Statistical Analysis Plan V2.0

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

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Statistical Analysis Plan

Study Title:	**A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VTX958 in Subjects with Moderate to Severe Psoriasis**
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STATISTICAL ANALYSIS PLAN, Final V2.0	
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This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

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ABBREVIATIONS

AE	adverse event
AIC	Akaike's information criteria
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR [1]	first-order autoregressive
ARH [1]	heterogenous first-order autoregressive
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BID	twice daily
BMI	body mass index
bpm	beats per minute
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
CTMS	Clinical Trial Management System
DB	double-blind
DBP	diastolic blood pressure
DILI	drug induced liver injury
DLQI	dermatology life quality index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EOS	end of study
ET	early termination

FAS	full analysis set
FCS	fully conditional specifications
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
IA	interim analysis
ICF	informed consent form
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
ITT	intent-to-treat
IWRS	interactive web response system
LOCF	last observation carried forward
LS	least square
LTE	long term extension
MAR	missing-at-random
MedDRA	medical dictionary for regulatory activities
MH	Mantel-Haenszel
MMRM	mixed model repeated measures
msec	millisecond
NR	non-responder
NRI	non-response imputation
NRS	numeric rating scale
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
PC	placebo-controlled
PD	pharmacodynamic
PD	protocol deviation
PDMP	protocol deviation management plan
PK	pharmacokinetic
PMM	predictive mean matching
PP	per-protocol
PR	PR interval
PSSD	psoriasis symptoms and signs diary
PT	preferred term
Q_1	first quartile
Q_3	third quartile
QD	once daily
QRS	Duration of ventricular muscle depolarization (ECG)
QT	QT interval
QTcF	Fridericia's correction formula for QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system®
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	system organ class
sPGA	static physician's global assessment
REML	restricted maximum likelihood
RR	respiratory rate
TB	tuberculosis
TBNK	T- and B-lymphocytes and natural killer cells

TEAE	Treatment-emergent adverse event
TLF	table, listing, and figure
TOEPH	heterogenous Toeplitz
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UN	unstructured
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the analyses that were to be performed and reported at the following timepoints for Ventyx Biosciences, Inc. clinical protocol VTX958-201 based upon protocol version 3.0, dated 05-May-2023:

- The Interim Analysis (IA) database lock (i.e. after all participants have either completed the placebo-controlled Week 16 visit or discontinued early from the study, whichever occurs first, and the study is unblinded, as described in Section 3.4). Refer to Section 6.4 for additional information concerning data that will be cleaned, locked, and analyzed as part of this analysis, referred to as the Main Analysis.
- The final database lock (i.e. after all participants have either completed the Open-Label Extension (OLE) period or discontinued early from the study, whichever occurs first).

Although the study achieved the primary and key secondary endpoints from the IA, the magnitude of efficacy observed did not meet the Sponsor's internal target to support advancement of VTX958 in psoriasis. Based on these results, the Sponsor has elected to terminate the ongoing activities in the study. In consequence, an abbreviated clinical study report (CSR) will be produced in lieu of a full CSR. This SAP was finalized before the IA database lock and study unblinding. Rather than eliminating the unneeded analyses for the abbreviated CSR, the subset of tables, listings, and figures (TLFs) to be performed are provided in Section 3.5. Unless otherwise specified in Section 3.5, the analysis method of the selected TLFs for the final analyses will follow what is stated in this SAP.

Analyses related to pharmacokinetic (PK) and pharmacodynamic (PD) endpoints are not covered in this SAP and will be described in separate documents. Similarly, analyses related to safety oversight and assessment of cardiovascular, embolic, and thrombotic adverse events (under the direction of an independent data monitoring committee [DMC] and cardiovascular adjudication committee) are not covered in this SAP and will be described in separate charters.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 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 at least 75% improvement from baseline in psoriasis area and severity index (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 adverse events (AEs) and serious AEs (SAEs) • Changes in vital signs, clinical laboratory parameters, and electrocardiograms (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 a static physician's global assessment (sPGA) score of 0 (clear) or 1 (almost clear) at Week 16 • Change and percent change from baseline in psoriasis area and severity index (PASI) at Week 16 • Proportion of participants achieving at least 90% improvement from baseline in PASI (PASI-90) at Week 16 • Proportion of participants achieving a 100% improvement from baseline in PASI (PASI-100) at Week 16 • Change from baseline in dermatology life quality index (DLQI) scores at Week 16 • Change from baseline in body surface area (BSA) at Week 16

OBJECTIVES	ENDPOINTS
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 achieving an sPGA score of 0 (clear) at Weeks 1, 2, 4, 8, 12 and 16 • 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 numeric rating scale (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 psoriasis symptoms and signs diary (PSSD) at Weeks 1, 2, 4, 8, 12, and 16

OBJECTIVES	ENDPOINTS
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 • Exposure-response relationship (PASI-75/90/100 and other measures as necessary)
To evaluate the effects of VTX958 on blood and skin biomarkers.	Exploratory PD endpoint:
	• Change in blood and skin biomarker levels

2.2 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 achieving an sPGA score of 0 (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

OBJECTIVES	ENDPOINTS
Exploratory objectives	
	• 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 • Exposure-response relationship (PASI-75/90/100 and other measures as necessary)

2.3 Open-Label Extension Period

OBJECTIVES	ENDPOINTS
Exploratory objectives	
To evaluate 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 1, 2, 4, 8, 12, and 16 • Change from baseline in sPGA at OLE Weeks 4, 8, 16, 24, 32, 36, and 40

OBJECTIVES	ENDPOINTS
Exploratory objectives	
	• 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 achieving an sPGA score of 0 (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

3 STUDY DESIGN

3.1 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 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: PASI score ≥ 12, sPGA score ≥ 3, and plaque psoriasis covering ≥ 10% of BSA.

All participants will read and sign an informed consent form (ICF) prior to any screening procedures being performed. Participants who fulfill all 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 electronic case report form (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 completed 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 (i.e., LTE Week 16 visit will occur on the same visit as the OLE Day 1 visit). However, a study product interruption of up to 28 days is permitted between the 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.

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.

Efficacy will be assessed using PASI, BSA, sPGA, pruritus NRS, and PSSD. Quality of life will be evaluated using the 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 pre-dose (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 periods, blood samples will be collected from all participants pre-dose (if applicable) to evaluate plasma concentration of VTX958.

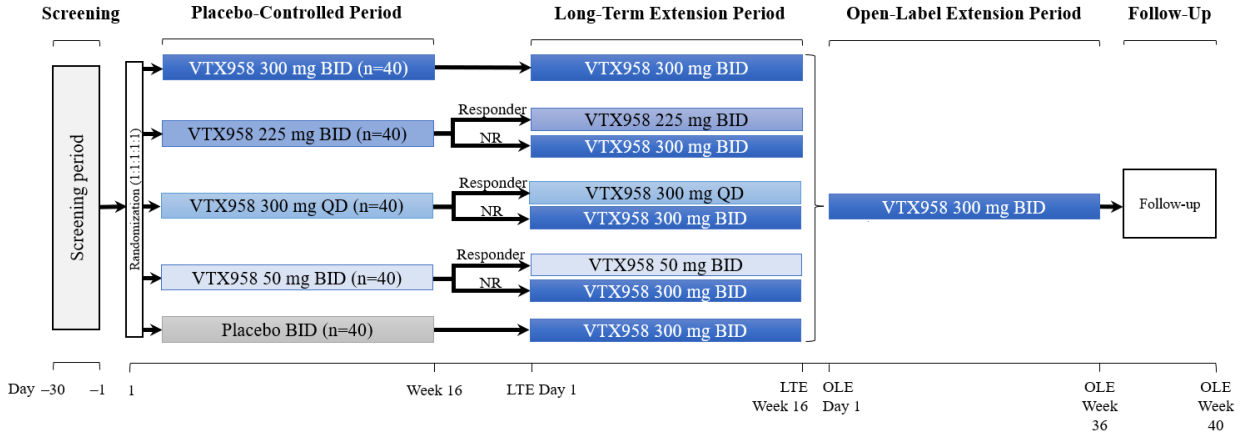
During the placebo-controlled period, the effect of VTX958 on skin biomarkers will be evaluated by collecting tape strips from all participants. At selected study centers, in a subset of participants who consent to the procedure, the effect of VTX958 on skin biomarkers will be evaluated by collecting 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.

Figure 1 provides an overview of the study.

Figure 1: Study Diagram



Abbreviations: 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.

3.2 Schedule of Events

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

The screening evaluations will only be performed after the participant has agreed to participate and signed and dated the ICF.

Unless specified otherwise, the study assessments scheduled during the study visits must be performed before the study product administration for visits with study product administration.

3.3 Treatment

3.3.1 Placebo-Controlled Period

At the end of the Day 1 visit of the placebo-controlled period, participants will be randomly assigned (refer to Section 3.4) to one of the treatment groups (refer to Table 1 for tablets administration information):

Table 1: Study Product Doses for the Placebo-Controlled Period

Treatment 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

Participants will be instructed to administer their study product BID, as assigned, for 68 weeks (including the LTE and OLE periods). Study products will 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 (refer to Section 3.2), 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 of the placebo-controlled period 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 the Placebo-Controlled period, treatment groups will be summarized as follows:

- VTX958 300 mg BID
- VTX958 225 mg BID
- VTX958 300 mg QD
- VTX958 50 mg BID
- All VTX958
- Placebo BID

3.3.2 Long-Term Extension Period

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 (LTE Day 1 visit). During that period, treatment will be assigned as described in Section 3.1 (refer to Table 2 for tablets administration information):

Table 2 Study Product Doses for the LTE Period

Treatment 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

For the LTE period, treatment groups will be summarized as follows:

- Placebo-Controlled (PC) VTX958 300 mg BID – LTE VTX958 300 mg BID
- PC VTX958 225 mg BID – LTE VTX958 300 mg BID
- PC VTX958 300 mg QD – LTE VTX958 300 mg BID
- PC VTX958 50 mg BID – LTE VTX958 300 mg BID

- PC Placebo BID – LTE VTX958 300 mg BID
- All LTE VTX958 300 mg BID (i.e., 5 previous treatment groups pooled together)
- PC VTX958 225 mg BID – LTE VTX958 225 mg BID
- PC VTX958 300 mg QD – LTE VTX958 300 mg QD
- PC VTX958 50 mg BID – LTE VTX958 50 mg BID
- All LTE VTX958 doses – All PC VTX958 doses
- All LTE VTX958 doses

3.3.3 Open-Label Extension Period

For participants without any study product interruption between the LTE and OLE periods, the dose administered on the day of the LTE Week 16 visit will be part of the OLE period (OLE Day 1 visit). During that period, all participants will receive VTX958 300 mg BID (refer to Table 3 for tablets administration information):

Table 3 Study Product Doses for the OLE Period

Treatment 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

For the OLE period, treatment groups will be summarized as follows:

- LTE VTX958 300 mg BID – OLE VTX958 300 mg BID
- LTE VTX958 225 mg BID – OLE VTX958 300 mg BID
- LTE VTX958 300 mg QD – OLE VTX958 300 mg BID
- LTE VTX958 50 mg BID – OLE VTX958 300 mg BID
- All OLE VTX958 300 mg BID

3.4 Randomization, Replacement, and Unblinding Procedures

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, which will be assigned in sequential order at the screening visit after consent.

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.

This study will be double-blinded for the placebo-controlled period. Randomization will occur prior to first dosing, at the Day 1 visit of the placebo-controlled period. 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.

Treatment and randomization information will be kept confidential and will not be released to the contract research organization's (CRO) and sponsor's study teams until after the IA database lock (refer to Sections 1 and 6.4). At the time of the IA database lock, the study will be unblinded, but the individual participant randomization information will not be shared with the investigators, site personnel, and participants until after the final database lock.

Breaking the blind on a participant level should only be considered 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.

The participant for whom the blind has been broken may be discontinued from the study and undergo the early termination (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.

Participants who discontinue will not be replaced.

3.5 Changes to the Analysis from the Protocol

The proportion of participants achieving an sPGA score of 0 (clear) will also be examined as an exploratory endpoint in placebo-controlled, LTE and OLE periods.

With the termination of the study after the interim analysis, sponsor requested only a subset of analysis with data from LTE and OLE period.

- Disposition table
- Efficacy: Primary analysis of PASI 75/90/100 and sPGA 0/1 and sPGA 0
    - Handling of missing data will be done based on a modified non-responder imputation (mNRI) method. Participants with missing data prior to the termination of the study by the sponsor will be considered as non-responders (i.e., not achieving the endpoint criteria). Therefore, the denominator for the calculation of the proportion will be the total number of participants who were not terminated by the sponsor for the visit. For example, a participant who completed the LTE Week 8 visit prior to study termination will be part of the denominator up to LTE Week 8 and will be missing for subsequent visits.
- Safety:
    - Study Drug Exposure
    - Adverse Events
    - CTCAE grade shift tables
    - Frequency tables of maximum hepatic enzyme elevations
    - Evaluation of drug-induced serious hepatotoxicity (eDISH) plots

4 ANALYSIS SETS

For the analysis sets used to summarize and analyze data collected during the placebo-controlled period, the participants to be included in each analysis set will be reviewed and finalized by the Sponsor and CRO in a blinded fashion before the IA database lock.

For the analysis sets used to summarize data collected during the LTE and OLE periods, the participants to be included in each analysis set will be determined based on the definitions in Sections 4.3 and 4.4. Given that none of the analysis sets that will be used to summarize data

collected during these study periods has a subjective definition, review by the sponsor and CRO will not perform.

4.1 All Screened Participants Set

The All Screened Set includes all participants who signed the ICF.

This analysis set will be used to summarize screening and screen failure.

4.2 Placebo-Controlled Period

4.2.1 Intent-to-Treat Set

The Intent-to-Treat (ITT) Set will include all participants who were randomized.

4.2.2 Full Analysis Set

The Full Analysis Set (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 set for efficacy. All participants will be analyzed according to the treatment group to which they were randomized.

4.2.3 Per Protocol Set

The Per Protocol (PP) Set will include all participants who were randomized, received at least one dose of study product and provided evaluable data for the primary endpoint with no major protocol deviations (refer to Section 7.2).

The PP Set will also be used for supportive analysis for the primary efficacy endpoint. All participants will be analyzed according to the treatment group to which they were randomized.

4.2.4 Safety Set

The Safety Set will include all participants who received at least one dose of the study product.

This analysis set will be used to summarize some baseline characteristics, including surgical and medical history and prior concomitant therapy, and safety data. In case a participant received more than one actual treatment, the first treatment received will be used for the safety analysis. All participants will be analyzed according to the treatment received.

4.3 Long-Term Extension Period

4.3.1 Long-Term Extension Safety Set

The LTE Safety Set will be a subset of the Safety Set and will include all participants who received at least 1 dose of study product in the LTE period.

This analysis set will be used to summarize both efficacy and safety data collected during the LTE period, unless specified otherwise. For efficacy data, participants will be analyzed according to the treatment they were assigned to while for safety data, participants will be analyzed according to the treatment received.

4.4 Open-Label Extension Period

4.4.1 Open-Label Extension Safety Set

The OLE Safety Set will be a subset of the Safety Set and will include all participants who received at least 1 dose of study product in the OLE period.

This analysis set will be used to summarize both efficacy and safety data collected during the OLE period. For efficacy data, participants will be analyzed according to the treatment they were assigned to while for safety data, participants will be analyzed according to the treatment received.

5 GENERAL CONSIDERATIONS

Formats and layouts of tables, listings, and figures (TLFs) will be provided in a separate document (output general layout is described in Appendix 1).

5.1 Baseline

5.1.1 Placebo-Controlled Period

Unless specified otherwise, the baseline value will be defined as the last non-missing assessment (including unscheduled/retest assessments) collected before the first dose of study product (VTX958 or Placebo). In the event a participant is randomized but never treated, the randomization date will be used instead of the date of first dose of study product. If the last non-missing assessment was performed on the same day as the first dose of study product and the time is not available, the assessment will be considered as baseline; however, AEs and medications starting on the same day as the first dose of study product will be considered post-baseline.

5.1.2 Long-Term Extension Period

For efficacy endpoints and baseline characteristics (except Weight and BMI), baseline will be defined as for the placebo-controlled period.

For safety assessments and unless specified otherwise, baseline will be defined as the last non-missing assessment (including unscheduled/retest assessments) collected before the first dose of the active study product (VTX958) across both the placebo-controlled and LTE periods. In other words, baseline will be defined as the last non-missing assessment (including unscheduled/retest assessments) collected before the first dose of VTX958 during the placebo-controlled period for participants who received VTX958 in the placebo-controlled period and before the first dose of the VTX958 during the LTE period for participants who received the placebo during the placebo-controlled period. If the last non-missing assessment was performed on the same day as the first dose of VTX958 and the time is not available, the assessment will be considered as baseline; however, AEs and medications starting on the same day as the first dose of VTX958 will be considered post-baseline.

5.1.3 Open-Label Extension Period

For efficacy endpoints and baseline characteristics (except Weight and BMI), baseline will be defined as for the placebo-controlled period.

For safety endpoints and unless specified otherwise, baseline will be defined as for the LTE period.

5.2 Change and Percent Change from Baseline

For each study period (i.e., placebo-controlled, LTE, and OLE periods), change from baseline is defined as the study period post-baseline value minus the study period baseline value.

Similarly, the percent change from baseline will be calculated for each study period using the following formula:

$$\frac{\text{(Study period post-baseline value at visit X – Study period baseline value)}}{\text{Study period baseline value}} \times 100$$

Percent change will not be calculated if the baseline value is zero (‘0’).

5.3 Study Day

For each study period (i.e., placebo-controlled, LTE and OLE periods), study days will be calculated from the first dose of study treatment during the concerned study period to show the start/end day of assessments or events during that study period. If an assessment/event start/end date is partially or completely missing, the period study start/end day will be missing.

If the date of an assessment or event is before the date of first dose of study product of a study period, the period study day will be calculated as follows:

Date of assessment/event – Date of first dose of study product of the study period

If the date of an assessment or event is on or after the date of first dose of study product of a study period, the period study day will be calculated as follows:

(Date of assessment/event – Date of first dose of study product of the study period) + 1

In the event a participant is randomized but was never treated, the randomization date will be used instead of the date of first dose of study product.

5.4 Handling of Retests, Unscheduled Visits, and Early Termination Data

For the outputs presented by visit, a retest or repeat measurement will be considered as unscheduled assessment. Unscheduled and ET assessments will be mapped to a scheduled visit as mentioned in Section 5.5.

For the outputs not presented by visit (e.g., AEs), all data will be considered, including retest, unscheduled, and early discontinuation measurements.

5.5 Windowing Conventions

For each study period, post-baseline scheduled visits (refer to Table 1, Table 2, and Table 3 of the protocol) will be summarized and analyzed as per their nominal visit name (e.g., Week 1, Week 2, Week 4, etc.). Data from unscheduled or ET visits will only be included in the by-visit summary and/or analysis if data from a scheduled visit is not available, and the unscheduled or ET visit falls within the scheduled visit analysis-adjusted visit window (also referred to as analysis visit window), as described in Table 4, Table 5, and Table 6 for the placebo-controlled, LTE, and OLE periods, respectively. If an assessment, measurement, or test is not planned to be collected at a scheduled visit as per Table 1, Table 2, or Table 3 from the protocol, data from unscheduled and ET visits falling within the scheduled visit analysis-adjusted visit window will not be mapped to that scheduled visit; thus, data collected during such unscheduled/ET visits will not be included in the summaries and/or analyses for that assessment, measurement, or test, but will be presented in the participant data listings.

If there is more than one unscheduled or ET visit that are mapped to a given scheduled visit with missing data, data from the unscheduled or ET visit closest to the scheduled visit target study day will be considered for the summary and analysis. If two unscheduled visits or an unscheduled and ET visits are equidistant from the scheduled visit target study day, data from the latest unscheduled/ET visit will be considered for the analysis.

All data from all visits (scheduled, retest, unscheduled, and ET) will be listed under their nominal visit name (e.g., Screening, Day 1, Week 4, unscheduled, ET, etc.). Should an unscheduled or ET visit has been mapped to a scheduled visit based on its analysis-adjusted visit window and used in the summary and analysis for that scheduled visit, the name of the scheduled visit under which the assessment, measurement or test has been summarized and analyzed will also be presented in the participant data listings.

Table 4: Analysis-Adjusted Visit Windows for the Placebo-Controlled Period

Scheduled Visit	Visit Target Study Day	Analysis-Adjusted Visit Window
Week 1	Day 8	Day 1 (post-dose) – Day 11
Week 2	Day 15	Day 12 – Day 22
Week 4	Day 29	Day 23 – Day 43
Week 8	Day 57	Day 44 – Day 71
Week 12	Day 85	Day 72 – Day 99
Week 16	Day 113	Day 100 – Day 127 (or prior to 1st dose day in LTE period for participants who continue into the LTE period)
Follow-up/Week 20*	Day 141	Day 128 – Day 155

*The 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.

Table 5: Analysis-Adjusted Visit Windows for the LTE Period

Scheduled Visit	Visit Target Study Day	Analysis-Adjusted Visit Window
LTE Week 1	LTE Day 8	LTE Day 1 (post-dose) – LTE Day 11
LTE Week 2	LTE Day 15	LTE Day 12 – LTE Day 22
LTE Week 4	LTE Day 29	LTE Day 23 – LTE Day 43
LTE Week 8	LTE Day 57	LTE Day 44 – LTE Day 71
LTE Week 12	LTE Day 85	LTE Day 72 – LTE Day 99
LTE Week 16	LTE Day 113	LTE Day 100 – LTE Day 127 (or prior to 1st dose day in the OLE period for participants who continue into the OLE period)
Follow-up/LTE Week 20*	LTE Day 141	LTE Day 128 – LTE Day 155

*The 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.

Table 6: Analysis-Adjusted Visit Windows for the OLE Period

Scheduled Visit	Visit Target Study Day	Analysis-Adjusted Visit Window
OLE Week 4	OLE Day 29	OLE Day 1 (post-dose) – OLE Day 43
OLE Week 8	OLE Day 57	OLE Day 44 – OLE Day 85
OLE Week 16	OLE Day 113	OLE Day 86 – OLE Day 141
OLE Week 24	OLE Day 169	OLE Day 142 – OLE Day 197
OLE Week 32	OLE Day 225	OLE Day 198 – OLE Day 239
OLE Week 36	OLE Day 253	OLE Day 240 – OLE Day 267
Follow-up	OLE Day 281	≥ OLE Day 268

5.6 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6 STATISTICAL CONSIDERATIONS

6.1 Sample Size

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) (refer to Appendix 5 for details).

6.2 Descriptive Statistics

All continuous endpoints will be summarized using descriptive statistics i.e., number of participants with non-missing data (n), mean, standard deviation (SD), median, first quartile (Q_1), third quartile (Q_3), minimum, and maximum.

Categorical endpoints will be summarized using frequencies and percentages and, when applicable, a "Missing" category will be presented.

6.3 Handling of Dropouts or Missing data

With the exception of missing data described in the following sub-sections, no missing data will be imputed in the study.

6.3.1 Efficacy Endpoints

6.3.1.1 Non-Responder Imputation

All participants with missing data, regardless of reasons for missingness, will be considered as non-responders (i.e., not achieving the endpoint criteria).

The NRI method will also be used to impute missing post-baseline values for the analysis of secondary and exploratory efficacy endpoints that are dichotomous in nature (refer to Sections 12.2.2 and 12.3.2, respectively).

6.3.1.2 Multiple Imputation

As a sensitivity analysis to the method used to impute missing data for the main analysis of the primary efficacy endpoint (refer to Section 6.3.1.1), missing PASI scores will first be multiply imputed as follows under a missing at random (MAR) assumption.

All missing PASI scores at scheduled post-baseline visits of the placebo-controlled period up to Week 16, inclusively, will be imputed using a fully conditional specification[3,4] (FCS) predictive mean matching[5,6] (PMM) sequential regression multiple imputation model, where missing values for all visits are imputed sequentially one at the time, with observed and previously imputed PASI scores at preceding visits serving as covariates and treatment group as fixed effect. For each visit, the FCS PMM regression model will include the PASI score at that visit as the dependent variable and the treatment group, PASI score at baseline (refer to Section 5.1), and PASI scores (observed and previously imputed) at the previous scheduled post-baseline visits as independent variables, using a seed of 942967. The number of observed values whose predicted values are closest to the predicted value of a missing value will be the SAS default value (i.e., k = 5). Among those k observed values, randomly choose one and assign it to substitute for the missing value. This process will be repeated 100 times, resulting in a total of 100 complete analysis datasets.

For each multiply imputed dataset, the percent change from baseline in PASI score at each scheduled post-baseline visit will then be derived using observed and imputed PASI score values. The achievement of PASI-75 (yes/no) at each scheduled post-baseline visit will be determined as defined in Section 12.1.1 using the derived percent change from baseline in PASI score and the main analysis of the primary efficacy endpoint will be repeated (refer to Section 12.1.3) for each

scheduled post-baseline visit. Result from the analysis of all multiply imputed datasets will be combined into one multiply imputed inference for each scheduled post-baseline visit as follows:

- Common proportions of participants achieving PASI-75 for each treatment group, common Mantel-Haenszel (MH) proportion differences (and their associate common 95% CI) between each VTX958 treatment group and the placebo treatment group as well as common MH odds ratios (and their associated common 95% CI) of each VTX958 treatment group over the placebo treatment group will be combined using PROC MIANALYZE SAS procedure based on the Rubin's rule. Common MH odds ratios and their associated common 95% CIs will first be normalized using a log-transformation before being combined using PROC MIANALYZE. The resulting combined common MH odds ratios (and their associated combined common 95% CI) will be back-transformed to the arithmetic scale before being presented in a table.
- For the combined common proportion of participants achieving PASI-75, the associated combined common 95% CI will be calculated as per Lott and Reiter multiple imputation Wilson interval method[7].
- For the comparison of each VTX958 treatment group against the placebo treatment group, the p-value will be obtained from a multiple imputation Cochran–Mantel–Haenszel (CMH) test, adjusted for the randomization stratification factor of prior treatment with biologics for psoriasis (yes/no), where the CMH general association statistics and their standard errors (SEs) obtained from the analysis of each multiply-imputed dataset will first be transformed using Wilson-Hilferty[8,9] transformation before being combined using PROC MIANALYZE based on Rubin's rule. Because the Wilson-Hilferty is a monotone transformation, the p-value for the multiple imputation CMH test is the one-sided p-value from the t distribution[10].
- The comparison of all VTX958 doses (4 active arms) combined versus placebo will also be tested as exploratory.

6.3.1.3 Mixed-Model for Repeated Measurements

For the main analysis of the secondary and exploratory efficacy endpoints that are continuous in nature (refer to Sections 12.2.2 and 12.3.2, respectively), missing post-baseline data will not be imputed before being analyzed using a Mixed-Model for Repeated Measurements (MMRM) model since, under a MMRM model, missing data are predicted by the observed data via the model of conditional mean.

6.3.1.4 Last Observation Carried Forward

As a sensitivity analysis to the composite strategy used for the main analysis of the primary efficacy endpoint (refer to Section 12.1.3), a different composite strategy will be used only for participants who discontinued early from study treatment due to a reason other than lack of efficacy or AE related to plaque psoriasis (e.g., worsening of plaque psoriasis). In this analysis, missing data will be imputed as per the Last Observation Carried Forward (LOCF) imputation method, under which a missing post-baseline value is imputed by the last non-missing post-baseline assessment (including retest, unscheduled, and ET assessments) collected prior to the missing assessment.

For participants who discontinued early from study treatment due to lack of efficacy or AE related to plaque psoriasis (e.g., worsening of plaque psoriasis), the same composite strategy as for the main analysis of the primary efficacy endpoint will be used for this sensitivity analysis. Similarly, participants who discontinued early after randomization and do not have any post-baseline assessments available or completed the placebo-controlled period but with missing data will be imputed using the same imputation method as for the main analysis of the primary efficacy endpoint (refer to Section 6.3.1.1).

6.3.2 Safety Endpoints

Partially or completely missing AEs and medication start and stop dates will be imputed as per the algorithm described in Appendix 2. This imputation will only be performed to classify the treatment-emergent status of an AE (refer to Section 13.1) and the concomitant status of a medication (refer to Section 10). The imputed AE and medication dates will not be used for the derivation of any other variables (e.g., AE start study day, AE duration, medication start study day, etc.) and will not be presented in the participant data listing.

6.4 Interim Analysis

An unblinded interim analysis (IA), corresponding to the Main Analysis of the study (refer to Section 1), will be performed after the following 2 conditions are met:

1) All participants complete the placebo-controlled period Week 16 visit or discontinue early from the study, whichever occurs first.

2) All data for the placebo-controlled period are captured as follows:

    a. Through the placebo-controlled Week 16 visit for participants who complete the placebo-controlled period and entered the LTE and through the ET visit for participants who discontinue early from the study during the placebo-controlled period (before placebo-controlled Week 16 visit)

b. Through the Follow-up visit at Week 20 for participants who complete the placebo-controlled period but do not enter into the LTE period (e.g. participant declined participation in the LTE period or discontinued from study due to an interruption of study treatment > 14 days between the placebo-controlled and LTE periods), provided that the Follow-up visit is performed prior to or on the data cutoff date.

The data cutoff date for the Main Analysis of the study is defined as the date of the Week 16 visit of the last participant completing the placebo-controlled period i.e., scheduled around 13-Sep-2023. Once the data has been cleaned and locked, the study will then be unblinded and analyses will be performed on the unblinded data. This Main Analysis will be the final analysis for the placebo-controlled period of the study. All efficacy analyses issued for the Main Analysis will not be re-issued at the time of the final analysis of the study after completion of the LTE and OLE periods. More details can be found in section 6.9.

6.5 Data Monitoring Committee

As part of its role, the Data Monitoring Committee (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. Refer to the DMC Charter for more details.

After approximately 40-50 participants in this study have reached 4 weeks of study product treatment, the Data Monitoring Committee 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. Refer to the DMC Charter for more details.

6.6 Multicenter Studies

Participants from all study centers will be combined for the summaries and analyses.

6.7 Adjustment for Fixed Effect and Covariate

The randomization stratification factor of prior treatment with biologics for psoriasis (yes/no) will be included as a fixed effect in the different statistical models/tests and the appropriate baseline value will be included as a covariate in the statistical models for the analyses of the continuous secondary and exploratory efficacy endpoints (refer to Sections 12.2.2 and 12.3.2).

6.8 Statistical Tests

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified. Confidence intervals (CIs) will be two-sided with 95% coverage.

6.9 Multiple Comparisons/Multiplicity

For the Main Analysis (refer to Section 6.4), 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 Week16 of the placebo-controlled period (refer to Section 12.1.1). The p-values will be nominal for the secondary and exploratory efficacy endpoints of the placebo-controlled period (refer to Sections 12.2.1 and 12.3.1). To account for the multiple comparisons of the multiple active treatment groups against the placebo treatment group, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group, and ending with the lowest dose group (i.e., VTX958 300 mg BID**,** VTX958 225 mg BID, VTX958 300 mg QD, and VTX958 50 mg BID). This procedure is further explained in Section 12.1.2.

As for the Final Analysis, only descriptive statistics will be provided for this analysis. No p-values will be presented for any of the 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 multiplicity between the Main Analysis and Final Analysis.

6.10 Examination of Subgroups

To explore whether the treatment effects are consistent across different subgroups, subgroup analyses will be performed for the primary efficacy endpoint for the following subgroups:

- Participants who received prior treatment with biologics (Yes/No) as per IWRS (stratification factor); Among participants receiving Prior biologics, target IL-12/-23/-23 (Yes/No)
- Participants who received prior treatment with biologics (Yes/No) as per data collected on the eCRF. This subgroup analyses will only be performed if at least 10% of the participants were mis-stratified at the time of randomization (e.g., participant was randomized under the 'Yes' stratum, but they actually did not receive any prior treatment with biologics and vice-versa).
- Sex at birth (male/female)
- Race (White/non-White)
- Age at informed consent (< median/≥ median)

- BMI (< median/≥ median)
- Duration of disease, in years, at informed consent (< median/≥ median), calculated as the date of signed informed consent minus the date of diagnosis plus 1, and divided by 365.25 days.
- PASI score at baseline (< median/≥ median)
- sPGA at baseline (moderate/severe)

For any subgroup with less than 10% of participants in a treatment group, only descriptive statistics will be provided.

7 STUDY PARTICIPANTS

7.1 Disposition of Participants

All participants who provided informed consent will be accounted for in this study. The total number of participants screened and rescreened will be presented. The total number and percentage of screen failure participants will be presented based on total number of screened participants, except for those who were rescreened and did not fail the second screening. The total number and percentage of screen failure participants by reason for screen failure will also be provided based on total number of screen failure participants.

For the placebo-controlled period, the number of participants randomized will be presented for each treatment and overall. For randomized participants, the number and percentage of participants included in each analysis set (refer to Section 4) and who completed the placebo-controlled period or discontinued early during the placebo-controlled period will be presented for each treatment and overall. For participants who completed the placebo-controlled period, the number and percentages of participants who declined to participate in the LTE period, had study product interruption > 14 days, and received at least one dose of study product during the LTE period will be provided. For participants who discontinued early during the placebo-controlled period, the number and percentage of participants by reason for discontinuation will be provided by treatment group and overall.

For the LTE period, the number and percentage of participants with and without an interruption of study product between the placebo-controlled and LTE periods will be provided by treatment group, as defined in Section 3.3.2, and overall based on the LTE Safety Set. Descriptive statistics will be provided for the duration of study drug interruption between the placebo-controlled and LTE periods, where duration of study treatment interruption will be calculated as the date of first dose of study product during the LTE period minus the date of last dose of study product during

the placebo-controlled period. LTE period completion status, discontinuation from study during the LTE period, and reason for study discontinuation for the LTE period will be presented. For participants who completed the LTE period, the number and percentage of participants who declined to participate in the OLE period, had study product interruption > 28 days, and received at least one dose of study product during the OLE period will be provided by treatment group , as defined in Section 3.3.2, and overall.

For the OLE period, the number and percentage of participants with study product interruption between the LTE and OLE periods will be presented by treatment group as defined in Section 3.3.3 based on the OLE Safety Set. Descriptive statistics will be provided for the duration of study product interruption between the LTE and OLE periods, where duration of study treatment interruption will be calculated as the date of first dose of study product during the OLE period minus the date of last dose of study product during the LTE period. Completion status of study period and reason for study discontinuation will be presented.

Completion status of study across all study periods and reason for study discontinuation will be presented for each treatment and overall based on the FAS.

Duration (in days) in the placebo-controlled, LTE, and OLE periods, and across all periods of the study will be summarized by treatment group as defined in Section 3.3 and overall using descriptive statistics, and will be calculated as follows:

Duration in placebo-controlled period (FAS) =
Date of completion/discontinuation from the placebo-controlled period – Date of first dose of study product in placebo-controlled period +1

Duration in LTE period (LTE Safety Set) =
Date of completion/discontinuation from the LTE period – Date of first dose of study product in the LTE period +1

Duration in OLE period (OLE Safety Set) =
Date of study completion/discontinuation from the OLE period – Date of first dose of study product in the OLE period +1

Duration in study across all periods (FAS) =
Date of study completion/discontinuation from study – Date of first dose of study product in the placebo-controlled period +1

For the placebo-controlled and LTE periods, date of completion of a study period is either the Week 16 visit (participants without study product interruption between two study periods), or the date of first dose of study treatment during the next study period minus 1 day (participants with study product interruption between two study periods).

A listing of participant disposition will be provided. Information on the initial screening for participants who were rescreened, including the rescreened participants identifier, will be presented under the first screening participant identifier.

A listing of participant randomization information and a listing of participants for each of the analysis sets will also be provided, including reason(s) for exclusion from the analysis set, if applicable.

7.2 Protocol Deviations

Protocol deviations (PDs) will be attributed to a study period as follows:

Placebo-Controlled Period

- For participants without an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the PD ≤ First dose of study product of the LTE period.

- For participants with an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the PD < First dose of study product of the LTE period.

- For participants who did not enter in the LTE period (either due to discontinuation of study before entering the LTE period or because the participant declined participation to the LTE period):

  All PDs for those participants will be attributed to placebo-controlled period.

- Protocol deviations occurring from the signing of the ICF to the day before first dose of study product of the placebo-controlled period will be attributed to this period.

LTE Period

- For participants without an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the PD ≤ First dose of study product of the OLE period.

If participant had an interruption between placebo-controlled period and LTE period, then:

First dose of study product of the LTE period ≤ Start Date of the PD ≤ First dose of study product of the OLE period.

- For participants with an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the PD < First dose of study product of the OLE period.

  If participant had an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period ≤ Start Date of the PD < First dose of study product of the OLE period.

- For participants who entered in the LTE period, but not in the OLE period (either due to discontinuation of study before entering the OLE period or because the participant declined participation to the OLE period):

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the PD

  If participant had an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period ≤ Start Date of the PD

OLE Period

- For participants without an interruption between LTE and OLE periods:

  First dose of study product of the OLE period < Start Date of the PD.

- For participants with an interruption between LTE and OLE periods:

  First dose of study product of the OLE period ≤ Start Date of the PD.

All protocol deviations will be reported based on Ventyx classification. The protocol deviations will be classified as Important and Non-Important in Clinical Trial Management System (CTMS). A blinded data review will be conducted before each database lock (refer Section 6.4) by the Medical Monitor and Sponsor to finalize the classification. During the review, the important protocol deviation during the placebo-controlled period will also be further classified as major PD if the PD is expected to have an impact on datasets, study results, efficacy endpoints, and populations that leads to the exclusion of the participants from the Per-Protocol Set.

Major protocol deviations may include, but are not limited to:

- Violation of eligibility criteria.
- Receiving incorrect study product
- Receiving a prohibited therapy or procedure during the study
- Compliance with study treatment < 80%

The classification of important protocol deviation as major PD will also be finalized in a blinded fashion before each database lock. Refer to the protocol deviation management plan (PDMP) for more details.

The number of events and the number and percentage of participants with at least one important protocol deviation will be summarized by protocol deviation category and sub-category by treatment group as defined in Section 3.3 and overall based on the appropriate safety set for each study period separately. An important protocol deviation occurring at the site-level will be counted once for each site participant that was ongoing in the study at the time the site-level protocol deviation occurred. Major protocol deviations for the placebo-controlled period will be summarized similarly.

A listing of all protocol deviations, including non-important and minor, will also be provided. Important and major deviations will be flagged in this listing. A listing of all protocol deviations associated with COVID-19 will also be provided.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized with descriptive statistics by treatment group as defined in Section 3.3 and overall, for each study period separately. The list of demographic and other baseline characteristics to be summarized include:

- Age (years) at informed consent, as collected on the eCRF (continuous and categorical)
- Sex at birth

- Ethnicity
- Country (from IWRS)
- Race (Participants who reported more than one race will be summarized under the 'Multiple' race category, but all races selected will be displayed in the listing.)
- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (BMI; kg/m^2)
- Duration of disease, in years, at informed consent (continuous and categorical [< median/≥ median]), as defined in Section 6.10
- Baseline PASI score
- Baseline sPGA score (continuous and categorical [moderate/severe])
- Baseline BSA
- Baseline DLQI
- Baseline Pruritus NRS
- Baseline PSSD total score
- Prior treatment with biologics for psoriasis (Yes/No) as per IWRS (stratification factor)
- Prior treatment with biologics for psoriasis (Yes/No) as per eCRF
- Prior treatment with IL-12/23 or IL-23 inhibitors (Yes/No) as per IWRS

Demographic and other baseline characteristics will be summarized using the Safety Set for the placebo-controlled period, the LTE Safety Set for the LTE period, and the OLE Safety Set for the OLE period.

Listings of all demographics and other baseline characteristics will be provided.

9 SURGICAL AND MEDICAL HISTORY

Surgical and medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.1.

The frequency and percentage of participants reporting at least one surgical and/or medical event will be summarized by system organ class (SOC) and preferred term (PT) by treatment group as defined in Section 3.3 and overall based on the Safety Set for the placebo-controlled period. A participant who experienced the same event multiple times within the same SOC will be counted only once for that SOC. Similarly, if a participants experienced multiple events within the same PT, the participants will be counted only once for that PT. Surgical and medical history events will be sorted alphabetically by SOC and within each SOC, the PT will be presented by decreasing order of overall frequencies.

A listing of all surgical and medical history events will be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), GLOBAL B3, Sep 1, 2022.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose.

Concomitant medications are defined as any medication taken on or after the first dose of study treatment, including those who started prior to the date of the first dose of study treatment and continued past that date (refer to Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications).

Concomitant medications will be attributed to a study period as follows:

Placebo-Controlled Period

- For participants without an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the concomitant medication ≤ First dose of study product of the LTE period; including those started before the date of first dose of study treatment during the placebo-controlled period and continued past that date.

- For participants with an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the concomitant medication < First dose of study product of the LTE period; including those started before the date of first dose of study treatment during the placebo-controlled period and continued past that date.

- For participants who did not enter the LTE period (either due to discontinuation of study before entering the LTE period or because the participant declined participation to the LTE period):

  All concomitant medications of those participant will be attributed to placebo-controlled period.

LTE Period

- For participants without an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

First dose of study product of the LTE period < Start Date of the concomitant medication ≤ First dose of study product of the OLE period; including those started on or before the date of first dose of study treatment during the LTE period and continued past that date.

If participant had an interruption between placebo-controlled period and LTE period, then:

First dose of study product of the LTE period ≤ Start Date of the concomitant medication ≤ First dose of study product of the OLE period; including those started before the date of first dose of study treatment during the LTE period and continued past that date.

- For participants with an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the concomitant medication < First dose of study product of the OLE period; including those started on or before the date of first dose of study treatment during the LTE period and continued past that date.

  If participant had an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period ≤ Start Date of the concomitant medication < First dose of study product of the OLE period; including those started before the date of first dose of study treatment during the LTE period and continued past that date.

- For participants who entered in the LTE period, but not in the OLE period (either due to discontinuation of study before entering the OLE period or because the participant declined participation to the OLE period):

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the concomitant medication; including those started on or before the date of first dose of study treatment during the LTE period and continued past that date.

If participant had an interruption between placebo-controlled period and LTE period, then:

First dose of study product of the LTE period ≤ Start Date of the concomitant medication; including those started before the date of first dose of study treatment during the LTE period and continued past that date.

OLE Period

- For participants without an interruption between LTE and OLE periods:

  First dose of study product of the OLE period < Start Date of the concomitant medication; including those started on or before the date of first dose of study treatment during the OLE period and continued past that date.

- For participants with an interruption between LTE and OLE periods:

  First dose of study product of the OLE period ≤ Start Date of the concomitant medication; including those started before the date of first dose of study treatment during the OLE period and continued past that date.

The frequency and percentage of participants with at least one prior medication will be summarized by anatomical therapeutic chemical (ATC) class level 3 term and preferred drug name by treatment group received during the placebo-controlled period (refer to Section 3.3.1) and overall using the Safety Set. A participant with the same medication taken multiple times within the same preferred drug name will be counted only once for the corresponding preferred drug name. Similarly, if a participant has taken more than one medication within the same ATC class level 3 term, then the participants will be counted only once for that ATC class level 3 term. Medications will be sorted alphabetically by ATC class level 3 term and within each ATC class level 3 term, the preferred drug name will be presented by decreasing order of overall frequencies. Concomitant medications will be summarized using the Safety Set, LTE Safety Set, and OLE Safety Set for the placebo-controlled, LTE, and OLE periods, respectively.

Additionally, a shift table describing changes in the antihypertensive therapy response (Yes/No) of participants from baseline to post-baseline visits will be provided for the placebo-controlled period.

A listing of all prior and concomitant medications will be provided.

11 EXPOSURE AND COMPLIANCE WITH TREATMENT PERIOD

Duration of exposure to study treatment, in days, will be computed as follows for each study period:

(Date of last known dose of study product during a study period
– Date of first dose of study product during a study period) + 1

Compliance with study treatment, in percentage, will be computed as follows for each study period:

$$\frac{\text{Total number of tablets taken during a study period}}{\text{Expected number of tablets to be taken during a study period}} \times 100$$

where the expected number of tablets to be taken during a study period will be calculated using the formula below:

Duration of exposure, in days, during a study period x Number of expected tablets per day during a study period

If the information captured in the eCRF indicates that a bottle was "Not returned" at all, then it will be assumed that all tablets were taken.

Descriptive statistics for the duration of exposure and compliance with study treatment will be presented by treatment group as defined in Section 3.3 based on the Safety Set for placebo-controlled period, LTE Safety Set for the LTE period, and OLE Safety Set for the OLE period. Frequency and percentage of participants in each of the following compliance categories will also be presented: <80%, 80% to 120%, >120%.

Compliance with actual dose for active groups, in percentage, will be computed as follows at each scheduled visit, and each study period:

$$\frac{\sum \text{Strength of tablet x number of tablets taken}}{\text{Expected total doses}} \times 100$$

where the expected total doses will be calculated using the formula below:

Duration of exposure in days x total dose per day during the visit or study period

For the compliance by visit, it will be calculated only when information on the number of tablets dispensed and returned between 2 adjacent visits is available for all related bottles.

Compliance with actual dose for placebo, in percentage will be computed at each scheduled visit using the same formula for the compliance with study treatment.

Compliance with actual dose will be summarized using descriptive statistics based on the Safety Set for placebo-controlled, LTE Safety Set for the LTE period, and OLE Safety Set for the OLE period.

A listing of drug accountability, including bottle number, number of tablets dispensed/re-dispensed, number of tablets returned, whether participant was compliant with the bottle, and reason for non-compliance when applicable will be provided. Study treatment on site, dose interruption, exposure, compliance with study treatment, and compliance with actual dose will also be provided in listings.

12 EFFICACY ANALYSIS

Unless otherwise indicated, all efficacy summaries and analyses will be performed by treatment group and visit, when applicable, based on the FAS (refer to Section 4.1) for the placebo-controlled period, based on the LTE Safety Set for the LTE period, and based on the OLE Safety Set for the OLE period. Listings for all efficacy data will be provided.

12.1 Primary Efficacy Endpoint

12.1.1 Definition of Primary Efficacy Endpoint

The primary endpoint is a responder analysis, where a participant will be classified as responder if the participant achieves PASI-75 i.e., at least 75% improvement from baseline in PASI at Week 16.

The PASI score is a composite score ranging from 0 to 72[11], where higher scores represent worse disease severity, that takes into account the degree of erythema, induration/infiltration, and desquamation 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. The PASI will be evaluated at scheduled visits specified in Table 1, Table 2, and Table 3 of the protocol and its score will be derived programmatically as described below.

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 graded 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 numeric 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

After assessing each of the above-mentioned parts, the PASI score is then obtained by using the following formula:

$$0.1\,(E_h + I_h + D_h)\,A_h + 0.2\,(E_u + I_u + D_u)\,A_u + 0.3\,(E_t + I_t + D_t)\,A_t + 0.4\,(E_l + I_l + D_l)\,A_l$$

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. The PASI score will be set as missing if at least one question value is missing. The derived PASI score will be set with one decimal.

For a participant, achievement of PASI-75 is "Yes", if the participant has an improvement in PASI score equal to or greater than 75% compared to baseline. If the participant has a worsening, no improvement, or an improvement in PASI score below 75% compared to baseline, the achievement of PASI-75 is set to "No".

12.1.2 Hypothesis Testing

Up to four set of hypotheses will be tested in the following pre-defined sequential order:

H_1: H_{10}: $P_{V300\ BID} = P_P$ versus H_{11}: $P_{V300\ BID} \neq P_P$

H_2: H_{20}: $P_{V225\ BID} = P_P$ versus H_{21}: $P_{V225\ BID} \neq P_P$

H_3: H_{30}: $P_{V300\ QD} = P_P$ versus H_{31}: $P_{V300\ QD} \neq P_P$

H_4: H_{40}: $P_{V50\ BID} = P_P$ versus H_{41}: $P_{V50\ BID} \neq P_P$

where, P_V = Proportion of participants achieving PASI-75 at Week 16 in a VTX958 treatment group and P_P = Proportion of participants achieving PASI-75 at Week 16 in Placebo treatment group.

To be more specific, the following hierarchical testing procedure will be followed (refer to Figure 2 for a visual representation):

Step 1: Test the null hypothesis of equal treatment effect of VTX958 300 mg BID vs placebo of the first set of hypotheses (H_1) at a significance level of 0.05.

If this null hypothesis is rejected, conclude that VTX958 300 mg BID treatment effect and placebo treatment effect are not equal and proceed to step 2. Otherwise, accept H_1 null hypothesis and stop further testing.

Step 2: Test the null hypothesis of equal treatment effect of VTX958 225 mg BID vs placebo of the second set of hypotheses (H_2) at a significance level of 0.05.

If this null hypothesis is rejected, conclude that VTX958 225 mg BID treatment effect and placebo treatment effect are not equal and proceed to step 3. Otherwise, accept H_2 null hypothesis and stop further testing.

Step 3: Test the null hypothesis of equal treatment effect of VTX958 300 mg QD vs placebo of the third set of hypotheses (H_3) at a significance level of 0.05.

If this null hypothesis is rejected, conclude that VTX958 300 mg QD treatment effect and placebo treatment effect are not equal and proceed to step 4. Otherwise accept the H_3 null hypothesis and stop further testing.

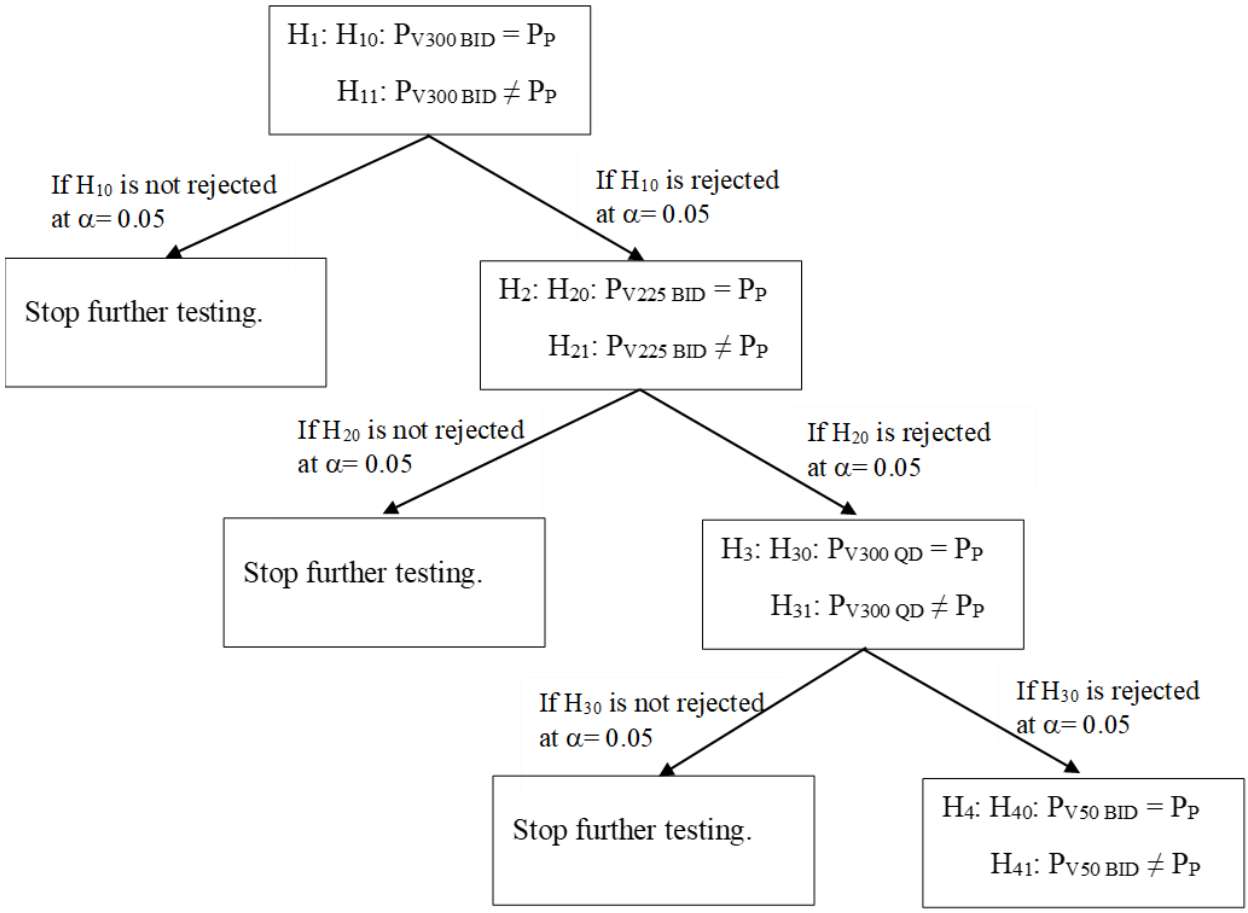
Step 4: Test the null hypothesis of equal treatment effect of VTX958 50 mg BID vs placebo of the fourth and last set of hypotheses (H_4) at a significance level of 0.05.

If this null hypothesis is rejected, conclude that VTX958 50 mg BID treatment effect and placebo treatment effect are not equal. Otherwise accept H_4 null hypothesis.

No adjustment to alpha level will be made to account for multiple testing between treatment groups for the secondary efficacy endpoints of the placebo-controlled period since only nominal p-values

will be reported for these efficacy endpoints. The comparison of all VTX958 doses (4 active arms) combined versus placebo will also be tested as exploratory.

Figure 2: Hierarchical Testing Procedure



Abbreviations: PASI-75 = Achievement of an improvement from baseline of at least 75% in the Psoriasis Area and Severity Index. Pv = Proportion of participants achieving PASI-75 at Week 16 in a VTX958 treatment group. P_P = Proportion of participants achieving PASI-75 at Week 16 in the Placebo treatment group. V50 BID = VTX958 50 mg BID. V225 BID = VTX958 225 mg BID. V300 BID = VTX958 300 mg BID. V300 QD = VTX958 300 mg QD.

12.1.3 Primary Estimand

Estimand	Definition	Attributes			
		Population	**Endpoint**	**Intercurrent Event Handling Strategy**	**Population-Level Summary Measure**
Primary estimand	Efficacy of eachVTX958 dose on PASI-75 at Week 16	Randomized participants who receive at least one dose of study product	Proportion of participants achieving PASI-75 at Week 16	Participants with missing data, regardless of reasons for missingness, will be considered as non-responders	Difference between each VTX958 dose and placebo in the endpoint at Week 16.

12.1.4 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy analysis for PASI-75 will be performed for the FAS. Number and proportion of participants achieving PASI-75 (and associated two-sided 95% Clopper-Pearson exact CIs) will be reported for each treatment group. The Cochran-Mantel-Haenszel (CMH) test will be used, stratified by the prior treatment with biologics (Yes/No). Reported randomization stratum will be used in the model. The proportion differences (with 95% CI), odds ratios (with 95% CI), and p-values from the CMH test will be reported.

Participants with missing data, regardless of reasons for missingness, will be imputed by Non-Responder Imputation (section 6.3.1.1).

12.1.5 Sensitivity Analysis of Primary Efficacy Endpoint

The following sensitivity analyses to handle missing data and intercurrent events will be performed:

1. Multiple Imputation (MI): Refer to Section 6.3.1.2.

2. NRI with Last Observation Carry Forward (LOCF): Same as for the primary analysis, except for participants who discontinued early from study treatment during the placebo-controlled period due to a reason other than lack of efficacy and AE related to plaque psoriasis (e.g., worsening of plaque psoriasis). For these participants, a different approach (LOCF) will be used as defined in Section 6.3.1.4.

3. NRI with Prohibited Medication (PM): Same as for the primary analysis, except for participants with any used of prohibited medications potentially having an impact on the

assessment of the primary efficacy endpoint. That is, should a participant started to use such prohibited medications during the placebo-controlled period, all achievement of PASI-75 status collected on and after the start of the prohibited medication will be set to 'No'. Such use of prohibited medications will be documented in the protocol deviation report (Section 7.2).

4. Observed Cases (OC): The primary analysis will be repeated based on observed data without imputation.

12.1.6 Supportive Analysis of Primary Efficacy Endpoint

The following supportive analyses will be performed:

- The primary analysis will be repeated (refer to Section 12.1.4) using the PP Set.
- The primary analysis will be repeated for each subgroup specified in Section 6.10 using the FAS. A Chi-Square test will be performed instead of a CMH test for subgroup analyses related to prior treatment with biologics (Yes/No).

12.2 Secondary Efficacy Analyses

12.2.1 Definition of Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of participants achieving a sPGA score of 0 (clear) or 1 (almost clear) at Week 16
- Change and percentage 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

Proportion of Participants Achieving an sPGA score of 0 (clear) or 1 (almost clear) at Week 16

The sPGA[12] of disease severity will be assessed at the visits specified in Table 1, Table 2, and Table 3 of the protocol. The sPGA is a 5-point rating scale of global assessment of the current disease severity. A detailed description of each sPGA score is provided in Table 7.

Table 7: 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
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

At each post-baseline visit, the achievement of a sPGA score of 0 or 1 (Yes/ No) will be determined. The visit of interest will be Week 16.

Change and Percent Change from Baseline in PASI Score at Week 16

PASI will be assessed at the visits specified in Table 1, Table 2, and Table 3 of the protocol. Change and percent change from baseline in PASI score at each post-baseline visit will be computed based on the definition provided in Section 5.2. The visit of interest will be Week 16.

Proportion of Participants Achieving PASI-90 at Week 16

At each post-baseline visit, the participant's PASI-90 status (Yes/No) will be determined in a similar way as achievement of PASI-75 (refer to Section 12.1.1). To be more specific, for any post-baseline visit, achievement of PASI-90 status will be Yes, if the participant has an improvement in PASI score equal to or greater than to 90% comparing to the baseline score. If the participant has a worsening, no improvement or an improvement in PASI score below 90% compared to baseline, the achievement of PASI-90 response status will be "No". The visit of interest will be Week 16.

Proportion of Participants Achieving PASI-100 at Week 16

At each post-baseline visit, the participant's PASI-100 status (Yes/No) will be determined in a similar way as achievement of PASI-75 (refer to Section 12.1.1). To be more specific, for any post-baseline visit, achievement of PASI-100 status will be Yes, if the participant has 100% improvement in PASI score compared to the baseline score. If the participant has a worsening, no

improvement or an improvement in PASI score below 100% compared to baseline, the achievement of PASI-100 will be set to "No". The visit of interest will be Week 16.

Change from Baseline in DLQI at Week 16

The DLQI will be assessed at the visits specified in Table 1, Table 2, and Table 3 of the protocol. The DLQI is a simple 10-question validated questionnaire[13] including questions concerning symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. All questions relate "to the last week" and each question is rated from 0 (Not at all) to 3 (Very much). The DLQI questions are provided in Appendix 3

The DLQI total score is defined as the sum of the 10 item scales, ranging from 0 to 30. If missing answers, the following rules will be followed:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
4. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If it is answered 'no', but the second half is left incomplete, the score will remain 0.

The DLQI total score will be derived programmatically. Change in DLQI total score at each post-baseline visit will be computed as defined in Section 5.2. The visit of interest will be the Week 16 visit.

Change from Baseline in BSA at Weeks 16

The overall percentage of BSA affected by plaque psoriasis will be evaluated from 0% to 100% at the visits specified in Table 1, Table 2, and Table 3 of the protocol. The palmar surface of one hand (using the participant's hand and including the fingers) represents 1% of his or her total BSA[14].

Change from baseline in BSA score at each post-baseline visit will be computed as defined in Section 5.2. The visit of interest will be Week 16.

12.2.2 Primary Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints involving proportions will be summarized and analyzed in the same manner as the primary efficacy endpoint (refer to Section 12.1.4). Missing data will be handled using NRI method (refer Section 6.3.1.1).

Each continuous secondary efficacy endpoint will be summarized using descriptive statistics by treatment group based on observed data and analyzed using a MMRM. This model will include the stratification factor of prior treatments with biologics (Yes/No), treatment, visit, and treatment-by-visit interaction as fixed effects, baseline score as a covariate, and participants as a random effect. An unstructured covariance structure will be used to model the within-participant error and the Kenward-Roger approximation to estimate the degrees of freedom will be used to test the fixed effects derived from the MMRM model. If this analysis fails to converge, the following covariance structure will be tested and the covariance structure converging to the best fit will be used [as determined by the Akaike's information criteria corrected (AICC)]: heterogenous Toeplitz (TOEPH), heterogenous first-order autoregressive (ARH[1]), and first-order ante dependence (ANTE[1]).

The least square (LS) mean estimate and associated standard error (SE) and two-sided 95% CI will be provided for each treatment group at each visit. The difference in LS means between each VTX958 dose and placebo along with their associated SE, two-sided 95% CI, and p-value will be reported for each visit. The contrast of interest will be Week 16. The comparison of all VTX958 doses (4 active arms) combined versus placebo will also be tested as exploratory.

12.2.3 Sensitivity Analysis of Secondary Efficacy Endpoints

The following sensitivity analyses will be performed on the dichotomous secondary endpoints.

PASI-90 and PASI-100

1) Multiple Imputation (MI) approach (refer to Section 6.3.1.2 for details).
2) Observed Cases (OC) approach (based on observed data without imputation)

sPGA

1) Observed Cases (OC) approach (based on observed data without imputation)

12.2.4 Supportive Analysis of Secondary Efficacy Endpoints

The proportion of participants achieving a sPGA score of 0 or 1 without presence of scaling (Scaling = 'No') at Week 16 will be summarized as described in Section 12.2.2. No supportive analyses will be performed for the other secondary efficacy endpoints.

12.3 Exploratory Efficacy Analyses

12.3.1 Definition of Exploratory Efficacy Endpoints

Placebo-Controlled Period:

The exploratory efficacy endpoints in the placebo-controlled period are:

- 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 percentage 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 achieving an sPGA score of 0 (clear) at Weeks 1, 2, 4, 8, 12 and 16
- 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

LTE Period:

The exploratory efficacy endpoints in the LTE period are:

- 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 and percent change from baseline in PASI 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 achieving an sPGA score of 0 (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

OLE Period:

The exploratory efficacy endpoints in the OLE period are:

- 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 and percent change from baseline in PASI 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 achieving an sPGA score of 0 (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

For following definitions, calculation of post-baseline visits definition differs for each study period and are defined in Section 5.2.

Proportion of Participants Achieving PASI-75

At each post-baseline visit, the participant's PASI-75 score status will be determined based on the procedure described in Section 12.1.1.

Proportion of Participants Achieving PASI-90

At each post-baseline visit, the participant's PASI-90 score status will be determined as described in Section 12.2.1.

Proportion of Participants Achieving PASI-100

At each post-baseline visit, the participant's PASI-100 score status will be determined as described in Section 12.2.1.

Change and Percentage Change from Baseline in PASI

Change and percent change from baseline in PASI score at each post-baseline visit will be computed based on the definition provided in Section 5.2.

Change from Baseline in sPGA

The change from baseline in sPGA score at each post-baseline visit will be computed as defined in Section 5.2. The description of sPGA scores is displayed in Table 7.

Proportion of Participants Achieving an sPGA score of 0 (clear) or 1 (almost clear)

At each post-baseline visit, the achievement of a sPGA score of 0 or 1 (Yes/ No) is defined as having a sPGA score of 0 or 1.

Proportion of Participants with at Least a 2-grade Decrease from Baseline in sPGA

At each post-baseline visit, the achievement of a decrease from baseline in sPGA score ≤ 2 will be determined. Change from baseline sPGA score will be computed as defined in Section 5.2.

Change from Baseline in BSA Affected

The change from baseline in % of BSA affected by plaque psoriasis at each post-baseline visit will be computed as defined in Section 5.2.

Change from Baseline in pruritus NRS

The intensity of pruritus will be recorded at the visits specified in Table 1, Table 2, and Table 3 of the protocol 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 change from baseline in pruritus NRS at each post-baseline visit will be computed as defined in Section 5.2.

Proportion of Participants with at Least a 4-point Decrease from Baseline in Pruritus NRS among Participants with a Baseline Pruritus NRS of at Least 4

For participants with a baseline pruritus NRS score of 4 or greater, the achievement of at least a 4-point decrease from baseline score (Yes or No) will be determined. Change from baseline in pruritus NRS will be calculated as defined in Section 5.2.

Change from Baseline in DLQI

The change from baseline in DLQI total score at each post-baseline visit will be computed as defined in Section 5.2. A detailed description of the DLQI measurement is given in Section 12.2.1.

Change from Baseline in PSSD

The PSSD will be evaluated at the visits specified in Table 1, Table 2, and Table 3 of the protocol. The PSSD is an 11-item validated questionnaire that assesses 5 symptoms (itch, pain, stinging, burning, and skin tightness) and 6 patient-observable signs (dryness, cracking, scaling, shedding/flaking, redness, and bleeding) of moderate to severe plaque psoriasis.[16,17] 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 questions are provided in Appendix 4. Questions 1, 4, 9, 10 and 11 in the questionnaire are related to symptom score and questions 2, 3, 5, 6, 7 and 8 are related to sign score. The symptom and sign PSSD scores are a composite score calculated based on the scores for each related question.

A symptom score will be derived by averaging the 5 symptom-related questions and multiplying by 10. If 3 or more questions are missing, the symptom score will be considered as missing.

The sign score will be derived by averaging the 6 sign-related questions and multiplying by 10. If more than 3 questions are missing, the sign score will be considered as missing.

Both scores range from 1-100, where 0 represents the least severe symptom/sign and 100 the most severe symptom/sign.

A total PSSD score with a 0-100 range will be derived from taking the average of the symptom and sign scores. If one of the two scores is missing, then the total PSSD score will be considered as missing.

The symptom, sign and total scores will be derived programmatically with one decimal. The change from baseline in symptom, sign, and total PSSD scores at each post-baseline visit will be computed as defined in Section 5.2.

12.3.2 Analysis of Exploratory Efficacy Endpoints

For the placebo-controlled period, exploratory efficacy endpoints will be summarized and analyzed in the same manner as the secondary efficacy endpoints (refer to Section 12.2.2).

For the LTE and OLE periods, exploratory efficacy endpoints will be summarized in the same manner as the secondary efficacy endpoints. For all the dichotomous exploratory endpoints, including PASI-75/90/100 and sPGA-0 or 1 and others in the LTE and OLE periods, response rate will be presented based on the observed data and using NRI approach. No inferential statistical testing will be performed for the exploratory efficacy endpoints of the LTE and OLE periods.

12.3.3 Sensitivity Analyses of Exploratory Efficacy Endpoints

No sensitivity analyses will be performed for the exploratory efficacy endpoints.

12.3.4 Supportive Analyses of Exploratory Efficacy Endpoints

For the placebo-controlled period, the exploratory endpoint PASI-75 at Weeks 1, 2, 4, 8 and 12 will be summarized in the same manner as the sensitivity analysis and the supportive analysis described in Sections 12.1.5 and 12.1.6, respectively. The exploratory endpoints PASI-90, PASI-100 and sPGA (0/1) at Weeks 1, 2, 4, 8 and 12 will be summarized in the same manner as the

sensitivity analysis described in Section 12.2.3. In a supportive analysis of sPGA, the proportion of participants achieving an sPGA score of 0 (clear) at Weeks 1, 2, 4, 8, 12 and 16 will be summarized in the same manner as the sensitivity analysis described in Section 12.2.2. No other supportive analyses will be performed for other placebo-controlled period related-exploratory efficacy endpoints.

For the LTE and OLE periods related-exploratory efficacy endpoints, analyses described in Section 12.3.2 will be performed excluding participants who experienced a study treatment interruption between study periods. Note that these supportive analyses will be performed only if more than 10% of participants enrolled in the safety set across all treatment groups had a study treatment interruption.

In a supportive analysis of PASI-75 and sPGA (0/1) to evaluate up to 32 weeks continuous treatment of same dose regimen of VTX-958 in placebo-controlled and LTE periods, participants who did not receive VTX958 300 mg BID during the placebo-controlled period and switched to 300 mg BID in the LTE period will be considered as non-responders. Analysis will be performed on FAS. Participants who did not enter in the LTE period will be considered as non-responders.

13 SAFETY ANALYSIS

Safety data will be summarized for each study period separately. For the placebo-controlled period, summaries will be based on the Safety Set while summaries for the LTE and OLE periods will be based on the LTE Safety Set and OLE Safety Set, respectively. No statistical inferences will be performed on the safety endpoints.

13.1 Adverse Events

All AEs will be coded according to the MedDRA Version 25.1.

A treatment-emergent adverse event (TEAE) is defined as 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, resolved, and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated). See Appendix 2 for handling of completely or partially missing AE start and stop dates. In cases where it is not possible to define an AE as treatment-emergent or not, the AE will be classified as treatment-emergent, except for AEs associated with a pre-dose assessment which will not be classified as treatment-emergent.

AEs will be attributed to a study period as follows:

Placebo-Controlled Period

- For participants without an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the AE ≤ First dose of study product of the LTE period.

- For participants with an interruption between placebo-controlled and LTE periods:

  First dose of study product of the placebo-controlled period ≤ Start Date of the AE < First dose of study product of the LTE period.

- For participants who did not enter in the LTE period (either due to discontinuation of study before entering the LTE period or because the participant declined participation to the LTE period):

  All AEs for those participants will be attributed to placebo-controlled period.

- Adverse events occurring from the signing of the ICF to the day before first dose of study product of the placebo-controlled period will be attributed to this period. Also, if the time of a laboratory assessment associated with an adverse event on Day 1 is before the time of first dose of study product, then the adverse event will be considered as non-TEAE.

LTE Period

- For participants without an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the AE ≤ First dose of study product of the OLE period.

  If participant had an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period ≤ Start Date of the AE ≤ First dose of study product of the OLE period.

- For participants with an interruption between LTE and OLE periods:

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the AE < First dose of study product of the OLE period.

If participant had an interruption between placebo-controlled period and LTE period, then:

First dose of study product of the LTE period ≤ Start Date of the AE < First dose of study product of the OLE period.

- For participants who entered in the LTE period, but not in the OLE period (either due to discontinuation of study before entering the OLE period or because the participant declined participation to the OLE period):

  If participant did not have an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period < Start Date of the AE

  If participant had an interruption between placebo-controlled period and LTE period, then:

  First dose of study product of the LTE period ≤ Start Date of the AE

OLE Period

- For participants without an interruption between LTE and OLE periods:

  First dose of study product of the OLE period < Start Date of the AE.

- For participants with an interruption between LTE and OLE periods:

  First dose of study product of the OLE period ≤ Start Date of the AE.

An overall summary table of AEs will be provided for each study period separately. The number of events and the frequency and percentage of participants who experienced at least one AE, TEAE, TEAE by greatest reported relationship with study treatment (related or not related), TEAE by maximum reported Controlled Terminology Criteria for Adverse Event (CTCAE) toxicity grade (version 5.0), AE with an outcome of death, non-serious TEAE, serious TEAE, TEAE leading to study treatment interruption and TEAE leading to study treatment discontinuation, and TEAE leading to study discontinuation will be presented by treatment group for each study period separately. TEAE with an unknown relationship with study treatment will be considered as related and TEAE with an unknown severity will be considered as severe.

Frequency and percentage of participants who experience at least one TEAE will be summarized by treatment group, SOC, and PT for each study period separately. A participant experiencing multiple TEAEs within the same SOC will be counted only once for that SOC. Similarly, a participant experiencing multiple TEAEs within the same PT will be counted only once for that

PT. TEAEs will be sorted alphabetically by SOC and within each SOC, PTs will be presented by decreasing order of total frequency. Participants who experience at least one non-serious TEAE, treatment-emergent SAE, TEAE leading to study treatment interruption, and TEAE leading to study treatment discontinuation will be summarized similarly. TEAEs will also be summarized by treatment group and PT only for each study period separately.

Frequency and percentage of participants who experience at least one TEAE will also be summarized by treatment group, SOC, PT, and greatest relationship for each study period separately. For these summaries, each participant will be counted only once within a SOC or a PT by using the TEAE with the greatest reported relationship.

Similarly, frequency and percentage of participants who experience at least one TEAE will be summarized by treatment group, SOC, PT, and maximum reported CTCAE toxicity grade for each study period separately. For these summaries, each participant will be counted only once within a SOC or a PT by using the TEAE with the maximum reported CTCAE toxicity grade.

Frequency and percentage of participants who experience at least one treatment-emergent AE of special interest (AESIs) will be summarized by SOC and PT for each study period separately (similar to the summary of participants who experience at least one TEAE). The search list for AESIs will be provided by the sponsor prior to the interim analysis and database locks.

Listings of all AEs, all AESIs, all AEs with an outcome of death, all serious AEs, all TEAEs leading to study treatment interruption, all TEAEs leading to study treatment discontinuation, and all TEAEs leading to study withdrawal will be provided.

13.2 Clinical Laboratory

Laboratory data will be presented as per the international system of units (SI). If numerical results include symbol "<", ">", "≤" or "≥" (ex.: <125), then the numerical portion will be used for the analysis.

For each biochemistry (incl. fasting lipids), hematology (incl. coagulation), quantitative urinalysis, and serum immunoglobulin laboratory test (refer to Table 8), the observed value and change from baseline will be summarized using descriptive statistics by visit (refer to Table 1, Table 2, and Table 3 of the protocol) and treatment group for each study period separately. For qualitative urinalysis tests, number and percentage of participants in each result category will be provided by visit and treatment group for each study period separately.

Shift tables from baseline to each post-baseline visit, and overall using the maximum post-baseline value describing shifts to out-of-normal range (Low: below the lower bound of the parameter normal range or High: above the upper bound of the parameter normal range), according to the

central laboratory, will be provided for each biochemistry and hematology laboratory test by treatment group for each study period separately. Only participants with a baseline result and a result at the specified post-baseline visit will be considered for each laboratory test.

The grade shift tables based on CTCAE (version 5.0) from baseline to overall using the maximum post-baseline value will be provided for the following events for each study period separately:

- Alanine aminotransferase increased,
- Alkaline phosphatase increased,
- Anemia,
- Aspartate aminotransferase increased,
- Blood bilirubin increased,
- Cholesterol high,
- CPK increased,
- Creatinine increased,
- GGT increased,
- Hypertriglyceridemia,
- INR increased,
- Lymphocyte count decreased,
- Neutrophil count decreased,
- Platelet count decreased,
- White blood cell decreased.

The table will present Grades 0 to 4 and total. The laboratory value will be graded 0 if it does not belong to Grade 1 to 4 as defined in the table in Appendix 6. The quantitative thresholds for Grade 5 of all events and Grade 4 of Anemia and INR increased are not available.

Frequency of maximum hepatic enzyme elevations (i.e., using the maximum post-baseline value) will be provided for the following events for each study period separately:

- 1×, 2×, 3×, 5×, 8×, 10×, 20× ULN elevation in ALT
- 1×, 2×, 3×, 5×, 8×, 10×, 20× ULN elevation in AST

- 3×, 5×, 10×, 20× ULN elevation in either ALT or AST
- 1×, 1.5×, 2×, 3× ULN elevation in total bilirubin
- 1×, 1.5×, 2×, 3×, 5×, 8× ULN elevation in ALP
- 1×, 2×, 3×, 5×, 8× ULN elevation in GGT
- 3× ULN elevation in either ALT or AST and > 1.5× ULN elevation in total bilirubin (on the same day)
- 3× ULN elevation in either ALT or AST and > 2× ULN elevation in total bilirubin (on the same day)
- 3× ULN elevation in either ALT or AST and > 1.5× ULN elevation in INR (on the same day)
- 3× ULN elevation in either ALT or AST and > 1.5× ULN elevation in ALP (on the same day)

For events with multiple categories (ex.: 1×, 2×, 3×, 5×, 8×, 10×, 20× ULN), participant will be counted only once in the highest one.

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots for the following laboratory assessments (using values after the first administration of study treatment) will be provided for each study period separately:

- Maximum aspartate aminotransferase (AST) versus same-day total bilirubin
- Maximum alanine aminotransferase (ALT) versus same-day total bilirubin
- Maximum gamma-glutamyl transferase (GGT) versus same-day total bilirubin
- Maximum alkaline phosphatase (ALP) versus same-day total bilirubin

In addition, eDISH plots adjusted for elevated baseline will also be provided. If a participant had an elevated value (ALT, AST, GGT, ALP, Bilirubin) at baseline > ULN, the elevated baseline value of the corresponding parameter will be replacing the original ULN when calculating the "value/ULN". Otherwise, the original lab ULN will be used when calculating "value/ULN".

Separate listings of data for biochemistry and hematology laboratory tests will be provided for each laboratory test for which a participant had at least one abnormal result.

In addition, separate listings of all data for biochemistry, hematology, urinalysis, serum immunoglobulin, pregnancy test, FSH, β-hCG, serology, and tuberculosis laboratory tests will also be provided.

Table 8: Clinical Laboratory Tests

Laboratory Test	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.

13.3 Vital Signs

The observed value and change from baseline for each vital sign (systolic blood pressure [SBP; mmHg], diastolic blood pressure [DBP; mmHg], pulse [beats/min], respiratory rate [RR;

breaths/min], body temperature [°C], weight [kg], height [cm], and BMI [kg/m^2]) will be summarized using descriptive statistics by treatment group and visit (refer to Table 1, Table 2, and Table 3 of the protocol) for each study period separately.

Shift tables from baseline to each post-baseline visit, and overall using the worst post-baseline value describing shifts to abnormality (abnormal but not clinically significant or abnormal and clinically significant), will be provided for each vital sign by treatment group for each study period separately. Only participants with a baseline result and a result at the specified post-baseline visit will be considered for each vital sign.

A listing of all vital sign assessments will be provided.

13.4 Electrocardiogram

ECG intervals/tests will be summarized using descriptive statistics by treatment group and visit (refer to Table 1, Table 2, and Table 3 from the protocol) for each study period separately. Change from baseline values in each ECG interval/test to each post-baseline scheduled visit will also be presented by treatment group for each study period separately.

Shift tables from baseline to each post-baseline visit and overall using the worst post-baseline value, ECG overall interpretation (as per Investigator's judgment), describing shifts to abnormality (normal/abnormal NCS/abnormal CS at baseline versus normal/abnormal NCS/abnormal CS at post-baseline visit), will be provided by treatment group for each study period separately. Only patients with a baseline result and a result at the specified post-baseline visit will be considered.

A listing of all ECG assessments will be provided.

13.5 Physical Examination

Information for all physical examinations will be included in the source documents. Per protocol, any significant change in physical examination findings will be reported as an AE in the source document and eCRF.

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15 APPENDICES

Appendix 1

Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1-inch margins and 9 pt. Courier New font.

The header section will comprise the sponsor's name, the protocol number, the delivery description, the data cut-off date (if applicable), TLF number, TLF title, analysis set, and page number (Page X of Y). The footer section will include the TLF footnotes, the CRO's name, date, and time of the execution of the program, reference listings and the name of the program.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1" while percentages between 99.9 and 100 (both exclusive) will be displayed as ">99.9". The denominator for each percentage will be the number of Participants within the population per treatment group unless otherwise specified.

For continuous endpoints, the mean, median, and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error, and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies. For change from baseline, the decimal will be the same as the original value. For percent change from baseline, 1 decimal will be presented.

P-values from ≥ 0.001 to ≤ 0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999".

Listings will be ordered by treatment group, participant number, date, and visit (where applicable). Imputed dates and imputed missing data will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Appendix 2

Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date
- Completely missing: Impute to the first study treatment date
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date

Event End Date Imputation

- Completely missing (and not flagged as "ongoing"): Impute to the last contact date
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date

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 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 □

Appendix 4

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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PSSD - United States/English - Original version
PSSD_7d_AU1.0_eng-USori.doc

Appendix 5

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 allow for a post-randomization dropout rate of approximately 10%, 200 participants will be randomized (40 participants/treatment group).

Software

SAS® (version 9.4; SAS Institute Inc.; Cary, NC, USA).

Input & Output

```
PROC POWER;
      twosamplefreq test=PCHI
      alpha=0.05
      sides=2
      power=0.87
      groupproportions = (0.15 0.48)
      npergroup=.;
RUN;
```

The POWER Procedure
Pearson Chi-square Test for Proportion Difference

Fixed Scenario Elements

Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	2
Alpha	0.05
Group 1 Proportion	0.15
Group 2 Proportion	0.48
Nominal Power	0.87
Null Proportion Difference	0

Computed N per Group

Actual Power	N per Group
0.870	36

Appendix 6

Common terminology criteria for adverse events (CTCAE) for the study

CTCAE Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	ALT	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline	
Alkaline phosphatase increased	Alkaline phosphatase [ALP]	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	
Anemia	Hemoglobin	Hgb<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences: urgent intervention indicated	Death

CTCAE Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	AST	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if	
Blood bilirubin increased	Total Bilirubin	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	
Cholesterol high	Cholesterol	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	Creatine Phosphokinase (CPK)	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	
GGT increased	GGT	>ULN - 2.5 x ULN if baseline	>2.5 - 5.0 x ULN if baseline	>5.0 - 20.0 x ULN if baseline	>20.0 x ULN if baseline was	

CTCAE Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
		was normal; 2.0 - 2.5 x baseline if baseline was abnormal	was normal; >2.5 - 5.0 x baseline if baseline was abnormal	was normal; >5.0 - 20.0 x baseline if baseline was abnormal	normal; >20.0 x baseline	
Hypertriglyceridemia	Triglycerides	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
INR increased	PT-INR	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding		
Lymphocyte count decreased	Lympho [Lymphocyte]	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Neutrophil count decreased	Neutro [Neutrophil]	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	

CTCAE Term	Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	Platelet	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
White blood cell decreased	White blood cell [WBC]	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	

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PPD Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 1/18/2024 1:55:20 PM Viewed: 1/18/2024 1:56:05 PM Signed: 1/18/2024 1:56:51 PM
Electronic Record and Signature Disclosure: Accepted: 7/26/2022 10:21:45 AM ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/18/2024 1:56:52 PM Viewed: 1/18/2024 2:31:03 PM Signed: 1/18/2024 2:31:37 PM
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Signer Events	Signature	Timestamp
PPD Security Level: Email, Account Authentication (Required), Logged in	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/18/2024 2:31:38 PM Viewed: 1/18/2024 2:46:13 PM Signed: 1/18/2024 2:49:56 PM
Electronic Record and Signature Disclosure: Accepted: 4/12/2023 12:12:29 PM ID: PPD		
PPD Security Level: Email, Account Authentication (Required), Logged in	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 1/18/2024 2:49:58 PM Viewed: 1/18/2024 4:17:28 PM Signed: 1/18/2024 4:17:52 PM
Electronic Record and Signature Disclosure: Accepted: 1/18/2024 4:17:28 PM ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/18/2024 1:55:20 PM
Certified Delivered	Security Checked	1/18/2024 4:17:28 PM
Signing Complete	Security Checked	1/18/2024 4:17:52 PM
Completed	Security Checked	1/18/2024 4:17:52 PM

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