	
Pregnancy test[b]	X		X	X	X	X	X	X	X
Serum chemistry and hematology	X	X	X	X	X	X	X	X	X
Coagulation	X						X	X	X
Urinalysis	X						X		X
hsCRP	X			X	X	X	X		X
TSH	X						X		
Fasting lipid panel	X						X		X
Serum IgM, IgG, IgA, IgE	X			X	X	X	X		X
Physical examination[c]	X	X	X	X	X	X	X	X	X
Weight measurements	X			X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X	X	X	X	X		X
PASI	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X
Pruritus NRS	X	X	X	X	X	X	X	X	X
PSSD	X	X	X	X	X	X	X	X	X
DLQI	X			X	X	X	X	X	X
Study product assignment	X								
Study product administration[d]	X———						———X[e]		
Study product dispensing/redispensing	X	X[f]	X[f]	X	X	X			
Study product accountability		X	X	X	X	X	X		X
Dosing diary distribution/collection/review	X	X	X	X	X	X	X		X
Blood sampling for VTX958 concentration[g]	X	X	X	X	X	X	X	X	X
Concomitant medication, procedures, and non-drug therapies	X	X	X	X	X	X	X	X	X
AE evaluation	X[h]	X	X	X	X	X	X	X	X

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Study Visits	Long-Term Extension Period							Follow-up[i]	ET
	LTE Day 1[a]	LTE Day 8	LTE Day 15	LTE Day 29	LTE Day 57	LTE Day 85	LTE Day 113	LTE Day 141	
	LTE Week 0[a]	LTE Week 1	LTE Week 2	LTE Week 4	LTE Week 8	LTE Week 12	LTE Week 16	LTE Week 20	
Window (days)	–	(±2)	(±2)	(±2)	(±3)	(±3)	(±3)	(±4)	

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; ET, Early Termination; hsCRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; LTE, long-term extension; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants without any study product interruption, the LTE Day 1 visit should occur on the same day of the Week 16 visit. In this case, assessments that are common to both visits (Week 16 and LTE Day 1) will be performed only once. However, at Week 16, some participants may have their treatment interrupted for up to 14 days, if needed, and in this case LTE Day 1 will have to be conducted in its entirety. In both cases, participants will not have to perform a screening visit to enter in the LTE period.

[b] For WOCBP only, urine pregnancy test at all visits.

[c] Complete physical examination at LTE Day 1 and LTE Week 16 (end of LTE treatment). Targeted physical examination at all other visits.

[d] On study visit days within the LTE period, the morning dose of the study product will be administered at the clinic, under the supervision of the study staff, after completion of all assessments on the day of visit (if applicable). However, if a study visit must occur in the afternoon, participants may take their morning dose at the regular scheduled time at home, and do not have to wait to take the dose at the clinic; during the afternoon visit, all assessments will be performed accordingly, except study product will not be administered in the clinic if the last dose occurred less than 8 hours prior.

[e] Study product administration for the LTE period will not be given during the LTE Week 16 visit. After all LTE Week 16 visit assessments are completed, the first dose of study product of the OLE will be given, and this will be considered Day 1 of the OLE period.

[f] Participants may be redispensed their returned study product after compliance is reviewed if there are adequate amounts of study product returned to last until the next study visit.

[g] Blood samples will be collected predose (as applicable). If needed, a blood sample may also be obtained at unscheduled visits to assess VTX958 plasma levels.

[h] In case of a study product interruption between the Week 16 visit and the LTE Day 1 visit, any AEs reported during the study product interruption will be reported under the placebo-controlled period. Any AEs reported after the LTE Day 1 morning dose will be reported in the LTE period.

[i] A follow-up visit after the LTE period is only applicable to participants who withdraw or are withdrawn from the study prior to continuation into the OLE period (eg, participant who withdraws consent during the possible study product interruption).

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Table 3: Schedule of Events – Open-Label Extension Period

Study Visits	Open-Label Extension Period							Follow-up	ET
	OLE Day 1[a]	OLE Day 29	OLE Day 57	OLE Day 113	OLE Day 169	OLE Day 225	OLE Day 253	OLE Day 281	
	OLE Week 0	OLE Week 4	OLE Week 8	OLE Week 16	OLE Week 24	OLE Week 32	OLE Week 36 (EOT)	OLE Week 40 (EOS)	
Window (days)	–	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±4)	
Pregnancy test[b]	X	X	X	X	X	X	X	X	X
Serum chemistry and hematology	X	X	X	X	X	X	X	X	X
Coagulation	X						X	X	X
Urinalysis	X						X		X
hsCRP	X	X	X	X	X	X	X		X
Fasting lipid panel	X			X			X		X
Serum IgM, IgG, IgA, IgE	X	X	X	X	X	X	X		X
Physical examination[c]	X	X	X	X	X	X	X	X	X
Weight measurements	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X		X
PASI	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X
sPGA	X	X	X	X	X	X	X	X	X
Pruritus NRS	X	X	X	X	X	X	X	X	X
PSSD	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X
Study product administration[d]	X ———						———X		
Study product dispensing	X	X	X	X	X	X			
Study product accountability		X	X	X	X	X	X		X
Dosing diary distribution/collection/review	X	X	X	X	X	X	X		X
Blood sampling for VTX958 concentration[e]	X	X	X	X	X	X	X	X	X
Concomitant medication, procedures, and non-drug therapies	X	X	X	X	X	X	X	X	X
AE evaluation	X[f]	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, Early Termination; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A;

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Study Visits	Open-Label Extension Period							Follow-up	ET
	OLE Day 1[a]	OLE Day 29	OLE Day 57	OLE Day 113	OLE Day 169	OLE Day 225	OLE Day 253	OLE Day 281	
	OLE Week 0	OLE Week 4	OLE Week 8	OLE Week 16	OLE Week 24	OLE Week 32	OLE Week 36 (EOT)	OLE Week 40 (EOS)	
Window (days)	–	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±4)	

IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; LTE, long-term extension; NRS, Numeric Rating Scale; OLE, open-label extension; PASI, Psoriasis Area Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment; TB, tuberculosis; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

[a] For participants without any study product interruption, the OLE Day 1 visit should occur on the same day of the LTE Week 16 visit. In this case, assessments that are common to both visits (LTE Week 16 and OLE Day 1) will be performed only once. However, at LTE Week 16, some participants may have their treatment interrupted for up to 28 days, if needed, and in this case OLE Day 1 will have to be conducted in its entirety.

[b] For WOCBP only, urine pregnancy test at all visits.

[c] Complete physical examination at OLE Day 1 and OLE Week 36 visits. Targeted physical examination at all other visits.

[d] On study visit days within the OLE period, the morning dose of the study product will be administered at the clinic, under the supervision of the study staff, after completion of all assessments on the day of visit (if applicable). However, if a study visit must occur in the afternoon, participants may take their morning dose at the regular scheduled time at home, and do not have to wait to take the dose at the clinic; during the afternoon visit, all assessments will be performed accordingly, except study product will not be administered in the clinic if the last dose occurred less than 8 hours prior. The last study product administration of the OLE is the evening prior to the OLE Week 36 visit. No study product will be administered at OLE Week 36 visit.

[e] Blood samples will be collected predose (as applicable). If needed, a blood sample may also be obtained at unscheduled visits to assess VTX958 plasma levels.

[f] In case of a study product interruption between the LTE Week 16 visit and the OLE Day 1 visit, any AEs reported during the study product interruption will be reported under the LTE period. Any AEs reported after the OLE Day 1 morning dose will be reported in the OLE period.

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2 INTRODUCTION

2.1 Background

2.1.1 Psoriasis

Psoriasis is a chronic inflammatory skin disease with a high prevalence worldwide, affecting approximately 125 million people in the global population.[3] Psoriasis is equally prevalent in men and women, and can develop at any age with onset often between the ages of 15 and 30 years.[4] It presents with many dermatologic manifestations but is most commonly observed in the form of plaque psoriasis. Plaque psoriasis is characterized by thickened erythematous scaly patches of skin often on extensor surfaces on the knees or elbows, but can also be found in intertriginous areas, palms, soles, and nails.[3,5] The role of the inflammatory process in plaque psoriasis is well established and elevated levels of Type I interferon (IFN), tumor necrosis factor (TNF), T helper (Th)17, interleukin (IL)-22, and IL-23 have been observed.[6-8]

Psoriasis is associated with elevated risk to many comorbidities, including psoriatic arthritis, obesity, and hypertension, as well as decreased quality of life.[3,4] Patients presenting mild to moderate symptoms often find topical therapies such as topical corticosteroids to be effective treatments; however, patients experiencing more severe symptoms usually need further systemic treatments such as systemic or biologic therapies.[4]

2.1.2 VTX958

2.1.2.1 Nonclinical studies

VTX958 is a potent, selective allosteric inhibitor of Tyrosine kinase 2 (TYK2) that binds selectively to the pseudokinase domain (JH2) of TYK2. VTX958 is highly selective with no effects on the other homologous proteins in the Janus kinase (JAK) family (JAK1, JAK2, and JAK3).

Tyrosine kinase 2, as other JAK members, associates with the intracellular domains of various cytokine receptors and transduce these receptor-mediated signals via the signal transducer and activator of transcription (STAT) pathways.[9,10] Tyrosine kinase 2 phosphorylation has been observed upon dimerization of many cytokine receptors, including Type I IFN, IL-12, IL-23, IL-10, IL-22, and IL-6, and is essential for Type I IFN, IL-12, and IL-23 signaling transduction.[11]

VTX958's binding to TYK2-JH2 potently inhibits TYK2-driven cytokine signaling pathways including interferon alpha (IFNα), IL-12, and IL-23, by inhibiting downstream phosphorylation of STAT proteins. Further downstream of STAT phosphorylation, VTX958 also inhibits protein transcription, such as interferon gamma (IFNγ) production induced by IL-12. Therefore, selective inhibition of TYK2 kinases may present an optimal therapeutic intervention to treat inflammatory diseases, such as plaque psoriasis, while preserving anti-pathogen immune functions involving the other JAK members.

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2.1.2.2 Clinical studies

VTX958 in suspension and tablet forms has been evaluated in four Phase 1 studies in healthy subjects. A total of 94 healthy subjects received at least one dose of VTX958, and 24 received placebo. Overall, the administration of VTX958 at single doses up to 500 mg, or multiple doses over 14 days ranging from 50 mg BID to 350 mg BID was well tolerated. There were no SAEs or dose-limiting safety and tolerability concerns reported.

Safety and Pharmacodynamic Effects

In the single ascending dose (SAD) study (VTX958-101), and in the multiple ascending dose (MAD) study (VTX958-102), the primary objective was to evaluate the safety and tolerability of single and multiple doses of VTX958, and the secondary objective was to assess the pharmacokinetic profile of VTX958 administered as a suspension. Both studies also included exploratory pharmacodynamic assays to evaluate the ability of VTX958 to block the effect of an injection of IFNα on biomarkers (ie, CXCL10, ISG20 and IFI27, genes responsive to IFNα), and to block the production of IFNγ after ex vivo stimulation with IL-12 and IL-18.

In VTX958-101, overall, 52 of 56 subjects (92.9%) reported a total of 139 TEAEs during the study. Four subjects (7.1%) experienced headache that were considered related to VTX958 and 1 subject (1.8%) experienced headache that was related to placebo. One subject (1.8%) experienced diarrhea that was considered related to VTX958. Fifty-one subjects (91.1%) experienced 125 TEAEs that were considered related to IFNα. The most common TEAEs, which mostly occurred after IFNα administration, were headache (39 subjects [69.6%], 44 events), chills (29 subjects [51.8%], 29 events), pyrexia (18 subjects [32.1%], 18 events), myalgia (11 subjects [19.6%], 11 events), and back pain (6 subjects [10.7%], 6 events).

In VTX958-102, in total, 219 TEAEs were reported by 35 of 40 subjects (87.5%) subjects over the course of the study. As in the SAD study, in the MAD most of the TEAEs occurred after IFNα, which was administered on Day 13. TEAEs considered related to IFNα and reported by at least 3 subjects receiving study drug were headache, chills, body temperature increased, myalgia, feeling cold, nausea, dizziness, decreased appetite, heart rate increased, pyrexia, fatigue, and feeling hot.

In VTX958-102, a total of 44 TEAEs were judged as related to study drug (Section 5.4.1.2 of the IB); of these, the ones reported by at least 2 subjects overall were headache (7 subjects [17.5%], 7 events in VTX958; 1 event in placebo), diarrhea (4 subjects [10.0%], 4 events in VTX958; no events in placebo), constipation (3 subjects [7.5%], no events in VTX958; 3 events in placebo), nausea (3 subjects [7.5%], 2 events in VTX958; 1 event in placebo), abdominal pain (2 subjects [5.0%], 2 events in VTX958; no events in placebo), alanine aminotransferase (ALT) increased (2 subjects [5.0%], 2 events in VTX958; no events in placebo), dry mouth (2 subjects [5.0%], 2 events in VTX958; no events in placebo), , feces soft (2 subjects [5.0%], 1 event in VTX958; 1 event in placebo), oral herpes (2 subjects [5.0%], 2 events in VTX958; no events in placebo).

In both the SAD and MAD studies, no deaths or SAEs were reported, and none of the TEAEs were judged to be severe. No subjects were discontinued from the studies due to a TEAE.

Results from the pharmacodynamic assay with IFNα showed that administration of VTX958 reduced the upregulation of CXCL10, ISG20 and IFI27 in a dose-related manner, and the

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production of IFNγ following stimulation with IL-12 and IL-18, confirming that VTX958 effectively inhibited TYK2 in healthy volunteers.

Pharmacokinetics

In the SAD study, the geometric mean maximal plasma concentrations (C_{max}) for the various dose levels were between 35.9 ng/ml to 2690 ng/ml after a single dose of VTX958. The median time to peak plasma exposure (T_{max}) under fasting conditions was 1 to 1.5 hours at the 5, 15, 50, 100 and 200 mg dose levels, and 2 to 3 hours for 350 and 500 mg dose levels. Plasma concentrations of VTX958 declined with geometric mean effective half-lives of 1.43 to 5.59 hours between 5 mg and 350 mg dose levels. Inter-subject variability (geometric CV) in the extent of systemic exposure to VTX958 in fasted conditions (C_{max}, AUC [area under the curve]$_{0\text{-}t}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-}inf}$) was generally high, ranging from 24.2% to 145.0% across all dose levels. Although there was some fluctuation and slight deviations from dose proportionality between adjacent dose levels, systemic exposure to VTX958 generally increased in an approximately dose-proportional manner over the 5 to 500 mg dose range. Under fed conditions, C_{max} and $AUC_{0\text{-}t}$ were increased 1.26-fold and 1.71-fold, respectively, in comparison to the fasting state.

In the MAD study, geometric mean C_{max} values were between 396.18 ng/ml and 4645.24 ng/ml for the various dose groups on Day 1 and Day 14. The median T_{max} was between 1.5 and 2 hours following multiple doses given once a day (QD; 250 mg QD and 500 mg QD). When VTX958 was dosed twice a day (BID; 50 mg BID, 175 mg BID and 350 mg BID), with the second dose given 8 hours after the first dose, T_{max} was between 9 and 12 hours on Day 1, and 1.5 to 12 hours on Day 14. The mean elimination half-lives ($T_{1/2}$) for QD cohorts were between 2.91 and 3.87 hours on Day 1, and 5.34 and 5.54 hours on Day 14. For the BID cohorts, $T_{1/2}$ ranged from 2.38 to 2.97 hours on Day 1, and 3.15 to 3.61 hours on Day 14. Based on available results, the steady state was attained by Day 10. Assessment of dose proportionality suggested a trend toward a less than dose-proportional increase for QD cohorts; and for a 7-fold increase in BID dosing, the PK exposure for Cohort 5 was more than dose-proportional on Day 1 and approximately dose-proportional on Day 14.

In VTX958-102 pilot drug-drug interaction (DDI) studies were performed to assess induction of cytochrome P450 (CYP)1A2 and CYP3A4 and to assess organic anion transporting polypeptide (OATP)1B1 and OATP1B3 transporter inhibition. On Day 1, subjects in Cohort 3 (VTX958 175 mg BID) were dosed with caffeine and midazolam, substrates of CYP1A2 and 3A4, respectively, and subjects in Cohort 5 (VTX958 350 mg BID) were dosed with pitavastatin, a substrate for both OATP1B1 and 1B3. This was followed by serial blood samples to provide baseline PK data for these CYP enzyme and drug transporter substrates. On Day 7, Cohorts 3 and 5 were dosed with the same substrates again and serial blood PK samples were obtained. Results of these pilot studies showed no evidence for VTX958 to inhibit or induce CYP3A4 but were consistent with inhibition of CYP1A. VTX958 demonstrated a low level of inhibition of OATPB1 and/or OATPB3 transporters which is considered to be clinically insignificant.

Relative Bioavailability

In study VTX958-103, the bioavailability of two extended-release tablet forms of VTX958 were compared to that of the suspension formulation used in the SAD and MAD studies. Development of these modified-release tablet forms was discontinued.

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In study VTX958-104, the bioavailability of immediate-release tablet forms of VTX958 were given at doses of 125 mg BID or 250 mg BID were compared to that of the suspension formulation dosed at 250 mg BID. This study also evaluated the effect of food on the bioavailability of VTX958 immediate-release tablets.

Results showed that the PK exposure for tablet vs suspension at the same dose level indicated by the geometric mean ratios for C_{max}, AUC_{0-t} and AUC_{0-inf} were 0.88, 0.83 and 0.82, respectively.

In the fed state, absorption of VTX958 as measured by C_{max}, AUC_{0-inf} and AUC_{0-t} were approximately 24%, 39% and 49% higher when given fasted. These results suggest that the absorption of VTX958 given as a tablet is modestly increased in the presence of food.

Detailed information on each study conducted with VTX958 can be found in Section 5 of the Investigator's Brochure (IB).

2.1.3 Study Rationale

There are currently a very limited number of small oral molecule therapies available to patients with plaque psoriasis. A safe, well-tolerated, and highly efficacious oral therapy for plaque psoriasis would provide an appealing treatment option for both patients and physicians.

VTX958 has the potential to add value to the treatment algorithm of psoriasis, particularly considering the lack of highly efficacious oral agents. Specific inhibition of TYK2 by VTX958 is expected to impact psoriasis pathogenesis primarily through its effects on IFNα, IL-12, and IL-23 signaling pathways. This specific inhibition has the potential to be more efficacious and safer than any current oral therapies and could be comparable to the efficacy observed for some biologic therapies currently in use.

2.2 Risk/Benefit Assessment

VTX958 is a potent, selective allosteric inhibitor of TYK2, being developed as an oral therapy for immune-mediated and inflammatory disorders including psoriasis, psoriatic arthritis and Crohn's disease. TYK2 is essential for the signaling of interferon alpha (IFNα), IL-12, and IL-23, key cytokines that promote innate, Th1 and Th17 immune responses in immune-mediated and inflammatory disorders. IL-12 and/or IL-23 signaling inhibition is a well-characterized and clinically validated target for the treatment of psoriasis, psoriatic arthritis, and inflammatory bowel disease. Another TYK2 inhibitor, deucravacitinib, has shown efficacy in patients with psoriasis, psoriatic arthritis, and systemic lupus erythematosus, demonstrating the relevance of this mechanism in the pathogenesis of these conditions. Thus, it is possible that patients with similar immune-mediated diseases may obtain therapeutic benefit from treatment with VTX958.

In nonclinical studies, VTX958 reduced pathological immune cell infiltration and led to resolution of inflammation. In phase 1 clinical studies, VTX958 administered as single or multiple oral doses showed dose-dependent on-target pharmacodynamic effects. The administration of VTX958 at single doses up to 500 mg, or multiple doses ranging from 50 mg BID to 350 mg BID, was well tolerated, and no important identified risks have emerged from the studies in healthy volunteers. There were no SAEs or dose-limiting safety and tolerability events reported.

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Based on the mechanism of action of VTX958, and experience with agents in the same class (TYK2 inhibitors), potential risks may include an increased risk of infections, and skin reactions (eg, acne, rash).

Risks associated with deucravacitinib, a product that was recently approved for the treatment of moderate-to-severe plaque psoriasis, may include hypersensitivity, infections, tuberculosis, malignancy, rhabdomyolysis, elevated creatine phosphokinase (CPK), laboratory abnormalities (including serum triglyceride and liver enzyme elevations), and potential risks related to JAK inhibition. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition.

Adverse events of special interest (AESIs) for VTX958 as detailed in Section 8.4.8 will be monitored.

In this Phase 2 study, it is anticipated that participants will see an improvement in their psoriatic condition, if they are randomized to active study product. Participation in this study may help generate future benefit for larger groups of patients with psoriasis if VTX958 proves to be successful in treating this disease.

In summary, the preclinical and clinical data to date and the potential risks outlined above indicate a favorable benefit/risk assessment which supports further clinical development of VTX958. Detailed information regarding the possible benefits and risks and reasonably expected adverse events of VTX958 can be found in the IB.

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3 OBJECTIVES AND ENDPOINTS

3.1 Placebo-Controlled Period

OBJECTIVES	ENDPOINTS
Primary objectives	
To determine the efficacy of VTX958 after treatment for 16 weeks in participants with moderate to severe psoriasis.	Primary efficacy endpoint: • Proportion of participants achieving PASI-75 at Week 16
To evaluate the safety and tolerability of VTX958 during the placebo-controlled period in participants with moderate to severe psoriasis.	Primary safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
Secondary objective	
To evaluate the efficacy of VTX958 on improvement of various measures of psoriasis after treatment for 16 weeks in participants with moderate to severe psoriasis.	Secondary efficacy endpoints: • Proportion of participants achieving an sPGA score of 0 (clear) or 1 (almost clear) at Week 16 • Change and percent change from baseline in PASI at Week 16 • Proportion of participants achieving PASI-90 at Week 16 • Proportion of participants achieving PASI-100 at Week 16 • Change from baseline in DLQI scores at Week 16 • Change from baseline in BSA at Week 16
Exploratory objectives	
To examine the efficacy of VTX958 at various timepoints during the first 16 weeks of treatment in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Proportion of participants achieving PASI-75 at Weeks 1, 2, 4, 8, and 12 • Proportion of participants achieving PASI-90 at Weeks 1, 2, 4, 8, and 12 • Proportion of participants achieving PASI-100 at Weeks 1, 2, 4, 8, and 12

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OBJECTIVES	ENDPOINTS
	• Change and percent change from baseline in PASI at Weeks 1, 2, 4, 8, and 12 • Change from baseline in sPGA at Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving an sPGA score of 0 (clear) or 1 (almost clear) at Weeks 1, 2, 4, 8, and 12 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in BSA at Weeks 1, 2, 4, 8, and 12 • Change from baseline in pruritus NRS at Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at Weeks 1, 2, 4, 8, 12, and 16 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at Weeks 4, 8, and 12 • Change from baseline in PSSD at Weeks 1, 2, 4, 8, 12, and 16
To evaluate the plasma concentration of VTX958 during the placebo-controlled period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: • Measurement of plasma concentrations of VTX958 in participants receiving active treatment
To evaluate the effects of VTX958 on blood and skin biomarkers.	Exploratory PD endpoint: • Change in blood and skin biomarker levels

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PASI-75, at least 75% improvement from baseline in Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PD, pharmacodynamic; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

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3.2 Long-Term Extension Period

OBJECTIVES	ENDPOINTS
Exploratory objectives	
To evaluate the efficacy of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Change and percent change from baseline in PASI at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-75 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-90 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving PASI-100 at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in sPGA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in BSA at LTE Weeks 1, 2, 4, 8, 12, and 16 • Change from baseline in pruritus NRS at LTE Weeks 1, 2, 4, 8, 12, and 16 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at LTE Weeks 1, 2, 4, 8, 12, and 16 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at LTE Weeks 4, 8, 12, and 16 • Change from baseline in PSSD at LTE Weeks 1, 2, 4, 8, 12, and 16
To evaluate the safety and tolerability of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory safety endpoints: • Incidence of AEs and SAEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the plasma concentration of VTX958 during the LTE period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: Measurement of plasma concentrations of VTX958

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; LTE, long-term extension; NRS, Numeric Rating Scale; PASI, Psoriasis Area Severity Index; PASI-75, at least 75%

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OBJECTIVES	ENDPOINTS
Exploratory objectives	

improvement from baseline in Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

3.3 Open-Label Extension Period

OBJECTIVES	ENDPOINTS
Exploratory objectives	
To examine the efficacy of VTX958 during the OLE period in participants with moderate to severe psoriasis.	Exploratory efficacy endpoints: • Change and percent change from baseline in PASI at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-75 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-90 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving PASI-100 at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in sPGA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants with at least a 2-grade decrease from baseline in sPGA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in BSA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in pruritus NRS at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Proportion of participants with at least a 4-point decrease from baseline in pruritus NRS at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 for participants with a baseline pruritus NRS of at least 4 • Change from baseline in DLQI at OLE Weeks 4, 8, 16, 24, 32, 36, and 40 • Change from baseline in PSSD at OLE Weeks 4, 8, 16, 24, 32, 36, and 40
To evaluate the safety and tolerability of VTX958 during the OLE period in	Exploratory safety endpoints: • Incidence of AEs and SAEs

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OBJECTIVES	ENDPOINTS
Exploratory objectives	
participants with moderate to severe psoriasis.	• Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the plasma concentration of VTX958 during the OLE period in participants with moderate to severe psoriasis.	Exploratory PK endpoint: Measurement of plasma concentrations of VTX958

Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; NRS, Numeric Rating Scale; OLE, open-label extension; PASI, Psoriasis Area Severity Index; PASI-75, at least 75% improvement from baseline in Psoriasis Area and Severity Index; PASI-90, at least 90% improvement from baseline in Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in Psoriasis Area and Severity Index; PK, pharmacokinetic; PSSD, Psoriasis Symptoms and Signs Diary; SAE, serious adverse event; sPGA, static Physician's Global Assessment.

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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of VTX958 in participants with moderate to severe psoriasis. This study will also evaluate the plasma concentrations of VTX958 and explore the immune response to VTX958 in participants with moderate to severe psoriasis.

Approximately 200 male and female participants, aged 18 or older, with moderate to severe plaque psoriasis will be randomized in this study. To be eligible for the study, participants will need to have a history of plaque psoriasis for at least 6 months prior to the screening visit. In addition, participants will need to have the following characteristics at screening and on Day 1: Psoriasis Area Severity Index (PASI) score ≥ 12, static Physician's Global Assessment (sPGA) score ≥ 3, and plaque psoriasis covering ≥ 10% of body surface area (BSA).

All participants will read and sign an ICF prior to any screening procedures being performed. Participants who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible participants will be randomized (1:1:1:1:1) on Day 1 to receive VTX958 at 300 mg twice daily (BID), 225 mg BID, 300 mg once daily (QD), or 50 mg BID, or placebo BID orally administered for 16 weeks during the placebo-controlled period. Randomization will be stratified based on prior treatment with biologics for psoriasis (yes/no). The number of participants with prior treatment with biologics targeting IL-12/-23 or IL-23 to be randomized into this study will be capped at 20% of the total number of participants.

Participants who complete the placebo-controlled period will continue into the LTE period. At the conclusion of the placebo-controlled period, participants may have a study product interruption of up to 14 days if needed to allow for flexibility in starting the LTE period. In such cases, rescreening would not be necessary, but any change in the participants' condition should be reported in the eCRF. If study product interruption is longer than 14 days, the participant may be discontinued from the study and will be asked to come back for a follow-up visit. Participants who decide to withdraw or are withdrawn after completing the placebo-controlled period will undergo a 4-week follow-up period. Participants who were assigned to placebo during the placebo-controlled period will receive the highest dose of VTX958 (300 mg BID) during the LTE period. Participants who were assigned to VTX958 225 mg BID, 300 mg QD, or 50 mg BID in the placebo-controlled period and were assessed as being responders to treatment will continue on the same assigned treatment dose during the LTE period. Participants who were assigned to VTX958 225 mg BID, 300 mg QD, or 50 mg BID in the placebo-controlled period and were non-responders to treatment will receive the highest dose of VTX958 (300 mg BID) during the LTE period. Participants who were assigned to the highest dose of VTX958 (300 mg BID) in the placebo-controlled period will continue on the same assigned treatment dose during the LTE period. A responder is defined as a participant who achieves at least 75% improvement from baseline in Psoriasis Area and Severity Index (PASI-75) at Week 16.

Participants who complete the LTE period will continue into the OLE period. Participants who continue into the OLE period will receive VTX958 at 300 mg BID and continue study treatment (ie, LTE Week 16 will occur on the same visit as OLE Day 1). However, a study product

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interruption of up to 28 days is permitted between LTE and OLE periods if needed to allow for flexibility in starting the OLE period. In such cases, rescreening would not be necessary, but any change in the participants' condition should be reported in the eCRF. If study product interruption is longer than 28 days, the participant will be discontinued from the study and will be asked to come back for a follow up visit. Participants who decide to withdraw or are withdrawn after completing the LTE period will also be asked to come back for a follow up visit as described in the Schedule of Events for the LTE period (Table 2).

The OLE period will be followed by a 4-week follow-up period. For scheduled study visits, participants will come to the study centers on up to 23 occasions, as described in the Schedule of Events (Table 1, Table 2, and Table 3).

Efficacy will be assessed using PASI, BSA, sPGA, pruritus Numeric Rating Scale (NRS), and Psoriasis Symptoms and Signs Diary (PSSD). Quality of life will be evaluated using the Dermatology Life Quality Index (DLQI).

Safety will be assessed by collecting AEs, recording vital signs, performing complete and targeted physical examinations, and evaluating clinical laboratory and ECG results.

During the placebo-controlled period, blood samples will be collected from all participants predose (if applicable) to evaluate plasma concentrations of VTX958 and the effect of VTX958 on inflammatory biomarkers and lymphocyte subsets (T- and B-lymphocytes, and natural killer cells [TBNK]). Optional blood samples for genetic testing (for analysis of deoxynucleic acid [DNA]) will be collected before administration of the study treatment. In addition, optional blood samples for PK analysis will be collected in a subset of participants who consent to the additional blood collection at the Week 4 visit at 1, 2, 4, 6, and 24-hours after the morning dose.

During the LTE and OLE period, blood samples will be collected from all participants predose (if applicable) to evaluate plasma concentrations of VTX958.

During the placebo-controlled period, the effect of VTX958 on skin biomarkers will be evaluated by collecting tape strips from all participants. Skin tape strips (from lesional skin and from nonlesional skin in the vicinity of the lesional skin) will be collected on Day 1, and from the same lesional skin at Week 16 (even if the lesion has cleared).

During the placebo-controlled period, at selected study centers, in a subset of participants who consent to the procedure, the effect of VTX958 on skin biomarkers will be evaluated by collecting six or eight optional skin biopsies. The target for this study is to reach approximately 100 participants who consent to collection of biopsies. Four 4-mm punch biopsies (two from lesional skin and two from nonlesional skin in the vicinity of the lesional skin) will be collected on Day 1, and two 4-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsies, at least 1 cm away from the previous scars, even if the lesions have cleared) at Week 16. In addition, two 4-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsies, at least 1 cm away from the previous scars) at Week 4 in participants who consent to eight skin biopsies.

During the placebo-controlled period, at selected study centers, in a subset of participants who consent, optional medical photographs (full body, front and back) will be taken to illustrate the outcome of the trial.

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During the placebo-controlled period, at selected study centers, in a subset of participants who consent, optional SkinCam photographs (one lesional and one nonlesional area) will be taken at various timepoints to illustrate the progress throughout the trial.

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy, safety, and tolerability of VTX958 (at 300 mg BID, 225 mg BID, 300 mg QD, or 50 mg BID) compared with placebo in participants with moderate to severe plaque psoriasis.

The first part of this study will be randomized to ensure random allocation of participants to treatment groups to reduce bias. Randomization will be stratified based on prior treatment with biologics for psoriasis (yes/no). Because efficacy assessments of plaque psoriasis have a high degree of subjectivity, the study will be double-blinded. The highest degree of participant and assessor blinding should be sought to achieve credible inference. It is also important to have a placebo control in this Phase 2 study to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied.

After completion of the placebo-controlled period, participants will have the opportunity to continue into the LTE period and to receive the active drug for a period of 16 weeks. At the conclusion of the placebo-controlled period, participants may have a study product interruption of up to 14 days if needed to allow for flexibility in starting the LTE period. The LTE period will enable assessment of study product safety for up to 32 weeks, and the efficacy results from the LTE period are intended to be descriptive only (with no inferential analyses planned in the LTE). The possible drug interruption is therefore deemed acceptable based on the objective of the LTE.

After completion of the LTE period, participants will have the opportunity to continue into the OLE period and to receive the active drug (VTX958 300 mg) for an additional 36 weeks. At the conclusion of the LTE period, participants may have a study product interruption of up to 28 days if needed to allow for flexibility in starting the OLE period. The OLE period will enable assessment of study product safety for up to 68 weeks, and the efficacy results from the OLE period are intended to be descriptive only (with no inferential analyses planned in the OLE). The possible drug interruption is therefore deemed acceptable based on the objective of the OLE. In the OLE, all participants will receive VTX958 at 300 mg BID to enable understanding of the long-term safety of VTX958.

4.3 Justification for Dose

Dose and dosing regimens for this Phase 2 study were selected with the objective of evaluating VTX958 across a range of doses for its efficacy on improving PASI score in participants with moderate to severe plaque psoriasis. Participants enrolled in this study will receive one of five treatments: placebo BID, 50 mg VTX958 BID, 300 mg VTX958 QD, 225 mg VTX958 BID or 300 mg VTX958 BID.

The anticipated therapeutic dose is expected to provide drug levels that exceed the IC50 for the inhibition of the human whole blood assay for IL-12 stimulated STAT4 phosphorylation (~300 nM/130 ng/mL) for 24 hours and the IC90 (~2000 nM/865 ng/mL) for that assay for

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16 hours or greater. The range of doses being evaluated in this study will enable optimal understanding of exposure-efficacy and exposure-safety relationships for VTX958 in patients with psoriasis.

Doses were selected based on the PK profile of VTX958 in human volunteers and on the estimated drug levels needed for efficacy in psoriasis.VTX958 was evaluated as a suspension in Phase 1 studies in the range of 5 mg to 500 mg as single doses (study VTX958-101 SAD), and in the range of 100 mg to 700 mg total daily dose for 14 days (study VTX958-102 MAD). In both studies, VTX958 was generally safe and well tolerated.

VTX958 was also evaluated in the form of immediate-release tablets given at doses of 125 mg BID or 250 mg BID in a study that compared the bioavailability of the tablets to that of the suspension formulation (study VTX958-104). This study also evaluated the effect of food on the bioavailability of VTX958 immediate-release tablets. Results showed that the PK exposure for tablet vs powder at the same dose level indicated by the geometric mean ratios for $AUC_{0\text{-}inf}$ was 0.82, or approximately 20% lower exposure for tablets than the suspension. Thus, considering this lower exposure for the tablets, the planned dose groups of 50 mg, 225 mg, and 300 mg are predicted to behave as effective doses of 40 mg, 180 mg, and 240 mg doses. In the fed state, absorption of VTX958 as measured by $AUC_{0\text{-}inf}$ was approximately 39% higher than when given fasted.

The expected C_{max} and AUC resulting from the selected dose levels are within the observed preclinical and clinical exposures in the Phase 1 studies. The geometric mean C_{max} (3380 ng/ml) and geometric mean AUC (34160 ng*h/mL) observed in study VTX958-104 for the suspension formulation given at 250 mg BID is equivalent to the highest effective dose to be evaluated in this Phase 2 study. The predicted geometric mean C_{max} (5070 ng/mL) is anticipated to approximate the highest observed geometric mean C_{max} in the MAD (5319 ng/ml). The predicted geometric mean AUC (61488 ng*h/mL) is approximately 20% lower than the highest observed AUC in the MAD (75294 ng*h/mL). The toxicokinetic exposures at the NOAEL in the 39-week toxicology study in cynomolgus monkeys, the most sensitive species, were 8510 ng/mL for C_{max} and 145,000 ng*h/mL for AUC, provide margins of 1.7-fold and 2.4-fold, respectively, for the highest expected C_{max} and AUC in the proposed Phase 2 trial.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedules of Events, Table 1, Table 2, and Table 3.

The end of the study is defined as completion of the last visit or procedure shown in the schedule of event for the last enrolled participant in the trial globally for all sites.

4.5 Interruption/Stopping Criteria

If a participant experiences any of the following AEs or laboratory abnormalities, treatment should be stopped and the participant should not receive any additional doses of study product. These participants should remain in the trial and be followed until the AE resolves or stabilizes. A

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decision to temporarily discontinue treatment with the study product and/or to reinstate study treatment must be discussed with the medical monitor.

- Common Terminology Criteria for Adverse Events (CTCAE; v5.0) Grade ≥ 3 AE, or any Grade ≥ 2 cardiac AE, regardless of relationship to study product. Abnormal laboratory results should be repeated and confirmed at the central laboratory.
- Serious infections: Participants should be closely monitored for the development of signs and symptoms of infection during and after treatment with study product. A participant who develops a new infection during treatment with study product 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 product must be permanently discontinued if a participant develops a serious infection. Participants who develop active tuberculosis must be permanently discontinued from study product.
- Abnormal liver function: Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined below or if the investigator believes that it is in best interest of the participant.
    - ALT or AST > 8 × ULN
    - ALT or AST > 5 × ULN for > 2 weeks
    - ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5
    - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

4.6 Data Monitoring Committee

Safety oversight will be under the direction of an independent DMC composed of individuals with the relevant expertise and who will not be directly involved in the ongoing management of the study. The roles and responsibilities of the DMC will be described in detail in the DMC Charter. As part of its role, the DMC will conduct reviews of accumulating unblinded safety data at specified intervals during the conduct of the trial, according to the guidelines detailed in the DMC Charter. The DMC will provide their recommendations in a blinded fashion (ie, treatment assignment for individual participants will not be shared) to the Study Team regarding the continuation, modification, or termination of the study.

After approximately 40-50 participants in this study have reached 4 weeks of study product treatment, the DMC will conduct an exploratory assessment of the safety and tolerability of VTX958 in participants with moderate to severe psoriasis. This exploratory analysis is not powered for any specific adverse event(s); there are no a priori analyses planned since TYK2 inhibition with VTX958 in Phase 1 studies in healthy volunteers was well tolerated without dose limiting toxicity, and Phase 2 and 3 studies with another TYK2 inhibitor, deucravacitinib, in participants with moderate to severe psoriasis did not demonstrate class related SAEs or AESIs. Provided no safety concerns are identified by the DMC, study enrollment and conduct will continue as planned.

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4.7 Cardiovascular Adjudication Committee

An independent, external committee of physician experts in cardiac event adjudication will be utilized to assess cardiovascular, embolic, and thrombotic adverse events in a blinded manner as defined by the Cardiovascular Adjudication Committee charter.

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5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria, at both the screening visit and Day 1, unless it is noted in the criterion at only one of the specified visits (screening or Day 1):

1. Male or female participant aged 18 years or older at the time of consent.
2. Participant has a history of primarily plaque psoriasis for at least 6 months prior to the screening visit.

   Note: Participants with concomitant guttate or inverse psoriasis may be included in the study; however, it should not be a predominant form.
3. Participant has had stable psoriasis conditions for at least 3 months before screening (information obtained from medical chart or participant's physician, or directly from the participant).
4. Participant has moderate to severe plaque psoriasis as defined by a PASI score of ≥ 12 and an sPGA score of ≥ 3 at screening and Day 1.
5. Participant has plaque psoriasis covering ≥ 10% of the total BSA at screening and Day 1.
6. Participant is deemed by the investigator to be eligible for phototherapy or systemic therapy.
7. For female participant of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 4 weeks after the last dose of study product. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided his vasectomy was performed ≥ 4 months prior to screening, with surgical success confirmed by the participant), tubal ligation, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.
   Note: Participants using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to participants who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.

   Note: A female participant of nonchildbearing potential is defined as follows:
   - Female participant who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
   - Female participant who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels)

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Note: Female participants must agree to not have egg retrieval from Day 1 until at least 4 weeks after the last dose of study product.

8. For male participant involved in any sexual intercourse that could lead to pregnancy: the participant must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 7 from Day 1 until at least 90 days after the last dose of study product. If the female partner of a male participant uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 90 days after the last dose of study product.

   Note: Male participants must refrain from donating sperm from Day 1 until at least 90 days after the last dose of study product.
9. Female participant of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
10. Participant has a negative tuberculosis (TB) infection test result at screening. Participant will be evaluated for active or latent TB infection with a purified protein derivative test or a QuantiFERON-TB Gold test. Participants who demonstrate evidence of latent TB infection (either purified protein derivative ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study, unless documentation of prior and complete anti-TB treatment, appropriate in duration and type according to current local country guidelines, can be provided.
11. Participant has a body mass index (BMI) within the range of 18 to 40 kg/m^2, inclusive, and a total body weight > 50 kg (110 lbs).
12. Participant is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
13. Participants must be willing to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

A participant who meets any of the following criteria at the screening visit and/or Day 1, as applicable, will be excluded from participation in this study:

1. Participant is a female who is breastfeeding, pregnant, lactating, or who is planning to become pregnant during the study.
2. Participant has evidence of erythrodermic, pustular, predominantly inverse or guttate psoriasis, or drug-induced psoriasis.
3. Participant has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Participant is known to have immune deficiency or is immunocompromised.
5. Participant has immune-mediated conditions commonly associated with psoriasis, such as psoriatic arthritis, active uveitis, inflammatory bowel disease, that currently require systemic treatment (including corticosteroids, immunosuppressants, or biologics).

   Note: Participants with immune-mediated conditions commonly associated with psoriasis that do not require systemic treatment may be included in the study.
6. Participant has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine,

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pulmonary, immunologic, or local active infection/infectious illness, or thromboembolic disease), psychiatric condition, or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with interpretation of study results.

7. Participant has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months prior to screening.
8. Participant had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
9. Participant has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
10. Participant has uncontrolled arterial hypertension characterized by a systolic blood pressure (BP) >160 mm Hg or diastolic BP >100 mm Hg at screening, confirmed by 3 measurements.
11. Participant has been hospitalized in the past 3 months for asthma, has ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or has required more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within 6 months prior to Day 1.
12. Participant has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Participants with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
13. Participant has a history or evidence of an active systemic infection and/or febrile illness within 7 days prior to Day 1.
14. Participant has a history of serious infections that led to hospitalization and/or intravenous antibiotic treatment within 12 weeks prior to Day 1, or requiring oral antibiotic treatment within 4 weeks prior to Day 1.
15. Participant has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection, recurrent urinary tract infection, fungal infection (with the exception of superficial fungal infection of the nailbed), or infected skin wounds or ulcers.
16. Participant has a history of infected prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.
17. Participant has an active herpes simplex infection that occurs more frequently than monthly or that requires suppressive therapy, or active herpes zoster infection identified on examination and/or medical history within 8 weeks prior to Day 1.
18. Participant has a positive result for hepatitis B virus (HBV; positive for hepatitis B surface antigens [HBsAg] or positive for hepatitis B antibodies to core antigens [anti-HBc]; participants having a negative HBsAg and a positive anti-HBc may enroll if they have a positive hepatitis B surface antibody [anti-HBs] demonstrating natural immunity), hepatitis C virus (HCV; positive for HCV antibodies; however, a participant with documented proof of cure from HCV may be enrolled), or human immunodeficiency virus (HIV) at screening.
19. Participant has any of the following laboratory values at the screening visit:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 2.0 times the upper limit of normal (ULN);
    - Hemoglobin (Hgb) < 9.0 g/dL (< 90.0 g/L);

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- White blood cell count (WBC) < 3.0 x 10^9/L (< 3000/mm^3);
- Absolute neutrophil count of < 1.0 x 10^9/L (< 1000/mm^3);
- Absolute lymphocyte count of < 0.5 x 10^9/L (< 500/mm^3);
- Platelet count < 100 x 10^9/L (< 100,000/mm^3);
- Total bilirubin ≥ 1.5 times the ULN.

20. Participant has thyroid-stimulating hormone (TSH) levels outside the normal range that is deemed clinically significant by the investigator at the screening visit.
21. Participants who have given > 50 ml of blood or plasma within 4 weeks of screening or > 499 mL of blood or plasma within 8 weeks prior to screening (during a clinical trial or at a blood bank donation).
22. Participant has used any topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar) within 2 weeks prior to Day 1.
23. Participant has used any systemic treatment that could affect psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, anakinra, methotrexate, cyclosporine, oral JAK inhibitors, or apremilast) within 4 weeks prior to Day 1.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
24. Participant has received any ultraviolet B (UVB) phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
25. Participant has had psoralen and ultraviolet A (PUVA) treatment within 4 weeks prior to Day 1.
26. Participant has received any live or live-attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live or live-attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last dose of study product.

    Note: Nonlive-attenuated vaccines (eg, ribonucleic acid [RNA]-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive-attenuated vaccines or boosters for coronavirus disease-2019 (COVID-19), are allowed during the study. The study site should follow local guidelines related to COVID-19.
27. Participant is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
28. Participant has received any marketed or investigational biologic agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criterion 32 that are to be excluded as specified).
29. Participant is currently receiving sensitive substrates of CYP1A2, 2C9 and 2B6, or strong inducers of CYP3A4 (as listed in Table 9) that would, in the opinion of the investigator in consultation with the sponsor and medical monitor, put the participant at undue risk or interfere with interpretation of study results.
30. Participant has received treatment with an investigational or marketed TYK2 inhibitor.
31. Participant has a history of loss of response to > 2 marketed biologic agents for psoriasis of any mechanism of action, when administered after at least 12 weeks of therapy.
32. Participant has received rituximab or other immune-cell depleting therapy within 6 months prior to Day 1.

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33. Participant is currently receiving terbinafine, lithium, antimalarials, leflunomide, or intramuscular (IM) gold, or have received terbinafine, lithium, antimalarials, or IM gold within 4 weeks or leflunomide within 12 weeks prior to Day 1.
34. Participant has had excessive sun exposure, is planning a trip to a sunny climate, has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Note: Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.
35. Participant has a known or suspected allergy to VTX958 or any component of the investigational product.
36. Participant has a known history of clinically significant drug or alcohol abuse in the last year prior to screening.
37. For participants consenting to biopsy collection only:
    - Participant has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    - Participant has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    - Participant has taken anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin ≤81 mg which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

5.3 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to the study treatment in the placebo-controlled period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in the placebo-controlled period of this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened participants should be assigned a different participant number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

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6 TREATMENT

6.1 Study Products

This study involves a comparison of VTX958 at 300 mg BID, 225 mg BID, 300 mg QD, or 50 mg BID, orally administered, with a placebo BID. VTX958 film coated immediate release (FCIR) tablets will be available in 125 mg and 50 mg strength tablets. VTX958 FCIR are blue with a round shape. Placebo tablets will be identical to the active tablets in size, shape, and color. All tablets contain tartrazine as an ingredient in the film coating. Tartrazine may cause allergic reactions in people who are particularly sensitive to this substance. During the LTE period, all participants will receive VTX958 and the dose to be administered will depend on their initial treatment in the placebo-controlled period and/or the participant's response status (based on PASI-75) at Week 16. During the OLE period, all participants will receive VTX958 at 300 mg BID.

All study products will be provided by the sponsor.

Further details regarding the study products can be found in Table 4.

Table 4: Study Products

	Study Products	
Product name	VTX958	Placebo
Dosage form	Tablet	Tablet
Unit dose strength(s)	50 mg and 125 mg	N/A
Route of administration	Oral	Oral
Dosing instructions	Study product should be taken with approximately 240 mL (one cup) of water in the morning and evening (12 hours apart), with or without food.	Study product should be taken with approximately 240 mL (one cup) of water in the morning and evening (12 hours apart), with or without food.
Physical description	The study product is a blue tablet with a round shape.	Placebo is identical to the active tablets in size, shape, and color.
Storage temperature	Kept in accordance with the label condition.	Kept in accordance with the label condition.
Source of procurement	Provided centrally from sponsor	Provided centrally from sponsor

Abbreviations: N/A, not applicable.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2 Dosage and Administration

Dosage and tablet administration information for the placebo-controlled period, LTE period, and OLE period can be found below in Table 5, Table 6, and Table 7, respectively.

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Table 5: Study Product Doses for the Placebo-Controlled Period

Group	Dosing regimen	
	Morning dose	**Evening dose**
VTX958 300 mg BID	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg
VTX958 225 mg BID	1 tablet of VTX958 125 mg 2 tablets of VTX958 50 mg	1 tablet of VTX958 125 mg 2 tablets of VTX958 50 mg
VTX958 300 mg QD	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg	3 tablets of placebo
VTX958 50 mg BID	1 tablet of VTX958 50 mg 2 tablets of placebo	1 tablet of VTX958 50 mg 2 tablets of placebo
Placebo BID	3 tablets of placebo	3 tablets of placebo

Table 6: Study Product Doses for the Long-Term Extension Period

Group	Dosing regimen	
	Morning dose	**Evening dose**
VTX958 300 mg BID	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg
VTX958 225 mg BID	1 tablet of VTX958 125 mg 2 tablets of VTX958 50 mg	1 tablet of VTX958 125 mg 2 tablets of VTX958 50 mg
VTX958 300 mg QD	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg	3 tablets of placebo
VTX958 50 mg BID	1 tablet of VTX958 50 mg 2 tablets of placebo	1 tablet of VTX958 50 mg 2 tablets of placebo

Table 7: Study Product Doses for the Open-Label Extension Period

Group	Dosing regimen	
	Morning dose	**Evening dose**
VTX958 300 mg BID	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg	2 tablets of VTX958 125 mg 1 tablet of VTX958 50 mg

Participants will be instructed to administer their study product BID, as assigned, for 68 weeks (including the LTE and OLE). Study products should be self-administered orally with water at home, except on study visit days when the morning dose of study product will be administered at the study site after completion of all assessments (if applicable). However, if a visit must occur in the afternoon, participants may take their morning dose at the regular scheduled time at home, and do not have to wait to take the dose at the clinic; during the afternoon visit, all assessments will be performed as per the Schedules of Events, including fasting (when applicable), except study product will not be administered in the clinic if the last dose occurred less than 8 hours prior. Afternoon visits will not be applicable at the Week 4 visit for participants who consent to the optional PK blood sampling procedure. Evening doses of study product will be taken at home on study visit days.

For participants without any study product interruption between the placebo-controlled and LTE periods, the dose administered on the day of the Week 16 visit of the placebo-controlled period will be part of the LTE period. For participants without any study product interruption between

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the LTE and OLE periods, the dose administered on the day of the LTE Week 16 visit will be part of the OLE period. Details on treatment assignment for the LTE and OLE periods can be found in Section 6.6.

The date and time of the study product administration will be collected by the study site during study visits or recorded by the participant via a daily diary. The participant should be instructed to take the study product at approximately the same time of the day, approximately 12 hours apart.

Additional details on dosage and administration are provided in separate study documentation.

6.3 Instructions for Missed Doses

Participants who forget to take a dose should take their missed dose as soon as they realize the dose has been missed, as long as the next planned dose is at least 8 hours away; otherwise, they should skip their missed dose and they should take their next dose at the regular time. Participants should contact the investigator if they miss 6 or more consecutive doses. If the participant vomits the study product, he/she should not take another dose in the same day, but take the next dose at the regular time on the next day.

6.4 Dose Interruptions

All study product interruptions of 3 or more consecutive days during a treatment period will be noted in the electronic case report form (eCRF), with the start date, duration, and reason for interruption (if known) specified. If the interruption was caused by an AE, only the primary AE leading to interruption of the study product, per the judgement of the investigator, should have an action taken of study product interrupted. If study product interruption greater than 3 days is required for a medical reason during a treatment period, the investigator must contact the medical monitor.

Study product interruptions are permitted between study periods as described in Section 4.1.

6.5 Preparation/Handling/Storage/Accountability

6.5.1 Preparation/Storage/Handling

All study products must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study products may only be supplied by authorized site staff and may only be given to participants enrolled into the study.

Study products will be dispensed by the study site to the participant at the visits specified in Table 1, Table 2, and Table 3. Participants are to return all study products (used and unused) to the stud site. The tablets will be counted prior to dispensing and upon return, and the counts will be recorde in the source documents and eCRF. Each participant will be instructed on the importance o returning the study product at the next study visit and on taking the study product as prescribed. I a participant does not return the study product, he or she will be instructed to return it as soon a possible. The study product returned at Weeks 1 and 2 of both the placebo-controlled period and

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the LTE period may be redispensed to participants if there is an adequate amount of study product returned to last until the next study visit.

6.5.2 Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. Any study product accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained. At the conclusion of the study, all used and unused study products and all medication containers will be returned and destroyed as per approved arrangements by the sponsor.

All study product accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained, as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of study products are provided in separate study documentation.

6.6 Randomization

At the study site, each screened participant will be assigned a participant identifier number during screening that will be used on all participant documentation. The participant identifier number will contain the study number (201), site number and the participant number and will be assigned in sequential order at the screening visit after consent (eg, the first participant at US site 840001 will be assigned the identifier number 201-840001-001).

Approximately 200 participants will be randomized 1:1:1:1:1 to VTX958 at 300 mg BID, 225 mg BID, 300 mg QD, or 50 mg BID, or placebo BID (approximately 40 participants/arm) during the placebo-controlled period (see dosing regimen in Table 5).

During the LTE period, treatment will be administered as follows (see dosing regimen in Table 6):

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During the OLE period, all participants will receive VTX958 at 300 mg BID (see dosing regimen in Table 7).

Randomization will occur prior to first dosing, at the Day 1 visit. The randomization list will be generated using a validated software and will be stratified based on prior treatment with biologics for psoriasis (yes/no). The number of participants with prior treatment with biologics targeting IL-12/-23 or IL-23 to be randomized into this study will be capped at 20% of the total number of participants. The master randomization list will be kept secured until the study blind is broken at the end of the study. This list will be uploaded into an Interactive Web Response System (IWRS). The investigator or designee will be able to acquire a randomization number for eligible participants by connecting to the IWRS.

Further guidance and information can be obtained in separate study documentation.

6.6.1 Blinding

This study will be double-blinded for the placebo-controlled period. Treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until the database lock at the end of the placebo-controlled period is completed. After the first database lock at Week 16, the study will be unblinded, but the individual participant randomization information will not be shared with sites, investigators, and participants until the final database lock (see Section 9.3.8 for more details). A second lock will occur at the end of the study in order to produce the exploratory endpoint descriptive results for the LTE and the OLE periods.

Details regarding the unblinding procedures for this study will be detailed in the Unblinding Plan.

Safety oversight will be under the direction of an independent DMC, who will remain unblinded during the study.

Breaking the blind should be considered only when knowledge of the treatment assignment is deemed essential for the participant's care. In such case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the medical monitor and the sponsor must be notified within 24 hours after breaking the blind. The date and reason for breaking the blind must be documented.

In cases of accidental unblinding, the investigator should contact the medical monitor and ensure every attempt is made to preserve the blind. Any request to unblind a participant for nonemergency purposes must be discussed with the medical monitor prior to unblinding.

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The participant for whom the blind has been broken may be discontinued from the study and undergo the ET procedures specific to the period when the participant was discontinued. In cases where there are ethical or safety reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor or its designee for the participant to continue in the study. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

6.6.2 Study Product Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the assigned regimen must be recorded in the eCRFs. Study product compliance will be measured by tablet count per bottle or blister card only. At each visit, site staff will retrieve the previously dispensed study product and assess compliance to ensure participants are taking the study product as instructed.

Overall study noncompliance is defined as taking less than 80% or more than 120% of study product during the entire treatment period. Participants will record tablet intake in the study diary.

Participants exhibiting poor compliance should be counseled on the importance of good compliance to the study dosing regimen. Participants who are persistently noncompliant (< 80% or > 120%) should be discussed with the medical monitor to determine whether they should be withdrawn from the study.

6.7 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded. Any prior use of biologic agents to treat psoriasis must be recorded in the eCRF. In addition, the use of any prohibited medications must be recorded within the timeframe described in the exclusion criteria. Any prior and completed anti-TB treatment must also be recorded, if applicable, as per inclusion criterion 10 in Section 5.1.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

Participants that are on stable antihypertensive therapy at baseline and information regarding any changes in their antihypertensive treatment during the study will be captured in the eCRF.

6.7.1 Permitted Therapies

6.7.1.1 Emollients

Participants can apply an emollient of their choice (except those containing salicylic acid) on their skin, **including on psoriasis lesions**. However, on the day of scheduled visits, participants cannot apply emollient before their scheduled visit time.

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Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF.

6.7.1.2 Other Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided. However, on the day of scheduled visits, participants cannot apply sunscreen products before their scheduled visit time.

6.7.2 Prohibited Therapies or Procedures

Table 8 lists prohibited medications that are not to be used from the defined washout periods before the first administration of study product at the Day 1 visit through the last study visit. In addition, any previous treatment with an investigational or marketed TYK2 inhibitor is prohibited.

Participants who start prohibited medications or therapies that have been demonstrated to be effective for treatment of psoriasis during the study will be withdrawn from study product. Participants who start prohibited medications or therapies for other reasons during the study may be withdrawn from study treatment if an impact on efficacy assessment or safety of the participants is expected. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 8: Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose of study product
Rituximab or other immune-cell depleting therapy	6 months
Any marketed or investigational biological agent (except those specifically listed in this table)	12 weeks or 5 half-lives (whichever is longer)
Leflunomide	12 weeks
Intravenous antibiotic treatment	12 weeks
Oral antibiotic treatment	4 weeks
Nonbiological investigational product or device	4 weeks
Any live and live-attenuated vaccines Note: Nonlive-attenuated vaccines (eg, RNA-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines), including nonlive attenuated vaccines or boosters for COVID-19, are allowed during the study. The study site should follow local guidelines related to COVID-19.	4 weeks or 5 half-lives (whichever is longer)
Systemic treatment that could affect psoriasis (including corticosteroids, oral retinoids, immunosuppressive medication, anakinra, methotrexate, cyclosporine, oral JAK inhibitors, or apremilast)	4 weeks

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Prohibited medications, products, and procedures	Washout period prior to first dose of study product
PUVA treatment, UVB phototherapy (including tanning beds) or excimer laser, or tanning booths	4 weeks
Terbinafine, lithium, antimalarials, or IM gold	4 weeks
Topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar)	2 weeks
For participants consenting to biopsy collection only: Anticoagulant medication, such as heparin, LMW-heparin, warfarin, antiplatelets (except low-dose aspirin ≤ 81 mg which will be allowed). NSAIDs will not be considered antiplatelets and will be allowed.	2 weeks

Abbreviations: COVID-19, coronavirus disease-2019; IL, interleukin; IM, intramuscular; JAK, Janus kinase; LMW, low molecular weight; NSAID, nonsteroidal anti-inflammatory drug; PUVA, psoralen and ultraviolet A; RNA, ribonucleic acid; UVB, ultraviolet B.

6.7.3 Restricted Therapies

Preliminary in vitro studies suggested that VTX958 has the potential to induce CYP2B6 and to inhibit CYP2C9, and a pilot human DDI study suggested that VTX958 may be an inhibitor of CYP1A2. In vitro data indicate that multiple CYP pathways are implicated in the metabolic clearance of VTX958. Therefore, any necessary concomitant use of the restricted medications as listed in Table 9 should be discussed with the medical monitor and approved by the sponsor to confirm eligibility.

Table 9: Restricted Therapies

Interaction	Enzyme	Drugs
Sensitive substrates	CYP1A2	alosetron, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine
	CYP2C9	celecoxib
	CYP2B6	buproprion
Strong inducers	CYP3A4	rifampin, St. John's wort, carbamazepine, phenytoin, lumacaftor, apalutamide, enzalutamide, mitotane, ivosidenib

Abbreviations: CYP, cytochrome P450

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7 DISCONTINUATION AND LOST TO FOLLOW-UP

Participants have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw participants from the study if he or she feels it is in the best interest of the participant or if the participant is uncooperative or noncompliant.

Should a participant decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit specific to the period when the participant was withdrawn.

The investigator or one of his or her staff members should contact the participant to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the study. If the reason for removal of a participant is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 Discontinuation

Participants who discontinue the study after the first dose will be asked to come for a last assessment (ET visit with procedures specific to the period when the participant was withdrawn) within 3 days of last dose of study product. However, participants who discontinue the study during a study product interruption before the LTE or OLE will be asked to come for a last assessment (follow-up visit) 4 weeks after last dose of study product. Participants who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up.

Participants who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the participant should be withdrawn. If this decision is made because of an SAE, the study product is to be discontinued in that participant immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The attending physician requests that the participant be withdrawn from the study.
- The study product interruption duration is >14 days between the placebo-controlled and the LTE periods or >28 days between the LTE and OLE periods.
- The participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The participant is lost to follow-up. In this case, reasonable attempts to contact the participant and ascertain his or her status must be made, and these attempts must be documented.
- The participant becomes pregnant at any time during the study.

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- The participant withdraws their consent.
- Other: the participant may withdraw from the study for any other reason.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all participants will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical trial site, inform both the participants and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of participants or other persons.

7.2 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit. The site will then counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three 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 or study file.
- If all attempts to contact the participant fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

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8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Clinical evaluations of plaque psoriasis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given participant whenever possible.

8.1.1 Psoriasis Area and Severity Index

The PASI will be evaluated at the visits specified in Table 1, Table 2, and Table 3. This index quantifies the severity of a participant's psoriasis based on both lesion severity and the percentage of BSA affected.[12] The PASI is a composite score ranging from 0 to 72 that that takes into account the degree of erythema, induration/infiltration, and desquamation (each scored from 0 to 4 separately) for each of four body regions, with adjustments for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. Refer to APPENDIX 1 for a complete description of this scale. To be eligible for this study, participants must have a PASI score ≥12 at the screening visit and Day 1 of the placebo-controlled period.

8.1.2 Static Physician's Global Assessment

The sPGA of disease severity will be assessed at the visits specified in Table 1, Table 2, and Table 3. The sPGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity. A detailed description of sPGA[13] scores is provided in Table 10. To be eligible for this study, participants must have an sPGA score ≥ 3 at the screening visit and Day 1 of the placebo-controlled period.

For participants with an sPGA score of 1, the following details will also be recorded.

Presence (yes/no) of:

- Erythema
- Scaling

Table 10: Static Physician's Global Assessment

Score	Grade	Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling

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Score	Grade	Description
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red; clearly distinguishable to moderate erythema; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

8.1.3 Body Surface Area

The overall BSA affected by plaque psoriasis will be evaluated (from 0% to 100%) at the visits specified in Table 1, Table 2, and Table 3. The palmar surface of one hand (using the participant's hand and including the fingers) represents 1% of his or her total BSA.[14] To be eligible, participants must have a BSA affected by plaque psoriasis ≥ 10% at the screening visit and Day 1 of the placebo-controlled period.

8.1.4 Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded at the visits specified in Table 1, Table 2, and Table 3 using an NRS (Itch NRS [v2.0][15]). This will be evaluated by asking participants to assign a numerical score representing the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pruritus is presented in APPENDIX 2.

8.2 Quality-of-Life Assessments/Patient Reported Outcomes

8.2.1 Dermatology Life Quality Index Questionnaire

The DLQI will be assessed at the visits specified in Table 1, Table 2, and Table 3. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions.[16] Its use has been described in more than 1,000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in APPENDIX 3.

8.2.2 Psoriasis Symptoms and Signs Diary

The PSSD will be evaluated at the visits specified in Table 1, Table 2, and Table 3. The PSSD is an 11-item validated questionnaire that assesses symptoms (itch, pain, stinging, burning, and skin tightness) and patient-observable signs (dryness, cracking, scaling, shedding/flaking, redness, and bleeding) of moderate to severe plaque psoriasis.[17,18] These symptoms and signs will be evaluated by asking participants to assign a numerical score representing of the worst intensity over the last 7 days on a scale from 0 to 10, with 0 indicating absence of symptoms or signs and 10 indicating the worst imaginable symptoms or signs. The PSSD is a composite score calculated based on the scores for each question. The questionnaire is provided in APPENDIX 4.

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8.3 Safety and Other Assessments

8.3.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1, Table 2, and Table 3 with the participant in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), respiratory rate (RR), and body temperature (°C).

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a participant from the study. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.3.2 Physical Measurements

Weight (kg) and height (cm) will be recorded at screening, and BMI at screening and Day 1. Weight (kg) will also be recorded at the other visits specified in Table 1, Table 2, and Table 3.

8.3.3 Physical Examination

The following sites/systems will at least be included in the complete physical examination, which will be performed at the visits specified in Table 1, Table 2, and Table 3:

- General appearance
- Dermatological (except plaque psoriasis)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a participant from the study. Any significant change will be reported as an AE in the source document and eCRF.

8.3.4 Targeted Physical Examination

The targeted physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.

If deemed appropriate by the investigator based on the participant's condition, a complete physical examination as described in Section 8.3.3 can be performed instead of a targeted examination.

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Information for all targeted physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the targeted physical examination will exclude a participant from the study. Any significant change will be reported as an AE in the source document and eCRF.

8.3.5 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1, Table 2, and Table 3. The tests will include serology, urinalysis, hematology, coagulation testing, a standard chemistry panel (chemistry includes liver function tests and cholesterol), fasting lipids, serum immunoglobulin (immunoglobulin M [IgM], immunoglobulin G [IgG], immunoglobulin A [IgA], immunoglobulin E [IgE]), and serum pregnancy test (screening) for women of childbearing potential (WOCBP). At the visit specified in Table 1, Table 2, and Table 3, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). At the visits specified in Table 1, Table 2, and Table 3, participants should be fasted for at least 8 hours before their visit and up to the time of the blood draw for fasting lipid panel. The specific tests in these panels are listed in Table 11.

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Table 11: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, PLT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute) TBNK at specified visits only
Coagulation	aPTT, INR, prothrombin time
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, cholesterol (nonfasting), CK, creatinine (enzymatic), direct bilirubin, GGT, glucose random, LDH, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, urea (BUN), uric acid hsCRP and TSH at specified visits only
Fasting lipids	Cholesterol (total, LDL, and HDL), triglycerides (all fasting)
Serum immunoglobulin	IgM, IgG, IgA, IgE
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen Microscopic analysis (as required)
Urine pregnancy test	For WOCBP (at each visit, except screening)
Laboratory tests required at screening only	FSH levels for female participants who have had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause β-hCG for WOCBP Tuberculosis test (purified protein derivative or QuantiFERON-TB Gold) Serology (HBV, HCV, HIV)

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; CK, creatine kinase; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl-transferase; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; HDL, high-density lipoprotein; Hgb, hemoglobin; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; RBC, red blood cell (count); TBNK, T- and B-lymphocytes and natural killer cells; TSH, thyroid-stimulating hormone; WBC, white blood cell (count); WOCBP, women of childbearing potential.

In case of a screening laboratory value abnormality, the test can be repeated once within the original screening time window, if the investigator believes there is a reasonable possibility that the participant would be eligible if re-tested. Laboratory safety tests may also be performed at unscheduled visits during the course of the study, if deemed necessary by the investigator.

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If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a participant from the study. Any clinically significant value will be reported as an AE.

8.3.6 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1, Table 2, and Table 3. Clinically significant findings in the ECG should exclude a participant from the study (as deemed appropriate by the investigator). Any clinically significant value will be reported as an AE.

8.3.7 Plasma Concentration of VTX958

A blood sample to assess VTX958 plasma trough levels will be collected predose at the visits specified in Table 1, Table 2, and Table 3. If needed, a blood sample may also be obtained at unscheduled visits to assess VTX958 plasma levels.

Additionally, optional blood samples for PK analysis will be collected in a subset of participants who consent to the additional blood collection at the Week 4 visit of the placebo-controlled period at the following timepoints:

- 1 hour (± 10 mins) post morning dose
- 2 hours (± 10 mins) post morning dose
- 4 hours (± 10 mins) post morning dose
- 6 hours (± 10 mins) post morning dose
- 24 hours (± 45 mins) post morning dose, but prior to the morning dose of the next day

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of plasma samples will be provided in the laboratory manual.

8.3.8 Biomarker Assessments in Blood

Blood samples to assess inflammatory biomarkers will be collected at the visits specified in Table 1 (predose, if applicable).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of blood samples will be provided in the laboratory manual.

8.3.9 Genetic Testing in Blood

Optional blood samples will be collected for genetic testing (for analysis of DNA) at the visit specified in Table 1, before administration of the study treatment.

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of blood samples will be provided in the laboratory manual.

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8.3.10 Biomarker Assessments in Skin Tape Strips

Skin tape strips (from lesional skin and from nonlesional skin in the vicinity of the lesional skin) will be collected on Day 1, and from same lesional skin at Week 16 (even if the lesion has cleared) as specified in Table 1.

Details about the collection, processing, handling, storage, and shipping of the samples will be provided in the laboratory manual.

8.3.11 Biomarkers Assessments in Skin Biopsies

At selected study centers, in a subset of participants who consent to the procedure, six or eight optional skin biopsies will be collected at the visits specified in Table 1 (predose, if applicable, and after all other assessments). The target for this study is to reach approximately 100 participants who consent to collection of biopsies. Four 4-mm punch biopsies (two from lesional skin and two from nonlesional skin in the vicinity of the lesional skin) will be collected on Day 1, and two 4-mm punch biopsies will be collected from the same lesional skin (outside the scar of the previous biopsies, at least 1 cm away from the previous scar, even if the lesions have cleared) at Week 16. In addition, two 4-mm punch biopsies will be collected from the same lesional skin (outside the scar of the previous biopsies, at least 1 cm away from the previous scars) at Week 4 in participants who consent to eight skin biopsies.

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary. An additional optional visit may be required for suture removal, if needed, 10-14 days after the skin biopsy collection.

Details about the collection, processing, handling, storage, and shipping of biopsy samples will be provided in the laboratory manual.

8.3.12 Medical Photography

Medical photographs (full body, front and back) will be performed at selected sites in a subset of participants who consent to the procedure at the visits specified in Table 1.

Photographs will be identified as follows: study number, participant number, visit name, and date. Additional information on photography will be described in the manual provided to sites.

8.3.13 SkinCam Photography

At the visits specified in Table 1, medical photographs using the SkinCam (two photos; one lesional area and one nonlesional area) will be performed at selected sites in a subset of participants who consent to the procedure. Photographs of the same lesional and nonlesional areas should be taken throughout the study, even if the lesions have cleared.

Participants will have their photos taken on site at each visit. Between visits, participants will take their own photos at home, daily from Day 2 to Day 14 and weekly from Day 16 to Day 28. Participants who consent to the procedure will take the SkinCam home after Day 1 and be

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instructed to bring it back at each visit until returned to the site at Week 4. After Week 4, SkinCam photographs will only be taken during site visits. A total of approximately 42 photos will be taken throughout the study (30 by the participant at home and 12 during on-site visits).

Additional information on SkinCam photography will be described in a manual provided to the selected sites.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not considered related to the study product.

8.4.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.4.3 Definition of Serious Adverse Event

An SAE or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

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Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.4.4 Classification of an Adverse Event

8.4.4.1 Relationship to Study Treatment

The investigator will establish causality of the AE to the experimental treatment. The investigator should take into account the participant's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: Temporal relationship of the onset of the AE, relative to the experimental treatment, is not reasonable, or another cause can explain the occurrence of the AE.
- Related: Temporal relationship of the onset of the AE, relative to the experimental treatment, is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

8.4.4.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions from the National Cancer Institute (NCI) CTCAE, Version 5.0, published 27-Nov-2017 are to be used to rate the severity of an AE or SAE. If a CTCAE criterion does not exist for a given event, the investigator should grade the severity according to the following criteria:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note: A Semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.4.3 Expectedness

PPD pharmacovigilance department will assess the expectedness of each SAE in relation to the study product.

8.4.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), date of resolution/stabilization of the event, and the AE outcome (not recovered/not resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, fatal, and unknown). All AEs occurring while on study must be documented appropriately regardless of relationship.

Study site personnel will note the occurrence and nature of each participant's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the study participant's condition deteriorates after the consent signature, it will be recorded as an AE.

Should a participant experience an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the study until the end of participation in the study.

The investigator is responsible for appropriate medical care of participants during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The participant should be followed until the event is resolved or stable. If an AE is ongoing at EOS, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test. (eg, lymphopenia rather than low lymphocyte count).

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8.4.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of the participants who are in this study and for alerting the sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

8.4.7 Serious Adverse Event Reporting

PPD will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this study. All SAEs, related to the experimental treatment or not, occurring during the course of the study must be reported on an SAE form to the pharmacovigilance unit (see below contact information) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends at the end of the follow-up period or if the participant begins an alternative therapy.

Reporting should be done by sending the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

PPD pharmacovigilance department:

Email: EMEAAsiaSafetyCentral.SM@ppd.com

SAE Hotline: +44 1223 374 240

SAE Fax Line: +44 1223 374 102

The pharmacovigilance unit will inform the medical monitor, the sponsor, and Innovaderm within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the sponsor if needed, will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The pharmacovigilance unit will manage the expedited reporting of relevant safety information to concerned regulatory agencies in accordance with local laws and regulations.

The expedited reporting of relevant safety information to concerned regulatory agencies and ethic committee will be performed in accordance with local laws and regulations and will be defined in the Safety Management Plan.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

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8.4.8 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs for a particular product or class of products that a sponsor may wish to monitor carefully. AESIs may be serious or nonserious. Such events may require further investigation to better characterize and understand them. While VTX958 is an inhibitor of TYK2 and TYK2 is a member of the JAK family, it is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Therefore, additional information related to safety data will be systematically collected to better characterize and understand any potential risk of VTX958 in participants with psoriasis.

The following AESIs including related safety data will be monitored during the study:

- Adjudicated cardiovascular events
  - Major adverse cardiovascular event (eg, cardiovascular death, nonfatal myocardial infarction, stroke)
  - Other adjudicated cardiovascular events
- Adjudicated embolic and thromboembolic events
  - Venous thromboembolic events (eg, deep vein thrombosis, pulmonary embolism)
  - Other venous thrombosis
  - Arterial thromboembolic events (noncardiac, nonneurologic)

8.4.9 Potential Drug-Induced Liver Injury

An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.

Discontinuation of study product should occur if a CTCAE v5.0 Grade ≥ 3 for abnormal liver function occurs, and additionally should be considered by the investigator when a participant meets one of the conditions outlined below or if the investigator believes that it is in best interest of the participant.

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for > 2 weeks
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

All events of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN (> 35% direct bilirubin), or ALT or AST > 3 × ULN and INR > 1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. See Section 8.4.7 for follow-up and reporting of SAEs.

Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of study

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treatment upon finding a greater than 3 × ULN elevation of ALT or AST may be unnecessary. Abnormal liver function tests should be repeated and confirmed at the central laboratory.

8.4.10 Pregnancy Reporting

If a female participant or a female partner of a male participant becomes pregnant during the study and up to 4 weeks after the end of the study, the participant should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female participant will be discontinued from the study. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the sponsor, and Innovaderm in a timely manner. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify the pharmacovigilance unit of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.4.11 Overdose

Study product overdose is any accidental or intentional use of study product in an amount higher than the dose indicated per protocol for a given participant. Study product compliance (see Section 6.6.2) should be reviewed to detect potential instances of overdose (intentional or accidental). Any study product overdose during the study will be evaluated. All AEs and SAEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.4.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Using published data from 2 Phase III studies (POETYK-PSO-1 and POETYK-PSO-2 - Deucravacitinib 6 mg QD)[1,2], a two group χ^2 test with a 5% two-sided significance level will have 87% power to detect the difference between a placebo PASI-75 responder rate of 0.15 and a PASI-75 responder rate of at least 0.48 (odds ratio of 5.231) in each active treatment group at Week 16 when the sample size in each group is 36. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group (VTX958 300 mg BID), and ending with the lowest dose group (VTX958 50 mg BID). To allow for a post-randomization dropout rate of approximately 10%, 200 participants will be randomized (40 participants/treatment group).

9.2 Analysis Sets

For the placebo-controlled period, the efficacy will be evaluated based on the Full Analysis Set (FAS). A supportive analysis will also be conducted on the Per-Protocol (PP) Set.

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Intent-to-treat (ITT) analysis set: This analysis set will include all participants who were randomized. All participants will be analyzed according to the treatment group to which they were randomized. Supportive and sensitivity analyses of efficacy endpoints may be performed using this analysis population, with participants treated according to their randomized treatment.

Full Analysis Set (FAS): The FAS will include all participants who were randomized and who received at least one dose of study product. The FAS will be used as the primary analysis population for efficacy. All participants will be analyzed according to their randomized treatment.

Per-Protocol Set: The Per-Protocol Set will include all participants who were randomized, who received at least one dose of study product and who provided evaluable data for the primary endpoint with no major protocol deviations affecting the efficacy evaluations. All participants will be analyzed according to the treatment group to which they received.

Safety Set: The Safety Set will include all participants who received at least one dose of the study product. All participants will be analyzed according to the treatment that they actually received.

In addition, for the LTE Period and OLE Period, the following analysis set will be used for all efficacy and safety analyses:

Long-Term Extension (LTE) Set: The LTE Set is a subset of the Safety Set who receive at least 1 dose of study treatment in the LTE period. The LTE Set will be used for summarizing both efficacy and safety data for those participants who entered the LTE period. For efficacy data, participants will be analyzed according to the treatment they were assigned to while for safety data, participants will be analyzed as treated.

Open-Label Extension (OLE) Set: The OLE Set is a subset of the safety analysis set who receive at least 1 dose of study treatment in the OLE period. The OLE Set will be used for summarizing both efficacy and safety data for those participants who entered the OLE period.

Other analysis sets, including the Pharmacokinetic Set and Pharmacodynamic Set, may be defined in a separate analysis plan.

9.3 Statistical Analyses

9.3.1 General Approach

Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in a separate statistical analysis plan (SAP) that will be finalized and signed off before the database is locked and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final clinical study report, as appropriate.

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All statistical tests will be two-sided and will be performed with a significance (alpha) level of 0.05, unless otherwise specified in the SAP. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group (VTX958 300 mg BID), and ending with the lowest dose group (VTX958 50 mg BID). No adjustment to alpha level will be made to account for multiple testing between treatment groups for the secondary and exploratory efficacy endpoints.

9.3.2 Baseline Definitions

Placebo-Controlled Period:

Unless specified otherwise, baseline is defined as the last non-missing assessment (including unscheduled/retest assessments) collected before the first dose of study product (VTX958 or placebo). If the last non-missing assessment was performed on the same date as the first dose of study product and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the same day than the first dose of study treatment which will be considered as post-baseline.

Long-Term Extension Period:

For efficacy endpoints, baseline is defined as for the placebo-controlled period.

For non-efficacy assessments and unless specified otherwise, baseline is defined as the last nonmissing-assessment (including unscheduled/retest assessments) collected before the first dose of the active study product (VTX958) on Day 1 for participants who received VTX958 in the placebo-controlled period (regardless of their responder/non-responder status at Week 16) or before the first dose of the active study product (VTX958) at LTE Day 1 for participants who received the placebo. If the last non-missing assessment was performed on the same date as the first dose of VTX958 and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the first dose date which will be considered post-baseline.

Open-Label Extension Period:

For efficacy endpoints, baseline is defined as for the placebo-controlled period. For non-efficacy assessments and unless specified otherwise, baseline is defined as for the LTE period.

9.3.3 Efficacy Analyses

Placebo-Controlled Period:

The primary endpoint can be translated as a responder analysis, where a participant will be classified as responder if he or she achieves PASI-75 at Week 16. The pairwise comparisons between treatment groups for the primary endpoint will be done using an adjusted Cochran-Mantel-Haenszel (CMH) test, the adjustment factor will be prior treatment with biologics for psoriasis (yes/no). The comparisons of interest are:

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- VTX958 300 mg BID vs. Placebo
- VTX958 225 mg BID vs. Placebo
- VTX958 300 mg QD vs. Placebo
- VTX958 50 mg BID vs. Placebo

The comparison between the highest dose of VTX958 (300 mg BID) versus placebo will be performed first and will be followed with the comparisons involving the lower doses (as per hierarchical testing procedure).

The primary analysis of the primary efficacy endpoint will be performed on the FAS, while the Per-Protocol Set analysis set will be used to perform a supportive analysis. For the primary analysis of the primary efficacy endpoint, missing data will be handled through the non-response imputation (NRI). For the supportive analysis on the Per-Protocol Set, participants with missing observation will be excluded from the analysis**.** Additional supportive and sensitivity analyses will be performed and will be described in the SAP.

The primary analysis of secondary and exploratory endpoints involving proportions of participants will be analyzed using the same approach (adjusted CMH test) as described for the primary analysis of the primary efficacy endpoint, at each time point and based on the FAS. Missing data imputation for the primary analysis of these endpoints will be handled through the NRI. Additional supportive and sensitivity analyses may be performed and will be described in the SAP.

The continuous secondary and exploratory endpoints involving change from baseline will be analyzed using the mixed effect model for repeated measures (MMRM). The model will include treatment group, analysis visit, treatment-by-visit interaction, and prior treatment with biologics for psoriasis (yes/no) as fixed effects and baseline value as a covariate. An unstructured covariance matrix will be specified for the MMRM model. LS means at visits and LS mean differences between treatment groups with p-value and corresponding 95% CIs will be reported. Supportive and sensitivity analyses related to missing data imputation for these endpoints will be described in the SAP.

Long-Term Extension Period:

For the efficacy variables collected during the LTE period, descriptive summaries by treatment sequence (treatment received during the placebo-controlled period – treatment received during the LTE period), by dose, and by visit, when applicable, will be provided based on LTE analysis set. No inferential statistical testing will be performed on the efficacy variables for the LTE period. A sensitivity analysis excluding participants who experienced a study product interruption between the placebo-controlled period and the LTE period may be performed. More details on this will be provided in the SAP.

Open-Label Extension Period:

For the efficacy variables collected during the OLE period, descriptive summaries by treatment sequence, all combined, and by visit, when applicable, will be provided based on the OLE Set. No inferential statistical testing will be done on the efficacy variables for the OLE period. A sensitivity

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analysis excluding participants who experienced a study product interruption between the LTE period and the OLE period may be performed. More details on this will be provided in the SAP.

9.3.4 Safety Analyses

Safety analyses will be performed by study period using the study population related to the analysis time period (Safety Set for the placebo-controlled period, LTE Set for the LTE period, and OLE Set for the OLE period).

AEs and SAEs will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification by treatment group. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, action taken with respect to the study product, and the outcome. The focus in this protocol will be the prevalence of TEAEs. The detailed definition of the TEAE will be provided in the SAP.

Adverse events will be reported in the placebo-controlled period, LTE period, or OLE period depending on the onset. If the AE onset was before Day 1 dosing of the LTE period, the AE will be considered in the placebo-controlled period. If the AE had an onset on or after LTE Day 1 dosing and before OLE Day 1 dosing (if applicable), the AE will be considered in the LTE period. If the AE had an onset on or after OLE Day 1 dosing, the AE will be considered in the OLE period.

Reported AEs will be summarized by the number of participants reporting the events, as well as by System Organ Class (SOC), Preferred Term (PT), severity, seriousness, and relationship to study product. For the summary of AEs by severity, each participant will be counted only once within an SOC or a PT by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each participant will be counted only once within an SOC or a PT by using the AEs with the greatest reported relationship within each category.

All information pertaining to AEs noted during the study will be listed by treatment group, participant, detailing verbatim, SOC, PT, start date, stop date, intensity, outcome, action taken with respect to study product, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. Serious adverse events will be tabulated by treatment group and a reference to the occurrence of the SAEs to the relative day of dosing.

Results from laboratory analyses, vital signs, and ECGs will be tabulated by treatment group and visit using descriptive statistics. The observed value at each visit as well as the change from baseline will be presented descriptively.

Clinically significant changes in laboratory analyses, vital signs, ECGs, and new findings on physical examination will be recorded as AEs.

Shift tables describing shifts to out-of-normal range may be provided for clinical laboratory results, and normal-abnormal shift tables may be provided for vital signs.

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Concomitant medications will be coded with the WHO-Drug Dictionary and listed by participant. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

9.3.5 Pharmacokinetic Analyses

Analyses of pharmacokinetic data will be described in a separate analysis plan.

9.3.6 Pharmacodynamic Analyses

Analyses of blood and skin biomarkers will be described in a separate analysis plan.

9.3.7 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data and prior concomitant therapy, and of participant disposition will be presented by treatment group for each study period. In addition, a list of participants who discontinued from the study along with discontinuation reason will be provided.

Protocol deviations will be summarized by treatment, category, and study period.

9.3.8 Planned Interim Analyses

An unblinded interim analysis (Main Analysis) will be performed for this study after all participants complete the Week 16 visit or discontinue from the study, whichever occurs first. Since the only efficacy endpoint to be inferentially tested with a controlled alpha is the primary efficacy endpoint of the proportion of participants achieving PASI-75 at Week 16, and all secondary and exploratory efficacy endpoints for which nominal statistical inferences will be performed are before or at Week 16, the Main Analysis will be the final analysis for the placebo-controlled period of the study. All efficacy analyses up to Week 16 performed for the Main Analysis will not be re-issued at the time of the final analysis of this study after completion of the LTE and OLE periods. Furthermore, only descriptive statistics will be provided for the exploratory efficacy and safety endpoints collected during the LTE and OLE periods. Therefore, no adjustment to the overall alpha level of the study is needed for the Main Analysis.

Additionally, unblinded safety data will be generated and reviewed by the DMC during the study.

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10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a REB/IRB. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor or CRO before initiation of the study and whenever subsequent modifications to the protocol are made.

10.3 Informed Consent Process

An ICF describing in detail the study treatment, study procedures, and risks will be given to the participant.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/REB approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research participant. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures.

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The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a participant to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/REB. All participants (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

10.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study participants and the IRB/REB, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB, and/or regulatory agencies.

10.5 Confidentiality and Privacy

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the participants' anonymity will be maintained and that participants' identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, participants should not be identified by their names, but by an identification code. The investigator should keep a participant log relating codes with the names of participants. The investigator should maintain in strict confidence documents not for submission to Ventyx Biosciences, Inc. (eg, participants' written consent forms).

All research activities will be conducted in a setting as private as possible.

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Blood and/or skin samples from this study that are collected and analyzed may be stored by the sponsor, in a secure storage space to protect participant confidentiality, for possible future analyses to better understand the effects of VTX958 and to measure psoriasis. Samples may be stored for up to, but no longer than, 15 years from the end of the main study.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB, institutional policies, or sponsor requirements.

10.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan.

Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study product accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The study site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

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10.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories: investigator's study files and participant clinical source documents.

The investigator must maintain source documents for each participant in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the participant's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Participant data will be entered by site personnel using Medrio, a web-based electronic data capture (EDC) and reporting system. This application will be set up for remote entry. Medrio is the developer and owner of Medrio. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

10.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The clinical research associate must ensure that a prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human participant protection or reliability of trial results is discovered, the CRO and the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

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10.10 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first participant being dosed.

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APPENDIX 1: Psoriasis Area and Severity Index

PASI Scoring

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (plaque thickness), and desquamation (scaling), as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = no symptoms
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10% to <30%
- 3 = 30% to <50%
- 4 = 50% to <70%
- 5 = 70% to <90%
- 6 = 90% to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head.
- Buttocks: include with the lower extremities.
- Axillae: include with the trunk.
- Genitals: include with the trunk.
- The inguinal canal separates the trunk and legs anteriorly.

The PASI score for each body region is obtained by using the formula below:

$$\text{PASI} = 0.1\,(E_h + I_h + D_h)\,A_h + 0.2\,(E_u + I_u + \mathrm{D}_u)\,\mathrm{A}_\mathrm{u} + 0.3\,(E_t + I_t + \mathrm{D}_\mathrm{t})\,A_t + 0.4\,(E_l + I_l + \mathrm{D}_l)\,A_l$$

Where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

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APPENDIX 2: Pruritus Numeric Rating Scale

ITCH NUMERIC RATING SCALE (NRS)

Subject # _ _ _ _
Site # _ _ _
Visit or Date _____

Please rate your itching severity due to your psoriasis by circling the number that best describes your worst level of itching in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

0 = No itch 10 = Worst itch imaginable

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APPENDIX 3: Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	□ □ □ □	Not relevant □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	□ □	Not relevant □
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little	□ □ □	

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		Not at all	☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

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Please check you have answered EVERY question. Thank you.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.

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APPENDIX 4: Psoriasis Symptoms and Signs Diary

Psoriasis Symptom and Sign Diary

Please answer each question to the best of your ability. There are no right or wrong answers.
Please pay close attention to the time period of interest. These questions ask you to think about the **past 7 days**.

Individuals with psoriasis may experience a range of symptoms. Please indicate how severe each of the following skin symptoms was in the **past 7 days.** Please select only one number for each item on the 0 to 10 scale (0=Absent and 10= Worst imaginable).

1. Rate the severity of itch in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2. Rate the severity of dryness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3. Rate the severity of cracking in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4. Rate the severity of skin tightness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5. Rate the severity of scaling (build-up of skin) in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6. Rate the severity of shedding or flaking in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7. Rate the severity of redness in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8. Rate the severity of bleeding in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9. Rate the severity of burning in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10. Rate the severity of stinging in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11. Rate the severity of pain from your psoriasis lesions in the past 7 days.	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

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