Janssen EMEA *

Clinical Protocol

Protocol Title
A Phase 4, Interventional, Single-arm, Open-label Study Evaluating the Effect of Guselkumab on Cardiovascular Risk Surrogate Markers in Participants With Moderate to Severe Plaque Psoriasis

G-CARE

Short Title
Effect of Guselkumab on Cardiovascular Risk Surrogate Markers in Participants With Moderate to Severe Plaque Psoriasis

Protocol CNTO1959PSO4015; Phase 4
Amendment 2

CNTO1959 (guselkumab)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	13 May 2022
Amendment 1	12 May 2021
Original Protocol	1 April 2021

Amendment 2 (13 May 2022)

Overall Rationale for the Amendment: To ensure exclusion criterion regarding low density lipoprotein (LDL) cutoff value (above which statin therapy should be initiated) is in line with the guidelines for management of dyslipidemia by the European Society of Cardiology.

Section Number and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria.	Updated the LDL cutoff-value from 160 mg/dL to >190 mg/dL in Exclusion Criterion 1.	To bring cutoff value in line with the guidelines for management of dyslipidemia by the European Society of Cardiology.
Section 3 Objectives And Endpoints.	Updated secondary endpoint from "Change from baseline in coronary flow reserve (CFR) at Week 16 **and Week 24** among participants with CFR in the ranges of 2 to 2.49, 2.5 to 3, and 3.01 to 3.5 at baseline" to "Change from baseline in CFR at Week 16 **and Week 32** among participants with CFR in the ranges of 2 to 2.49, 2.5 to 3, and 3.01 to 3.5 at baseline".	To ensure consistence with all other endpoints throughout the protocol.
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (12 May 2021)

Overall Rationale for the Amendment: The protocol was amended to include tests and measurements to screen study participants for metabolic syndrome. In addition, the method used for calculation of body surface area (BSA) affected by psoriasis was updated, and the latest versions of the patient reported outcomes (PRO) questionnaires were added to the protocol.

Section Number and Name	Description of Change	Brief Rationale
Schedule of Activities.	• Measurement of waistline circumference was added as part of physical examination at Screening Visit S1. • The lipid panel was changed to include metabolic tests, and serum glucose and serum insulin tests were added to the panel.	To screen study participants for metabolic syndrome.
Schedule of Activities.	Foot note "g" pertaining to cardiology assessments was updated.	To ensure participant comfort and compliance, participants who have fasted for the lipid and metabolic panel at Weeks 16 and 32 will be permitted to have a non-caffeinated drink prior to the cardiology assessments.
Section 8: Study Assessments and Procedures.	Text in the "Study Visits Weeks 16 and 32" section was updated.	To ensure participant comfort and compliance, participants who have fasted for the lipid and metabolic panel at Weeks 16 and 32 will be

Section Number and Name	Description of Change	Brief Rationale
		permitted to have a non-caffeinated drink prior to the cardiology assessments.
Section 8.1.2: Psoriasis Assessments.	The section "Body Surface Area" was updated, and a new reference was added.	Text consistent with the updated "Rule of 9" calculation for BSA measurement was added.
Section 8.2.1: Physical Examination.	Measurement of waistline circumference was added to the list of physical examinations.	To screen study participants for metabolic syndrome.
Section 10.2 Appendix 2: Clinical Laboratory Tests.	The lipid panel was changed to include metabolic tests, and serum glucose and serum insulin tests were added to the panel.	To screen study participants for metabolic syndrome.
Section 10.7 Appendix 7.	A new "Appendix 7: Body Surface Area" was added.	The new appendix is consistent with the updated "Rule of 9" used for BSA measurement.
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 4, Interventional, Single-arm, Open-label Study Evaluating the Effect of Guselkumab on Cardiovascular Risk Surrogate Markers in Participants With Moderate to Severe Plaque Psoriasis

Effect of Guselkumab on Cardiovascular Risk Surrogate Markers in Patients With Moderate to Severe Plaque Psoriasis

Guselkumab is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 protein subunit of human interleukin 23 (IL-23) with high specificity and affinity. Binding of guselkumab to the IL-23 p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. Guselkumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. However, there may be potential benefits for guselkumab beyond those related to skin clearance. The promising results of IL-12/23 inhibition in the Vascular Inflammation in Psoriasis-Ustekinumab (VIP-U) study, combined with the role of IL-23 in the early stages of atherogenesis, suggest a potential benefit of IL-23 inhibition on vascular inflammation. This study aims to investigate the effect of guselkumab on surrogate markers of cardiovascular risk in participants with moderate-to-severe plaque psoriasis.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the effect of guselkumab on CFR measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk*.	• Change from baseline[‡] in CFR at Week 32.
Secondary	
To evaluate the short-term effect of guselkumab on CFR measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in CFR at Week 16.
To evaluate the effect of guselkumab on GLS as a surrogate marker of left ventricular function in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in GLS at Week 32. • Change from baseline in GLS at Week 16.
To evaluate the effect of guselkumab on arterial stiffness in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in cfPWV at Week 32. • Change from baseline in cfPWV at Week 16.
To evaluate the effect of guselkumab on CFR among participants in the different CFR categories.	• Change from baseline in CFR at Week 16 and Week 32 among participants with CFR in the ranges of 2 to 2.49, 2.5 to 3, and 3.01 to 3.5 at baseline.
To evaluate the effect of guselkumab on surrogate CV risk markers among nicotine users and non-users in the participant population.	• Change from baseline in CFR at Week 16 and Week 32 among nicotine users and non-users. • Change from baseline in GLS at Week 16 and Week 32 among nicotine users and non-users. • Change from baseline in cfPWV at Week 16 and Week 32 in nicotine users and non-users.

Objectives	Endpoints
To assess the safety and tolerability of guselkumab in participants with moderate-to-severe plaque psoriasis and intermediate cardiovascular risk.	• Rate of AEs among participants treated with guselkumab.

*Intermediate cardiovascular risk defined by CFR ≥2 and ≤3.5 at Screening Visit S2.
† cfPWV, GLS and CFR measurements at Week 0 will be considered as the baseline value. CFR must not be <2 or >3.5 at both Screening Visit S2 and Week 0.
Abbreviations: AE= Adverse event; cfPWV = carotid-femoral pulse wave velocity; CFR= Coronary Flow Reserve; GLS: Global Longitudinal Strain

Hypothesis

The primary hypothesis of this study is that guselkumab (administered as 100 mg at Weeks 0, 4, 12, 20 and 28) is effective in reducing surrogate markers of cardiovascular risk as assessed by the change from baseline in CFR at Week 32.

OVERALL DESIGN

This is an interventional, single-arm, open-label, oligocentric study to evaluate the effect of guselkumab on cardiovascular risk surrogate markers in adult men and women diagnosed with moderate-to-severe plaque psoriasis (with or without PsA) for at least 6 months prior to study entry. Eligibility of the participants will be assessed at 2 screening visits; at Screening Visit S1, participants will be screened at the dermatology department based on skin assessments, medical history, and laboratory parameters. Participants fulfilling eligibility criteria at Screening Visit S1 will be referred to the cardiology department, and will undergo cardiologic assessments (GLS, CFR [via transthoracic doppler echocardiography] and cfPWV) at Screening Visit S2, and again at Week 0. Only participants with CFR ≥2 and ≤3.5 at both these time-points will be enrolled in the study. The CFR measurement at Week 0 will be considered as the baseline value.

NUMBER OF PARTICIPANTS

Following screening for inclusion into the study, approximately 50 participants will be enrolled to receive subcutaneous injections of guselkumab (100 mg). The number of dropouts in the study are expected to be low; however, additional participants will be entered to maintain the sample size and ensure that the protocol-specified number of participants complete the study.

Approximately 20 of the enrolled participants should be active nicotine users. All participants will be instructed to abstain from nicotine-containing and caffeinated products for at least 12 hours prior to the cardiology assessments.

INTERVENTION AND DURATION

Participants will receive guselkumab 100 mg SC injections at Weeks 0, 4, 12, 20 and 28.

The first dose of the guselkumab will always be administered at the site and by a health care professional (HCP). Subsequent doses can be self-administered at the site under supervision by site-staff after the participant has been adequately trained in the procedure.

The total duration of the study will be 40 weeks, including 28 weeks of treatment and a Final Efficacy Visit 4 weeks later (Week 32). A Final Safety Visit will occur 12 weeks after the last dose of the guselkumab (Week 40). For participants continuing to receive guselkumab commercially after the end of the study, the Final Safety Visit will occur on the same day as the first dose of guselkumab outside the study, ie, at Week 36.

EFFICACY EVALUATIONS

The following key assessments will be carried out as detailed in the Schedule of Activities. Efficacy assessments will be done locally at the sites. Results of the GLS and CFR assessments, along with other cardiology data, will be reviewed by a cardiology core lab for blinded analysis of endpoints.

- Carotid-femoral Pulse Wave Velocity
- Global Longitudinal Strain for left ventricular function
- Coronary Flow Reserve

SAFETY EVALUATIONS

The safety and tolerability of guselkumab will be monitored by collecting information on adverse events, clinical laboratory tests, physical examinations, vital signs, and concomitant medication review through Week 40.

STATISTICAL METHODS

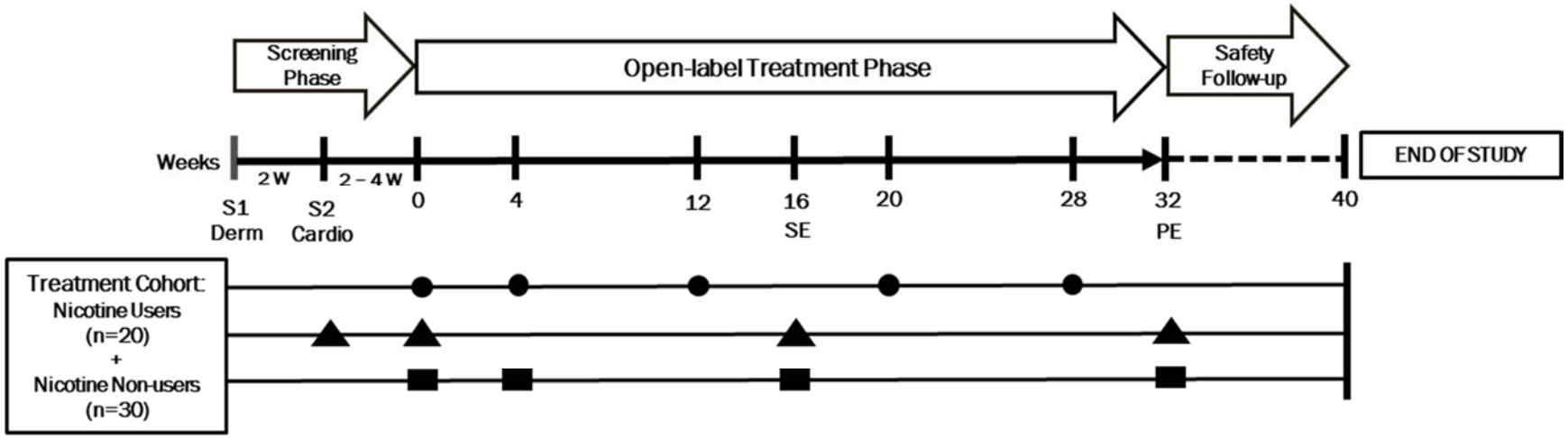
The sample size calculation is based on the assumption that participants will show an average improvement of 20% in CFR at Week 32. To detect a CFR mean change of 0.3 from baseline with 80% power, and assuming a standard deviation of 0.8 and a 5% dropout rate, 50 participants are expected to be enrolled in the study. Sample size may be increased if the dropout rate is higher than expected, in accordance with the sample size assumptions stated above.

INTERIM ANALYSIS

An interim analysis will be performed after a sufficient proportion of the participants (to be defined during the study) have accrued Week 16 CFR measurements. The scope of the interim analysis will be developed and documented in a statistical analysis plan. Other interim analyses may be planned based on specific questions from the medical field. The data from these interim analyses will allow for assessment of coverage and follow-up of participant types and treatment modalities to investigate specific research questions.

1.2. Schema

Figure 1: Schematic Overview of the Study



● = Guselkumab 100 mg s.c.

▲ = Cardiology Assessments (cfPWV, GLS and CFR)

■ = Biomarker Assessments

Visit Window between Screening Visit 1 and Screening Visit 2 = maximum of 2 weeks
Visit Window between Screening Visit 2 and Week 0 = minimum of 2 weeks and maximum of 4 weeks
CFR, GLS and cfPWV measurements at Week 0 will be considered as the baseline measurements

cfPWV = carotid-femoral pulse wave velocity; CFR = coronary flow reserve; GLS = global longitudinal strain; PE = Primary Endpoint; S1 = Screening Visit 1 (Dermatology Assessments); S2 = Screening Visit 2 (Cardiology Assessments); SE = Secondary Endpoint

1.3. Schedule of Activities (SoA)

Phase	Screening Visit S1 (Dermatology)	Screening Visit S2 (Cardiology)	Treatment Phase						Final Efficacy Visit [a]	Final Safety Visit [b]	Comments
Week	**Maximum of 2 weeks prior to Screening Visit S2**	**Minimum of 2 weeks and maximum of 4 weeks prior to Week 0**	**0**	**4**	**12**	**16**	**20**	**28**	**32**	**40**	
Visit Window (days)				**±7**		**-7 to +14**	**±7**		**-7 to +14**	**±7**	
Screening/Administrative											
Informed consent form	X										Must be signed before first study-related activity.
Review of inclusion/exclusion criteria	X	X	X								Refer to Section 5 to see the eligibility criteria assessed at each screening visit. Cardiology criteria to be assessed at the cardiology department at Screening Visit S2.
Demography/ medical history	X	X									At Screening Visit S1, presence of PsA, psoriasis and IBD to be recorded at the Dermatology Department. At Screening Visit S2, family history and first-degree relatives with cardiovascular events to be recorded at the cardiology department.
QuantiFERON-TB Gold test	X										Tests performed within 2 months before Week 0 are permitted.
HBV/HCV serology	X										
HIV antibody test	X										
Chest radiograph	X										May be taken within 3 months prior Week 0.
Guselkumab Administration											
Guselkumab SC [c]			X	X	X		X	X			Must be administered only on completion of all the laboratory tests, efficacy assessments, PROs and other procedures scheduled for that visit.

Phase	Screening Visit S1 (Dermatology)	Screening Visit S2 (Cardiology)	Treatment Phase						Final Efficacy Visit [a]	Final Safety Visit [b]	Comments
Week	**Maximum of 2 weeks prior to Screening Visit S2**	**Minimum of 2 weeks and maximum of 4 weeks prior to Week 0**	**0**	**4**	**12**	**16**	**20**	**28**	**32**	**40**	
Visit Window (days)				**±7**		**-7 to +14**	**±7**		**-7 to +14**	**±7**	
Safety Assessments											
Physical examination (including skin)	X		X	X	X	X	X	X	X	X	Waistline circumference must be measured and documented at Screening Visit S1.
TB	X		X	X	X	X	X	X	X	X	Specific questions about history of TB or known occupational/personal exposure to individuals with active TB to be asked.
Vital signs	X		X	X	X	X	X	X	X	X	Blood pressure, pulse/heart rate and temperature to be recorded at the dermatology study site prior to Screening Visit S2.
Height	X										
Weight [d]	X		X			X			X		
12-lead ECG	X										
Pregnancy test [e]	X	X	X	X	X	X	X	X	X	X	
Injection-site reaction evaluation			X	X	X		X	X			
Clinical Laboratory Tests											
Hematology, chemistry	X		X	X	X	X	X	X	X	X	Laboratory tests are described in Appendix 2.
Lipid and metabolic panel	X					X			X		Participants must fast (ie, no food or beverages, except water) for at least 8 hours before blood is drawn. Glucose and insulin will be measured as part of this panel.
HbA1c	X					X			X		
hsCRP	X		X			X			X		
Urinalysis	X		X			X			X		If there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally, protein and glucose levels must not

Phase	Screening Visit S1 (Dermatology)	Screening Visit S2 (Cardiology)	Treatment Phase						Final Efficacy Visit [a]	Final Safety Visit [b]	Comments
Week	**Maximum of 2 weeks prior to Screening Visit S2**	**Minimum of 2 weeks and maximum of 4 weeks prior to Week 0**	**0**	**4**	**12**	**16**	**20**	**28**	**32**	**40**	
Visit Window (days)				**±7**		**-7 to +14**	**±7**		**-7 to +14**	**±7**	
											exceed trace levels, one re-test is allowed.
Urine nicotine test [f]		X	X			X			X		
Efficacy Assessments											
cfPWV [g]		X	X			X			X		
GLS [g]		X	X			X			X		
CFR [g]		X	X			X			X		Must be measured before administration of guselkumab at Week 0. Measured by Transthoracic Doppler Echocardiography with adenosine as vasodilator. CFR should be conducted regardless of a positive urine nicotine test.
PASI	X		X	X	X	X	X	X	X		
BSA	X		X	X	X	X	X	X	X		
IGA	X		X	X	X	X	X	X	X		
PSQI			X			X			X		Paper PROs completed before any other tests, procedures, evaluations, or guselkumab administration on the day of the visit for Week 0 and other scheduled visits.
DLQI			X			X			X		
HADS (if available)			X			X			X		
AUDIT			X			X			X		
Biomarkers											
Serum sample collection			X	X		X			X		Including but not limited to: hsCRP, NT-proBNP, Cytokine-levels including IL-6, IL-17A, IL-17F, IL-22, IL-23, SAA1, SAA2, Olink analysis.
Plasma sample			X	X		X			X		Concentration of oxidative lipid damage (8-Isoprostane) and malondialdehyde, concentration of antioxidants (Vitamin C and Vitamin E), adipokines (leptin and adiponectin).

Phase	Screening Visit S1 (Dermatology)	Screening Visit S2 (Cardiology)	Treatment Phase						Final Efficacy Visit [a]	Final Safety Visit [b]	Comments
Week	**Maximum of 2 weeks prior to Screening Visit S2**	**Minimum of 2 weeks and maximum of 4 weeks prior to Week 0**	**0**	**4**	**12**	**16**	**20**	**28**	**32**	**40**	
Visit Window (days)				**±7**		**-7 to +14**	**±7**		**-7 to +14**	**±7**	
Urine sample			X	X		X			X		DNA damage markers (8-Oxo-7,8-dihydro2'-desoxyguanosine)
Ongoing Participant Review											
Concomitant therapy			X (throughout the study)								
Adverse events			X (throughout the study)								

Abbreviations: AUDIT= Alcohol Use Disorders Identification Test; BSA = body surface area affected by psoriasis; cfPWV = carotid-femoral pulse wave velocity; CFR= Coronary Flow Reserve; DLQI = Dermatology Life Quality Index; DNA= deoxyribonucleic acid; ECG = electrocardiogram; GLS: Global Longitudinal Strain; IL: interleukin; HADS: Hospital Anxiety and Depression Scale; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP= high-sensitivity C-reactive protein; IBD: Inflammatory bowel disease; IGA= Investigator Global Assessment; LV= left ventricular; NT-proBNP= N-terminal pro b-type natriuretic peptide; PASI = Psoriatic Area and Severity Index; PRO= Patient-reported Outcome; PsA= psoriatic arthritis; PSQI= Pittsburg Sleep Quality Index; SAA1=Serum amyloid A1; SAA2= Serum amyloid A2; SC= subcutaneous

Footnotes:

a. The Final Efficacy Visit should occur 4 weeks after the last dose of the guselkumab within the study. If a participant permanently discontinues guselkumab before Week 28, the Final Efficacy Visit should take place at the time of discontinuation, or as soon as possible, and all assessments scheduled for the Final Efficacy Visit should be performed.

b. The participant should return for a Final Safety Visit, 12 weeks after the last guselkumab dose. For participants opting to receive commercially available guselkumab after Week 28, the first dose of guselkumab outside the study (Week 36) should be considered as the Final Safety Visit.

c. Administered at the site by health care professional (HCP) at Week 0. Subsequent doses may be self-administered at the site under supervision up to Week 28.

d. BMI calculation is done automatically in the eCRF at each time-point when the weight is measured.

e. Women of childbearing potential who are dosed at the clinic must have a negative serum pregnancy test at Screening Visit S1 and a negative urine pregnancy test at all other visits. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the participation in the study.

f. Urine nicotine test to be done before any cardiology measurements (cfPWV, GLS and CFR). CFR should be conducted regardless of a positive urine nicotine test.

g. At the Week 16 and Week 32 visits, participants who have been fasting for the lipid and metabolic panel are permitted to have a non-caffeinated drink prior to the cardiology assessments. Cardiology assessments (cfPWV, GLS, CFR and other assessments) must be performed at the same lab using the same machines and software, and preferably by the same cardiologist/technician at every visit. If CFR measurement is unsuccessful, ie, if the acoustic window of the coronary artery cannot be properly found, 2 attempts to measure a CFR can be made on different days. In such cases, the visit window can be extended by 7 additional days (CFR visit window=-7/+14 days). Guselkumab must not be administered at Week 0 before a CFR measurement is successfully obtained.

2. INTRODUCTION

Psoriasis is a common chronic inflammatory disease that affects 2% 3% of the population and has an impact on physical and emotional health-related quality-of-life that is comparable to major illnesses such as cancer, heart disease and depression.[50] It is also increasingly viewed as a systemic inflammatory syndrome due to its association with serious comorbidities including:

- cardiovascular disease (CVD); including risk factors such as obesity, diabetes, hypertension, dyslipidemia,
- inflammatory bowel disease (IBD),
- mood disorders,
- kidney disease and
- malignancy.[55,61]

Psoriasis and Cardiovascular Comorbidities

Cardiovascular disease is of particular concern since it is a leading cause of death in people with psoriasis, who have an increased risk over healthy individuals; the absolute and excess risk of death is highest for cardiovascular disease (61.9 deaths/1000 and 3.5 deaths/1000 person years, respectively).[11] It is now considered likely that psoriasis confers an independent risk of myocardial infarction (MI),[23] which is relatively higher in young patients with severe psoriasis, whose risk of cardiovascular death increases from 5.5% to 8.2% compared with a control population (relative risk 57%).[41]

Research has revealed atherosclerosis to be a complex inflammatory and immune-mediated longitudinal process, occurring on a continuum over decades. In its earlier stages, coronary microvascular dysfunction, wherein the coronary microvasculature becomes increasingly less able to control delivery of blood to the myocardium by adjusting blood flow to meet demand, is a reversible event.[39] It is also associated with increased vascular smooth muscle tone, arterial stiffening, and thickening of vascular walls, which culminates in irreversible structural changes in the large pericardial vessels that are associated with adverse clinical outcomes such as myocardial ischaemia.[17,20,53,57]

The microvascular endothelium is capable of rapid and sensitive response to blood flow, physical stress, and a vast range of mediators including hormones, metabolites and neurotransmitters.[17,20,26] Classical vascular dysfunction and remodeling follows the disturbed blood flow model, which is based on dynamic endothelial responses that attempt to normalize altered shear stress and preserve constant coronary blood flow.[26,57] Chronic abnormalities in blood flow, such as uncontrolled hypertension, lead to adverse remodeling and thickening of medial walls and intima.[17,26,58] Endothelial shear stress also causes expression of inflammatory mediators and cellular adhesion molecules, which can amplify into a chronic inflammatory situation.[58]

More recent research has also shown that chronic systemic inflammation can also cause such coronary microvascular dysfunction, as is seen in diseases with elevated levels of pro-inflammatory cytokines such as psoriasis.[20] Emerging evidence shows overlap of the pathophysiological processes underlying psoriasis and atherogenesis. The interleukin (IL)-23/IL-17 axis is a key factor in psoriasis development and persistence, with IL-23 driving a downstream Th17 immune response involving an array of pro-inflammatory cytokines such as IL-17, IL-22 and Tumor necrosis factor (TNF).[13,23,31,41,43,45] There is also evidence for involvement of IL-23 in atherogenesis,[37,40,55] and high plasma levels of IL-23 have been associated with increased mortality during follow-up of patients with carotid plaques,[11] leading to its proposal as a novel target for treating atherosclerosis.[40]

As with shear stress-mediated remodeling, this inflammation-induced microvascular dysfunction is associated with increased incidence of major adverse cardiovascular events (MACE).[57] It is therefore likely that better clinical outcomes will be seen if the early stages of endothelial dysfunction and atheroma development can be limited, before irreversible structural changes occur. Accordingly, it has been proposed that patients with psoriasis should be candidates for early cardiovascular risk factor modification.[47]

The European Academy of Dermatology and Venereology (EADV) states that dermatologists are in a position for early CVD detection or referral of those at risk due to unhealthy lifestyle behavior.[46] In accord with the increased cardiovascular risk in these patients, European and North American psoriasis guidelines state that adults with severe psoriasis of any type should undergo a cardiovascular risk assessment at presentation and provide recommendations for continued monitoring, management, and patient education.[19,33,43,44,46,55] However, despite such recommendations, cardiovascular comorbidities in patients with psoriasis remain consistently underdiagnosed and undertreated.[12,23,37] Furthermore, given that psoriasis confers an independent risk for CVD, there is a need to evaluate the interactions between psoriasis therapies and markers of inflammation and cardiovascular health.[29]

Measurement of vascular dysfunction is challenging, as no technique can visualize the human coronary microvasculature in vivo. Therefore, indirect measurements must be used, many of which are invasive.[17]

Coronary Flow Reserve and Measurement of Cardiovascular Dysfunction

The concept of coronary flow reserve (CFR) was first introduced by Gould et al in 1974. It describes the ability of coronary blood flow to increase substantially when demanded by metabolic requirements, which may be up to 4- or 5-times resting values during normal exercise and even more by administration of pharmacological substances.[19] CFR assessment is conducted via transthoracic ultrasound of the coronary vasculature and provides an integrated measure of flow through both the large epicardial arteries and the coronary microcirculation.[17] This is a key factor to its relevance in G-CARE, because effective diagnosis and management of atherosclerosis is now thought to depend on interaction of both macro- and microvessels in the coronary circulation.[57] A normal CFR implies maximal dilation of resistance vessels, ie, an inability to further increase myocardial blood flow.[47] Causes of altered CFR include obstructive coronary

atherosclerosis (primary cause) and other diseases involving the microcirculation, sometimes occurring with angiographically normal arteries, in conditions such as psoriasis, diabetes and systemic sclerosis.[47]

It is essential that during measurement of coronary blood flow, maximal flow is stimulated and that both basal and maximal flow measurements are accurately assessed.[19] Pharmacological stimulation of maximal flow may be done with agents that act directly on, or bypass, the endothelium. Endothelium-dependent agents, such as acetylcholine, stimulate vasodilation in the presence of a healthy endothelium. Endothelium-independent agents, such as dipyridamole, can bypass the endothelium and directly stimulate relaxation of vascular smooth muscle cells,[20] which may be advantageous in the case of an unhealthy endothelium and can also counteract the autoregulatory mechanisms controlling coronary vasodilation.[39] The hyperemic action of adenosine, a commonly used agent in CFR assessment that is often thought of as endothelium-independent, may in fact partly depend on an intact healthy endothelium.[20,39] Use of adenosine may thus identify endothelial dysfunction and early microvascular wall pathology, as both are contributors to reduced myocardial perfusion reserve. [20]

Other studies have used alternative methods of measuring cardiovascular impact. The Vascular Inflammation in Psoriasis (VIP) study series have investigated the effects of adalimumab, secukinumab, apremilast, and ustekinumab on aortic inflammation, with mixed results in completed studies to date: VIP and VIP-S showed a neutral effect of adalimumab and secukinumab, respectively, on aortic inflammation at Week 12 using 18-FDG positron emission tomography/computed tomography (PET/CT),[29,43] whereas in the VIP-U study, ustekinumab improved aortic inflammation versus placebo at 12 weeks.[30]

The Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab (CARIMA) study used the flow-mediated dilation (FMD) technique to assess the impact of secukinumab on endothelial dysfunction.[60] FMD is another non-invasive method of assessing microvascular dysfunction, via external vascular ultrasound assessment of the brachial artery during reactive hyperaemia.[56] Hence, FMD records peripheral arterial function and often cannot be translated to coronary vessels due to different mechanisms of microvascular activation or regulation between the two beds,[49] which certainly exist in terms of cellular anatomy and vasodilatory function.[26] Despite numerous studies often correlating FMD with presence of coronary artery disease, it has been demonstrated that pathologic FMD does not always identify individuals with coronary microvascular dysfunction that has otherwise been assessed by CFR, notably in a similar CVD phenotype to that proposed for G-CARE.[25] Conversely, functional remodeling of the coronary microvasculature is a key cause of CFR reduction in patients with inflammatory disease and reflective of pathologies such as impaired vasodilation, enhanced vasoconstriction and structural remodeling, as well as MACE risk.[20,57] Thus, CFR is capable of detecting coronary microvascular dysfunction in the absence of detectable obstructive atherosclerosis, which may be missed by FMD.[20,25,57] Indeed, these patients are now proposed to present a prevalent phenotype of CVD with unique prognostic and therapeutic implications.[57]

Therefore, CFR has been chosen over other methods as a primary outcome measure in G-CARE, because it detects the sensitive early changes in the cardiac microvasculature in patients with chronic inflammatory diseases, before onset of irreversible structural changes.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) for guselkumab.

The term "study intervention" throughout the protocol, refers to guselkumab as defined in Section 6.1, Study Interventions Administered.

The term "Sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject", describing patients with psoriasis participating in this study.

2.1. Study Rationale

Guselkumab is an IL-23 inhibitor which has been approved for the treatment of adults with moderate-to-severe plaque psoriasis and active psoriatic arthritis. Guselkumab has also demonstrated superiority to inhibitors of TNF-α, IL-17, and IL-12/23 in terms of long-term efficacy and safety.[13,33,41,50] However, there may be potential benefits for guselkumab beyond those related to skin clearance. The promising results of IL-12/23 inhibition in the Vascular Inflammation in Psoriasis-Ustekinumab (VIP-U) study,[28] combined with the role of IL-23 in the early stages of atherogenesis,[24] suggest a potential benefit of IL-23 inhibition on vascular inflammation. However, additional research is necessary to further determine the effects of IL-23 inhibition on surrogate markers of cardiovascular outcomes and therefore improve understanding of a major serious comorbidity in patients with plaque psoriasis.

This study aims to investigate the effect of guselkumab on surrogate markers of cardiovascular risk, primarily CFR, in participants with moderate-to-severe plaque psoriasis.

2.2. Background

Nonclinical Studies

Refer to the IB[19] for guselkumab for information about nonclinical studies.

Clinical Studies

Psoriasis

In guselkumab Phase 3 studies in moderate-to-severe plaque psoriasis, the key efficacy findings are summarized below:

- In 2 large placebo- and active-controlled studies (CNTO1959PSO3001 [VOYAGE-1] and CNTO1959PSO3002 [VOYAGE-2]),

The proportion of participants who demonstrated improvements in psoriasis as assessed by all 4 Psoriasis Area and Severity Index (PASI) (PASI 100, PASI 90, PASI 75, and PASI 50) and investigator global assessment (IGA) responses was higher among those receiving guselkumab 100 mg subcutaneously (SC) at Weeks 0, 4, and q8w compared with the placebo and adalimumab groups. Responses were observed up to Week 252.

In participants with baseline physician's global assessment of psoriasis on the hands and/or feet (hf-PGA) scores ≥2, guselkumab treatment led to a significantly higher ($p<0.001$) proportion of participants with hf-PGA scores of clear (0) or almost clear (1) at Week 16 and Week 48, compared with the adalimumab group.

Most participants experienced clinically meaningful improvements in psoriasis symptoms (erythema, induration, and scaling) and involved body regions (head, trunk, upper extremities, and lower extremities) as measured by PASI 75 response. Following sustained treatment, the proportions of participants achieving PASI 90 response within 5 months after initiation, and PASI 100 response within 7 months were maintained through 5 years.

- In a plaque psoriasis study (CNTO1959PSO3003: NAVIGATE), participants with an inadequate response to ustekinumab benefitted from switching to guselkumab, and approximately twice as many participants receiving guselkumab achieved clinical responses compared with participants receiving ustekinumab, with significant improvement in PASI and IGA scores as early as 4 weeks after switching.
- In a plaque psoriasis study in Japan (CNTO1959PSO3004), in general, clinical responses obtained at Week 16 in the guselkumab 50 mg and 100 mg groups either continued to improve or were maintained after Week 16 through Week 52 for all endpoints. In addition, the body surface area (BSA) involvement which was assessed over time from baseline through Week 52, demonstrated improvement with guselkumab treatment (50 and 100 mg) in all treatment groups (including placebo-crossover participants).
- Efficacy of guselkumab in the treatment of generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) has been demonstrated (CNTO1959PSO3005). A majority of participants with GPP (77.8%) and EP (90.9%) achieved treatment success with guselkumab at Week 16, with maintenance of effect of guselkumab through Week 52.
- In participants with moderate-to-severe plaque psoriasis (CNTO1959PSO3006: ORION), guselkumab treatment using a novel self-injection device gave rise to significantly higher proportions of participants achieving an IGA score of 0 or 1 (80.6% versus 0.0%, $p<0.001$) and a PASI 90 response (75.8% versus 0.0%, $p<0.001$), compared with placebo. In addition, significantly higher proportions of participants receiving guselkumab achieved an IGA score of 0 (56.5% vs 0.0%, $p<0.001$) and a PASI 100 response (50.0% vs 0.0%, $p<0.001$) at Week 16, compared with placebo.
- In participants with moderate-to-severe plaque psoriasis (CNTO1959PSO3008) who had not received any prior systemic therapy, the study comparing guselkumab with the active-comparator (fumaric acid esters) met its primary and major secondary endpoints, with significantly higher proportions of participants treated with guselkumab achieving PASI 90 (81.7% vs 13.6%, $p<0.0001$) and PASI 75 (90.0% vs 27.1%, $p<0.0001$) response at Week 24 compared with the active-comparator.

Psoriatic Arthritis

There are 3 Phase 3 studies evaluating the efficacy of guselkumab in participants with active psoriatic arthritis (PsA) who have inadequate response to standard therapies (CNTO1959PSA3001- DISCOVER-1), in biologic naïve population with inadequate response to non-biologic therapies (CNTO1959PSA3002-DISCOVER-2), and in participants who have had an inadequate response to anti-tumor necrosis factor alpha (anti-TNFα) (CNTO1959PSA3003-COSMOS). In the DISCOVER-1 study, the primary endpoint was met: American College of Rheumatology (ACR) 20 at Week 24 was achieved by significantly greater proportions of participants in the guselkumab every 4 weeks group (76 [59%] of 128 [95% CI 50 68]) and every 8 weeks group (66 [52%] of 127 [43 61]) than in the placebo group, with significant percentage differences versus placebo for the every 4 weeks group and the every 8 weeks group (both p<0.0001). In the DISCOVER-2 study, significantly greater proportions of participants in the guselkumab every 4 weeks group (156 [64%] of 245 [95% CI 57 70]) and every 8 weeks group (159 [64%] of 248 [58 70]) than in the placebo group achieved an ACR 20 response at Week 24; both p<0.0001). In the COSMOS (CNTO1959PSA3003) study, treatment with guselkumab 100 mg at Week 0 and Week 4, and then every 8 weeks in this study demonstrated the superiority of guselkumab over placebo with respect to the primary endpoint of ACR 20 response. At Week 24, a significantly higher proportion of participants in the guselkumab group achieved ACR 20 response compared with the placebo group (44.4% [n 84] versus 19.8% [n 19] p<0.001). Superiority of guselkumab was also established in terms of all 4 key secondary endpoints at Week 24, based on a predefined hierarchical testing procedure: HAQ-DI, ACR 50 response, SF36 PCS, and PASI 100.

Palmoplantar Pustulosis

In a Phase 3 study (CNTO1959PPP3001) evaluating the efficacy of guselkumab for the treatment of palmoplantar pustulosis, the study achieved the primary endpoint, with both guselkumab dose groups showing superior efficacy to the placebo group at Week 16 as measured by change from baseline in the Palmoplantar Psoriatic Area and Severity Index (PPPASI) total score (p 0.017 for guselkumab 200 mg versus placebo and p<0.001 for guselkumab 100 mg versus placebo). The proportion of PPPASI-50 responders in the guselkumab 100 mg and the guselkumab 200 mg groups continued to increase through Week 52 and reached a maximum of 83.3% and 84.6%.

Safety

The safety of guselkumab was analyzed in participants from placebo- and active-controlled Phase 3 studies for up to 156 weeks of treatment (CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003, CNTO1959PSO3005, CNTO1959PSO3006, CNTO1959PSO3008 and CNTO1959PPP3001).

- Serious adverse events (SAEs) were relatively infrequent among guselkumab-treated participants, with most SAEs consisting of infection-related events; rates of SAEs did not increase with longer duration of guselkumab exposure.

- Serious infections with guselkumab were infrequent, with most being single events without a clear pattern. No events of tuberculosis (TB) or opportunistic infection were reported with guselkumab treatment.
- The incidences of malignancies, MACE, and suicidal ideation and behavior through 3 years of treatment with guselkumab were low and did not increase with increased duration of exposure. These results demonstrate that with additional guselkumab exposure through approximately 3 years, the rates of infections, serious infections, malignancies, and MACE remained stable, suggesting that there is no increased risk of these events with prolonged guselkumab exposure.
- The analyses of pooled data support the conclusion that guselkumab is well tolerated through 3 years of treatment, and the safety profile remains consistent when compared with Week 48 data, at the approved dose regimen of 100 mg, administered SC at Weeks 0, 4, and then q8w, in adult participants with moderate-to-severe plaque psoriasis.

A review of the cumulative safety data and risk-benefit analysis did not identify any change to the risk-benefit profile of guselkumab.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of guselkumab may be found in the IB.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential Risks Due to Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C virus (HBV, HCV), will be excluded from the study. Similarly, participants with evidence of active or untreated latent tuberculosis (TB) will be excluded from the study (Section 5.2). • Participants who have received a live viral or bacterial vaccination within 12 weeks of Week 0 will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of guselkumab (Section 5.2). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including TB (Section 8.2.5). • Discontinuation of a participant's guselkumab must be strongly considered if the participant develops a serious infection, including but not

		limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and guselkumab should be withheld until the clinical assessment is complete (Sections 5.2, 7.1).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in post-marketing experience with guselkumab in psoriasis patients.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study. • Sites are instructed that before any administration of guselkumab, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue guselkumab (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety labs to assess for any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from guselkumab (Section 7.1).
Liver injury	A SAE of 'toxic hepatitis' was reported in the ongoing Phase 2/3 guselkumab Crohn's disease program in a participant who received guselkumab 1200 mg IV at Weeks 0, 4, and 8, and 200 mg SC at Week 12. Based on the hepatocellular pattern of injury, temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event may represent drug-induced liver injury possibly related to guselkumab.	• Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury (Section 5.1).

Immunosuppression	Although guselkumab has been studied with other immunosuppressives in other diseases, there may be an increased risk of infection or malignancy.	In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, participants who have previously or are currently receiving allergy immunotherapy, IL-12/23, IL-17, or IL-23 inhibitors, B or T-cell modulators or systemic immunosuppressants will be excluded from the study (Section 5.2).
Potential Risks due to Study Procedure (Adenosine Injection)		
Potential Risks of Clinical Significance	**Indications for Stopping Adenosine Infusion and/or Administering Aminophylline**	**Mitigation Strategy**
• Vascular related: Flushing • Thoracic related: dyspnea (shortness of breath), chest discomfort • Nervous system related: Headache, dizziness, light-headedness, paresthesia • Gastrointestinal related: Nausea • Cardiac related: bradycardia, sinus pause, skipped beats, atrial extrasystoles, Atrio-Ventricular block, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia	Stopping Adenosine and/or further medical intervention is at the discretion of the cardiology investigator and should be considered in case of: • Severe hypotension: Systolic pressure <80 mm Hg or 20 mmHg fall which persists • ST depression: >3 mm beyond baseline ECG without angina or >2 mm with angina • Persistent 2nd or 3rd degree heart block • Severe chest discomfort, dizziness, dyspnea, headache, nausea, syncope or dysrhythmia	The half-life of adenosine is less than 10 seconds. Thus, the adverse effects are generally rapidly self-limiting. Treatment of any prolonged adverse effect should be individualized and directed toward the specific effect. • Stop infusion – most effects resolve within 30-60 seconds post infusion • If symptoms persist, administer aminophylline, 125 mg, IV by slow infusion (1 minute) on cardiology investigator's direction. Dosage may be repeated in five minutes if there is no response to the first dose. **Note:** Adverse events (AEs) should be reported if medical intervention beyond stopping adenosine infusion is necessary. Please refer Appendix 13 for further information.

2.3.2. Benefits for Study Participation

Guselkumab was first approved for the treatment of moderate-to-severe plaque psoriasis by the United States Food and Drug Administration on 13 July 2017 and has since been approved in several other countries worldwide (including the EU, Canada, and Japan). Since 14 July 2020, guselkumab has been approved for the treatment of active psoriatic arthritis

It has been shown that serum levels of IL-12 and IL-23 are augmented in patients with CVD.[35] IL-12 and IL-23 are present in atherosclerotic plaques, thereby affecting the pro-inflammatory status in these patients.[24] Taken together, this evidence suggest that targeting IL-12/23 could represent a valid therapeutic option for psoriatic disease, with benefits on cutaneous involvement and on cardiovascular comorbidities.

2.3.3. Benefit-Risk Assessment for Study Participation

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants with moderate-to-severe plaque psoriasis with intermediate cardiovascular risk.

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB. The collective efficacy and safety results of the Phase 1, Phase 2, and Phase 3 clinical studies in healthy volunteers and participants with plaque psoriasis and active psoriatic arthritis established a favorable benefit-risk profile for guselkumab in the treatment of plaque psoriasis and active psoriatic arthritis and regulatory approval for these indications.

Potential risks of guselkumab, including those of serious infection and malignancy, are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the studies.

In summary, the collective preclinical and clinical evidence for the anti-IL-23 mechanism of action, and the benefit-risk profile of guselkumab established to date in psoriasis and other immune mediated diseases provide a strong scientific and clinical rationale for investigating the efficacy of guselkumab in reducing vascular inflammation.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the effect of guselkumab on CFR measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk*.	• Change from baseline ǂ in CFR at Week 32.
Secondary	
To evaluate the short-term effect of guselkumab on CFR measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in CFR at Week 16.
To evaluate the effect of guselkumab on GLS as a surrogate marker of left ventricular function in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in GLS at Week 32. • Change from baseline in GLS at Week 16.
To evaluate the effect of guselkumab on arterial stiffness in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.	• Change from baseline in cfPWV at Week 32. • Change from baseline in cfPWV at Week 16.
To evaluate the effect of guselkumab on CFR among participants in the different CFR categories.	• Change from baseline in CFR at Week 16 and Week 32 among participants with CFR in the ranges of 2 to 2.49, 2.5 to 3, and 3.01 to 3.5 at baseline.
To evaluate the effect of guselkumab on surrogate CV risk markers among nicotine users and non-users in the participant population.	• Change from baseline in CFR at Week 16 and Week 32 among nicotine users and non-users. • Change from baseline in GLS at Week 16 and Week 32 among nicotine users and non-users. • Change from baseline in cfPWV at Week 16 and Week 32 in nicotine users and non-users.
To assess the safety and tolerability of guselkumab in participants with moderate-to-severe plaque psoriasis and intermediate cardiovascular risk.	• Rate of AEs among participants treated with guselkumab.

* Intermediate cardiovascular risk defined by CFR ≥2 and ≤3.5 at Screening Visit S2.

ǂ cfPWV, GLS and CFR measurements at Week 0 will be considered as the baseline value. CFR must not be <2 or >3.5 at both Screening Visit S2 and Week 0.

Abbreviations: AE= Adverse event; cfPWV = carotid-femoral pulse wave velocity; CFR= Coronary Flow Reserve; GLS: Global Longitudinal Strain

The G-CARE study will also investigate the following exploratory objectives:

- To evaluate the correlation between skin improvement and cardiovascular risk surrogate markers in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.
- To evaluate the effect of guselkumab on disease-related quality-of-life in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.
- To evaluate the effect of guselkumab on quality of sleep, alcohol intake patterns and depression and anxiety in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.
- To evaluate the effect of guselkumab on biomarkers in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.

Refer to Section 8, Study Assessments and Procedures for evaluations related to the endpoints.

HYPOTHESIS

The primary hypothesis of this study is that guselkumab (administered as 100 mg at Weeks 0, 4, 12, 20 and 28) is effective in reducing surrogate markers of cardiovascular risk as assessed by the change from baseline in CFR at Week 32.

4. STUDY DESIGN

4.1. Overall Design

This is an interventional, single-arm, open-label, oligocentric study to evaluate the effect of guselkumab on cardiovascular risk surrogate markers in adult men and women diagnosed with moderate-to-severe plaque psoriasis (with or without PsA) for at least 6 months prior to study entry. Participants will be assessed for eligibility at 2 screening visits; at Screening Visit S1, dermatology, medical history, and laboratory parameters will be assessed. Participants fulfilling eligibility criteria at Screening Visit S1 will be referred to the cardiology department and will undergo cardiologic assessments (cfPWV, GLS and CFR [via transthoracic doppler echocardiography]) at Screening Visit S2, and again at Week 0. Only participants with CFR ≥2 and ≤3.5 at both these time-points will be enrolled in the study. The CFR measurement at Week 0 will be considered as the baseline value.

Approximately 50 participants are planned to be enrolled, and will receive guselkumab (100 mg) SC at Weeks 0, 4, 12, 20 and 28. Approximately 20 of the enrolled participants should be active nicotine users. The number of nicotine users for enrollment in the study is capped at 20. Once this number is reached, only non-users may be enrolled to fulfil the sample size. Enrollment of nicotine users versus non-users will be stratified on a site-by-site basis. All participants will be instructed to abstain from caffeinated and nicotine-containing products at least 12 hours prior to any scheduled cardiology assessments.

The first dose of the guselkumab will always be administered at the site and by a health care professional (HCP). Subsequent doses can be self-administered under the supervision of site-staff after the participant has been adequately trained in the procedure.

Key efficacy evaluations will be carried out at the time-points detailed in the Schedule of Activities, and will include cardiology assessments (cfPWV, GLS and CFR), and skin assessments (IGA, PASI and BSA). Efficacy assessments will be done locally at the sites. The CFR assessments for eligibility will be immediately evaluated on-site at Screening Visit S2 and Week 0. All the CFR and GLS assessments in the study will be reviewed by a cardiology core lab for blinded analysis of endpoints. Quality-of-life and lifestyle changes during the study will be measured using the Dermatology Life Quality Index (DLQI), Pittsburg Sleep Quality Index (PSQI) and Alcohol Use Disorders Identification Test (AUDIT) questionnaires, and mood and anxiety will be assessed using the Hospital Anxiety and Depression Scale (HADS, if available).

Safety evaluations will include monitoring of vital signs, 12-lead electrocardiogram (ECG) at Screening Visit S1, monitoring of tuberculosis status, pregnancy testing at each visit, and recording of AEs throughout the study. Biomarker assessments will include the evaluation of relevant markers in serum, plasma, and urine for all participants.

For participants completing the study, the total duration will be 40 weeks, including 28 weeks of treatment and a Final Efficacy Visit 4 weeks later (Week 32). The Final Safety Visit will occur 12 weeks after the last dose of the guselkumab (Week 40). Participants who discontinue guselkumab prior to Week 28 will be considered to have completed the study if they complete all the assessments of the Final Efficacy Visit at the time of discontinuation (or soon after), and the Final Safety Visit scheduled 12 weeks after the last guselkumab dose. For participants who opt to receive commercially available guselkumab from their healthcare provider after Week 28, the visit at which the first dose of guselkumab is received outside the study (Week 36) will be considered as the Final Safety Visit.

An interim analysis will be conducted after a sufficient proportion of the participants (to be defined during the study) have accrued Week 16 CFR measurements. The scope of the interim analysis will be developed and documented in a statistical analysis plan.

The GLS and CFR assessments throughout the study will be conducted per the echocardiology protocol provided by the cardiology core lab. The results from GLS, CFR and other cardiology assessments will be securely transmitted to the cardiology core lab for blinded independent review of endpoints, per guidelines laid down in the process document of the core lab. Further details regarding materials to be forwarded to the core lab can be found in the core lab Standard Operating Procedures and process documents.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Eligibility Criteria for Inclusion in the Study

The eligibility criteria for inclusion in the study are aligned with those in pivotal clinical trials evaluating the efficacy of guselkumab for the treatment of moderate-to-severe plaque psoriasis. Participants with renal disease and coagulopathies are excluded as there is strong evidence that they have independent effects on epithelial dysfunction and thereby the primary endpoint. In addition, participants with a history or currently suffering from certain cardiovascular conditions are excluded to reduce the risk of cardiovascular AEs during the study (please refer Section 5.2, Exclusion Criteria).

Rationale for Study Duration

Previous studies investigating the effects of adalimumab and phototherapy,[43] and secukinumab (VIP-S),[28] on psoriasis and surrogate cardiovascular risk markers by evaluating the primary endpoint after 12 weeks of intervention, failed to demonstrate a significant change in vascular inflammation. A study using flow mediated dilatation of the brachial artery also failed to demonstrate a significant improvement at 12 weeks versus placebo (primary endpoint) but clearly

showed a dose and time dependent effect with a statistically significant effect at 52 weeks of secukinumab treatment.[60] Ustekinumab, an IL-12/23 blocker has demonstrated a significant improvement of vascular inflammation after 12 weeks.[28] In all studies the effect on skin improvement was in line with previous results in clinical trials.

These observations hint towards the assumption that cardiovascular inflammation of peripheral arteries assessed by surrogate markers improve slower than the skin parameters (eg, PASI, IGA). Therefore, the rationale for G-CARE is to assess the primary endpoint at Week 32 and assess a secondary endpoint at Week 16 for a detailed investigation of the timeline of effects of guselkumab on the coronary system. Further, these results will be correlated with the timeline of skin improvement. These results will help to better understand the effect of long-term treatment and the effects on cardiovascular endpoints like myocardial infarction, stroke, and cardiovascular death.

Biomarker Collection

Biomarker samples will be collected to evaluate the mechanism of action of guselkumab and help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. Markers of cardiovascular risk and psoriasis will be analyzed in the study, along with the effect of guselkumab treatment on these markers over 40 weeks of treatment.

Guselkumab has been shown to selectively inhibit IL-23 in psoriasis and produce substantial clinical responses.[32] The association between IL-23 and disease progression in patients with carotid atherosclerosis has been previously shown, with a potential involvement of IL-17-related mechanisms.[11] Interleukin-6 and high-sensitivity C-reactive protein (hsCRP) levels will be analyzed in the study, as they are related to the prevention of CV events and death, independent of lowering serum lipids.[51,52]

Olink high-throughput proteomic assays will be utilized to better define serum inflammatory and cardiovascular risk proteins in psoriasis.[15] Additional proteomic research assays (eg, Somascan) may also be applied. Psoriasis pathogenesis via SAA production and its role in maintaining a cutaneous inflammatory environment will be investigated.[18]

Malondialdehyde in combination with oxidative lipid damage [8-Isoprostane (GC-MS)], concentration of antioxidants (Vitamin C and Vitamin E) and nucleotide damage markers (8-Oxo-7,8-dihydro2'-desoxyguanosine) will provide a clearer picture of oxidative stress at baseline and during treatment,[22,34] Vitamin D, which has been shown to play a role in metabolic syndrome and improve psoriatic skin lesions,[27] will be investigated.

Cytokines (TNF-α, IL-6, IL-17A and F, IL-22, IL-23) have been shown to be involved in the pathogenesis of psoriasis, but little is known about their potential role in microvascular inflammation. Adipocytokines (leptin and adiponectin) are increasingly recognized as important regulators of inflammation, and a dysregulation of their levels and/or functions has been shown in psoriasis.[21]

HbA1c levels will be analyzed because inflammation-induced insulin resistance and endothelial dysfunction provide a pathogenetic link between psoriasis and atherosclerosis.[14]

N-terminal pro b-type natriuretic peptide (NT-proBNP) is a biomarker of CV disease in both normo- and hyperlipidemic groups, and is elevated in patients with psoriasis. NT-proBNP levels in the current study population will be useful to investigate the risk of cardiovascular disease associated with psoriasis.[48,54]

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected (approximately 185 mL) is considered to be an acceptable amount of blood over this time period for the population in this study.

4.3. Justification for Dose

Participants will receive guselkumab at Weeks 0, 4, 12, 20 and 28. This dosing regimen is approved for use in patients with moderate-to-severe plaque psoriasis based on the data from global Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002).

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study at Week 40. The final data from the study-site will be sent to the Sponsor (or designee) after completion of the final participant visit at that study-site, in the time frame specified in the clinical trial agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 40 of the study.

Participants who prematurely discontinue guselkumab for any reason before Week 28 will be considered to have completed the study once all assessments scheduled for the Final Efficacy Visit are performed at the time of discontinuation, or as soon as possible. For these participants, the last study visit will be the Final Safety Visit 12 weeks after last guselkumab administration.

5. STUDY POPULATION

Eligibility of the participants will be assessed at 2 screening visits:

- At Screening Visit S1, participants will be assessed by the dermatology investigator based on dermatology, medical history, and laboratory parameters.
- Screening Visit S2 will occur a maximum of 2 weeks after Screening Visit S1, where eligibility based on the CFR performed by the cardiology investigator will be assessed.
- A minimum of 2 weeks, and a maximum of 4 weeks after Screening Visit S2, the Week 0 visit will occur, and the cardiology assessments will be repeated by the cardiology investigator. Participants fulfilling all the eligibility criteria at Screening Visit S1, Screening Visit S2 and Week 0 will be enrolled, and will receive the first dose of guselkumab.

Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed. Please refer to Schedule of Activities for details on the assessments at each study time-point.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Inclusion criteria will be assessed by the dermatologist, unless otherwise indicated below. Each potential participant must satisfy all the following criteria to be enrolled in the study:

Participant population-related inclusion criteria

The participant

1. Is male or female (according to their reproductive organs and functions assigned by chromosomal complement), 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) and above.

2. Has a diagnosis of moderate-to-severe plaque psoriasis (with or without PsA) for at least 6 months prior to the first dose of guselkumab at Week 0. Moderate-to-severe plaque psoriasis is defined as PASI ≥12, IGA ≥3 and involved BSA ≥10% at Screening Visit S1. Participants with a predominantly non-plaque form of psoriasis (eg, erythrodermic, guttate, or pustular) will not be eligible for inclusion in the study.

3. Has intermediate cardiovascular risk defined by CFR ≥2 to ≤3.5 (Criterion to be assessed by cardiologist at Screening Visit S2 and Week 0).

4. Is a candidate for systemic treatment for psoriasis (either naïve or history of previous treatment).

5. Does not have any abnormalities in physical examination, medical history, clinical laboratory tests, vital signs, and 12-lead ECG performed at screening that are not consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator. The 12-lead ECG must be assessed by the dermatologist at Screening Visit S1.

6. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Reproduction-related inclusion criteria

7. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at Screening Visit S1.

8. A woman must be

    a. not of childbearing potential

    b. of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and must agree to remain on a highly effective method while receiving guselkumab and until 12 weeks after the last dose the end of relevant systemic exposure. Examples of highly effective methods of contraception are described in Appendix 14, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.

9. A woman using oral contraceptives must use an additional contraceptive method (as detailed in Appendix 14, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

10. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 12 weeks after receiving the last administration of guselkumab.

11. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

12. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 12 weeks after receiving the last dose of guselkumab.

Infectious disease-related inclusion criteria

The participant

13. Is considered eligible according to the following TB screening criteria:

    a. Has no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB before the first administration of guselkumab, or have documentation of having completed appropriate treatment for latent TB within 3 years before the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.

    b. Has no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study agent.

       Within 2 months before the first administration of guselkumab, has a negative QuantiFERON-TB Gold test result, or has a newly identified positive QuantiFERON-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of guselkumab. A participant whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the participant may be enrolled without treatment for latent TB, if active TB is ruled out, his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor's Medical Monitor and recorded in the participant's source documents and initialed by the investigator.

       The QuantiFERON-TB Gold test is not required at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; participants with documentation of having completed adequate treatment as described above **are not** required to initiate additional treatment for latent TB.

14. Has a chest radiograph (posterior-anterior view), taken within 3 months before the first administration of study agent and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

15. Agrees not to receive a live virus or live bacterial vaccination during the study, or within 12 weeks after the last administration of guselkumab.

16. Agree not to receive a BCG vaccination during the study, and within 12 months after the last administration of guselkumab.

Clinical laboratory-related inclusion criteria

The participant

17. Has screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single re-test of laboratory values is permitted:

• Hemoglobin	≥10 g/dL	(SI: ≥100 g/L)
• White blood cells	≥3.5 x 10^3/μL	(SI: ≥3.5 GI/L)
• Neutrophils	≥1.5 x 10^3/μL	(SI: ≥1.5 GI/L)
• Platelets	≥100 x 10^3/μL	(SI: ≥100 GI/L)
• Serum creatinine	≤1.5 mg/dL	(SI: ≤135 μmol/L)

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be ≤2 × upper limit of normal (ULN) for the laboratory conducting the test.

Other inclusion criteria

The participant must

18. Agree to reduce risk of sun burn, and avoid use of tanning booths or other ultraviolet (UV) light sources during study.

19. Be willing to refrain from the use of complementary therapies for plaque psoriasis including ayurvedic medicine, traditional Taiwanese, Korean, or Chinese medications and acupuncture within 2 weeks before the first guselkumab administration and through Week 40.

20. Be willing to refrain from using or consuming any caffeinated and nicotine-containing products including but not limited to smoking, vaping, chewing tobacco, nicotine gum and patches 12 hours before the cardiology assessments.

21. Be willing and able to adhere to the Schedule of Activities, comply with protocol requirements, and the prohibitions and restrictions specified in this protocol.

22. It is recommended that participants are up to date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study participants who received locally approved COVID-19 vaccines recently prior to study entry, follow applicable local labelling, guidelines, and standards of care for participants receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrolment (please refer Section 6.5, Concomitant Therapy).

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Participant population-related exclusion criteria

1. Changed per Amendment 2.

1.1 Has low-density lipoprotein (LDL) >190 mg/dL.

2. Has uncontrolled hypertension that needs immediate medication (criterion to be assessed by the dermatologist at Screening Visit S1 and by the cardiologist at Screening Phase 2).

3. Has any clinically significant evidence of cardiac functional or valvular abnormalities, other than intermediate cardiovascular risk defined by CFR ≥2 and ≤3.5, including but not limited to: coronary stenosis, history of any MI or transient ischemic attacks, stroke, cerebrovascular disease, peripheral atherosclerosis, congestive heart failure, chronic pulmonary disease, fast atrial fibrillation, supraventricular arrhythmia, valvular abnormalities, ventricular wall movement abnormalities observed during the CFR assessment (Criterion to be assessed by the dermatologist at Screening Visit S1, and to be confirmed by the cardiologist at Screening Visit S2).

4. Has any contraindications to adenosine infusion, including but not limited to asthma with ongoing wheezing, hypersensitivity to adenosine, known or suspected bronchoconstrictive or bronchospastic lung disease (history of acute respiratory distress syndrome, emphysema), greater than first degree heart block without a pacemaker or sick sinus syndrome, systolic blood pressure <90 mmHg and severe sinus bradycardia (heart rate <40 bpm), or other contraindications listed in the SmPC (Criterion to be assessed by the dermatologist at Screening Visit S1 and confirmed by the cardiologist at Screening Visit S2).

5. Unable or unwilling to abstain from caffeine- or nicotine-containing products including but not limited to smoking, vaping, chewing tobacco, nicotine gum and patches for 12 hours prior to the cardiology assessments.

6. Has diabetes or has HbA1c >6.5.

7. Has a predominantly non-plaque form of psoriasis (eg, erythrodermic, guttate, or pustular).

8. Has a history of liver or renal insufficiency (estimated creatinine clearance below 60 mL/min); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (except PsA), psychiatric, metabolic

disturbances or coagulopathies. Participants with AS, RA, SLE, BD, Sjögren's syndrome, etc. will not be permitted.

9. Has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

10. Has a diagnosed severe chronic mental disorder, including but not limited to major depression, anxiety disorder, and schizophrenia.

11. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the IB).[19]

12. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.

13. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.

14. Has contraindications to the use of guselkumab per local prescribing information.

Concomitant or previous medical therapies-related exclusion criteria

15. Has taken any prohibited therapies before the planned first dose of guselkumab (as noted in Section 6.5, Concomitant Therapy and Table 1).

16. Has had major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study, or within 16 weeks after the last dose of guselkumab.
    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

17. Is currently undergoing or has previously undergone allergy immunotherapy for a history of anaphylactic reactions.

18. Has received any anti-TNFα biologic within 3 months or 5 half-lives of the first administration of guselkumab, whichever is longer.

19. Has previously received IL-23 inhibitors (guselkumab, tildrakizumab or risankizumab).

20. Has received any therapeutic agent directly targeted to IL-12/23 or IL-17 within 6 months of the first administration of guselkumab (including but not limited to ustekinumab, tildrakizumab [MK3222], secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG 827]).

21. Has received natalizumab, belimumab, or agents that modulate B-cells or T-cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months of the first administration of guselkumab.

22. Has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus) or anakinra within 4 weeks of the first administration of guselkumab.

23. Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 (calcitriol), psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of guselkumab. Oral vitamin D supplements (ergocalciferol and/or cholecalciferol) are permitted.

24. Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or have received lithium, antimalarials, or IM gold within 4 weeks of the first administration of guselkumab.

25. Has received an experimental antibody or biologic therapy within the previous 6 months, or received any other experimental therapy or new investigational agent within 30 days or 5 half-lives (whichever is longer) of any guselkumab administration or is currently enrolled in another study using an investigational agent or procedure.

26. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of guselkumab.

27. Has had a BCG vaccination within 12 months of screening.

Infections or predisposition to infections-related exclusion criteria

28. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of guselkumab).

29. Has a history of an infected joint prosthesis, or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

30. Has or has had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening.

31. Has or has had herpes zoster within the 2 months before screening.

32. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta-blockers, calcium channel blockers, or lithium).

33. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criterion 13 for information regarding eligibility with a history of latent TB.

34. Has a chest radiograph within 3 months before the first dose of guselkumab that shows an abnormality suggestive of a malignancy or current active infection, including TB.

35. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

36. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody).

37. Tests positive for hepatitis B virus (HBV) infection or is seropositive for antibodies to hepatitis C virus (HCV) at screening.

38. During the 4 weeks prior to Week 0, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

    Exception: if recommended by local guidelines and as part of standard of care in the respective country, participants may be included with a documented negative result for a validated SARS-CoV-2 test (direct detection methods)

    (1) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the Week 0 study visit

    The field of COVID-related testing (for presence of, and immunity to, the SARS CoV 2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

Other exclusion criteria

39. Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 5 months after the last dose of guselkumab.

40. Plans to father a child while enrolled in this study or within 12 weeks after the last dose of guselkumab.

41. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments (Criterion to be assessed by both dermatologist and cardiologist during Screening Visits 1 and 2).

42. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.

43. Lives in an institution on court or authority order.

44. Is an employee of the investigator or study-site, with direct involvement in the proposed study or other studies under the direction of that investigator or study-site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at both Screening Visit S1 and Screening Visit S2. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of guselkumab is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 12, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. This study will enroll both nicotine users and non-users. Those using tobacco products and/or nicotine products including, but not limited to cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum, etc, will be considered nicotine users. To be considered a nicotine non-user, the participant must have refrained from using the above tobacco/nicotine products for at least 3 months before Screening Visit S1. Participants will be instructed to abstain from nicotine-containing products for at least 12 hours before the scheduled cardiology assessments. A urine nicotine test will be conducted before measurement of CFR to confirm tobacco/nicotine use.

4. Caffeine is a potent antagonist of adenosine. All eligible participants must abstain from consuming coffee, tea, cola drinks, energy drinks, other caffeinated beverages, food, or using any substances containing caffeine for at least 12 hours prior to the scheduled cardiology assessments during the study.

5. Agree to use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen), limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from Screening Visit S1 until the last dose of guselkumab.

6. Participants will be instructed not to make significant changes in their exercise routines, diet, and their nicotine consumption, drinking, or sleeping habits during the study, outside the requirements of the study eligibility criteria.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date of Screening Visit S1 and age at initial informed consent will be used.

Screening Visit S2 must occur no later than 2 weeks after Screening Visit S1, and the Week 0 visit must occur a minimum of 2 weeks and a maximum of 4 weeks after Screening Visit S2. Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once within the 2-week period. Eligibility may be reassessed at a single unscheduled visit during the screening period, or at Screening Visit S2 along with the scheduled cardiology assessments. If the CFR measurement is unsuccessful during Screening Visit S2, ie, if the acoustic

window of the coronary artery cannot be properly found, 2 attempts to measure a CFR can be made on different days within the 2-week screening period.

In general, if a participant is a screening failure but, in the future, meets all the eligibility criteria, the participant may be re-screened after a new informed consent has been obtained. Participants who are re-screened will be assigned a new participant number and will restart a new Screening Visit. Re-screening will be permitted once.

6. STUDY INTERVENTION

6.1. Guselkumab Administration

Guselkumab administration must be captured in the source documents and the case report form (CRF). Guselkumab will be manufactured and provided under the responsibility of the Sponsor. Refer to the IB for a list of excipients.

Participants enrolled in the study will receive guselkumab 100 mg at Weeks 0, 4, 12, 20 and 28.

The first dose of guselkumab will always be administered at the site and by a health care professional (HCP). Subsequent doses can be self-administered at the site under supervision by site-staff after the participant has been adequately trained in the procedure.

Study intervention administration must be captured in the source documents and the CRF.

For a definition of guselkumab overdose, refer to Section 8.4, Treatment of Overdose.

Guselkumab 100 mg will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U). Malfunctions of the syringe must be detected, documented, and reported by the investigator throughout the study.

6.1.1. Combination Product

- The Sponsor-manufactured combination product (or those manufactured for the Sponsor by a third party) provided for use in this study is guselkumab 100 mg provided in a single use PFS assembled with the UltraSafe PLUSTM Passive Needle Guard (PFS-U).
- Instructions for use of the PFS and PFS-U will be provided.
- All deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) of the PFS and PFS-U shall be documented and reported by the investigator throughout the study. For studies in combination product, these deficiencies will be reported as product quality complaints (PQC) (see Appendix 13: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting and appropriately managed by the Sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Guselkumab must be stored according to the labeled storage conditions, at 2°C to 8°C (36ºF to 46ºF) and protected from exposure to light. Vigorous shaking of the product should be avoided. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during administration.

Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on guselkumab preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all the guselkumab doses received at the site are inventoried and accounted for throughout the study. Guselkumab administered to the participant must be documented on the intervention accountability form. Guselkumab will be stored and disposed of according to the Sponsor's instructions. Study-site personnel must not combine contents of the guselkumab containers.

Guselkumab must be handled in strict accordance with the protocol and the container label, and must be stored at the study-site in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused guselkumab must be available for verification by the Sponsor's study-site monitor during on-site monitoring visits. The return to the Sponsor of unused guselkumab, or used returned guselkumab for destruction, will be documented on the intervention return form. When the study-site is an authorized destruction unit and guselkumab supplies are destroyed on-site, this must also be documented on the intervention return form.

Guselkumab should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Guselkumab will be supplied only to participants participating in the study. Guselkumab may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense guselkumab from, nor store it at, any site other than the study sites agreed upon with the Sponsor. Further guidance and information for the final disposition of unused guselkumab are provided in the pharmacy manual/study-site investigational product and procedures manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Randomization will not be used in this study.

Blinding

As this is an open-label study, blinding procedures are not applicable.

The GLS and CFR assessments throughout the study will be conducted per the echocardiology protocol provided by the cardiology core lab. The results from GLS and CFR assessments will be securely transmitted to the cardiology core lab for blinded review of endpoints, per guidelines laid down in the process document of the core lab. The received images and examinations will be loaded and copied to the ultrasound software at the core lab. Both the computer and the software used for analysis will have restricted access and will be password protected, with only responsible physicians and biomedical technicians having access to the password.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive guselkumab directly from the investigator or designee, under medical supervision. The date of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of guselkumab and study participant identification will be confirmed at the time of dosing by a member of the study-site personnel other than the person administering the guselkumab.

Compliance will be assessed during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF. A record of the number of guselkumab doses dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Guselkumab start and stop dates, including dates for delays will also be recorded in the CRF.

6.5. Concomitant Therapy

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of guselkumab up to 12 weeks after the last dose of guselkumab. Concomitant therapies should also be recorded beyond Week 40 only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

When considering the use of locally approved COVID-19 vaccines in study participants, follow applicable local labelling, guidelines, and standards of care for participants receiving immune-targeted therapy. For study participants receiving a locally approved COVID-19 vaccine, it is recommended where possible that the vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

6.5.1. Concomitant Medications for Treatment of Psoriasis

6.5.1.1. Topical Therapy

Use of topical psoriasis treatment (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus) is permitted at the investigator's discretion from Screening Visit S1 up to Week 4. The treatment should only cover a maximum of 20% body surface area, ie, for the scalp, the intertriginous regions, palms/soles. However, Class IV topical corticosteroids (alone or in combination) and phototherapy are prohibited until end of the study. Shampoos (containing tar or salicylic acid only) and topical moisturizers are allowed throughout the study, but participants should not use these topical agents (shampoos, moisturizers) on the day of a study visit. Nonmedicated shampoos may be used on the day of the study visit. Traditional Taiwanese, Korean, or Chinese medicines are prohibited during the study.

6.5.1.2. Phototherapy or Systemic Therapy for Psoriasis

The use of phototherapy or systemic antipsoriatic medications is not permitted at any time during the study. These medications include those targeted for reducing TNF (including but not limited to infliximab or etanercept), drugs targeted for reducing IL-12/23, IL-17, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab, secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), steroids, any conventional systemic therapy that could affect psoriasis or the IGA evaluation (including but not limited to MTX, cyclosporine, acitretin), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis or the IGA evaluation.

6.5.2. Concomitant Medications for Conditions Other than Psoriasis

Every effort should be made to keep participants on stable concomitant medications. If the medication is temporarily discontinued because of abnormal laboratory values, side-effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the participant's medical record. The use of stable doses of nonsteroidal anti-inflammatory drugs is allowed. However, disease-modifying agents such as MTX, sulfasalazine, or IM gold are prohibited during the study. Antimalarial agents, except for chloroquine, may be used after Week 40. The use of corticosteroids for indications other than psoriasis should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for $\leq$2 weeks. Longer-term use of corticosteroids should be discussed with the Medical Monitor or designee and may require discontinuation of study drug. Inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

6.5.3. Concomitant Medications of Special Interest

Every effort should be made to keep participants on stable concomitant medications. If the medication is temporarily discontinued because of abnormal laboratory values, side-effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly

documented in the participant's medical record. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Details on permitted and prohibited concomitant medication relevant to the study is presented in Table 1. The medications detailed in the table are prohibited as they are known to affect CFR measurements or interact adversely with adenosine.

Table 1: Concomitant Medication of Special Interest

Drug class	Effect on CFR	Strength of evidence	Study rules
Products containing short-acting xanthine derivates eg, caffeine, etc. This includes beverages such as coffee, black/green tea, cola drinks	Decreases	Good	Allowed in the study but prohibited 12 hours before CFR procedure.
Drugs containing long-acting xanthine derivates eg, theophylline, diprophylline	Decreases	Good	Prohibited in study
Phenylephrine containing products	Increases	Good	Prohibited in study
NSAIDs*	Increases	Good	Allowed in stable dosing for at least 3 months before study. Prohibited are intermediate use >14 days and use on the day before and day of CFR measurement
ACEi	Increases	Good	Allowed in stable dosing for at least 3 months before study
ARBs	Losartan, no effect Candesartan, increases	Moderate	Allowed in stable dosing for at least 3 months before study
Thiazide diuretics	No data available		Allowed in stable dosing for at least 3 months before study
Loop diuretics	No data available		Allowed in stable dosing for at least 3 months before study
Vitamin K antagonists	No data available		Prohibited in study
Platelet inhibitors (including ≤100mg ASA/d)	Increases	Good	Prohibited in study
Beta-blockers	First and second generation: Contradictory data Third generation: Increased	Good Moderate	Prohibited in study
Aldosterone blockers	Increases	Moderate	Prohibited in study
Calcium antagonists	Increases	Good	Prohibited in study
Sodium channel inhibitors (ranolazine)	Increases	Moderate	Prohibited in study
Statins	Increases (if therapy >8 weeks)	Good	Prohibited in study
Glucose lowering drugs	Insulin: Increases DPP4i: Mixed effects GLP 1 RA: No effect SU: Decreases/no effect Metformin: Increases	Moderate Moderate Moderate Moderate/good Moderate/good	Prohibited in study

Table 1: Concomitant Medication of Special Interest

Drug class	Effect on CFR	Strength of evidence	Study rules
Products containing short-acting xanthine derivates eg, caffeine, etc. This includes beverages such as coffee, black/green tea, cola drinks	Decreases	Good	Allowed in the study but prohibited 12 hours before CFR procedure.
	TZD: No effect SGLT2 inhibitors: Increases	Moderate Good	
Hawthorn derivates	Increases	Good	Prohibited in the study

ACEi= angiotensin-converting enzyme inhibitors; ARB= angiotensin II receptor blockers; CFR= coronary flow reserve; DDP4i= Dipeptidyl peptidase 4 inhibitors; GLP-1 RA= Glucagon-like peptide-1 receptor agonists; NSAID= nonsteroidal anti-inflammatory drugs; SU= sulfonylurea; TZD= thiazolidinediones; SGLT2= sodium glucose co-transporter 2

6.6. Dose Modification

Dose or dosage adjustment of guselkumab is not permitted during the study.

6.7. Intervention After the End of the Study

No continued access to guselkumab is proposed for this study. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Guselkumab

A participant's guselkumab regimen must be discontinued if:

- The participant withdraws consent to receive guselkumab.
- The investigator believes that for safety reasons or tolerability reasons (eg, AEs) it is in the best interest of the participant to discontinue guselkumab.
- The participant becomes pregnant. Refer to Appendix 14, Contraceptive Guidance and Collection of Pregnancy Information.
- The participant is diagnosed with a malignancy (except 1-2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease).
- The participant meets any of the following TB screening criteria:

  A diagnosis of active TB.

  Has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.

  Has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of guselkumab and

continued to completion. Participants who have an indeterminate result should have the test repeated. Guselkumab must be discontinued for participants with persistently indeterminate QuantiFERON-TB Gold test results .

Discontinues treatment for latent TB prematurely or is noncompliant with the therapy.

- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant develops an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a guselkumab administration.
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of guselkumab. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Participants who develop a serious or opportunistic infection. Discussion of such participants with the Medical Monitor or designee should also be considered.
- The participant receives a concomitant medication that is prohibited by the protocol.
- The study is terminated by the Sponsor.

If a participant permanently discontinues guselkumab before Week 28, the Final Efficacy Visit should occur at the time of discontinuation or as soon as possible, and all assessments scheduled for the Final Efficacy Visit should be performed. The participant should also return for a Final Safety Visit, 12 weeks after the last guselkumab dose.

If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed. If a participant discontinues study treatment and starts another biologic treatment, an interval of at least 12 weeks between the last guselkumab administration and the start of the new treatment is recommended. The number of dropouts in the study are expected to be low; however, additional participants will be entered to maintain the sample size and ensure that the protocol-specified number of participants complete the study.

7.2. Participant Discontinuation/Withdrawal From the Study

Reasons for participant discontinuation/withdrawal from the study may include:

- Adverse event, eg, Major Adverse Cardiac Event (myocardial infarction, non-fatal stroke, or cardiovascular death)
- Lost to follow-up
- The investigator decides to withdraw the participant from the study
- Protocol violation
- Study termination by the Sponsor
- Pregnancy

- Lack of efficacy
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the CRF and in the source document. For each participant discontinuing the study, the investigator should attempt to obtain a CFR reading. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches) as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Withdrawal of consent should be an infrequent occurrence in clinical studies, therefore, prior to the start of the study the Sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Circumstances for Reduced Follow-up

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for reduced follow-up upon confirmation from the study Sponsor. These may include (as local regulations permit):

- Less frequent clinical visits
- Telemedicine
- Telephone, email, letter, social media, fax, or other contact with:
    - participant
    - relatives of the participant
    - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study-site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study-site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study-site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study-site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, biomarker, and safety measurements applicable to this study. Participants will provide informed consent before undergoing any study-related procedures or assessments.

Multiple assessments are scheduled for the same time-point. As a rule, all PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions. The PRO assessments should be completed in the order DLQI, PSQI, HADS (if available) and AUDIT.

The current study will integrate dermatological and cardiological aspects of the systemic disease psoriasis.

Screening Visit S1

At Screening Visit S1, participants presenting with moderate-to-severe plaque psoriasis at dermatology departments/sites will be assessed for eligibility by the dermatology investigator following informed consent. Demography and medical history will be recorded, and the

participants' TB, HIV and pregnancy status will be checked. Participants will undergo physical examinations, 12-lead ECG, dermatologic examinations and PASI, BSA, and IGA assessments.

The dermatology site will navigate the participants through the study, and will own the study documentation for the participants.

Screening laboratory samples will be obtained from eligible participants. Once the laboratory test results are available and the inclusion and exclusion criteria related to laboratory parameters are reviewed, the participant will be referred to the participating cardiology department for assessments related to Screening Visit S2. The participant may undergo Screening visit S2 while the QuantiFERON-TB Gold results are pending, however, the result must be reviewed and confirmed prior to enrolment at Week 0. All the other Screening Visit S1 laboratory parameters must be available and reviewed prior to the participant being referred for Screening Visit S2.

Screening Visit S2

Screening Visit S2 will occur no more than 2 weeks after Screening Visit S1. At the dermatology site, all participants will undergo a urine nicotine test to determine nicotine status (user/non-user) of the participant, and a urine pregnancy test (if applicable). The nicotine status (user/non-user) must be recorded in the eCRF. A positive pregnancy tests will lead to exclusion of the participant. The participants will then proceed with the cardiologic assessments performed by the cardiology investigator. A cardiologic anamnesis will be performed including cardiologic family history, vital signs and review of the relevant eligibility criteria.

Once eligibility is confirmed, the participant will undergo the cfPWV, GLS and CFR assessments. The preferred order of the cardiology assessments is cfPWV, GLS and CFR. If the participant is ineligible based on CFR results, the subsequent assessments can be deferred or avoided.

If the cardiology investigator is unsuccessful in obtaining a CFR measurement, eg, if the acoustic window of the coronary artery cannot be found, 2 additional attempts to measure the CFR can be made on different days.

Study Visit Week 0

The Week 0 visit will occur a minimum of 2 weeks and a maximum of 4 weeks after Screening Visit S2. At this visit, the eligibility criteria will be reviewed, and the participant will complete the PRO questionnaires prior to other assessments. A physical examination including PASI, BSA, and IGA will be performed by the dermatology investigator. The PASI and IGA values will be documented but not be considered as inclusion criteria. The participants will provide serum, plasma, and urine samples, and cardiology assessments (cfPWV, GLS and CFR) will be performed by the cardiologist following a urine nicotine test to determine nicotine use by the participant, and a negative urine pregnancy test (if applicable). Only participants with CFR $\geq$2 and $\leq$3.5 at both Screening Visit S2 and Week 0 will be enrolled in the study. The CFR measurement at Week 0 will be considered as the baseline value. Participants will then receive the guselkumab SC injection, and may receive training for self-administration of subsequent doses in the study, if applicable.

Study Visits Weeks 4, 12, 20 and 28

At these visits, participants will undergo PASI, BSA and IGA assessments as assessed by the dermatology investigator. Safety assessments including urine pregnancy test (where applicable) will be performed per the Schedule of Activities, and adverse events and concomitant therapy will be recorded. Guselkumab will be administered only after completion of all the assessments for that time-point.

Study Visits Weeks 16 and 32

At Week 16 and 32, the participant will complete the PRO questionnaires (DLQI first, followed by other PROs) prior to other assessments and procedures. The dermatological investigator will review the safety assessments and concomitant medication, and enquire about nicotine use in the 12 hours prior to the visit. The physical examination will include vital signs and PASI, BSA, and IGA assessments performed by the dermatology investigator. Serum, plasma, and urine samples will be drawn. After a urine nicotine test to determine nicotine use, and a negative urine pregnancy test (if applicable), the participant will proceed to the cardiology department, where the cfPWV, GLS, CFR and other assessments will be performed in arbitrary sequence by the cardiology investigator. Participants who have been fasting for the lipid and metabolic panel are permitted to have a non-caffeinated drink prior to the cardiology assessments.

If CFR measurement is unsuccessful at any time-point during the study, eg, if the acoustic window of the coronary artery cannot be properly found, 2 attempts to measure the CFR can be made on different days. At Weeks 16 and 32, the visit window can be extended by 7 additional days (CFR visit window -7/+14 days). If all 3 attempts to obtain CFR at Week 16 are unsuccessful, the participant may still proceed the study with all the scheduled procedures. Actual dates of assessments will be recorded in the source documentation and CRF.

Week 40 (Final Safety Visit)

This visit will occur 12 weeks after the last dose of guselkumab at the dermatology department. Participants will undergo physical examination and recording of vital signs. Pregnancy tests will be conducted, if applicable. Blood and urine sample will be provided for clinical laboratory tests. Concomitant therapy received and adverse events since the last visit will be recorded in the CRF.

For guidance on study conduct during a pandemic, please refer to Appendix 15.

Sample Collection and Handling

The actual dates of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

The total blood volume for the study is approximately 185 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study-site and procedures manual
- Laboratory manual and laboratory supplies
- Paper PRO questionnaires and PRO completion guidelines
- IWRS Manual
- eDC Manual
- Sample ICF and related participant materials
- Instructions for Use (IFU) for guselkumab

8.1. Efficacy Assessments

Every effort should be made to ensure that the cardiology physician or designee who performed the cardiology efficacy assessments (cfPWV, GLS and CFR) for a participant at Week 0 should also perform the evaluations for the participant at Week 16 and Week 32. Every effort must be made to perform the assessments at the same lab, on the same machine, using the same software for all the visits. Assessments should be processed per the guidelines from the core lab. All CFR and GLS assessments must be recorded. The results from GLS and CFR assessments will be securely transmitted to the cardiology core lab for blinded independent review of endpoints, per guidelines laid down in the process document of the core lab. To determine eligibility, the CFR results obtained at the study site will be used. The use of contrast media for assessments is not permitted. Sites staff will be trained by the Sponsor or designee to perform the CV assessments to ensure standardization of the procedures.

The following assessments will be carried out as detailed in the Schedule of Activities. The efficacy assessments will be performed locally at the sites.

8.1.1. Cardiovascular Evaluations

Carotid-femoral Pulse Wave Velocity

The measurement of cfPWV is accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness.[38] Carotid-femoral (cf) PWV is a direct measurement, and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant since the aorta and its first branches are what the left ventricle 'sees' and are thus responsible for most of the pathophysiological effects of arterial stiffness. cfPWV is usually measured using the foot-to-foot velocity method from various waveforms. These are obtained transcutaneously at the right common carotid artery and the right femoral artery (ie, 'carotid-femoral' PWV), and the time delay (Δt or transit time) measured between the feet of the 2 waveforms. A variety of different waveforms can be used including pressure, distension, and Doppler. The distance (D) covered by the waves is usually assimilated to the surface distance between the 2 recording sites. cfPWV is calculated as cfPWV D (meters)/ Δt (seconds).

Global Longitudinal Strain for Left Ventricular Function

In the G-CARE study, speckle tracking echocardiography (STE) will be employed for the detection of left-ventricular (LV) myocardial strain. Two-dimensional STE is based on the temporal and spatial tracking of naturally occurring intramyocardial reflectors of ultrasound (speckles) within the 2D echocardiographic images of the LV walls, and measures LV regional and global deformations as a marker of contractility and elasticity. The GLS and global longitudinal strain rate will be calculated at systole and diastole. The ratio of the arterial stiffness measured with cfPWV (described below) and the myocardial performance represented by GLS will be calculated as an index reflecting the arterial-ventricular interaction. In addition, the estimated LV peak twisting and untwisting at the time of mitral valve opening will be measured, and the percentage difference between LV twist and untwisting at the mitral valve opening will be calculated.[42]

The strain-pressure curves recorded from the GLS measurement may be used to calculate the myocardial work index at selected sites.

Coronary Flow Reserve

Coronary flow reserve will be measured non-invasively using transthoracic doppler echocardiography,[36] using a high-resolution ultrasound system with a suitable transducer and the respective software. The acoustic window will be around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. Long-axis views of the left ventricle will be obtained, and the ultrasound beam will then be angled laterally and superiorly to image the anterior interventricular groove. The coronary blood flow in the distal portion of the left anterior descending artery (LAD) will be examined with the help of color Doppler flow mapping. A sample volume will be positioned on the color signal in the LAD, and Doppler spectral tracings of flow velocity will be recorded. First, the baseline spectral Doppler signals in the distal portion of the LAD will be recorded. Then 140 µg/kg/min adenosine, a coronary vasodilator, will be administered for 5 minutes. Doppler signals will be recorded continuously at baseline and during the period of adenosine infusion. Measurements of hyperemic coronary flow velocity will be done continuously during the adenosine infusion, and the CFR measurement will be recorded based on the guidelines provided by the cardiology core lab.

Cardiac parameters, along with strain and coronary parameters will be assessed by the cardiology core lab as defined in the process document of the core lab.

8.1.2. Psoriasis Assessments

Investigator's Global Assessment

The IGA documents the investigator's assessment of the participant's psoriasis at a given time-point (Appendix 5). Overall lesions are graded for induration, erythema, and scaling. The participant's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Appendix 6). In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 to 72. A PASI 75 response is defined as ≥75% improvement in PASI score from baseline; PASI 90 and PASI 100 are similarly defined. A higher score indicates more severe disease.

The Sponsor will provide PASI training on assessment of PASI scores. Documentation of this training will be maintained in the site's training files. Previous PASI training by the Sponsor within the last 3 years with adequate documentation (eg, training certification) will be considered adequate for this study; however, repeat training prior to start of the study is encouraged.

Body Surface Area

The BSA score is the arithmetic mean of the affected skin surface. The most commonly used method to estimate the BSA 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, and 1% for the groin. The area of the palm can be used as a unit of measure which represents approximately 1% of the BSA. The number of patient hand areas affected can then be calculated. The formula for the calculation of BSA is provided in Appendix 7.

8.1.3. Patient-Reported Outcomes

Patient-reported outcomes will be assessed using paper PROs at the study sites.

Dermatology Life Quality Index

The DLQI is a dermatology-specific quality-of-life instrument designed to assess the impact of the disease on a participant's quality-of-life (Appendix 8). It is a 10 item PRO questionnaire that, in addition to evaluating overall quality-of-life, can be used to assess 6 different aspects that may affect quality-of-life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30. A higher score indicates more severe disease.

Pittsburg Sleep Quality Index

The PSQI is an effective instrument used to measure the quality and patterns of sleep in the older adult (Appendix 9). It differentiates "poor" from "good" sleep by measuring 7 domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The participant self-rates each of these 7 areas of sleep. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. A global sum of "5" or greater indicates a "poor" sleeper.

Alcohol Use Disorders Identification Test

The AUDIT is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems (Appendix 10). Both a clinician-administered version (page 1) and a self-report version of the AUDIT (page 2) are provided. Participants should be encouraged to answer the questions in terms of standard drinks. A chart illustrating the approximate number of standard drinks in different alcohol beverages is included. A score of 8 or more is considered to indicate hazardous or harmful alcohol use. The AUDIT has been validated across genders and in a wide range of racial/ethnic groups and is well suited for use in primary care settings.

The Hospital Anxiety and Depression Scale (if available)

The Hospital Anxiety and Depression Scale measures anxiety and depression which commonly coexist in a general medical population of patients (Appendix 11).[62] The HADS focuses on non-physical symptoms so that it can be used to diagnose depression in people with significant physical ill-health. The questionnaire comprises 7 questions for anxiety and 7 questions for depression, and takes 2-5 minutes to complete. Although the anxiety and depression questions are interspersed within the questionnaire, they are scored separately, and cut-off scores are available for quantification. The HADS questionnaire has been validated in many languages, countries and settings, including general practice and community settings.

8.1.4. Other Efficacy Evaluations

8.1.4.1. Biomarker Analysis

High levels of inflammatory markers are associated with atherosclerosis, coronary artery disease and are predictors of cardiovascular events. The following biomarkers will be analyzed at the time-points detailed in the Schedule of Activities:

Serum Samples:

- Inflammatory markers: hsCRP, IL-6, IL-17A/F, IL-22, IL-23, SAA1, SAA2
- Lipid biomarkers: LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides
- Metabolic biomarkers: HbA1c
- Markers of cardiovascular injury: NT-proBNP
- Olink cardiovascular and inflammatory panels

Plasma Samples:

- Oxidative stress markers:

  Concentration of oxidative lipid damage (8-Isoprostane) and malondialdehyde (HPLC, GC-MS)

  Concentration of antioxidants (Vitamins C and E)

  Adipokines- leptin and adiponectin

Urine samples:

- DNA damage markers (8-Oxo-7,8-dihydro2'-desoxyguanosine)

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 13, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time-points provided in the Schedule of Activities.

8.2.1. Physical Examinations

Physical examinations, including skin and recording of height, weight and waistline circumference will be performed by the investigator or designated physician as specified in the Schedule of Activities. Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document.

8.2.2. Vital Signs

Temperature (axillary, tympanic or forehead), pulse/heart rate, blood pressure will be assessed by the dermatologist. Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Vital signs measured during the CV procedures at the cardiology department may be recorded and used for data analysis.

8.2.3. Electrocardiograms

Standard 12-lead electrograms will be taken at Screening Visit S1 at the dermatology department. During the collection of the 12-lead ECG, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time-point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 2, Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

8.2.5. Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Schedule of Activities) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:

  Persistent fever?

  Unintentional weight loss?

  Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB Gold test, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted.

Guselkumab administration should be interrupted during the study. A positive QuantiFERON-TB Gold test result should be considered detection of latent TB. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 8.2.5. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of guselkumab and be encouraged to return for all subsequent scheduled study visits according to the Schedule of Activities.

8.2.6. Pregnancy Testing

Serum pregnancy tests will be performed at Screening Visit S1. Further urine pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at all the study visits as detailed in the Schedule of Activities.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

The usual pharmacodynamic actions and expected effects of adenosine administration during CFR assessment are not considered as AEs.

As guselkumab is classified as a combination product, malfunctions or deficiencies of the device constituent will be reported as PQC.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as PQCs, refer to Appendix 13, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of guselkumab, must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate Sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study-site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax) via a secure transmission system.

Any possible Hy's law case (AST or ALT ≥3x ULN together with bilirubin ≥2X ULN or INR >1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event form, even before all other possible causes of liver injury have been excluded. The INR criterion is not applicable to participants receiving anticoagulants.

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 13, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or Sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

All AEs will be recorded in the CRF and will be reported to the Sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the Sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further doses of guselkumab.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.5. Disease-Related Events and Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of a serious adverse event will be reported as SAEs, regardless of whether they are protocol-specific assessments.

The cause of death of a participant in a study ≤24 hours of the last dose of guselkumab, regardless of causality or association with guselkumab, is considered a SAE.

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the participant's first guselkumab administration must be reported within 24 hours by the investigator according to the procedures in Section 8.3 and Section 8.3.1. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of a SAE.

8.4. Treatment of Overdose

No clinical studies in humans have been conducted to assess a toxic threshold for guselkumab. The highest single SC dose of guselkumab investigated in humans was 300 mg. The maximum IV dose (10 mg/kg) in humans was 987 mg.

In the event of an overdose (any dose greater than that prescribed for the study), the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and appropriate symptomatic treatment instituted immediately.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetics will not be evaluated for this study.

8.6. Pharmacodynamics

Pharmacodynamics will be assessed as described in the endpoints.

8.7. Biomarkers

Biomarker sample collections will be conducted at the time-points presented in the Schedule of Activities to measure serum markers. Data collected from these samples will be used for exploratory research that will include the following objectives:

- To understand the molecular effects of guselkumab.
- To understand psoriasis.

- To understand why people may respond differently to guselkumab.
- To develop tests related to guselkumab or psoriasis.

Instructions for the collection and shipment of these samples can be found in the appropriate Laboratory Manual.

8.8. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

Descriptive statistics, such as mean, standard deviation (SD), median, inter quartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

In general, for continuous or ordinal efficacy endpoints, a Mixed-Effect Model Repeated Measures (MMRM) model will be used. Covariates such as BMI, smoking status, presence, or absence of PsA, age, gender, left ventricular mass index and hypertension diagnosis will be incorporated into these models. For binary efficacy endpoints, 95% confidence intervals for binomial proportions will be provided using exact methods, such as Clopper-Pearson or Chan-Zhang.

In general, all statistical tests will be performed at a 2-sided significance level of α 0.05.

9.1. Statistical Hypotheses

The primary hypothesis of this study is that guselkumab is effective in reducing surrogate markers of cardiovascular risk as assessed by the change from baseline in CFR at Week 32.

9.2. Sample Size Determination

The sample size calculation is based on the assumption that participants will show an average increase of 20% in CFR at Week 32. To detect a CFR mean change of 0.3 from baseline with 80% power, and assuming a SD of 0.8 and a 5% dropout rate, 50 participants are expected to be enrolled in the study.[42]

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
Full Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab.
Safety Analysis Set	All enrolled participants who receive at least 1 dose of guselkumab.

9.4. Statistical Analyses

This section of the protocol is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. The Statistical Analysis Plan will be finalized within 3 months of "first patient in" (FPI). It will include a more technical and detailed description of the planned statistical analyses.

9.4.1. Primary Endpoint

The primary endpoint for the study is the change from baseline in CFR at Week 32. The treatment effect of guselkumab will be analyzed as described in Section 9.

Further analysis of CFR data will be described in detail in the Statistical Analysis Plan.

9.4.2. Secondary Endpoints

Secondary endpoints will be analyzed with the appropriate methods as described in Section 9.

9.4.3. Exploratory Endpoints

Please refer to the Statistical Analysis Plan for details on the analysis of exploratory endpoints.

9.4.4. Safety Analyses

All safety analyses will be made on the Safety Analysis Set.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for all laboratory analyte at Week 0 and for observed values and changes from Week 0 at each scheduled time-point. Changes from Week

0 results will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

All clinically relevant abnormalities in ECG waveform that are changes from the Screening Visit S2 readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves). The effects on ECG variables may be evaluated by means of descriptive statistics and frequency tabulations.

Vital Signs

Vital signs including temperature, pulse/heart rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.5. Other Analyses

Biomarker Analyses

Changes in serum biomarkers over time will be summarized. Associations between Week 0 levels and changes from Week 0 in select markers and clinical response will be explored. Biomarker analyses will be summarized in separate technical reports.

9.5. Interim Analysis

An interim analysis will be performed after a sufficient proportion of the participants (to be defined during the study) have accrued Week 16 CFR data. The scope of the interim analysis will be developed and documented in a statistical analysis plan. Other interim analyses may be planned based on specific questions from the medical field. The data from these interim analyses will allow for assessment of coverage and follow-up of participant types and treatment modalities to investigate specific research questions.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AE	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUDIT	Alcohol use disorders identification test
BCG	Bacillus Calmette-Guérin
BMI	Body mass index
BSA	Body surface area
cfPWV	Carotid-femoral pulse wave velocity
CFR	Coronary flow reserve
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form(s) (paper or electronic as appropriate for this study)
CVD	Cardiovascular disease
DLQI	Dermatology life quality index
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
EADV	European Academy of Dermatology and Venereology
ECG	Electrocardiogram
eDC	Electronic data capture
EU	European Union
FMD	Flow-mediated dilation
FSH	Follicle stimulating hormone
GC-MS	Gas chromatography-mass spectrometry
GCP	Good clinical practice
GLS	Global longitudinal strain
GPP	Generalized pustular psoriasis
HADS	Hospital anxiety and depression scale
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Health care professional
HCV	Hepatitis C virus
HDL	High-density lipoproteins
hf-PGA	Physician's global assessment of psoriasis on the hands and/or feet
HIV	human immunodeficiency virus
HPLC	High performance liquid chromatography
HRT	Hormonal replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IFU	Instructions for use
IL	Interleukin
INR	International normalized ratio
IRB	Institutional review board
IWRS	Interactive web response system
LAD	Left anterior descending artery
LC-MS	Liquid chromatography–mass spectrometry
LDL	Low-density lipoprotein
LV	Left ventricular
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities

MI	Myocardial infarction
MMRM	Mixed-effect model repeated measure
MTX	Methotrexate
NT-proBNP	N-terminal pro b-type natriuretic peptide
PASI	Psoriasis area and severity index
PFS	Prefilled syringe
PPP	Palmoplantar pustulosis
PPPASI	Palmoplantar pustulosis area and severity index
PQC	Product quality complaint
PRO	Patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	Psoriatic arthritis
PSQI	Pittsburg sleep quality index
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SoA	Schedule of activities
STE	Speckle tracking echocardiography
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TC	Total cholesterol
TG	Triglycerides
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VIP	Vascular inflammation in psoriasis
WBC	White blood cell
WHO	World health organization

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Bilirubin
Alkaline phosphatase (AP)
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
HbA1c
hsCRP

<u>Lipid and Metabolic Panel:</u>
Triglycerides
Magnesium
Low-density lipoproteins (LDL)
High-density lipoproteins (HDL)
Very-low-density lipoprotein (VLDL) (calculated)
Non-HDL (calculated)
Serum glucose
Serum insulin</td></tr>
<tr><td colspan="3">Note: Any possible Hy's law case (AST or ALT ≥ 3x ULN together with bilirubin ≥2X ULN or INR >1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event form, even before all other possible causes of liver injury have been excluded. INR criterion is not applicable to participants receiving anticoagulants.</td></tr>
</table>

<table>
<tr><td rowspan="2">Routine Urinalysis</td><td>Dipstick
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td>Sediment (if dipstick result is abnormal)
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria

DNA damage markers
(8-Oxo-7,8-dihydro2'-desoxyguanosine) Concentration of oxidative lipid damage [8-Isoprostane] and Malondialdehyde in plasma Concentration of antioxidants (Vitamins C, E).</td></tr>
<tr><td colspan="2">If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time.

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBCs, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="2">• Serum and Urine Pregnancy Testing for women of childbearing potential only
• Nicotine Dipstick
• TB QuantiFERON Test
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and HCV antibody)</td></tr>
</table>

10.3. Appendix 3: Hepatitis B Virus (HBV) Screening with HBV DNA

Participants must undergo screening for HBV. At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg , anti-HBc , and anti-HBs) ***are eligible*** for this study.
- Participants who test **negative** for surface antigen (HBsAg) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the participant ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this study.

For participants who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+
* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

10.4. Appendix 4: QuantiFERON®-TB GOLD TESTING

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in participants with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per participant, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each participant, and sites will be informed of the results. Participants who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable anti-tuberculosis treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

1. Barnes PF. Diagnosing latent tuberculosis infection: Turning glitter to gold [editorial]. Amer J Respir Crit Care Med. 2004;170:5-6.
2. Brock I, Weldingh K, Lillebaek T, et al. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med. 2004;170:65-69.
3. Cellestis. QuantiFERON-TB Gold clinicians guide and QuantiFERON-TB Gold In-Tube Method package insert. Downloaded from www.cellestis.com, February 2009.
4. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-λ assay for the development of active tuberculosis disease after recent infection with mycobacterium tuberculosis. Am J Respir Crit Care Med. 2008;177:1164-1170.
5. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003;361:1168-73.
6. Ferrara G, Losi M, Meacci M, et al. Routine hospital use of a new commercial whole blood interferon-γ assay for the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2005; 172:631-635.
7. Higuchi K, Nobuyuki H, Mori T, Sekiya Y. Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. Respirology. 2007;12:88-92.
8. Kobashi Y, Mouri K, Obase Y, et al. Clinical evaluation of QuantiFERON-TB-2G test for immunocompromised patients. Eur Respir J. 2007; 30:945-950.
9. Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon λ assay. Rheum Dis. 2008;67:84-90.
10. Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: An interferon-γ-based assay using new antigens. Am J Respir Crit Care Med. 2004;170:59-64.

10.5. Appendix 5: Investigator Global Assessment

10.6. Appendix 6: Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) is: 0 none, 1 slight, 2 moderate, 3 severe, and 4 very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 no involvement
1 1% to 9% involvement
2 10% to 29% involvement
3 30% to 49% involvement
4 50% to 69% involvement
5 70% to 89% involvement
6 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

PASI 0.1 (Eh + Ih + Sh) Ah + 0.3 (Et + It + St) At + 0.2 (Eu + Iu + Su) Au + 0.4 (El + Il + Sl) Al

Where E erythema, I induration, S scaling, and A area

10.7. Appendix 7: Body Surface Area

BSA calculation "Rule of nine"

Area of the palm = unit of measure

The palm of the patient's hand "Handprint" represents approximately 1% of the BSA.

This method is defined as:

9% coverage for the head and neck

9% for each arm (=18)

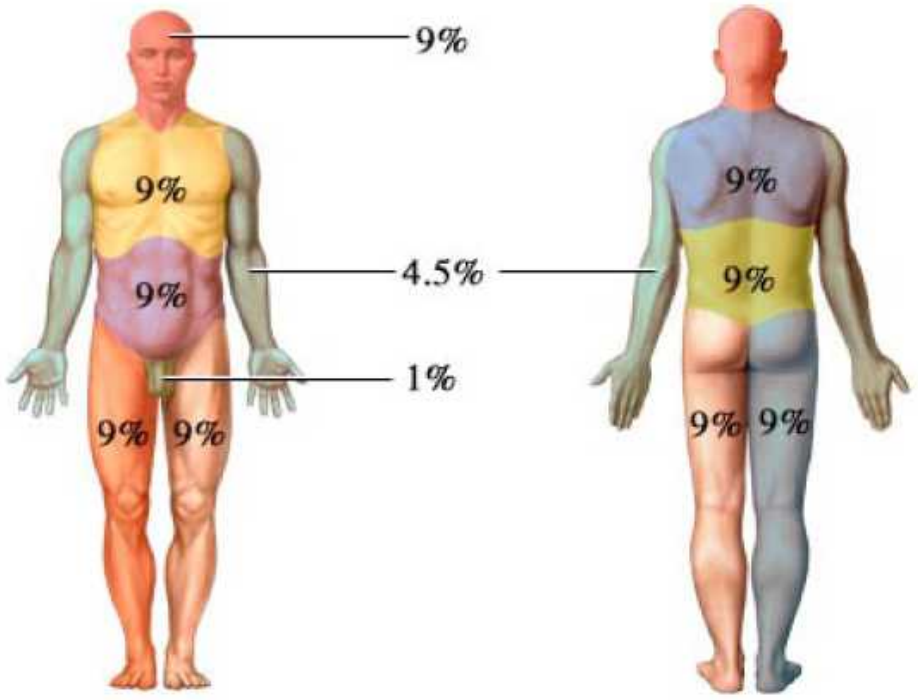
9% for the anterior and 9% posterior side of each leg (=36)

9% for each of 4 trunk quadrants (=36)

1% for the genitalia[1]

The sum of all palms will define the total BSA

Bożek A, et al. *Adv Clin Exp Med* 2017;26:851–856



10.8. Appendix 8: Dermatology Life Quality Index

CCI

[redacted]

CCI

10.9. Appendix 9: Pittsburgh Sleep Quality Index

Subject's Initials_____ID#_____Date_____Time_____AM PM

PITTSBURGH SLEEP QUALITY INDEX

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

Form Administration Instructions, References, and Scoring

Form Administration Instructions

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing, then any scores calculated using missing questions are also missing. Thus it is important to make sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

Scores – reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

PSQIDURAT **DURATION OF SLEEP**
IF Q4 $\geq$ 7, THEN set value to 0
IF Q4 < 7 and $\geq$ 6, THEN set value to 1
IF Q4 < 6 and $\geq$ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB **SLEEP DISTURBANCE**
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) $\geq$ 1 and $\leq$ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and $\leq$ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN **SLEEP LATENCY**
First, recode Q2 into Q2new thusly:
IF Q2 $\geq$ 0 and $\leq$ 15, THEN set value of Q2new to 0
IF Q2 > 15 and $\leq$ 30, THEN set value of Q2new to 1
IF Q2 > 30 and $\leq$ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new $\geq$ 1 and $\leq$ 2, THEN set value to 1
IF Q5a + Q2new $\geq$ 3 and $\leq$ 4, THEN set value to 2
IF Q5a + Q2new $\geq$ 5 and $\leq$ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS **DAY DYSFUNCTION DUE TO SLEEPINESS**

IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1
IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2
IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE **SLEEP EFFICIENCY**

Diffsec = Difference in seconds between day and time of day Q1 and day Q3
Diffhour = Absolute value of diffsec / 3600
newtib =IF diffhour > 24, then newtib = diffhour – 24
IF diffhour ≤ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0
IF tmphse < 85 and ≥ 75, THEN set value to 1
IF tmphse < 75 and ≥ 65, THEN set value to 2
IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL **OVERALL SLEEP QUALITY**

Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS **NEED MEDS TO SLEEP**

Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI **TOTAL**

DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL ≤ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality

10.10. Appendix 10: Alcohol Consumption Screening AUDIT Questionnaire in Adults

AUDIT questionnaire

Please circle the answer that is correct for you

1. How often do you have a drink containing alcohol?

· Never
· Monthly or less
· 2-4 times a month
· 2-3 times a week
· 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day when drinking?

· 1 or 2
· 3 or 4
· 5 or 6
· 7 to 9
· 10 or more

3. How often do you have six or more drinks on one occasion?

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

4. During the past year, how often have you found that you were not able to stop drinking once you had started?

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

5. During the past year, how often have you failed to do what was normally expected of you because of drinking?

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?

1

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

7. During the past year, how often have you had a feeling of guilt or remorse after drinking?

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

8. During the past year, have you been unable to remember what happened the night before because you had been drinking?

· Never
· Less than monthly
· Monthly
· Weekly
· Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?

· No
· Yes, but not in the past year
· Yes, during the past year

10. Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?

· No
· Yes, but not in the past year
· Yes, during the past year

Scoring the AUDIT

Scores for each question range from 0 to 4, with the first response for each question (eg never) scoring 0, the second (eg less than monthly) scoring 1, the third (eg monthly) scoring 2, the fourth (eg weekly) scoring 3, and the last response (eg. daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4 (from left to right).

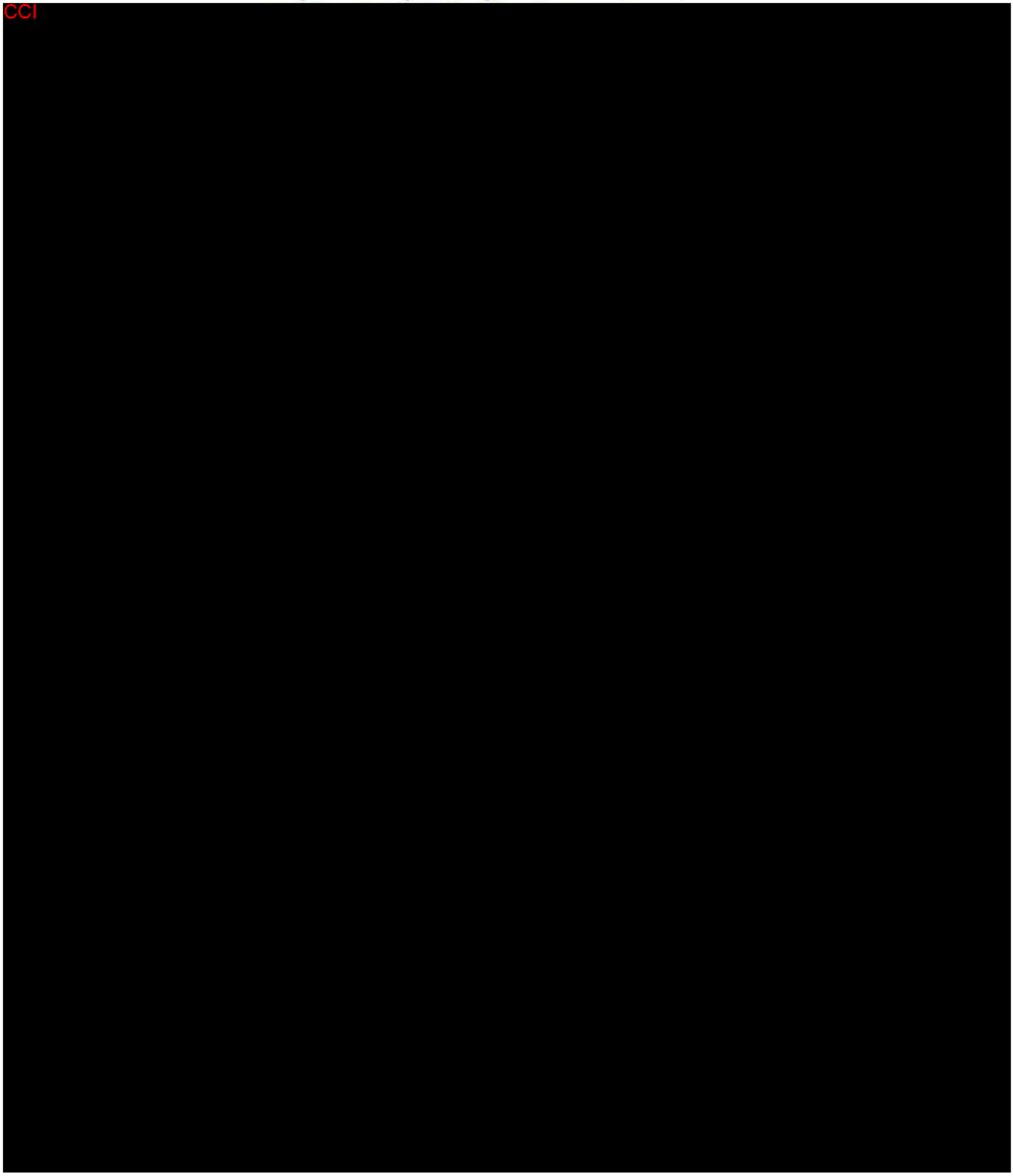
A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Saunders JB, Aasland OG, Babor TF et al. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption — II. Addiction 1993, 88: 791–803.

10.11. Appendix 11: Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

CCI



10.12. Appendix 12: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the Sponsor will modify this protocol without a formal amendment by the Sponsor. All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the Sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

In case of restrictions and limitations arising from a pandemic, study procedures and assessments may be executed as detailed in Appendix 15.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study intervention to the study-site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the Sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)

- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site

- Development Safety Update Report and Line Listings, where applicable
- Any other documents required by the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

INFORMED CONSENT PROCESS

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a

participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are re-screened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps

will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

The Sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand guselkumab, to understand plaque psoriasis, to understand differential intervention responders, and to develop tests/assays related to guselkumab and plaque psoriasis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding guselkumab or the Sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the Sponsor and will contain data from all study sites that participated in the study per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the Sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the Sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study-site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the Sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The Sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the Sponsor, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The Sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the Sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the Sponsor.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or Sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study-site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data :

- Race
- Blood pressure and pulse/heart rate

- Height and weight
- Details of physical examination

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The Sponsor will use a combination of monitoring techniques (risk-based, central, remote, or on-site monitoring) to monitor this study.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the Sponsor and study-site personnel and are accessible for verification by the Sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site and facilitate remote source data verification, where applicable.

Central monitoring will take place for data identified by the Sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the Sponsor's clinical quality assurance department may visit the study-site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE START AND CLOSURE

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- The study outcomes do not pass the criteria for futility analysis

10.13. Appendix 13: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The Sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may

require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

For combination products with a device constituent, serious adverse events include adverse device effects that resulted in any of the consequences characteristic of a serious adverse event. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

ATTRIBUTION DEFINITIONS

Assessment of Causality

The causal relationship to study treatment is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study treatment administration and the AE.

Not Related

There is not a reasonable causal relationship between study treatment administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a Sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study intervention
- Suspected abuse/misuse of a Sponsor study intervention
- Accidental or occupational exposure to a Sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a Sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a Sponsor study intervention
- Suspected transmission of any infectious agent via administration of a Johnson & Johnson medicinal product
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a Sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF, where possible. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local Sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the Sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.14. Appendix 14: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 13, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER-INDEPENDENT **Highly Effective Methods That Are User-Independent** *Failure rate of <1% per year when used consistently and correctly*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
4
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] oral injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

A female participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male participants included in the study will be reported. A male study participant is not required to discontinue study intervention if their partner becomes pregnant during the study.

Pregnancy Testing

A woman of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at all dosing visits prior to administration of study intervention. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

10.15. Appendix 15: Guidance on Study Conduct During a Pandemic

It is recognized that a pandemic situation (eg, Coronavirus Disease 2019 [COVID-19], or other) may have an impact on the conduct of this clinical study due to, for example: self-isolation/quarantine by participants and/or study-site personnel; travel restrictions and/or limited access to public places, including hospitals; and study-site personnel being reassigned to critical tasks.

In alignment with health authority guidance, the Sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. These recommendations do not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site-staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and follow-up will be conducted.

GENERAL GUIDANCE

Scheduled visits that cannot be conducted in person at a study-site will be performed remotely/virtually to the extent possible or may be delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Participants will also be questioned regarding their general health status.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the Sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the appropriate prefix (eg, "COVID-19-related" or other in accordance with Sponsor recommendations) in the case report form.

The Sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for a pandemic infection, the investigator should contact the Sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the pandemic should be summarized in the Clinical Study Report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

These emergency provisions are meant to ensure the safety of participants on study while site capabilities are compromised by pandemic restrictions. As restrictions are lifted, sites should revert to original protocol conduct as soon as feasible.

Enrollment of new participants may be halted at the Sponsor's discretion and restarted once the situation permits. The investigator's assessment of the risks versus benefit, depending on the situation at their particular site and the ability to monitor the safety of participants must be considered when restarting enrollment at a specific site.

The following provisions are being implemented by the Sponsor with respect to the following protocol mandated procedures to mitigate the impact of a pandemic:

1. Study intervention
2. Management of discontinuations and withdrawals due to a pandemic
3. Options for efficacy and other assessments
4. Options for safety assessments
5. Handling of missed assessments, visits or doses
6. Management of participants with COVID-19 infection
7. Statistical considerations

1. ***Study Intervention***

a. Study Intervention Administration: Home- or Self-administration

Study intervention should be continued if, in the assessment of the investigator, it does not result in risk to the participant. Remote medical consultation and alternatives to study medication dispensing, administration, and clinical safety laboratory assessments (including home health nursing) will allow continued study participation for participants in this study. In cases where site visits are not possible under the restrictions and limitations due to a pandemic, participants who have adequate experience and have been trained how to self-inject may self-administer subcutaneous (SC) study intervention outside a study-site (eg, at home) up to the time when pandemic-related restrictions are lifted, and site visits can be resumed. Participants must self-administer the study intervention in compliance with the Instructions for Use (IFU) document at the times instructed by the investigator. Site-staff will contact the participants by phone prior to, and 30 minutes after the administration of the study intervention for evaluation of AEs. The study-intervention must be self-administered only on completion of the phone contact with the site-staff.

Study-site personnel will instruct participants on how to store study intervention for at-home use, and disposal of used syringes. For each administration of study intervention, the time and date of injection, whether study intervention was self-administered, and if so, whether SC administration was complete will be recorded in the study participant drug administration card.

b. Preparation/Handling/Storage/Accountability

In case site visits are not possible due to the restrictions arising from a pandemic, any participant who will be self-administering study intervention outside of a study-site will receive detailed instructions on how to store study intervention, disposal of used syringes, and handling of unused study material. Participants will also receive a sharps container to dispose of used syringes and will be instructed to return the sharps container and all unused cartons with syringes.

Participants will maintain a record of the time and date of study intervention administrations in the study participant drug administration cards which will be shipped in advance to the participants. Study-site personnel will utilize the study participant drug administration card to ensure compliance and document at-home study intervention administrations in the CRF.

c. Notes on Shipment of Study Intervention to Participants

If it is necessary to ship the study intervention directly to study participants, shipment by the study-site itself is preferred under this exception due to a pandemic. Shipment should be made in a manner that allows tracking of both transport and delivery. The participant should acknowledge receipt of the shipment to the site (eg, by returning a dated and signed receipt form).

In case adequate shipment by the study-site is not possible (for example, owing to capacity limitations, logistics, or special transport conditions for the study intervention), direct transport by the Sponsor may be accepted in justified exceptional cases, provided that the Sponsor appoints a suitably qualified service provider as trustee. Both the transport and handover conditions for study intervention should be part of the contractual arrangements, so that pharmaceutical drug safety of study intervention as well as protection of the privacy and personal data of participants are adequately safeguarded. The study intervention must be delivered directly to the participant or a person authorized by the participant, and must not be given to neighbors or deposited at a storage location. Written confirmation of dose and dose regimens by the investigator should also be obtained prior to shipment.

The personnel of the service provider in charge of the transport should be trained and instructed accordingly. As personal data are transferred to the service provider, this requires a contract of assignment with the Sponsor or legal representative.

For direct shipment of study intervention to participants, instructions on storage and return of used and unused study intervention should be provided to participants. When shipped by study sites, the receipt, consumption and return of study intervention must be documented in a form that allows the study-site to meet its documentation requirements (ie, drug accountability), as defined in ICH GCP 4.6.3.

d. Discontinuation of Study Intervention

If at any time the safety of a participant is considered to be at risk, study intervention will be temporarily or permanently discontinued, while every effort should be made to maintain follow-up on study.

The benefit of continuing study treatment should be considered by the investigator for each individual participant, considering the potential impact of reduced direct clinical supervision on a participant's safety. A temporary interruption of study intervention might be considered based on investigator´s discretion and documented.

Discontinuations of study interventions due to pandemic-related reasons should be documented with a prefix (eg, "COVID-19-related" or in accordance with Sponsor recommendations) in the CRF.

2. Management of Discontinuations and Withdrawals due to a Pandemic

Withdrawal from the study due to pandemic-related reasons should be documented with a prefix (eg, "COVID-19-related" or in accordance with Sponsor recommendations) in the CRF. Study intervention assigned to the withdrawn participant may not be assigned to another participant. If the sample size is not achieved due to pandemic-related reasons or other emergency situations, enrollment of additional participants will be considered by the Sponsor.

3. Options for Efficacy and Other Assessments

To safely maintain participants on study treatment while site capabilities are compromised by pandemic or other emergency restrictions, participants may have tele-health visits (conducted via phone or video conversation per local regulation) until such time that on-site visits can be resumed.

Normal study procedures should be followed for the applicable visit as closely as possible, however it is recognized that remote visits may be limited to the collection of the following data:

- Concomitant therapy checks
- PROs

Patient-reported outcomes (PRO) questionnaires in paper format may be shipped to participants along with instructions for completion. The PROs must be completed on the day of the scheduled visit prior to administration of the study intervention and any tests, procedures or consultations and sent to the investigator by appropriate means per Sponsor instructions.

Actual dates of assessments will be recorded by the participants and transcribed to the CRF. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations.

If assessments are not possible as outlined in the Schedule of Activities, missed assessments should be documented as a deviation related to the pandemic and be made up as soon as possible.

4. Options for Safety Assessments

All efforts should be done to perform the following safety assessments, when applicable:

- Vital signs
- Weight
- Early Detection of Active Tuberculosis (per protocol Section 8.2.5)

- Urine pregnancy testing
- Safety assessments related to study intervention administration, including injection-site reactions evaluation
- Clinical Safety Laboratory Assessments (including through home collection of samples or at certified local laboratory, where possible)

At each contact/remote visit, participants will be interviewed to collect safety data per the list above. At drug administration time-points, site-staff will contact the participants by phone prior to, and 30 minutes after the administration of the study intervention (when done at home) for evaluation of AEs including injection-site reactions.

In cases where participants receive SC injections outside the study-site during the treatment period, participants are requested to contact their treating physician as soon as they experience any untoward medical occurrence. The treating physician should consider reporting any AEs.

Home testing may be employed for urine pregnancy tests. The urine pregnancy test will be shipped in advance to the participants. For women of childbearing potential, a negative pregnancy test must be recorded on the study participant drug administration card before self-administering the study intervention.

Clinical laboratory safety monitoring may be performed using home collection of samples or at a certified local laboratory rather than at the central laboratory. A copy of the external laboratory report should be reviewed by the investigator and retained, along with reference ranges, for source documentation and captured in the CRF.

5. Handling of Missed Assessments/Visits/Doses

Relevant study data elements impacted by a pandemic or other emergency situations should be documented (eg, "COVID-19-related" or in accordance with Sponsor recommendations) in CRFs and/or other study systems, as directed by Sponsor guidance; these may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.

6. Management of Participants Infected With SARS-CoV-2

If a participant develops SARS-CoV-2 infection or related disease, the investigator should contact the Sponsor to discuss plans for study intervention and follow-up. An interruption of study treatment should be considered by the investigator, depending on symptoms and concomitant medication used for the treatment of COVID-19. Treatment must be interrupted if prohibited medication is used. Standard adverse event and serious adverse event reporting requirements apply.

When a participant for whom study treatment has been interrupted recovers from suspected or confirmed SARS-CoV-2 infection or related disease and all toxicities improve to Grade ≤1, the investigator should discuss with the Sponsor about resuming study treatment.

Consenting and re-consenting of participants will be performed as applicable for the measures taken (including remote consenting by phone or video consultation) and according to local guidance for informed consent applicable during the COVID-19 pandemic.

7. *Statistical Considerations*

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is detailed in the protocol.

The Sponsor will evaluate the totality of impact of the restrictions and limitations arising from a pandemic on collection of key study data and additional data analyses will be outlined in the Statistical Analysis Plan(s).

In line with the protocol Section 8.9.2. the sample size may be further revised to compensate for major protocol deviations during a pandemic which could potentially impact the primary endpoint. The new sample size will also account for any future dropouts.

Note: In case of emergency situations where the recommendations specified in this protocol are insufficient, the investigator or site-staff are instructed to follow local guidelines and recommendations, or contact the Sponsor for guidance.

11. REFERENCES

11. Abbas A, Gregersen I, Holm S, et al. Interleukin 23 levels are increased in carotid atherosclerosis: possible role for the interleukin 23/interleukin 17 axis. Stroke. 2015 Mar;46(3):793-799.

12. Ahlehoff O, Skov L, Gislason G, et al. Pharmacological undertreatment of coronary risk factors in patients with psoriasis: observational study of the Danish nationwide registries. PLoS One. 2012;7(4):e36342.

13. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017 Mar;76(3):405-417.

14. Boehncke WH. Systemic Inflammation and cardiovascular comorbidity in psoriasis patients: causes and consequences. Front Immunol. 2018;9:579. Published 2018 Apr 5. doi:10.3389/fimmu.2018.00579

15. Bożek A, Reich A. The reliability of three psoriasis assessment tools: Psoriasis area and severity index, body surface area and physician global assessment. Adv Clin Exp Med. 2017 Aug;26(5):851-856. doi: 10.17219/acem/69804. PMID: 29068583.

16. Brunner PM, Suárez-Fariñas M, He H, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins [published correction appears in Sci Rep. 2018 May 29;8(1):8439]. Sci Rep. 2017;7(1):8707. Published 2017 Aug 18. doi:10.1038/s41598-017-09207-z

17. Camici PG, d'Amati G, Rimoldi O. Coronary microvascular dysfunction: mechanisms and functional assessment. Nat Rev Cardiol. 2015 Jan;12(1):48-62.

18. Couderc E, Morel F, Levillain P, et al. Interleukin-17A-induced production of acute serum amyloid A by keratinocytes contributes to psoriasis pathogenesis. PLoS One. 2017;12(7):e0181486. Published 2017 Jul 14. doi:10.1371/journal.pone.0181486

19. CNTO1959 (guselkumab). Investigator's Brochure Edition 9, Janssen Research and Development, LLC, December 2018 (EDMS-DEC-8340385).

20. Dal Lin C, Tona F, Osto E. Coronary microvascular function and beyond: the crosstalk between hormones, cytokines, and neurotransmitters. Int J Endocrinol. 2015;2015:312848.

21. Davidovici BB, Sattar N, Prinz J, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions [published correction appears in J Invest Dermatol. 2010 Oct;130(10):2517. Jörg, Prinz C [corrected to Prinz, Jörg C]]. J Invest Dermatol. 2010;130(7):1785-1796. doi:10.1038/jid.2010.103

22. Del Rio D, Serafini M, Pellegrini N. Selected methodologies to assess oxidative/antioxidant status in vivo: a critical review. Nutr Metab Cardiovasc Dis. 2002;12(6):343-351.

23. Eder L, Harvey P, Chandran V, et al. Gaps in diagnosis and treatment of cardiovascular risk factors in patients with psoriatic disease: an international multicenter study. J Rheumatol. 2018 Mar;45(3):378-384.

24. Fatkhullina AR, Peshkova IO, Koltsova EK. The Role of Cytokines in the Development of Atherosclerosis. Biochemistry (Mosc). 2016;81(11):1358-1370. doi:10.1134/S0006297916110134

25. Flintholm Raft K, Frestad D, Michelsen MM, et al. Peripheral endothelial function and coronary flow velocity reserve are not associated in women with angina and no obstructive coronary artery disease: The iPOWER Study. J Vasc Res. 2017;54(5):309-319.

26. Fonseca DA, Antunes PE, Cotrim MD. The morphology, physiology and pathophysiology of coronary microcirculation. DOI: 10.5772/64537

27. Fu LW, Vender R. Systemic role for vitamin D in the treatment of psoriasis and metabolic syndrome. Dermatol Res Pract. 2011;2011:276079. doi:10.1155/2011/276079

28. Gelfand JM, Shin DB, Alavi A, et al. A Phase IV, randomized, double-blind, placebo-controlled crossover study of the effects of ustekinumab on vascular inflammation in psoriasis (the VIP-U Trial). J Invest Dermatol. 2020;140(1):85-93.e2. doi:10.1016/j.jid.2019.07.679

29. Gelfand, J. et al. Presented at AAD 2019, LB abstract. #11304

30. Gelfand et al. Presented at AAD 2018 #LB abstract

31. Gooderham MJ, Papp KA, Lynde CW. Shifting the focus - the primary role of IL-23 in psoriasis and other inflammatory disorders. J Eur Acad Dermatol Venereol. 2018 Jul;32(7):1111-1119.

32. Gordon KB, Armstrong AW, Foley P, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 Study. J Invest Dermatol. 2019;139(12):2437-2446.e1. doi:10.1016/j.jid.2019.05.016

33. Griffiths CEM, Papp KA, Kimball AB, et al. Long-Term efficacy of guselkumab for the treatment of moderate-to-severe psoriasis: results from the Phase 3 VOYAGE 1 trial through two years. J Drugs Dermatol. 2018 Aug 1;17(8):826-832.

34. Grune T, Berger MM. Markers of oxidative stress in ICU clinical settings: present and future. Curr Opin Clin Nutr Metab Care. 2007;10(6):712-717. doi:10.1097/MCO.0b013e3282f0c97c

35. Heijden, T. & Bot, Ilze & Kuiper, Johan. The IL-12 cytokine family in cardiovascular diseases. Cytokine. 2017. 122. 10.1016/j.cyto.2017.10.010.

36. Kim SM, Shim WJ, Lim HE, et al. Assessment of coronary flow reserve with transthoracic Doppler echocardiography: comparison with intracoronary Doppler method. J Korean Med Sci. 2000 Apr;15(2):139-145. https://doi.org/10.3346/jkms.2000.15.2.139

37. Kimball AB, Szapary P, Mrowietz U, et al. Underdiagnosis and undertreatment of cardiovascular risk factors in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2012 Jul;67(1):76-85.

38. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006 Nov;27(21):2588-605.

39. Layland J, Carrick D, Lee M, et al. Adenosine: physiology, pharmacology, and clinical applications. JACC Cardiovasc Interv. 2014 Jun;7(6):581-91.

40. Liu W, Chang C, Hu H, Yang H. Interleukin-23: A new atherosclerosis target. J Interferon Cytokine Res. 2018 Oct;38(10):440-444.

41. Langley RG, Tsai TF2, Flavin S. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol. 2018 Jan;178(1):114-123.

42. Makavos G, Ikonomidis I, Andreadou I, et al. Effects of interleukin 17A inhibition on myocardial deformation and vascular function in psoriasis. Can J Cardiol. 2020 Jan;36(1):100-111.

43. Mehta NN, Shin DB, Joshi AA. effect of 2 psoriasis treatments on vascular inflammation and novel inflammatory cardiovascular biomarkers: a randomized placebo-controlled trial. Circ Cardiovasc Imaging. 2018 Jun;11(6):e007394.

44. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015 Dec;29(12):2277-2294.

45. Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest. 2004 Jun;113(12):1664-1675.

46. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009 Oct;23 Suppl 2:1-70.

47. Petretta M, Acampa W, Zampella E, et al. Imaging techniques for assessment of coronary flow reserve. Monaldi Arch Chest Dis. 2011 Dec;76(4):192-7.

48. Pietrzak A, Bartosinska J, Blaszczyk R, et al. Increased serum level of N-terminal Pro-B-type natriuretic peptide as a possible biomarker of cardiovascular risk in psoriatic patients. J Eur Acad Dermatol Venereol. 2015;29(5):1010-1014. doi:10.1111/jdv.12528

49. Pries AR, Habazettl H, Ambrosio G, et al. A review of methods for assessment of coronary microvascular disease in both clinical and experimental settings. Cardiovasc Res. 2008 Nov 1;80(2):165-174.

50. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999 Sep;41(3 Pt 1):401-407.

51. Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018;391(10118):319-328. doi:10.1016/S0140-6736(17)32814-3

52. Ridker PM, Libby P, MacFadyen JG, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018;39(38):3499-3507. doi:10.1093/eurheartj/ehy310

53. Sandfort V, Lima JA, Bluemke DA. Non-invasive imaging of atherosclerotic plaque progression: status of coronary computed tomography angiography. Circ Cardiovasc Imaging. 2015 Jul;8(7):e003316.

54. Shahidi-Dadras M, Niknezhad N, Niknejad N, et al. Can serum level of N-terminal pro B-type natriuretic peptide be used in patients with psoriasis as a predictor of cardiovascular disease?. Dermatol Ther. 2019;32(3):e12865. doi:10.1111/dth.12865

55. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009 Nov;161(5):987-1019.

56. Raitakari OT, Celermajer DS. Flow-mediated dilatation. Br J Clin Pharmacol. 2000 Nov;50(5):397-404.

57. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Nov 27;72(21):2625-2641.

58. Terui T, Kobayashi S, Okubo Y, Murakami M, Hirose K, Kubo H. Efficacy and Safety of Guselkumab, an Anti–interleukin 23 Monoclonal Antibody, for Palmoplantar Pustulosis: A Randomized Clinical Trial. JAMA Dermatol. 2018;154(3):309–316. doi:10.1001/jamadermatol.2017.5937

59. Thondapu V, Bourantas CV, Foin N, Jang IK, Serruys PW, Barlis P. Biomechanical stress in coronary atherosclerosis: emerging insights from computational modelling. Eur Heart J. 2017 Jan 7;38(2):81-92.

60. von Stebut E, Reich K, Thaçi D, et al. Impact of Secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. J Invest Dermatol. 2019 May;139(5):1054-1062.

61. World Health Organisation global report on psoriasis https://apps.who.int/iris/bitstream/handle/10665/204417/9789241565189 eng.pdf.psoriasis;jsessionid=352D8A96C9AC34EA9CBA35F2B39195E4?sequence=1 Accessed October 2019.

62. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–370.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutica NV

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-May-2022 08:27:43 (GMT)	Document Approval