Clinical Study Protocol

Study Title:	A Multi-Center, Randomized, Double-Blind, Placebo-controlled Proof-of-Activity Study with Orticumab in Subjects with Moderate-to-Severe Psoriasis and Cardiometabolic risk factors
Protocol Number:	Ort-2020-01
Study Phase:	2
Name of Investigational Product:	Orticumab
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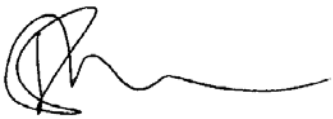
Protocol Version:	Version 2
Date:	March 05, 2021

SPONSOR APPROVAL PROTOCOL SIGNATURE PAGE

The undersigned have reviewed and approved the following protocol:



March 5th 2021

Kevin Bacon, PhD
Chief Executive Officer
Abcentra LLC

Signature

Date

INVESTIGATOR AGREEMENT

I have read this protocol and agree:

- I understand that all information concerning the product supplied to me by ABCENTRA LLC in connection with this study and not previously published, is confidential information. This information includes the Investigator's Brochure, protocol (and applicable amendments), Case Report Forms, assay methods, technical methodology, and basic scientific data.
- I will conduct the study according to the protocol and I understand that any changes to the protocol must be approved in writing by ABCENTRA and the Institutional Review Board (IRB) before implementation, except where necessary to eliminate apparent immediate hazards to the subjects.
- I confirm that I will report all adverse events (AE) following the regulations referenced in the protocol.
- I confirm that I will conduct this study in conformance with the principles of the Declaration of Helsinki, Good Clinical Practices (GCP), and US law and regulations.
- I confirm that I am informed of the need for records retention and that no data will be destroyed without the written consent of ABCENTRA.
- By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol.

Investigator Printed Name: Dr. Joel Neutel

Signature:  **Date:** March 5th, 2021

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with GCP as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- E6(R2) GCP: Integrated Addendum to International Conference on Harmonisation (ICH) E6(R1) (2018)

All key personnel (all individuals responsible for the design and conduct of this study) have completed GCP Training.

SYNOPSIS

Title	A Multi-Center, Randomized, Double-blind, Placebo-controlled, Proof-of-Activity Study with Orticumab in Subjects with Moderate-to-Severe Psoriasis and Cardiometabolic Risk factors.
Indication	Plaque Psoriasis
Clinical Phase	2
Study Treatment	Orticumab
Dose and Duration of Treatment	[redacted] orticumab or placebo, once weekly x 4 weeks, then once monthly x 2 months.
Route of Administration	Intravenous (IV; study subjects will receive [redacted] orticumab or placebo via an IV infusion).
Primary Safety Objective	• To assess the safety and tolerability of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors, as assessed by vital signs, clinical laboratory variables, and adverse events (AEs) monitoring, compared to placebo.
Primary Efficacy Objective	• To demonstrate the efficacy of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors with respect to both percent change in PASI and sIGA mod 2011 response at Week 15, compared to placebo.
Secondary Efficacy Objectives	• To demonstrate the efficacy of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors with respect to percent change in PASI and PASI response by looking at PASI 75 and 50 response rates and sIGA mod 2011 response at Weeks 1, 3, 7, and 11, compared to placebo. • Assess the effect of orticumab [redacted] on BSA, Dermatology Life Quality Index (DLQI), and Itch Numerical Rating Scale Score in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors.
Exploratory Objective	• Assess the effect of orticumab [redacted] on cardiometabolic and inflammatory biomarkers in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors.
Total Sample Size	Approximately 75 generally otherwise healthy men and women ≥ 30 years of age with moderate-to-severe psoriasis and cardiometabolic risk factors will be enrolled at 17 centers in the US to complete 60 subjects. Subjects will be randomized to receive orticumab or placebo in a 2:1 ratio.
Study Design	Following the Screening Period, participants will be enrolled into one of the two groups: [redacted] orticumab or placebo. Subjects will be randomized in a 2:1 ratio, orticumab to

	placebo and receive up to 11 weeks of treatment. Planned treatments are weekly for 4 weeks, then monthly IV infusions [redacted] of orticumab or placebo. The Internal Safety Review Committee (ISRC) will review the blinded safety data after the first subject completes the first dose (Day 1), the first five subjects complete the first dose (Day 1), and the first ten subjects complete the first dose (Day 1). The IRSC will review all adverse reactions to all administered doses at these times. Stopping criteria will be utilized in this study based on treatment-emergent AEs (defined as AEs that begin or worsen after the first dose of IP) in determining if infusions in existing and future subjects may continue.
Primary Safety Endpoints	• Number and percent of participants with one or more Treatment Emergent Adverse Events (TEAEs) or any serious adverse events (SAEs). • Change in hemodynamic parameters from Baseline to Weeks 3, 7, 11, and 15. • Change in blood chemistry and hematology from Baseline to Weeks 3 and 15. • Change in physical examination from Baseline to Weeks 3, 7, 11, and 15.
Primary Efficacy Endpoints	• Mean percent change from Baseline in PASI at Week 15, compared to placebo. • Percentage of participants achieving treatment success (clear =0 or almost clear =1) and greater than or equal to (>=) 2 Point Improvement at Week 15 on the 5-point static Investigator's Global Assessment modified 2011 version (sIGA).
Secondary Efficacy Endpoints	• Mean percent change from Baseline in PASI at Weeks 1, 3, 7, and 11. • Percentage of Participants achieving PASI75 and PASI50 from Baseline at Weeks 1, 3, 7, and 11, compared to placebo. • Percentage of participants achieving treatment success (clear =0 or almost clear =1) and greater than or equal to (>=) 2 Point Improvement at Weeks 1, 3, 7, and 11 on the 5-point static Investigator's Global Assessment modified 2011 version (sIGA). • Mean percent change from Baseline in BSA at Weeks 1, 3, 7, 11, and 15, compared to placebo. • Mean change from Baseline in Dermatology Life Quality Index (DLQI) at Weeks 3, 7, 11, and 15, compared to placebo. • Mean change from Baseline in Itch Numerical Rating Scale Score at Weeks 3 and 15, compared to placebo.
Exploratory Efficacy	• Mean change from Baseline in cardiometabolic and

Endpoints	inflammatory biomarkers at Weeks 3 and 15 in: o Blood serum lipid parameters ▪ ApoB, Apo A1, VLDL-c, oxLDL, oxHDL, Lp(a), oxLp(a), NMR-LP4 o Blood serum inflammation biomarkers ▪ Interleukin-6 (IL-6), IL-1β, IL-17, tumor necrosis factor-alpha (TNF-α), osteoprotegerin, high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), and monocyte chemoattractant protein-1 (MCP-1) o Blood serum HDL efflux efficiency ▪ ABCA-1 • Change in coronary artery perivascular fat attenuation index (FAI) measured by coronary computed tomographic angiography (CCTA) at Week 15 as compared to Baseline in active and placebo treated subjects. • Change in noncalcified and low attenuation coronary artery plaque volume, assessed by CCTA at Week 15 as compared to Baseline in active and placebo subjects. • Change in total plaque volume, assessed by CCTA at Week 15 as compared to Baseline in active and placebo subjects.
Pharmacokinetic (PK) Assessments	Blood samples for PK analysis will be obtained prior to dosing on Visits 1-6.
Subject Selection Criteria	**Inclusion Criteria:** Subjects may be enrolled if the following criteria are met: 1. Stable/chronic plaque psoriasis with PASI score of ≥ 12 AND involving ≥ 10% of the subject's BSA. 2. Males and Females ≥ 30 years of age at time of consent. 3. Females of childbearing age must use 2 forms of birth control. 4. BMI ≥ 30 kg/m^2. 5. LDL ≥ 100 mg/dL at Screening. 6. All females must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test at Day 1 (Visit 1) prior to dosing. **Exclusion Criteria:** Subjects are excluded from the study if any of the following criteria are met: 1. Past use of orticumab. 2. Any of the nonplaque forms of psoriasis: erythrodermic, guttate, or pustular. 3. Scalp, palmar or plantar psoriasis only, at Screening or Baseline.

	4. Have evidence of skin conditions (e.g., eczema) at the time of Screening or Baseline visit that would interfere with the evaluation of psoriasis. 5. Newly discovered Type 2 diabetes mellitus (T2DM) within 90 days of Screening (prior to study entry) or medical treatment for T2DM started < 90 days prior to Screening. 6. Moderate or high-intensity statin use or new use of a low-intensity statin therapy within 90 days of Screening. Low-intensity statin therapy is permitted provided it is limited to lovastatin, fluvastatin, pravastatin ≤ 40 mg daily, simvastatin ≤ 20 mg daily, or pitavastatin ≤ 2 mg daily AND the dose has remained stable and unchanged for ≥ 90 days prior to the Screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial (see Section 5.9.2 Prohibited Medication). No other non-statin lipid-modifying therapy is permitted. 7. No use of anti-coagulating or anti-thrombotic agents within 90 days prior to the Screening visit. Low dose aspirin limited to ≤ 81 mg daily provided the dose has remained stable and unchanged for ≥ 90 days prior to the Screening visit. Nonsteroidal anti-inflammatory drugs are not permitted for the duration of the trial from the Screening Visit. 8. Poorly controlled hypertension defined as: a. Systolic blood pressure (BP) > 160 mm Hg. b. Diastolic BP > 90 mm Hg. 9. Antihypertensive medication is permitted provided it is limited to two or less medications and all have been stable and unchanged for ≥ 90 days prior to the Screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial. 10. Use of topical therapies, phototherapy (UVA or UVB) or tanning salons for the treatment of psoriasis in the past 4 weeks. 11. Use of an IL-23 blocker in the past 180 days, an IL-17 blocker in the past 16 weeks, or a TNF blocker in the past 12 weeks. 12. Use of methotrexate, cyclosporine, or apremilast in the past 4 weeks. 13. History of hypersensitivity or allergies to any contents in the orticumab formulation. 14. Participation in any clinical study with an investigational. drug/device within 4 weeks prior to the first day of dosing

15. Is pregnant or breastfeeding.
16. Has an underlying condition that predisposes to infections (e.g. immunodeficiency, HIV, or splenectomy).
17. Chronic or acute hepatitis B and C, or carrier status.
18. History of tuberculosis, tuberculosis or a positive tuberculin skin test (TST) for tuberculosis. Participants who previously received BCG vaccination can participate in the study after showing negative responses in Interferon-Gamma Release Assays (IGRA).
19. History of malignancy in the past 5 years or suspicion of active malignant disease except treated cutaneous squamous cell or basal cell carcinoma and treated carcinoma in situ of the cervix uteri.
20. Diagnosis of major depressive disorder, schizophrenia, bipolar disorder, personality disorder or other DSM-V disorders which the investigator believes will interfere significantly with study compliance.
21. A history of any clinically important abnormalities in cardiac rhythm or conduction.
22. A history of prolonged QT intervals or a family history of long QT-syndrome at Screening.
23. A history of first, second or third-degree atrioventricular (AV) block, or AV dissociation.
24. A history of complete bundle branch block.
25. Unstable angina pectoris, myocardial infarction, transient ischemic attack, or stroke within 3 months prior to Screening, or participants who have undergone percutaneous coronary intervention or a coronary artery bypass graft within 6 months prior to Screening or who are due to undergo these procedures at the time of Screening.
26. Severe congestive heart failure (NYHA III or IV).
27. Prior history of contrast-induced nephropathy.
28. Known or suspected allergy to iodinated x-ray contrast.
29. Estimated GFR < 60 mL/min/1.73 m^2 {MDRD formula}.
30. Contraindications to intravenous metoprolol (beta adrenergic blocker) during CCTA imaging procedure.
31. Contraindications to sublingual nitroglycerine during CCTA imaging procedure.
32. Subject is a user of recreational or illicit drugs or has had a recent history (within 1 year of Screening) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by >3 drinks per day or >14 drinks per week, or binge drinking) at Screening. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during

	the 1 week prior to each visit.
Interim Analysis	This study will utilize a modified adaptive design model. There will be 2 planned stages for the analysis. Stage 1 will consist of the first 30 randomized subjects. After enrollment is completed for Stage 1, enrollment will begin for Stage 2 (there will be no pause in enrollment). In order to ensure an overall alpha of approximately 0.05, Stage 1 will be analyzed at an alpha level of 0.01 and the final analysis (Stage 1 and Stage 2 combined) will be analyzed at an alpha level of 0.04. A hierarchical testing strategy will be utilized in which the percentage change in PASI will be tested initially. If the p-value for this initial test is less than the indicated alpha level, the result will be concluded as real. If the percentage change in PASI is concluded as real, the change in sIGA will be tested at the indicated alpha level. In order to preserve type I error, the method presented by Cui, et al will be used to combine the data from Stage 1 and Stage 2. [22] The planned number of subjects for the study is 75. Stage 1 will consist of the first 30 subjects, so the weight given to Stage 1 in the analyses will be 30/75 (0.40). The weight given to Stage 2 in the analyses will be 45/75 (0.60). The combining of the Stage 1 and Stage 2 analyses will be performed as follows: • The Stage 1 p-value will be converted to a Z score (standard normal score). • The Stage 2 p-value will be converted to a Z score (standard normal score). • The Z scores will be combined using the weights previously indicated to create the combined Z score. • The combined Z score will be converted to a p-value.
Statistical Methods	**Analysis Sets** **Safety population:** All subjects who receive at least one dose of study drug will be included in the safety population. **PK/PD population**: All subjects who receive the study drug and for whom at least 1 trough PK concentration was collected. The safety population will be used for all summaries of subject accountability, demographic and Baseline data, and safety information, including adverse event incidence rates and laboratory

data.

The PK/PD population will serve as the basis for all efficacy analyses.

Primary Efficacy Evaluation

There are two primary endpoints for this study: Percent change in PASI and sIGA response rate.

Percent change in PASI will be analyzed using a linear mixed model analysis. The model will be implemented using PROC MIXED in SAS, and will include fixed effects for treatment, site and Baseline PASI as a covariate.

sIGA response rate will be analyzed using Fisher's Exact Test with treatment and response as the factors.

Secondary Efficacy Evaluation:

Continuous variables will be analyzed using a linear mixed model similar to the primary efficacy evaluation.

Response rates and other dichotomous variables will be analyzed using Fisher's Exact Test.

Categorical data that has more than two possible responses will be analyzed using the Cochran-Mantel-Haenszel Row Mean Score.

PK Evaluation:

Trough PK concentrations will be summarized using descriptive statistics at each visit in which PK is collected.

Safety Evaluation:

All AEs will be coded by Preferred Term using the MedDRA classification dictionary. The incidence of TEAEs will be summarized by treatment group, and by severity and relationship to study drug. Serious AEs (SAEs) and AEs leading to withdrawal from the study will be tabulated.

Other safety will be evaluated on the basis of vital signs, physical examinations, and clinical laboratory assessments. Changes from Baseline in vital signs, weight, and clinical laboratory values will be summarized by treatment group using descriptive statistics.

Shifts in clinical laboratory values (Low/Normal/High) will be

	presented. **Other Summaries:** Demographic and Baseline Characteristics will be summarized by sex and overall.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

No table of figures entries found.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABCA-1	adenosine triphosphate-binding cassette transporter A1
AE	Adverse Event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ApoA-1	apolipoprotein A-1
ApoB	apolipoprotein B
ApoB-100	apolipoprotein B-100
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
AUC_{τ}	area under the concentration-time curve for a dosing interval
BSA	body surface area
C_{max}	maximum concentration
CK	creatine kinase
CK-MB	creatine kinase-muscle/brain
CL	clearance
CL_{SS}	clearance at steady state
CRO	contract research organization
CCTA	coronary computed tomography angiography
CVD	cardiovascular disease
DLQI	dermatology life quality index
DOB	date of birth
eCRF	electronic case report form
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HDL	high-density lipoprotein
HED	human equivalent dose
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IGA	Investigator global assessment
IgG1	immunoglobulin G1
IGRA	Interferon-Gamma Release Assays

IL	interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISRC	Internal Safety Review Committee
IV	intravenous
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LOX-1	lectin-like oxLDL receptor-1
Lp(a)	lipoprotein(a)
Lp-PLA2	lipoprotein-associated phospholipase A2
MACE	major adverse cardiovascular events
MCP-1	monocyte chemoattractant protein-1
MDA	malondialdehyde
MedDRA	medical dictionary for regulatory activities
mg	milligram
NOAEL	no-observable-adverse-effect-level
oxLDL	oxidized low-density lipoprotein
oxHDL	oxidized high-density lipoprotein
oxLp(a)	oxidized lipoprotein(a)
PASI	psoriasis area and severity index
PD	pharmacodynamic
PK	pharmacokinetic
PT	prothrombin time
SAA	serum amyloid A
SAE	serious adverse event
SC	subcutaneous
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time of maximum concentration
TNFα	tumor necrosis factor-alpha
TPV	total plaque volume
TST	tuberculin skin test
VLDL	very low-density lipoprotein

WHO	World Health Organization

1 INTRODUCTION AND RATIONALE FOR DOSE SELECTION

1.1 Background Information

Orticumab is a fully human, recombinant monoclonal immunoglobulin G1 (IgG1) antibody that targets oxidized low-density lipoprotein (oxLDL) through binding to a specific epitope expressed in apolipoprotein B-100 (ApoB-100), the protein portion of LDL. It preferentially binds oxLDL over native LDL and reduces oxLDL-mediated inflammation[1]. Orticumab is being developed for the treatment of subjects with plaque psoriasis.

OxLDL is significantly increased in subjects with psoriasis and is found in lesional, but not in non-lesional skin of psoriatic subjects, and plasma levels of oxLDL correlate with the psoriasis area and severity index (PASI).[2-6] The main receptor for oxLDL (lectin-like oxLDL receptor-1 [LOX-1]) has been shown to be expressed in the epidermis.[7-10] The presence of LOX-1 perpetuates oxLDL-mediated inflammation in the skin, and because oxLDL also promotes LOX-1 upregulation, a feed-forward loop is created that stimulates chronic inflammation.[11] OxLDL promotes inflammation via endothelial dysfunction[12,13] and macrophage activation and the subsequent release of proinflammatory cytokines, including those identified as pathogenic mediators of psoriasis.[3,4] An in vitro assessment of TNFα-stimulated keratinocytes found that oxLDL was responsible for driving IL-23 expression, demonstrating that oxLDL upregulates a known pathogenic mediator of psoriasis, and the target of current standard of care therapeutics.[11] These data further suggest that targeting oxLDL may be an effective approach for treating psoriasis.

Non-clinical safety pharmacology and toxicology studies have been performed with orticumab in support of early clinical trials. During the conduct of these nonclinical studies, no toxicological findings were identified that could be related to drug treatment at exposures up to several orders of magnitude higher than those that appear to produce pharmacological effects in in vitro and in vivo animal models of cardiovascular disease.

Orticumab has been tested in humans in 3 clinical studies: two Phase 1 studies and one Phase 2 study. In the first-in-human Phase 1 study, orticumab was administered to 28 healthy volunteers as a single intravenous (IV) infusion at doses of 0.007 to 15 mg/kg or as a single SC injection at 1.25 mg/kg (n=6); in the multiple dose phase of this study, orticumab was administered weekly for 4 weeks via IV infusion at doses of 0.25 to 15 mg/kg or via SC injection at 1.25 mg/kg (n=6).

In the second (bioavailability) Phase 1 study, orticumab was administered as a single dose of 360 mg via IV or subcutaneous (SC) injection to (n=22) healthy volunteers. In both studies, orticumab demonstrated linear pharmacokinetics with a half-life of 2-3 weeks. Orticumab was safe and well tolerated in both studies without any reports of treatment-related serious adverse events (SAEs). Local injection site reactions were observed but were mild in intensity and resolved within a few days to slightly more than 1 week without medical intervention.

In the Phase 2 study, (n=49) subjects with stable atherosclerotic cardiovascular disease were administered orticumab via IV [redacted] as a single dose followed by [redacted]

[redacted] weekly for 3 weeks then monthly for 2 months. No SAEs due to study drug were reported. All adverse events (AEs) were mild or moderate in severity, with the most common AEs being dizziness, headache, and gastrointestinal (mainly diarrhea). No anti-therapeutic antibodies (ATAs) to orticumab were observed during or after treatment. No dose-limiting toxicities, deaths, or pregnancies were reported.

1.2 Rationale for Study and Dose Selection

OxLDL is an established driver of CVD and atherosclerotic plaque development.[14,15] OxLDL is also a potential target for the treatment of psoriasis. OxLDL promotes inflammation via macrophage activation and the subsequent release of proinflammatory cytokines, including those identified as pathogenic mediators of psoriasis,[3,4] and promotes endothelial dysfunction,[12] an important process implicated in the pathogenesis of psoriasis.[13] OxLDL is significantly increased in subjects with psoriasis and is found specifically in psoriatic skin lesions, but not unaffected skin from the same subject.[3-6] Furthermore, plasma levels of oxLDL correlate with the PASI score used to measure psoriatic disease activity.[2]

The dual role oxLDL plays in contributing to both psoriasis disease pathogenesis and its primary comorbidity (CVD), make oxLDL a promising target for the potential treatment of subjects with psoriasis.

In the Phase 2 study listed above (NCT01258907), 2 subjects with psoriasis reported improvements in psoriatic plaque lesions. Anecdotal information provided from the subjects to the Investigators were: 1) improvement after one dose of orticumab in one subject and 2) improvement in elbow and knee plaque psoriasis despite being refractory to both phototherapy and steroids in the second subject. Neither subject was receiving treatment for psoriasis during this study. While anecdotal and in only 2 subjects, this information along with the role of oxLDL in psoriasis suggest a study of orticumab in subjects with psoriatic disease is warranted.

Given that no information is known regarding optimized dosing regimen or route of administration, it is decided that IV administration of the maximal allowable dose of orticumab should be chosen to maximize the potential to observe a clinically relevant efficacy signal.

Orticumab administered IV or SC is well tolerated by cynomolgus monkeys after repeat dosing, including weekly SC doses of up to 150 mg/kg for 26 weeks. The NOAEL for orticumab derived from the pivotal repeat dose toxicology studies in cynomolgus monkeys was determined to be [redacted] after 4 or 26 weeks of administration. The HED of the monkey NOAEL is 4926 mg (or 59.4 mg/kg), based on a mean body weight of 83 kg obtained from the Phase 2 study of orticumab in subjects with stable atherosclerosis.

In the Phase 1 first-in-human study, a dose of 15 mg/kg IV weekly for 4 weeks was well tolerated by healthy volunteer subjects with elevated circulating oxLDL. Following multiple IV dose administration of orticumab in the Phase 2 proof of activity study in subjects with stable atherosclerosis (NCT01258907); [redacted] on Day 1 and [redacted] on Days 8, 15, 22, 50, and 78), the C_{max} was 286 and 197 ug/mL (resulting in ~19-fold safety margin based on Cmax) after the first and last dose, respectively. Mean trough serum concentrations on Days 22, 78, and 169 (12 weeks after the last dose administration) were 63.1, 15.4, and 2.47 ug/mL, respectively. No dose limiting SAEs were observed and orticumab was well-tolerated at this high dose by the patients.

The dosing regimen in the first month of this Phase 2 psoriasis proof-of-activity study involves fixed weekly doses of [redacted] IV. This approximates to [redacted] once weekly for a subject of relatively short stature and a BMI of 30 (the minimum BMI for eligibility for enrolment), with subjects of taller stature and higher BMI receiving lower doses on a mg/kg basis. Hence, the dosing regimen in the Phase 2 psoriasis proof-of-activity study can be supported by the favorable safety profile of the 15 mg/kg once weekly dose in healthy subjects in the first-in-human study. In addition, the atherosclerosis study (NCT01258907) provides relevant data on safety of more prolonged exposure (albeit at lower doses than proposed for the Phase 2 psoriasis proof-of-activity study). The NOAELs in the 4-week IV monkey study (Study2090-007) and 26-week SC monkey study (Study07-1492) of [redacted] q1w (the highest doses evaluated) correspond to a human equivalent dose (HED) of 48mg/kg q1w (for a 60kg human based on normalization to body surface area), which is approximately 3-fold higher than proposed for use during the first month of the Phase 2 proof of activity study.

Because the temporal relationship between orticumab PK and PD in humans is not known, our dosing regimen is designed to administer the maximal allowable concentration of orticumab to the subjects in the first 4 weeks of treatment. Given that the mean elimination half-life of orticumab at this dose is approximately 2-3 weeks, a weekly dosing regimen is consistent with the therapeutic goal of ensuring pharmacologically relevant blood concentrations of orticumab over the initial 4-week period. Because the link between PK and PD has not been established, blood samples are taken just prior to dosing (minimum concentration [Cmin]) on day 8, 15, 22, 29, 58 and 87 to confirm trough levels of orticumab to ascertain intersubject differences concentrations associated with potential differences in PD measures.

In summary, the results of the in vivo safety studies support the proposed clinical program and provide adequate safety factors to support x 4 weekly, followed by x 2 monthly administration of [redacted] orticumab in the planned Phase 2 study in psoriasis.

1.3 Rationale for Subject Population

Psoriasis is a risk factor for cardiovascular disease (CVD), and CVD is the primary cause of morbidity and mortality in subjects with psoriasis.[13,16,17] Subjects with psoriasis have a 25% increase in relative risk for CVD,[16,18] and those with severe psoriasis were found to have a 6.2% increase in the 10-year absolute risk of MACE compared with the general population.[16,17] The association between psoriasis and CVD is further demonstrated by the fact that improvement in psoriasis disease activity results in improvement in aortic vascular inflammation.[19]

OxLDL is significantly increased in subjects with psoriasis and is found specifically in psoriatic skin lesions, but not unaffected skin from the same subject. [3-6] The dual role oxLDL plays in contributing to both psoriasis disease pathogenesis and its primary comorbidity (CVD), make oxLDL a promising target for the potential treatment of subjects with psoriasis.

While mild-to-moderate psoriasis is typically controlled with topical creams and phototherapy, moderate-to-severe psoriasis requires oral, systemic anti-inflammatory medications (i.e., methotrexate) and/or injectable biologics. Although these therapies are effective at managing symptoms and improving healing in subjects with psoriasis, they are associated with significant side effects due to their broad, systemic immune-suppressing activity. Therefore, reducing disease activity while preventing off-target effects remains an unmet need in this subject

population. The moderate-to-severe psoriatic subjects with CVD comorbidities are therefore the most relevant target population to investigate the effects of orticumab on both local and systemic chronic inflammation.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Safety Objective:	**Primary Safety Endpoints:**
1. To assess the safety and tolerability of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors, as assessed by vital signs, clinical laboratory variables, and adverse events (AEs) monitoring, compared to placebo.	1. Number and percent of participants with one or more Treatment Emergent Adverse Events (TEAEs) or any serious adverse events (SAEs). 2. Change in hemodynamic parameters from Baseline to Weeks 3, 7, 11 and 15. 3. Change in blood chemistry and hematology from Baseline to Weeks 3 and 15. 4. Change in physical examination from Baseline to Weeks 3, 7, 11 and 15.
Primary Efficacy Objective:	**Primary Efficacy Endpoints:**
1. To demonstrate the efficacy of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors with respect to both percent change in PASI and sIGA mod 2011 response at Week 15, compared to placebo.	1. Mean percent change from Baseline in PASI at Week 15, compared to placebo. 2. Percentage of participants achieving treatment success (clear =0 or almost clear =1) and greater than or equal to (>=) 2 Point Improvement at Week 15 on the 5-point static Investigator's Global Assessment modified 2011 version (sIGA).
Secondary Efficacy Objectives:	**Secondary Efficacy Endpoints:**
1. To demonstrate the efficacy of orticumab [redacted] in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors with respect to percent change in PASI and PASI response by looking at PASI 75 and 50 response rates and sIGA mod 2011 response at Weeks 1, 3, 7, and 11, compared to placebo. 2. Assess the effect of orticumab [redacted] on BSA, Dermatology Life Quality Index (DLQI), and Itch Numerical Rating Scale Score in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors.	1. Mean percent change from Baseline in PASI at Weeks 1, 3, 7 and 11. 2. Percentage of Participants achieving PASI75 and PASI50 from Baseline at Weeks 1, 3, 7, and 11, compared to placebo. 3. Percentage of participants achieving treatment success (clear =0 or almost clear =1) and greater than or equal to (>=) 2 Point Improvement at Weeks 1, 3, 7, and 11 on the 5-point static Investigator's Global Assessment modified 2011 version (sIGA). 4. Mean percent change from Baseline in BSA at Weeks 1, 3, 7, 11, and 15, compared to placebo. 5. Mean change from Baseline in Dermatology Life Quality Index (DLQI) at Weeks 3, 7, 11, and 15, compared to placebo. 6. Mean change from Baseline in Itch Numerical Rating Scale Score at Weeks 3 and 15,

	compared to placebo.
Exploratory Objective:	**Exploratory Efficacy Endpoints:**
1. Assess the effect of orticumab [redacted] on cardiometabolic and inflammatory biomarkers in subjects with moderate-to-severe psoriasis and cardiometabolic risk factors.	1. Mean change from Baseline in cardiometabolic and inflammatory biomarkers at Weeks 3 and 15 in: o Blood serum lipid parameters ▪ ApoB, Apo A1, VLDL-c, oxLDL, oxHDL, Lp(a), oxLp(a), NMR-LP4 o Blood serum inflammation biomarkers ▪ Interleukin-6 (IL-6), IL-1β, IL-17, tumor necrosis factor-alpha (TNF-α), osteoprotegerin, high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), and monocyte chemoattractant protein-1 (MCP-1) o Blood serum HDL efflux efficiency ▪ ABCA-1 2. Change in coronary artery perivascular fat attenuation index (FAI) measured by coronary computed tomographic angiography (CCTA) at Week 15 as compared to Baseline in active and placebo treated subjects. 3. Change in Noncalcified and low attenuation coronary artery plaque volume, assessed by CCTA at week 15 as compared to Baseline, in active and placebo subjects. 4. Change in total plaque volume, assessed by CCTA at week 15 as compared to Baseline, in active and placebo subjects.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

This randomized, double-blind study is designed to compare the responses of orticumab [redacted] or placebo in subjects with moderate to severe psoriasis. A total of 75 subjects (enrolled in at least 17 study sites) with psoriasis will be randomized in a double-blind fashion to receive either an IV infusion of orticumab or placebo for up to 78 days. Before any study-related procedures are conducted, the subjects will sign a written informed consent. Subjects will be screened (Day -28 to -1) for the study, which will include clinical laboratory evaluations and CCTA. Prior to dosing on study Day 1, Baseline assessments will be performed. During treatment periods, dosing will be performed under supervision at the research center. Subjects will visit the research center on the morning of Days 1, 8, 15, 22, 50, and 78 for a pre-dose blood sample for PK purposes, Day 106 for End of Study assessments, and Day 120 for Follow-up assessments.

Following the Screening Period, participants will be enrolled into one of the two groups: [redacted] orticumab or placebo. Subjects will be randomized in a 2:1 ratio, orticumab to placebo and receive up to 11 weeks of treatment.

Planned treatments are weekly for 4 weeks, then monthly IV infusions of [redacted] orticumab or placebo. The Internal Safety Review Committee (ISRC) will review the blinded safety data after the first subject completes the first dose (Day 1), the first five subjects complete the first dose (Day 1), and the first ten subjects complete the first dose (Day 1). The IRSC will review all adverse reactions to all administered doses at these times. At the Investigator's discretion, subjects may be eligible for psoriasis rescue medications as discussed in Section 5.9.4.

Stopping criteria (see Section 12.2) will be utilized in this study based on treatment-emergent AEs (defined as AEs that begin or worsen after the first dose of IP) in determining if infusions in existing and future subjects may continue.

The following efficacy analyses measures will be assessed during the study:

- **Psoriasis Area and Severity Index (PASI)**

The PASI combines assessments of 4 body areas: the head and neck (H), the upper limbs (UL), the trunk (T) and the lower limbs (LL). The percentage of skin affected by psoriasis in each area is given a numerical score representing the Percentage involved: 1(0–9%), 2 (10–29%), 3 (30–49%), 4 (50–69%), 5 (70–89%) or 6 (90–100%). Within each area (H, UL, T, LL) the severity of 3 plaque signs –erythema (E), thickness/induration (I) and desquamation/scaling (D) –is assessed on a 5-point scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe) or 4 (very severe). The assessment of lesion severity and area affected are combined into single score. The final PASI will be = sum of severity parameters for each region*area score*weight of region (where head: 0.1, arms: 0.2, body: 0.3, legs: 0.4); total possible score range: 0=no disease to 72=maximal disease. The maximum PASI score that can be measured will be <72 since the PASI assessment will exclude scalp, palms, fingernails, soles, and toenails.

Video training will be mandatory for trial investigators involved in this assessment.

Reduction in PASI score from Baseline indicates improvement. The percentage change will be calculated by subtracting the weeks 1, 3, 7, 11 and 15 values from the Baseline values. The percentage change will be calculated for each entire treatment group (not for each participant). A positive percentage change from Baseline will indicate improvement (Bozek 2017).

- **Body Surface Area (BSA)**

Scored as the percentage body area affected by psoriasis; 0–100%. A commonly used method to estimate the body surface area of psoriatic lesions is the "rule of nines", which was originally developed for estimating the surface area of burns. It is defined as 9% coverage for the head and neck, 9% for each arm, 9% for the anterior and posterior legs, and 9% for each of 4 trunk quadrants, leaving 1% for the genitalia. The BSA can also be estimated by the number of a subject's hand areas affected, on the assumption that one "handprint" reflects approximately 1% of BSA (Bozek 2017, Spuls 2010).

Training will be mandatory for trial investigators involved in this assessment.

- **Investigator Global Assessment (IGA)**

The IGA is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consists of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque, and none to minimal focal scaling. The IGA captures and categorizes the global assessment of all clinical signs and symptoms of disease. This scale will be scored as a static assessment; i.e., without regard to a previous assessment. To have IGA success, one must have a designation of 'clear' or 'almost clear' and exhibit a two-point improvement from Baseline. Hence, if a subject has 'mild' disease at Baseline, he/she must reach 'clear'. If a subject has 'moderate' disease at Baseline, he/she must reach 'almost clear'.

And, if a subject is classified as 'severe' at Baseline, he/she must still reach 'almost clear', even though that requires a three-point improvement.

Training will be mandatory for trial investigators involved in this assessment.

- **Itch Numeric Rating Scale (I-NRS)**

The Itch NRS is a self-administered subject reported outcome questionnaire that is completed during protocol specified clinic visits. Participants indicate itch severity by circling the integer that best describes the worst level of itching due to psoriasis in the past 24 h on an 11-point scale anchored at 0, representing 'no itching' and 10, representing 'worst itch imaginable'.

- **Dermatology Life Quality Index (DLQI)**

DLQI is the dermatology-specific quality of life measure used for psoriatic population. The 10-item questionnaire assesses participant health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). The DLQI questions are rated by the participant as 0 (not at all/not relevant) to 3 (very much) with a total score range of 0 (best) to 30 (worst); higher scores indicate poor quality of life. Patient's Global

Assessment (PtGA)-The PtGA asks the participant to evaluate the overall cutaneous disease at that point in time on a single item, 5-point scale (0=clear; 1=almost clear;2=mild; 3=moderate; 4=severe).

3.2 Study Visits

For each subject, a maximum of 9 scheduled visits will be performed. The procedures and assessments to be performed during each period/time point are indicated in Table 1.

Further relevant details of the evaluations to be performed at each visit are described below.

3.2.1 Screening Period (Day -28 to Day -1)

3.2.1.1 Screening Visit

At Screening, potential subjects will be given a detailed oral presentation describing the nature, purpose, risks, and requirements of the study and will receive detailed written information. Subjects will be given ample time to consider participation and ask questions that will be adequately addressed by site personnel.

Once the subject is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study informed consent form (ICF) (refer to Section 11.2.4 for further detail regarding the ICF). The Investigational Site personnel obtaining written consent from the subject will also sign the form to confirm consent has been obtained.

Once signed, the Investigator will retain the original ICF for the subject's study records and provide the subject with a signed copy. The Investigator will verify that informed consent has been obtained from each subject prior to enrollment into the study and prior to the subject undergoing any study-related procedures.

Subjects will report to the clinic in the morning following a 10-hour fast. Screening activities after obtaining informed consent will be conducted and consist of the following:

- Review of eligibility criteria.
- Collection of demographic data (sex, date of birth (DOB), race, and ethnicity).
- Completion of medical history, including tobacco and alcohol use.
- Review of prior and concomitant medications and supplements.
- Physical examination will be performed.
- Height and weight will be measured.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- DLQI questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood samples for (see Section 6.3.2 for a list of tests):
    - Clinical laboratory tests (including serum pregnancy test for females and activated partial thromboplastin time (aPTT) test).
    - Serology (Hepatitis B and C, and HIV).

- CCTA will be performed.

For subjects who meet eligibility criteria based on the Screening assessments, instruction will be provided on the following:

- Use of adequate contraceptive methods (see Section 5.10.2) for the duration of the study (Screening through Follow-up Visit (Visit 8));
- Avoid use of concomitant medication unless deemed necessary by the Investigator, and avoid prohibited medications as defined in Section 5.9.2;
- Restraint from excessive alcohol use or binge drinking during the study, and restraint from drinking alcohol for 72 hours prior to all study visits.

3.2.2 Screen Failure

A screen failure is defined as a subject who has signed the ICF, does not meet all the entry criteria outlined in Section 4 of this protocol (note that this criteria includes assessments through Visit 1) and was not randomized to receive the study treatment (active or placebo). The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents and on the Screening log. Screen failure subjects will have only their consent, demographic and reason for screen failing (including, where applicable, the unmet inclusionary or exclusionary criteria) data entered into the electronic data capture (EDC) system, unless an adverse event was responsible for the subject's screen failure, in which case all electronic case report form (eCRF) data collected for that subject during the Screening process will be entered into the EDC system.

3.2.3 Baseline Period (Day 1)

3.2.3.1 Visit 1 (Week 0, Day 1 ± 1 day)

The morning of randomization (Day 1), subjects will report to the clinic in the morning following a 10-hour fast. The following activities will be performed:

- Review of eligibility criteria. *
- Review of concomitant medications and supplements.
- Physical examination will be performed. *
- Weight will be measured. *
- IGA will be performed. *
- PASI Score will be evaluated. *
- BSA will be measured. *
- DLQI questionnaire will be completed. *
- I-NRS questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate). *
- Collection of fasted blood and urine samples for (see Section 6.3.2 for a list of tests): *
    - Clinical laboratory tests (including urine pregnancy test for females, aPTT test, and biomarkers test).
    - Immunogenicity testing.
    - PK assessment.

- Subjects will be randomized to receive IV infusion of either orticumab [redacted] or placebo. *
- Subjects will receive IV infusion of either orticumab [redacted] or placebo and will be monitored for at least 1-hour after the infusion.
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 1 week for Visit 2.

* Assessments to be performed/samples to be collected prior to dosing.

3.2.3.2 Visit 2 (Week 1, Day 8 ± 1 day)

Subjects will and report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Review of eligibility criteria prior to dosing.
- Collection of fasted blood samples prior to dosing for:
  - PK assessment.
  - Biomarker testing.
- Subjects will receive IV infusion of either orticumab [redacted] or placebo and will be monitored for at least 1-hour after the infusion.
- Review of concomitant medications and supplements.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- Measurement of vital signs (SBP/DBP and heart rate).
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 1 week for Visit 3.

3.2.3.3 Visit 3 (Week 2, Day 15 ± 1 day)

Subjects will report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Review of eligibility criteria prior to dosing.
- Collection of fasted blood samples prior to dosing for:
  - PK assessment.
  - Biomarker testing.
- Subjects will receive IV infusion of either orticumab [redacted] or placebo and will be monitored for at least 1-hour after the infusion.
- Review of concomitant medications and supplements.
- Measurement of vital signs (SBP/DBP and heart rate).
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 1 week for Visit 4.

3.2.3.4 Visit 4 (Week 3, Day 22 ± 1 day)

Subjects will report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Review of eligibility criteria prior to dosing.
- Collection of fasted blood samples prior to dosing for (see Section 6.3.2 for a list of tests):
  - Clinical laboratory tests (including urine pregnancy test for females, biomarkers test, and aPTT test).
  - Immunogenicity testing.
  - PK assessment.
- Subjects will receive IV infusion of either orticumab [redacted] or placebo and will be monitored for at least 1-hour after the infusion.
- Review of concomitant medications and supplements.
- Physical examination will be performed.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- DLQI questionnaire will be completed.
- I-NRS questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate).
- Weight will be measured.
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 4 weeks for Visit 5.

3.2.3.5 Visit 5 (Week 7, Day 50 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Review of eligibility criteria prior to dosing.
- Collection of fasted blood samples prior to dosing for:
  - PK assessment.
  - Biomarker testing.
- Urine pregnancy test for females prior to dosing.
- Subjects will receive IV infusion of either orticumab [redacted]) or placebo and will be monitored for at least 1-hour after the infusion.
- Review of concomitant medications and supplements.
- Physical examination will be performed.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- DLQI questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate).
- Weight will be measured.

- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 4 weeks for Visit 6.

3.2.3.6 Visit 6 (Week 11, Day 78 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Review of eligibility criteria prior to dosing.
- Collection of fasted blood samples prior to dosing for:
  - PK assessment.
  - Biomarker testing.
- Urine pregnancy test for females prior to dosing.
- Subjects will receive IV infusion of either orticumab [redacted] or placebo and will be monitored for at least 1-hour after the infusion.
- Review of concomitant medications and supplements.
- Physical examination will be performed.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- DLQI questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate).
- Measurement of weight.
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 4 weeks for Visit 7.

3.2.4 End of Study/Early Termination Visit (EOS/ET Visit)

3.2.4.1 Visit 7 (Week 15, Day 106 ± 3 days)/ ET Visit

Subjects will report to the clinic in the morning following a 10-hour fast where the following activities will be performed:

- Collection of fasted blood samples for (see Section 6.3.2 for a list of tests):
  - Clinical laboratory tests (including urine pregnancy test for females, biomarkers test, and aPTT test).
  - Immunogenicity testing.
- Review of concomitant medications and supplements.
- Physical examination will be performed.
- IGA will be performed.
- PASI Score will be evaluated.
- BSA will be measured.
- DLQI questionnaire will be completed.
- I-NRS questionnaire will be completed.
- Measurement of vital signs (SBP/DBP and heart rate).
- Weight will be measured.

- CCTA will be performed.
- AEs will be recorded.
- Subjects will be instructed to return to the clinic in 2 weeks for Follow-up Visit 8 (or discharged from the study if terminated early).

3.2.5 Follow-up (FU) Visit

3.2.5.1 Visit 8 (Week 17, Day 120 ± 3 days)

A post-treatment Follow-up Visit will occur 14 ± 3 days after completion of the treatment period. Subjects will report to the clinic in the morning where the following activities will be performed:

- Review of concomitant medications and supplements.
- Physical examination will be performed.
- Urine pregnancy test will be performed.
- Measurement of vital signs (SBP/DBP and heart rate).
- AEs will be recorded.
- Subjects will be discharged from the study.

3.2.6 Unscheduled (UNS) Visit

Should there be a need for an unscheduled (UNS) visit, (e.g., to manage or Follow-up on unresolved AEs), the investigator will use their judgment and perform an adequate evaluation of the subject. Prior and concomitant medications and supplements, vital signs, physical examination, weight, adverse events assessment, and clinical lab tests will be performed as necessary and data will be recorded.

3.3 Schedule of Events

Table 1 presents the schedule of events for all study visits.

Table 1. Schedule of Events

Study Period	**SCR**	**BSL**								
Visit	**S**	**1**	**2**	**3**	**4**	**5**	**6**	**EOS/ET [7] 7**	**FU 8**	**UNS**
Study Week		**0**	**1**	**2**	**3**	**7**	**11**	**15**	**17**	
Study Day [1]	**-28 to -1**	**1** (± 1 day)	**8** (± 1 day)	**15** (± 1 day)	**22** (± 1 day)	**50** (± 3 days)	**78** (± 3 days)	**106** (± 3 days)	**120** (± 3 days)	
Informed Consent Form	X									
Eligibility Criteria	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]			
Demographic Data (sex, DOB, race, and ethnicity)	X									
Medical History (including tobacco and alcohol use)	X									
Prior and Concomitant Medications and Supplements [2]	X	X	X	X	X	X	X	X	X	X
Physical Examination [3]	X	X[a]			X	X	X	X	X	X
Height and Weight [$]	X	X			X	X	X	X		X
PASI, BSA and IGA	X	X[a]	X		X	X	X	X		
DLQI	X	X[a]			X	X	X	X		
I-NRS		X			X			X		
Vital Signs [4]	X	X[a]	X	X	X	X	X	X	X	X
Pregnancy Test [5]	X	X[a]			X[a]	X[a]	X[a]	X	X	
Blood Sample for Immunogenicity Assessment		X[a]			X[a]			X		
Blood Sample for PK assessment		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]			
Blood Sample for Clinical Lab Tests [#]	X	X[a]			X[a]			X		X
Serology (Hepatitis B and C, and HIV)	X									
Exploratory Biomarkers [6]		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X		
CCTA	X							X		
Randomization		X[a]								
IV Administration		X	X	X	X	X	X			
Adverse Events		X^	X	X	X	X	X	X	X	X

Table 1 Footnotes

BSL = Baseline; DOB = Date of Birth; CCTA = Coronary Computed Tomography Angiography; EOS = End of Study; ET = Early Termination; FU = Follow-up; UNS = Unscheduled; PASI = Psoriasis Area and Severity Index; IGA = Investigator Global Assessment; BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; I-NRS = Itch Numerical Rating Scale; PK = Pharmacokinetic; IV = Intravenous

[a]Assessment to be performed/samples to be collected prior to dosing.
[1] For Study Weeks 1-15: Clinic visits should occur within ± 1 days. Follow-up Visit should occur within ± 3 days.
[2] Prior and concomitant medications and supplements will be reviewed at Screening, Early Termination (ET) Visit (if applicable), and Unscheduled (UNS) Visit (if applicable). Concomitant medications and supplements will be reviewed as indicated.
[3] Physical examination will include the following organ or body system assessments: general appearance; eyes; ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological; and extremities.
[4] Heart rate and blood pressure.
[5] Serum pregnancy test at Screening, urine pregnancy test at Visits 1, 4, 5, 6, 7, and FU Visit.
[6] See Efficacy Assessment Section under "Cardiometabolic and Inflammatory Biomarkers".
[7] Subjects withdrawing prematurely from the trial at any visit will have the ET visit procedures completed.
[$] Height and weight will be measured at Screening and weight will be measured at Weeks 0, 3, 7, 11, 15, and Unscheduled (UNS) Visit (if applicable).
[#] Clinical lab tests will include hematology, serum chemistry (includes a standard lipid panel), and coagulation parameters (includes an activated partial thromboplastin time (aPTT) test).
[^] AE's will only be collected after dosing on Visit 1 (Week 0).

4 STUDY SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1 Number of Subjects

Approximately 75 subjects will be enrolled in at least 17 sites in the US to ensure that at least 60 subjects complete the study. Subjects will be randomized in a 2:1 ratio, orticumab to placebo. Subjects who discontinue prematurely will not be replaced.

4.2 Inclusion Criteria

Subjects may be enrolled if the following criteria are met:

1. Stable/chronic plaque psoriasis with PASI score of ≥ 12 AND involving ≥ 10% of the subject's BSA.
2. Males and Females ≥ 30 years of age at time of consent.
3. Females of childbearing age must use 2 forms of birth control.
4. BMI ≥ 30 kg/m^2.
5. LDL ≥ 100 mg/dL at Screening.
6. All females must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test at Day 1 (Visit 1) prior to dosing.

4.3 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria are met:

1. Past use of orticumab.
2. Any of the nonplaque forms of psoriasis: erythrodermic, guttate, or pustular.
3. Scalp, palmar or plantar psoriasis only, at Screening or Baseline.
4. Have evidence of skin conditions (e.g., eczema) at the time of Screening or Baseline visit that would interfere with the evaluation of psoriasis.
5. Newly discovered Type 2 diabetes mellitus (T2DM) within 90 days of Screening (prior to study entry) or medical treatment for T2DM started < 90 days prior to Screening.
6. Moderate or high-intensity statin use or new use of a low-intensity statin therapy within 90 days of Screening. Low-intensity statin therapy is permitted provided it is limited to lovastatin, fluvastatin, pravastatin ≤ 40 mg daily, simvastatin ≤ 20 mg daily, or pitavastatin ≤ 2 mg daily AND the dose has remained stable and unchanged for ≥ 90 days prior to the screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial. See Section 5.9.2 Prohibited Medication. No other non-statin lipid-modifying therapy is permitted.
7. No use of anti-coagulating agents or anti-thrombotic agents within 90 days prior to the Screening visit. Low dose aspirin limited to ≤ 81 mg daily provided the dose has remained stable and unchanged for ≥ 90 days prior to the Screening visit. Nonsteroidal anti-inflammatory drugs are not permitted for the duration of the trial from the Screening Visit.
8. Poorly controlled hypertension defined as:
    a. Systolic blood pressure (BP) > 160 mm Hg.

b. Diastolic BP > 90 mm Hg.

9. Antihypertensive medication is permitted provided it is limited to two or less medications and all have been stable and unchanged for ≥ 90 days prior to the screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial.
10. Use of topical therapies, phototherapy (UVA or UVB) or tanning salons for the treatment of psoriasis in the past 4 weeks.
11. Use of an IL-23 blocker in the past 180 days, an IL-17 blocker in the past 16 weeks, or a TNF blocker in the past 12 weeks.
12. Use of methotrexate, cyclosporine, or apremilast in the past 4 weeks.
13. History of hypersensitivity or allergies to any contents in the orticumab formulation.
14. Participation in any clinical study with an investigational drug/device within 4 weeks prior to the first day of dosing.
15. Is pregnant or breastfeeding.
16. Has an underlying condition that predisposes to infections (e.g. immunodeficiency, HIV, or splenectomy).
17. Chronic or acute hepatitis B and C, or carrier status.
18. History of tuberculosis, tuberculosis or a positive tuberculin skin test (TST) for tuberculosis. Participants who previously received BCG vaccination can participate in the study after showing negative responses in Interferon-Gamma Release Assays (IGRA).
19. History of malignancy in the past 5 years or suspicion of active malignant disease except treated cutaneous squamous cell or basal cell carcinoma and treated carcinoma in situ of the cervix uteri.
20. Diagnosis of major depressive disorder, schizophrenia, bipolar disorder, personality disorder or other DSM-V disorders which the investigator believes will interfere significantly with study compliance.
21. A history of any clinically important abnormalities in cardiac rhythm or conduction.
22. A history of prolonged QT intervals or a family history of long QT-syndrome at Screening.
23. A history of first, second or third-degree atrioventricular (AV) block, or AV dissociation.
24. A history of complete bundle branch block.
25. Unstable angina pectoris, myocardial infarction, transient ischemic attack, or stroke within 3 months prior to Screening, or participants who have undergone percutaneous coronary intervention or a coronary artery bypass graft within 6 months prior to Screening or who are due to undergo these procedures at the time of Screening.
26. Severe congestive heart failure (NYHA III or IV).
27. Prior history of contrast-induced nephropathy.
28. Known or suspected allergy to iodinated x-ray contrast.
29. Estimated GFR < 60 mL/min/1.73 m^2 {MDRD formula}.
30. Contraindications to intravenous metoprolol (beta adrenergic blocker) during CCTA imaging procedure.
31. Contraindications to sublingual nitroglycerine during CCTA imaging procedure.

32. Subject is a user of recreational or illicit drugs or has had a recent history (within 1 year of Screening) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by >3 drinks per day or >14 drinks per week, or binge drinking) at Screening. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during the 1 week prior to each visit.

4.4 Removal of Subjects from Therapy or Assessment

Subjects may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

Within the provisions of informed consent and good clinical judgment with respect to safety, every attempt will be made to have subjects complete the study. Reasons for subject discontinuation include, but are not limited to the following:

1. Subject experiences an AE that in the judgement of the Investigator poses a significant risk to the subject for continued participation in the study.
2. Subject uses a prohibited medication (listed in Section 5.9.2) that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of the study.
3. Subject becomes pregnant.
4. Significant protocol violation or noncompliance on the part of the subject or the Investigator.
5. Intercurrent illness requires treatment not consistent with the protocol requirements, or intercurrent illness and the associated treatment poses a significant risk to the subject for continued participation in the study in the judgment of the Investigator.
6. Subject meets one of the exclusion criteria during the study.
7. Subject wishes to withdraw for any reason.
8. Sponsor elects to end the study or the Investigational Site elects to end the study at their site.
9. Any other reason that in the judgment of the Investigator poses unacceptable risk to the subject.

Subjects who withdraw from the study prior to treatment may be replaced. Subjects who are withdrawn and have received at least one treatment will not be replaced.

Except in cases of emergency, the Investigator should consult with the Sponsor and the Medical Monitor before removing the subject from the study. In some circumstances, it may be necessary to temporarily interrupt treatment because of AEs that may have an unclear relationship to study treatment. The Investigator should obtain approval from the Sponsor and Medical Monitor before restarting study treatments that were temporarily discontinued for an AE.

If a subject discontinues the study prior to completion, the date the subject is withdrawn and the reason for discontinuation will be recorded in the source documents and eCRF. Although a subject will not be obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights.

All subjects who are randomized and treated (i.e., received any amount of study treatment) will be included in the safety analyses. Thus, every effort will be made to contact any subject who fails to attend any Follow-up appointments/contacts, to ensure that he/she is in satisfactory health. If a subject withdraws from the study as a result of meeting discontinuation criteria (Section 4.4) after the start of study treatment administration, reasonable efforts should be made to have the subject return for the early termination evaluations (Section 3.2.4). Any subject withdrawn due to a suspected study treatment-related AE should be followed until resolution or stabilization of the event.

If a subject becomes pregnant, study treatment will be discontinued immediately. The subject will be followed until delivery or other termination of pregnancy for outcome.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation among involved parties. The Investigator will notify the IRB in writing of a premature termination of a study or closure of Investigational Site and will send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, GCP violations, slow recruitment/low enrollment, or change in development plans for the study treatment.

Enrollment of new subjects and dosing of ongoing subjects will be temporarily stopped based on the stopping criteria (See Section 12.2). The Investigator, Sponsor, and the Medical Monitor will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IRB and FDA prior to re-starting the trial.

5 STUDY TREATMENT

5.1 Description of Investigational Drug

The study drug will be manufactured, bulk packaged, and labeled under good manufacturing practices (GMP). The study drug will be shipped to each study site by Sponsor or their designee.

Active:
Orticumab is a fully human recombinant IgG1 monoclonal antibody (molecular weight, approximately 146 kDa) that is expressed in Chinese hamster ovary cells. Orticumab will be provided as a sterile liquid for infusion and will contain no preservatives. Each single-use, 2 mL vial is designed to deliver 225 mg of orticumab (1.5 mL/vial). [redacted]

Placebo:
The placebo formulation is identical to the drug product, minus the active ingredient. For further details, see the Investigator Brochure.

5.2 Drug Packaging

Adequate supplies of medication will be made available to each investigational site. The study drug will be packaged into kits containing [redacted] vials of either orticumab [redacted] or placebo.

5.3 Drug Labeling

Each kit and vial will be labeled with the following information:

- Protocol number
- Name and address of the Sponsor
- Orticumab [redacted] or Placebo (1.5mL/vial), dosage form, route of administration, strength, and volume
- Unique 6-digit kit number
- Lot number
- Directions for use
- Storage conditions

5.4 Drug Storage

Glass vials containing study drug must be stored at a refrigerated temperature (2°C–8°C) and away from light until used. Since stability studies are ongoing, the study drug has an assigned re-test date that will be updated during the course of the clinical trial. The re-test date will be available in the Interactive Response Technology (IRT) system.

All study medication will be stored in a refrigerator placed in a secured area where access will be limited to the unblind pharmacist and his/her designated staff. Blinded investigators and site staff should not open the study drug kits.

5.5 Dosage and Administration of Treatment

Subjects will be randomly allocated in a 2:1 ratio to receive either orticumab [redacted] or placebo by a single IV infusion based on the Schedule of Visits (Table 1). Subjects will receive a total of six (6) IV infusions of either orticumab or placebo during the course of the study.

Preparation of a dose requires that a 10 mL syringe and needle withdraw 8.45 mL from the contents of [redacted] vials in the kit and injected into a 50 mL 0.9% Sodium Chloride IV bag. This will be prepared using aseptic technique by an unblinded pharmacist or other trained medical personnel designated by the Investigator. Allowing for an estimated 0.15 mL retained in the needle after injection into the IV bag, this will deliver [redacted] of orticumab. Consult the pharmacy manual for dose preparation instructions.

Orticumab will be diluted (in 50 mL of sterile normal saline) and administered over 30 minutes without premedication.

No dosage modification will be permitted in this trial. If a subject has a reaction while study drug is being infused and the injection is stopped, the volume infused prior to stopping study drug administration should be recorded and the Medical Monitor should be contacted.

5.6 Study Blinding and Randomization

Subjects who fulfill the eligibility criteria and provide informed consent will be enrolled into the study and randomized in a double-blind manner. Subjects will be randomized to receive orticumab or placebo in a 2:1 ratio. The randomization scheme will be generated by a qualified statistician designated by Sponsor or its designee.

5.7 Procedure for Unblinding

The randomization code may be broken by the investigator when this knowledge will affect the management of an urgent medical event.

If possible, before unblinding of a given single subject during the treatment period, the medical monitor should be contacted to discuss the case before the code is broken. For each subject, the treatment code will be held in the IRT system. The investigator will be able to unblind a subject by using the IRT system to identify the vial number dispensed to the subject. When the unblinding is completed, the sponsor and investigator shall receive written notification of the unblinding.

If it becomes necessary to unblind treatment information during the study, the reason for unblinding is to be documented in the IRT system. The investigator is to contact the medical monitor promptly and explain the reason for any premature unblinding (e.g., unblinding due to an SAE) and document this reason appropriately.

5.8 Drug Accountability

The Investigator or their designee will sign a receipt for the study drugs on the day they are delivered to the study site. A copy of this receipt must be filed in the investigator study file and the original returned as directed. A drug accountability record should be maintained by the person responsible for dispensing the study drug to the subject. This should record which supplies are issued to which subjects. The Investigator or their designee should be notified immediately of details of any supplies that are inadvertently damaged. Details of any supplies that are inadvertently damaged or unaccountable for any reason should be noted on this drug accountability record, which will be collected by the Investigator or their designee at the end of the study. Each clinical study site will be responsible for drug accountability once drug is received.

All drugs will be inventoried by the Investigator or their designee during and at the conclusion of the study. Secure disposal or return of unused supplies to the sponsor at the end of the study will be arranged.

5.9 Concomitant Medication

5.9.1 General Considerations

The Investigator is to record the use of all concomitant medications, both prescribed and over the counter, in the eCRF. Any medication must have been stopped in the time frame required in the inclusion and exclusion criteria prior to the first dose of study drug. Subjects should be advised against taking any new medication, both prescribed and over the counter, without consulting the investigator, unless the new medication is required for emergency use.

On Day 1, the study site personnel should ensure that subjects continue to meet the inclusion criteria and none of the exclusion criteria (including contraindicated medications). The prohibited and allowed medications with time frames where relevant are summarized below.

5.9.2 Prohibited Medication

- Prior or current use of orticumab (not a part of this trial).
- Any medical treatment for T2DM started < 90 days prior to study entry.
- Moderate or high-intensity statin use or new use of a low-intensity statin therapy within 90 days of Screening. Low-intensity statin therapy is permitted provided it is limited to lovastatin, fluvastatin, pravastatin ≤ 40 mg daily, simvastatin ≤ 20 mg daily, or pitavastatin ≤ 2 mg daily AND the dose has remained stable and unchanged for ≥ 90 days prior to the screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial.
- No use of anti-coagulating agents or anti-thrombotic agents within 90 days prior to the Screening visit. Low dose aspirin limited to ≤ 81 mg daily is permissible provided the dose has remained stable and unchanged for ≥ 90 days prior to the screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial. Nonsteroidal anti-inflammatory drugs are not permitted for the duration of the trial from the Screening Visit.
- Antihypertensive medication is permitted provided it is limited to two or less medications and all have been stable and unchanged for ≥ 90 days prior to the screening visit and NO DOSE change is anticipated for the approximate 20-week duration of the trial.
- Paracetamol (acetaminophen) or paracetamol-containing preparations is permitted for pain and fever control but not within 24-hours of a study visit.
- Antihistamines.
- Use of topical therapies, phototherapy (UVA or UVB) or tanning salons for the treatment of psoriasis in the past 4 weeks.
- Use of an IL-23 blocker in the past 180 days, an IL-17 blocker in the past 16 weeks, or a TNF blocker in the past 12 weeks.
- Use of methotrexate, cyclosporine, or apremilast in the past 4 weeks.
- Phosphodiesterase inhibitors (e.g. Viagra, Cialis, Levitra) for at least 72 hours prior to CCTA.
- Metformin for 48 hours after CCTA (day of and day after).

5.9.3 Permitted Medication

Psoriasis rescue medication, (in addition to their current blinded treatment), is limited to topical hydrocortisone 2.5% (cream or ointment) that can be applied twice daily if needed to the face and sensitive intertriginous regions (axilla, groin, breast). Over the counter (non-prescription) applications of coal tar and emollients may be used as necessary.

5.9.4 Rescue Medication

Up to week 15, any subject who, in the opinion of the Investigator, requires medication to treat their psoriasis (in addition to their current blinded treatment) may apply 2.5% hydrocortisone cream or ointment to the face and intertriginous regions (groin, axilla, breast). Over the counter (non-prescription) applications of coal tar and emollients may be used as necessary. The Investigator and qualified staff must direct the administration of this medication and record its use in the concomitant medication section of the source documents and eCRF.

5.10 General Restrictions

5.10.1 Behavioral Restrictions

Excessive alcohol use or binge drinking will be discouraged during the study, and alcohol will be prohibited 72 hours prior to each visit. Subjects should not use any recreational or illicit drugs within one year prior to Screening through Follow-up Visit. No cannabinoid products will be allowed 1 week prior to each visit.

5.10.2 Contraceptive Measures

The subject or their heterosexual partner (if applicable) should be surgically sterile (vasectomy, hysterectomy, bilateral tubal ligation [both tubes tied], or bilateral oophorectomy [both ovaries removed]). If not, and the female subject or partner is of childbearing potential (could become pregnant), the subject must agree to use highly effective contraception during heterosexual intercourse throughout the study period and for 90 days following last dose of study drug. Examples of a highly effective method of contraception include double barrier methods (e.g., use of a condom and spermicide along with [choose 1 of the following] a diaphragm; hormone-containing pill, injection or implant; or intrauterine device [IUD]). The male subject must not donate sperm while participating in this study and for 90 days after receiving the last dose of study drug.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 PHARMACOKINETIC EVALUATIONS

Blood samples will be collected at the time points indicated in Table 1. The concentration of orticumab in these samples will be analyzed by a contract bioanalytical laboratory. Aliquots of plasma samples from each time point will be stored frozen for potential future evaluation of additional biomarkers for preliminary information only. Full details of the methodology will be presented in the bioanalytical report, which will be appended to the clinical study report.

6.2 PHARMACOKINETIC SAMPLING

Samples of venous blood will be obtained in 10 mL K2EDTA tubes (a minimum of 8 mL per time point required) just prior to dose administration at the time points indicated in Table 1. The K2EDTA tubes and associated labels will be provided by the sponsor or their designee.

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at approximately 1500 × g. The plasma fraction will be withdrawn by pipette and divided into 2 polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the subject, the study period, and the collection time. Labels will be fixed to freezing tubes in a manner that will prevent the label from detaching after freezing. All plasma samples will be processed and placed into a freezer (-70°C) within 1 hour after collection.

All plasma samples will be stored frozen (-70°C) until they are shipped to the bioanalytical facility. Prior to shipping, the samples will be packed into thermal insulated containers (provided by Sponsor or their designee) and packed in sufficient dry ice to assure that they remain frozen for a minimum of 72 hours and protected from breakage during shipment. The bioanalytical facility will be notified of the shipment via e-mail or facsimile. Samples will be shipped by overnight priority courier. The samples will be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment will be sent.

All samples will be shipped to: PPD Labs Inc., Global Central Laboratories, 2 Tesseneer Drive, Highland Heights, KY 41076.

6.3 SAFETY EVALUATIONS

6.3.1 Adverse Events

The investigator will determine during the course of all study periods whether any AEs have occurred. The subjects will be questioned in a general way and no specific symptoms will be suggested. Section 7 contains additional information with regard to AEs.

6.3.2 Clinical Laboratory Tests

Blood for clinical safety laboratory assessments will be collected and processed using standard procedures as indicated in Table 1. Clinical laboratory tests will be performed by a central laboratory designated by the Sponsor.

The Principal Investigator will review all laboratory results and initial and date a copy for storage in the source document. A clinically significant abnormal lab test will be reported as an AE. In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether the abnormality is clinically significant.

A procedures manual for Screening and safety clinical laboratory sample collection, handling, and shipment to the central laboratory will be provided to each study site by Sponsor or Sponsor designee prior to the start of the study.

Laboratory reports received from the central laboratory should be reviewed, signed, and dated by the investigator or delegated physician. Each abnormal result will be assessed as clinically or not clinically significant and a comment will be provided for all out-of-range analytes deemed clinically significant (i.e., document probable cause for abnormal results). Laboratory data will be collected electronically by Sponsor or their designee and transferred to the contract research organization (CRO) handling the eCRF form data for integration with the eCRF data.

6.3.2.1 Clinical Safety Labs

The following clinical safety labs will be performed:

Hematology: Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, differentials (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes.

Chemistry: Albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, CO2, creatinine, direct bilirubin, gamma-glutamyl-transferase (GGT), glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, uric acid, standard lipid panel (Total Cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol).

6.3.2.2 Coagulation Parameters

An activated partial thromboplastin time (aPTT) test will be performed at Screening, Visits 1, 4, 7 and any unscheduled visit (if applicable) as indicated in (Table 1).

6.3.2.3 Pregnancy Test

For females, a serum pregnancy test will be performed at Screening and a urine pregnancy test at Visits 1 (Baseline), 4, 5, 6, 7, and 8 (post-treatment Follow-up Visit) as indicated in (Table 1).

6.3.2.4 Immunogenicity Testing

Immunogenicity will be assessed at Baseline (Day 1, prior to dosing), at Visit 4 (Week 3, prior to dosing), and at Visit 7 (Week 15) as indicated in (Table 1).

6.3.2.5 Additional Screening Bloodwork

In addition to the blood tests listed above serology (Hepatitis B and C, and HIV) will be performed at Screening (Table 1).

6.3.3 Vital Signs

Vital signs (blood pressure [BP] [mmHg] and heart rate [bpm]) will be measured at the clinic visits or time points indicated in Table 1. BP will be measured after at least a 5-minute rest in the sitting position. BP will be measured with a standard mercury sphygmomanometer. Whenever possible, the measurements should be made by the same personnel using the same device at each evaluation.

6.3.4 Physical Examination

A physical examination will be performed at the time points indicated in Table 1. This evaluation will include examination of the following body systems: general appearance; eyes; ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological; and extremities. Urogenital and psychiatric abnormalities will be accessed as part of the subject's medical history at Screening and any abnormalities (i.e., if the subject has a complaint for that system) in these systems during the treatment period will be recorded as AEs.

6.3.5 Height and Weight

Height and weight will be measured at Screening and weight will be measured at Weeks 0, 3, 7, 11, 15, and UNS Visit (Table 1).

6.3.6 Demographics and Medical History and Prior Medications

At Screening, demographics (sex, DOB, race, and ethnicity) and a brief medical history (including tobacco and alcohol use) will be collected by subject interview. Medications and supplements, recent blood donations, illnesses, and participation in other Investigational Drug trials or clinical trials will also be recorded.

6.4 Total Blood Volume

The total volume of blood obtained from an individual study participant is expected to be approximately 164 mL, including PK samples and clinical laboratory tests.

Table 2: Blood Draw Volumes

Assay	Volume per Sample (mL)	Total Number of Samples	Total Volume (mL)
Serum Pregnancy	4 mL	1	4 mL
Immunogenicity	4 mL	3	12 mL
PK	4 mL	6	24 mL
Hematology	4 mL	4	16 mL
Serum Chemistry^	8 mL	5	40 mL
aPTT	3 mL	4	12 mL
Biomarkers	8 mL	7	56 mL
Total blood volume (entire study)			164 mL
^Serum chemistry will include serology (Hepatitis B and C, and HIV) and a standard lipid panel			

6.5 Efficacy Assessments

6.5.1 Psoriasis Measures

Mean percent change from Baseline in PASI at Weeks 1, 3, 7, 11, and 15, compared to placebo.

Percentage of Participants achieving PASI75 and PASI50 from Baseline at Weeks 1, 3, 7, and 11, compared to placebo.

Percentage of participants achieving treatment success (clear =0 or almost clear =1) and greater than or equal to (>=) 2 Point Improvement at Weeks 1, 3, 7, 11, and 15 on the 5-point static Investigator's Global Assessment modified 2011 version (sIGA).

Mean percent change from Baseline in BSA at Weeks 1, 3, 7, 11, and 15, compared to placebo.

Mean percent change from Baseline in DLQ1 at Weeks 1, 3, 7, 11, and 15, compared to placebo.

Mean change from Baseline in Itch Numerical Rating Scale Score at Weeks 3 and 15, compared to placebo.

6.5.2 Cardiometabolic and Inflammatory Biomarkers

Mean change from Baseline in cardiometabolic and inflammatory biomarkers at Weeks 3 and 15 in:

- Blood serum lipid parameters
  - ApoB, Apo A1, VLDL-c, oxLDL, oxHDL, Lp(a), oxLp(a), NMR-LP-4
- Blood serum inflammation biomarkers
  - Interleukin-6 (IL-6), IL-1β, IL-17, tumor necrosis factor-alpha (TNF-α), osteoprotegerin, high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), and monocyte chemoattractant protein-1 (MCP-1)
- Blood serum HDL efflux efficiency
  - ABCA-1

6.5.3 Coronary Imaging

Change in coronary artery perivascular fat attenuation index (FAI) measured by CCTA at Week 15 for participants.

6.5.4 Plaque Burden and Characteristics

Change in Noncalcified and low attenuation coronary artery plaque volume, assessed by CCTA at week 15 as compared to Baseline, in active and placebo patients.

Change in total plaque volume, assessed by CCTA at week 15 as compared to Baseline, in active and placebo patients.

7 ADVERSE EVENTS AND SAFETY REPORTING

7.1 Safety and Tolerability Assessments

Safety and tolerability will be assessed on an ongoing basis by review of reported AEs, physical examinations, vital signs (SBP/DBP and heart rate), and clinical safety labs (hematology and serum chemistry).

7.2 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the pharmaceutical product treatment. An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the subject's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that subject. Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first randomized dose of study treatment (active or placebo).

Clinically meaningful (for a given subject) changes in physical examination findings and abnormal objective test findings (e.g., laboratory or X-ray) should also be recorded as AEs.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms or is of clinical concern.
2. Test result requires additional diagnostic testing or medical/surgical intervention.
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
4. Test result leads to any of the outcomes included in the definition of a SAE.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet condition 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

7.3 Definition of a Serious Adverse Event

A SAE is defined in 21 CFR 312.32(a) as follows:

> An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
>
> - Death.
> - Life-threatening AE.
> - Inpatient hospitalization or prolongation of existing hospitalization.
> - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or the subject requires medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

7.3.1 Life-Threatening Adverse Event

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

7.3.2 Hospitalization

This is defined as the subject being hospitalized overnight, or the subject’s hospital stay being prolonged for at least an additional overnight stay. Preplanned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization. “Twenty-three-hour hospitalizations” for observation should be discussed with the medical monitor to determine whether they are appropriate for SAE reporting.

7.3.3 Pregnancy

Female subjects must be surgically sterile (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or if a female subject is of childbearing potential, she must agree to use a medically acceptable highly effective method of contraception during the study and for 90 days after the last dose of study drug to be eligible for participation in the study (see Inclusion Criteria, Section 4.2; and Contraceptive Measures, Section 5.10.2). All female subjects must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at day 1 prior to dosing to be eligible for the study. A urine pregnancy test will also be performed at the end of study at the post-treatment Follow-up Visit.

7.3.4 Subject Withdrawal

If the subject discontinues study treatment due to an AE and withdraws from the study, the reason for the subject withdrawal is to be recorded as due to a specific AE.

7.4 Eliciting and Reporting of Adverse Events

AE monitoring will start immediately following the first dose at Visit 1 and will continue through the Follow-up Visit. Any subject with a possible study treatment-related AE at the Follow-up Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether related or unrelated to study treatment that occurs within 30 days following the last dose of study treatment will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded in the subject's source documentation and in the eCRF.

Subjects will be instructed to report all AEs experienced during the study, and subjects will be assessed in clinic for the occurrence of AEs throughout the study. To avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs, including pretreatment and TEAEs, reported by the subject, observed, or otherwise identified by the Investigator or other Investigational Site personnel will be documented.

Medical conditions existing at Screening should be recorded as medical history. New or worsening pre-existing medical conditions or diseases are considered AEs if they arise or worsen after dosing (Visit 1) and should be recorded as AEs.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected following the first dose of study treatment at Visit 1 through the Follow-up Visit. Conditions leading to planned surgical procedures are not AEs if the condition(s) was (were) known before study treatment. In the latter case, the condition should be reported as medical history.

7.4.1 Routine Reporting of Adverse Events

All AEs, whether or not associated with study treatment, that are observed by the Investigator, other Investigational Site personnel, or the subject will be recorded in the subject's source documentation and on the AE page of the eCRF. An SAE listing generated based on the eCRF pages will be submitted to the Sponsor at regularly scheduled intervals to allow the Sponsor to meet expedited regulatory reporting requirements under 21 CFR 312.32 and regular regulatory reporting requirements under 21 CFR 312.33.

For each AE, the following information will be entered in the eCRF:

- Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event).
- Date of onset of any new AE or worsening of a previously observed AE.
- Date of resolution of the event (or confirmation ongoing).
- Whether the event is serious (per definition in Section 7.3), and if so, the reason it is considered serious.
- Severity of AE (per definition in Section 7.6).
- Assessment of the causality of the AE to the study treatment (per definition in Section 7.5).
- Action taken in treating the AE (including concomitant medications or therapies administered) and/or change in the study treatment administration or dose (including whether the study treatment was temporarily interrupted or discontinued).
- Outcome of AE (per definition in Section 7.7.1).

7.4.2 Reporting of Serious Adverse Events, Including Death

The Sponsor will adhere to all expedited regulatory reporting requirements as per 21 CFR 312.32.

If an SAE, including death occurs during this study or within 30 days following the last dose of the study treatment, the Investigator must notify the Medical Monitor **within 24 hours** after becoming aware of the event.

Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE Form within the time frames outlined in the protocol. This timeframe also applies to additional new information (Follow-up) on previously forwarded SAE reports.

Medical Monitor:

Carmen Margaritescu, MD
Safety Office, Integrium, LLC
Office: 714-210-6665
Cellular: 714-328-7083
Email: carmen.margaritescu@integrium.com

SAE Forms will be provided by the Sponsor or Sponsor designated CRO. If all information is not known at the time of initial reporting, an initial report should still be made. In the event there is a question as to whether the experience is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. For all SAEs, the Investigator must pursue and provide information to the study Medical Monitor in accordance with the timeframes for reporting specified above. In general, this will include a description of the AE in enough detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Medical Monitor.

In the event of a medical emergency for an SAE that is unexpected (as defined in Section 7.7) and possibly related to the study treatment(s) (i.e., an adverse reaction or suspected adverse reaction as defined in Section 7.4), the Investigator in consultation with the Medical Monitor may request that a blind be broken in instances when the knowledge of the assigned treatment may impact the subjects' medical management.

The initial SAE Form and any subsequent Follow-up SAE Forms submitted to provide more accurate, corrected, or new information must be signed by the Investigator. The Investigator and Investigational Site Personnel must make every reasonable effort to obtain, from other institutions if necessary, all supporting medical case records as needed to comply with expedited Investigational New Drug application (IND) safety reporting requirements.

If the SAE involves expedited IND safety reporting (as determined by the Sponsor or designee), all supporting medical records must be submitted to the Sponsor or designee within 4-calendar days for death or life-threatening events, and 10 calendar days for all other events. In cases where medical records and supporting documentation are unobtainable, the Investigator must generate a narrative of the event utilizing, when necessary, interviews with the subject, their family members and care givers as appropriate.

The Investigator must also promptly inform the governing IRB of the SAE in accordance with the governing IRB's requirements. Any SAE that is determined by the Sponsor to be reportable

to the FDA as an IND Safety Report (as defined in 21 CFR 312.32) will be reported to FDA by the Sponsor or designee within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his/her IRB. Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor or designee within the specified time frames and will be provided to the Investigator for submission to his/her IRB.

The SAE report will evaluate the relationship of the adverse experience to study treatment and underlying disease. Based on this assessment, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study treatment raises concern over the safety of continued administration of study treatment, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol.
2. Discontinuation or suspension of the study.
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings.
4. Modification of previously identified expected adverse experiences, to include adverse experiences newly identified as study treatment related.

7.4.2.1 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study medication, the Investigator should report the pregnancy to Integrium within 24 hours of being notified. Safety personnel will then forward the Exposure In-Utero form to the Investigator for completion.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.5 Causality Assessment of Adverse Events

For all AEs, the Principal Investigator will provide an assessment of causal relationship to the study drug. The causality assessment must be recorded on the appropriate AE reporting page of the subject's CRF. Causal relationship will be classified according to the following criteria:

- *Unrelated*: The event is clearly due to causes other than the active study drug.
- *Unlikely*: The event is doubtfully related to active study drug. The event was most likely related to other factors such as the subject's clinical state, concomitant drugs or other therapeutic interventions.

- *Possible*: The event follows a reasonable temporal sequence from the time of active study drug administration but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.
- *Probable*: The event follows a reasonable temporal sequence from the time of active study drug administration and follows a known response pattern to the drug. The toxicity cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs.
- *Definite*: The event follows a reasonable temporal sequence from the time of active study drug administration, follows a known response pattern to the drug, cannot be reasonably explained by other factors such as the subject's condition, concomitant drugs or therapeutic interventions, AND either occurs immediately following active study drug administration, improves on stopping the study drug, or reappears on re-exposure.

7.6 Adverse Event Severity Assessment

The severity of each AE will be graded according to the NCI CTCAE, version 5. The severity of AEs that are not specifically listed in the CTCAE will be categorized according to the general guidelines provided in the CTCAE, and as summarized in the table below.

Table 3: General Guidelines for Severity Assessment of Adverse Events

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.].
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above in Section 7.3.

7.7 Expectedness of Adverse Event

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

> An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.7.1 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to International Council for Harmonisation (ICH) Topic E2B, ICH Guideline.

- **Recovered/Resolved:** The subject has recovered fully from the AE without any remaining effects or impairment.
- **Recovered/Resolved with Sequelae**: The subject has recovered, but with an after effect possibly due to disease or treatment.
- **Not Recovered/Not Resolved:** The condition is still present.
- **Fatal:** Fatal should only be used when death is possibly related to the AE.
- **Unknown**: If an outcome for an AE is not available at the time of the initial report, Follow-up will proceed until an outcome is known or followed up to the Final Study Visit. Any subject with a possible study treatment-related AE at the Final Study Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related to Study treatment (active or placebo), that occurs within 30 days following the last dose of Study treatment will be followed until resolution or stabilization of the event.

7.8 Clinical Findings

Any significant clinical findings at the Follow-up Visit will be followed until the condition returns to pre-study status, stabilizes, or can be explained as not being study treatment related. If the clinical finding is reported as an AE (per the criteria outlined in Section 7.4), the Follow-up procedures for AEs defined above will apply.

8 STATISTICAL METHODS

This section describes the statistical methods to be used for the analysis and reporting of data collected under Protocol No. Ort-2020-01. Additional details will be provided in the statistical analysis plan.

8.1 Sample Size Justification

No formal statistical assessment, in terms of sample size, was conducted for the endpoints analyzed in this study. Given the typical placebo response rates of 0-10% in psoriasis clinical trials, it is assumed that a 2:1 randomization involving at least 40 subjects on orticumab or placebo will allow for the exploration of meaningful measure of efficacy.

Subjects will be stratified by five geographic regions: Northeast, Southeast, Upper Midwest (including Alaska); Lower Midwest; and West Coast (Including Hawaii).

8.2 General Considerations

All data will be listed, and sorted by subject, visit, and time. Descriptive summaries will be presented using summary statistics and, where applicable, 95% confidence intervals (CIs), for continuous parameters or frequency distributions (n, %) for categorical parameters. Statistical Applications Software (SAS®) version 9.4 or later will be used to derive all calculations and generate all analyses.

8.3 Study Analysis Data Sets

Safety population: All subjects who receive at least one dose of study drug will be included in the safety population.

PK/PD population: All subjects who receive the study drug and for whom at least 1 trough PK concentration is collected will be included in the PK/PD population.

8.4 Efficacy Analysis

8.4.1 Primary Efficacy Evaluation

There are two primary endpoints for this study: Percent change in PASI and sIGA response rate.

Percent change in PASI will be analyzed using a linear mixed model analysis. The model will be implemented using PROC MIXED in SAS, and will include fixed effects for treatment, site and Baseline PASI as a covariate.

The sIGA response rate will be analyzed using Fisher's Exact Test with treatment and response as the factors.

8.4.2 Secondary Efficacy Evaluation

Continuous variables will be analyzed using a linear mixed model similar to the primary efficacy evaluation.

Response rates and other dichotomous variables will be analyzed using Fisher's Exact Test.

Categorical data that has more than two possible responses will be analyzed using the Cochran-Mantel-Haenszel Row Mean Score.

8.5 Demographic/Baseline Information

Demographic and Baseline characteristics will be summarized by treatment sequence, gender, and overall. For continuous variables, mean, standard deviation, median, minimum, and maximum will be presented. For categorical variables, N and % will be presented.

8.6 Analysis of Pharmacokinetic Data

Trough PK concentration will be summarized using mean, standard deviation, geometric mean, median, minimum and maximum values.

8.7 Analysis of Safety Data

8.7.1 Adverse Events

AEs will be coded using the most current version of MedDRA. The severity of AEs will be graded according to CTCAE version 5. AEs will be regarded as "pretreatment" if they occur prior to Visit 1/Day 1. Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first dose of the study drug on Visit 1/Day 1.

The incidence of TEAEs will be tabulated by MedDRA preferred term, system organ class, treatment group, severity, and assigned relationship to study drug. The incidence for each TEAE will be provided as the total number of subjects that experienced the TEAE, as well as the percentage of the population that this represents. If a TEAE is reported more than once for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

TEAEs will be listed for individual subjects, along with information regarding onset and end dates, onset time where available, severity, seriousness, relationship to study drug, action taken, and outcome. A similar listing will be prepared for the pretreatment AEs.

Pretreatment AEs and TEAEs that lead to withdrawal from the study will be separately listed and summarized. Similarly, separate tabulations and listings will be prepared for pretreatment and treatment emergent SAEs.

Descriptive statistics will be generated as appropriate (i.e., frequency for categorical data). Inferential statistical analysis comparing the AE data between active and Placebo is not planned.

8.7.2 Laboratory Evaluations

Individual clinical safety lab (hematology and serum chemistry) values will be listed by visit and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Individual change from Baseline (Screening) in laboratory values will be calculated and summarized descriptively. Shift tables from Baseline (Screening) to post-dose (Visit 7) will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from Baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.7.3 Vital Signs

Individual vital sign measurements (seated SBP/DBP and heart rate) will be listed by measurement time and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation). Individual change from Baseline (pre-dose Visit 1) in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from Baseline (pre-dose Visit 1) will be recorded as a TEAE if deemed appropriate by the Investigator.

8.7.4 Physical Examination

Individual physical examination findings will be listed by visit. A clinically significant change from Baseline (Screening to Visit 8) will be recorded as an AE if deemed appropriate by the Investigator.

8.7.5 Height and Weight

Height and weight will be listed by measurement time and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation).

8.7.6 Prior and Concomitant Medications and Supplements

Medications and supplements will be coded using the most current version of the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

All medications and supplements (other than the study drug) taken by the subject from Visit 1 through Visit 8 will be considered "concomitant" medications and supplements. Medications and supplements taken prior to Visit 1 that are no longer being taken at the time of Visit 1 will be considered "prior" medications and supplements.

Concomitant medications and supplements will be listed for individual subjects. A similar listing will be prepared for prior medications and supplements taken within 30 days prior to the first dose of study drug. The incidence of these prior and concomitant medications and supplements will be summarized.

8.7.7 Handling of Missing, Unused, or Spurious Data

Descriptive statistics and listings will be provided for all data. No substitution of missing data will be used in any calculations. Data points that appear to be spurious will be investigated and will not be excluded from the listings. Influential cases will be handled in an appropriate statistical manner.

8.8 Interim Analysis

This study will utilize a modified adaptive design model. There will be 2 planned stages for the analysis. Stage 1 will consist of the first 30 randomized subjects. After enrollment is completed for Stage 1, enrollment will begin for Stage 2 (there will be no pause in enrollment).

In order to ensure an overall alpha of approximately 0.05, Stage 1 will be analyzed at an alpha level of 0.01 and the final analysis (Stage 1 and Stage 2 combined) will be analyzed at an alpha level of 0.04. A hierarchical testing strategy will be utilized in which the percentage change in PASI will be tested initially. If the p-value for this initial test is less than the indicated alpha level, the result will be concluded as real. If the percentage change in PASI is concluded as real, the change in sIGA will be tested at the indicated alpha level.

In order to preserve type I error, the method presented by Cui, et al will be used to combine the data from Stage 1 and Stage 2. [22]

The planned number of subjects for the study is 75. Stage 1 will consist of the first 30 subjects, so the weight given to Stage 1 in the analyses will be 30/75 (0.40). The weight given to Stage 2 in the analyses will be 45/75 (0.60).

The combining of the Stage 1 and Stage 2 analyses will be performed as follows:

- The Stage 1 p-value will be converted to a Z score (standard normal score).
- The Stage 2 p-value will be converted to a Z score (standard normal score).
- The Z scores will be combined using the weights previously indicated to create the combined Z score.
- The combined Z score will be converted to a p-value.

9 DATA MANAGEMENT

9.1 Data Collection

All data required by the study protocol will be collected in a validated database according to the CRO's standard operating procedures (SOPs).

9.1.1 Electronic Data Capture

Data from the source documents will be entered into the EDC system by authorized Investigational Site personnel. Data Management staff, using both electronic and manual checks, will systematically check the data. Errors or omissions will result in queries (that can be issued by the Study Monitor or Data Management staff), which will be presented to the Investigational Site within the EDC system. The Investigational Site will resolve the queries within the EDC system. The Study Monitor and Data Management staff will review the responses as part of the query resolution process. The EDC system will track the queries with the corresponding responses.

Medications and supplements entered into the database will be coded in the EDC system using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. AEs and medical history will be coded in the EDC system using MedDRA terminology.

Laboratory samples will be processed by the Central Laboratory. Results will be reported to Integrium and imported into the database.

9.2 Quality Assurance and Database Lock

A 100% critical variable review of all key safety and secondary endpoint data in the database will be performed. Following this review, a data quality control audit or a random sample equal to 10% of subjects, with a minimum of 5 subjects will be performed.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, the Investigator, Integrium, and the study biostatistician.

10 AMENDMENTS/MODIFICATIONS OF THIS PROTOCOL

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. As the study progresses it may become necessary to change or modify parts of the protocol. The Sponsor or designee is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB. Approval by the IRB must be obtained before changes are implemented.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the study. The eCRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB will be notified in writing of such departure from protocol.

11 INVESTIGATOR OBLIGATIONS

11.1 Regulatory Documentation

Before the trial starts, Essential Documents, as defined in ICH E6 will be generated and placed in both the Investigator's and Sponsor's files. Additional Essential Documents will be added to both files as new information becomes available and at the completion or termination of the trial as defined in ICH E6.

11.2 Protection of Human Subjects

11.2.1 Declaration of Helsinki

The Investigator will conduct this study in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the October 2013 revision.

11.2.2 Good Clinical Practice and Regulatory Compliance

The Investigator will conduct this study in accordance with the principles of GCP (current ICH guidelines) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The study will be conducted as described in the approved protocol, with amendments and in accordance with the obligations of clinical Investigators set forth in the Form FDA 1572 and in 21 CFR 50, 54, 56, and 312.

11.2.3 Institutional Review Board

The Investigator is responsible for the submission of the protocol, ICF, and other written materials (such as advertisements and diaries), along with relevant supporting data (e.g., IB), to

the appropriate IRB for review and approval before the study can be initiated. The Investigator is also responsible for submitting amendments to the protocol and ICF to the IRB for review and approval prior to implementation of the change. The Investigator is responsible for providing the Sponsor with a letter documenting the IRB approval prior to initiation of the study or implementation of the changes, respectively.

The Investigator will not have authority to implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation from the approved protocol will be documented in the source documents and eCRF.

Any deviation or change to the protocol required to eliminate an immediate hazard prior to obtaining IRB approval/favorable opinion, will be submitted as soon as possible to:

- IRB for review and approval/favorable opinion.
- The Sponsor via appropriate designees.
- Regulatory Authorities, if required by local regulations.

Documentation of IRB approval signed by the chairperson or designee of the IRB will be provided to the Sponsor via appropriate designees.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the ICF will be revised and submitted to the IRB for review and approval/favorable opinion; (2) the revised ICF will be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new ICF will be used to obtain consent from any new subjects prior to enrollment.

The Investigator is responsible for informing the IRB of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB by the Investigator.

The Investigator is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The Investigator must inform the IRB when the study is completed or terminated. After completion or termination of the study, the Investigator will submit the final clinical study report to the IRB. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonised Tripartite Guideline, dated November 30, 1995).

11.2.4 Subject Informed Consent

The Investigator must comply with informed consent regulations (21 CFR Part 50) and relevant state regulations (i.e., California Bill of Rights for California subjects).

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and will include any

additional elements required by the Investigator's institution or local regulatory authorities. The ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Investigator will obtain the IRB's written approval/favorable opinion of the written ICF. The IRB approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The ICF and any other information provided to subjects will be revised whenever important new information becomes available that is relevant to the subject's consent, and the Investigator will obtain the IRB's written approval/favorable opinion prior to the use of the revised documents. The Investigator, or a person designated by the Investigator, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. Subjects will read and sign any and all revised ICFs.

11.3 General Aspects

All information concerning Sponsor, such as patent applications, formula, manufacturing processes, basic scientific data, or formulation information supplied by Sponsor and not previously published, are considered confidential and shall remain the sole property of Sponsor.

The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of Sponsor, except for official representatives, such as regulatory authorities.

It is understood by the investigator that the information derived from this clinical study, in connection with the development of orticumab, will be used by Sponsor and, therefore, may be disclosed by Sponsor as required to other clinical investigators, other pharmaceutical companies, and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to Sponsor complete test results and all data compiled in this study.

11.4 Subject Confidentiality and Data Protection

Sponsor and its designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be linked to the CRF via a unique identification number and the subject's initials. The data will be blinded correspondingly in all data analyses.

However, in compliance with the guidelines of the US FDA concerning the acceptance of clinical studies in support of a New Drug Application (NDA) and the ICH Guidelines (whether performed in the United States or elsewhere), and in fulfillment of its obligations to Sponsor to verify compliance with this protocol, Sponsor designee requires that the investigator permit its study monitor, representatives from FDA, Sponsor-designated auditors, IRBs, and other governmental regulatory authorities to review the subject's primary medical records (source data or documents), including but not limited to laboratory test result reports, admission and

discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports of deaths occurring during the study.

Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the investigator will obtain such permission in writing from the subject before the subject is entered into the study.

11.5 Compliance with the Protocol

The investigator will agree to implement the study protocol as written and adhere to the guidelines stated in the investigator's statement, which will be signed by the investigator prior to the start of the study. The study will be performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) GCP guidelines.

Any noncompliance to the protocol should be discussed with Sponsor. All deviations from the regimen defined above should receive written approval from the study medical monitor, must be explained, and the reason entered on the CRF. Sponsor retains the right to require the withdrawal of any subject who violates the protocol.

11.6 Case Report Forms

The eCRFs will be provided by validated electronic data capture screens. All subject data generated during the study will be recorded on the source documents and transcribed to the electronic data capture screens through a web browser for entry into a validated electronic database by way of a secure internet connection.

The investigator and clinical research associate (CRA) will ensure that all data are entered promptly, completely, and accurately, and conform to source documents, in accordance with specific instructions accompanying the eCRFs. Any corrections will be recorded by an audit trail. The audit trail will include the user identification of the person making the change and the date the change was made, and an explanation why the change was made.

The study monitor will verify the entered data against the source document and issue manual queries. The query text will be manually entered by the monitor. These queries will then be available for the site entry personnel for responses.

Integrium will only consider eCRFs to be complete when each eCRF has been reviewed and signed by the CRA, data manager and, ultimately, the investigator, indicating their assurance of the accuracy of all recorded data. It is expected that the investigator and his or her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

Laboratory data will be collected electronically and transferred to the CRO handling the eCRF data for integration with the eCRF data.

If data changes are required to the database, queries will be issued. If external data need to be modified, the laboratory vendor will provide updated data with appropriate documentation.

11.7 Verification Procedures

In fulfillment of their obligations to Sponsor and to verify compliance with this protocol, ICH GCP, and the FDA CFR, the investigator is required to authorize direct access to the subject's medical records by Integrium, IRBs, and regulatory authorities. It is the investigator's obligation to ensure the documentation of all relevant data in the subject's medical record. The subject's medical record will be considered the source document for the following information, which may not be recorded directly into the eCRF: medical history/concomitant disease, subject identification number, confirmation of informed consent and the date of study enrollment, visit dates, administration/compliance of study medications, AEs (start and stop dates), and all concomitant medications (start and stop dates).

The investigator will maintain a subject identification code list to enable unambiguous identification of each subject's name and corresponding subject number. The subject identification code list is an essential document and will be maintained according to ICH GCP guidelines.

11.8 Retention of Records

All documentation pertaining to the study will be kept by Integrium in accordance with FDA regulations until a transfer to Sponsor or their designee is requested in writing by Sponsor. The study site will maintain a study file, which should contain the IB; protocol; drug accountability records; correspondence with the IRB, Sponsor, and BAI; and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating subjects, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all CRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities and Sponsor or its designees.

The investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. However, these documents should be retained for a longer period if required by the applicable local regulatory requirement(s) or if needed by the sponsor. In addition, the investigator must make provision for the subject's medical records to be kept for the same period of time.

No data should be destroyed without the agreement of the sponsor. Sponsor will inform the investigator in writing when the trial-related records are no longer needed.

Subjects' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

11.9 Insurance and Indemnity

In the event that a subject suffers injury or death directly attributable to participation in this study, appropriate treatment and/or compensation will be provided by and/or paid to the subject by Sponsor in accordance with applicable federal and international laws and/or guidelines.

11.10 Clinical Study Report and Publication Policy

All information regarding this study shall be kept strictly confidential. All data derived from the study shall be the property of Sponsor. The investigators must not undertake submitting any part of the data from this study for publication without prior consent of Sponsor. Sponsor may disclose data derived from the study to other investigators and drug regulatory authorities.

After completion of the study, the investigator (upon agreement with Sponsor) may prepare a publication and shall send a draft manuscript of the publication to Sponsor to reach agreement between the investigator and Sponsor on the contents of the publication. The investigator shall receive written approval from Sponsor prior to submission of the final version for publication.

At the conclusion of the study, after the data are analyzed, Sponsor or their designee will prepare a final clinical study report.

12 STUDY ADMINISTRATION

12.1 Study Monitoring

This study will be monitored by the Sponsor or designee to evaluate the progress of the study, to verify the accuracy and completeness of the eCRFs, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the Study Monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each subject in the study.

The Study Monitor will compare the eCRF data against source documentation in order to verify its accuracy and completeness. The Investigator and Investigational Site staff will collaborate with the Study Monitor to resolve any identified data discrepancies in a timely manner.

The Study Monitor will record any protocol deviations identified, including, but not limited to, subjects that were enrolled even though they did not meet all eligibility criteria, subjects who took concomitant medications, subjects who received the wrong study drug or incorrect dose, and subjects who failed to comply with the protocol-defined dietary restrictions. The Investigator and Investigational Site staff will collaborate with the Study Monitor to identify the reason for each protocol deviation.

The Study Monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and Investigational Site staff will collaborate with the Study Monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

12.2 Internal Safety Review Committee

The ISRC will review the blinded safety data after the first subject completes the first dose (Day 1), the first five subjects complete the first dose (Day 1), and the first ten subjects complete the first dose (Day 1). The IRSC will review all adverse reactions to all administered doses at these times. Thus, all doses administered beyond the first dose will be reviewed in patients 1-4 and 1-9 at the time of the 5th and 10th subjects completing the first dose review.

The ISRC consists of the Principal Investigators (mainly those responsible for the subjects under review), the trial medical monitor, and the Sponsor.

The committee will focus on treatment-emergent AEs (defined as AEs that begin or worsen after the first dose of IP) in determining if infusions in existing and future subjects may continue.

Stopping Criteria:

1. A death within 30 days after study treatment administration where there is a reasonable possibility that the drug caused the event.

2. Any CTCAE Grade 4 (Life Threatening) event by Investigator judgment considered reasonably related to the study drug. (This does not include non-life threatening SAEs.)

3. Any two CTCAE Grade 3 (Severe) event considered related to the study drug.

12.3 On-Site Audits

The FDA, or other regulatory authorities, may request access to all study records for inspection and copying. The Principal Investigator and Investigational Site staff will cooperate with the

inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for the purpose of conducting an inspection.

The Sponsor or designee may also request to visit the Investigator's site to conduct an audit of the study. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Principal Investigator and Investigational Site staff will cooperate with the auditors and allow access to all source documents supporting the eCRFs and other study-related documents.

12.4 Data Quality Assurance

All eCRFs must be completed by authorized Investigational Site personnel who have undergone eCRF training. Data will be entered into the eCRF as information becomes available on a visit-by-visit basis. All data recorded on the eCRFs must be supported by source documentation. The Principal Investigator must verify that all data entries in the eCRF are accurate and correct by electronically signing and dating the eCRF.

All eCRF corrections must be made by the Principal Investigator or authorized Investigational Site personnel. The Principal Investigator must authorize changes to the recorded data, and this authorization must be documented in the source documents.

Refer to Section 9 for further details regarding Data Management quality assurance, including query generation and resolution, final data review, and database lock.

12.5 Final Report and Publication Policy

All information regarding this study shall be kept strictly confidential. All data derived from the study shall be the property of Sponsor. The investigators must not undertake submitting any part of the data from this study for publication without prior consent of Sponsor. Sponsor may disclose data derived from the study to other investigators and drug regulatory authorities.

After completion of the study, the investigator (upon agreement with Sponsor) may prepare a publication and shall send a draft manuscript of the publication to Sponsor to reach agreement between the investigator and Sponsor on the contents of the publication. The investigator shall receive written approval from Sponsor prior to submission of the final version for publication.

At the conclusion of the study, after the data are analyzed, Sponsor or their designee will prepare a final clinical study report.

12.6 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor and Integrium in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor and Integrium (protocols, IBs, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor and Integrium to the Investigator may not be disclosed to others without direct written authorization from the Sponsor and Integrium, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

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