Janssen Research & Development

Statistical Analysis Plan

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

Protocol CNTO1959PSO4015; Phase 4

CNTO1959 (guselkumab)

Status:	Approved
Date:	21 July 2023
Prepared by:	ClinChoice
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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	21 Jul 2023	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan (SAP) contains the definitions of analysis sets, key derived variables, and statistical methods to evaluate the safety and efficacy of guselkumab in adult participants with moderate to severe plaque psoriasis Protocol CNTO1959PSO4015. Analysis results titles, mock-ups, and programming instructions for all statistical outputs (tables, figures, and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS).

This current SAP covers the analyses to be performed following the Sponsor decision to prematurely terminate the study on 31 MAY 2023 due to slow enrollment.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of guselkumab on Coronary flow reserve (CFR) measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk*	• Change from baseline[†] in Coronary Flow Reverse (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 Global Longitudinal Strain (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 carotid femoral pulse wave velocity (cfPWV) as a surrogate marker of arterial stiffness in participants with	• Change from baseline in carotid-femoral pulse wave velocity (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 2.74, and 2.75 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.

* 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.

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

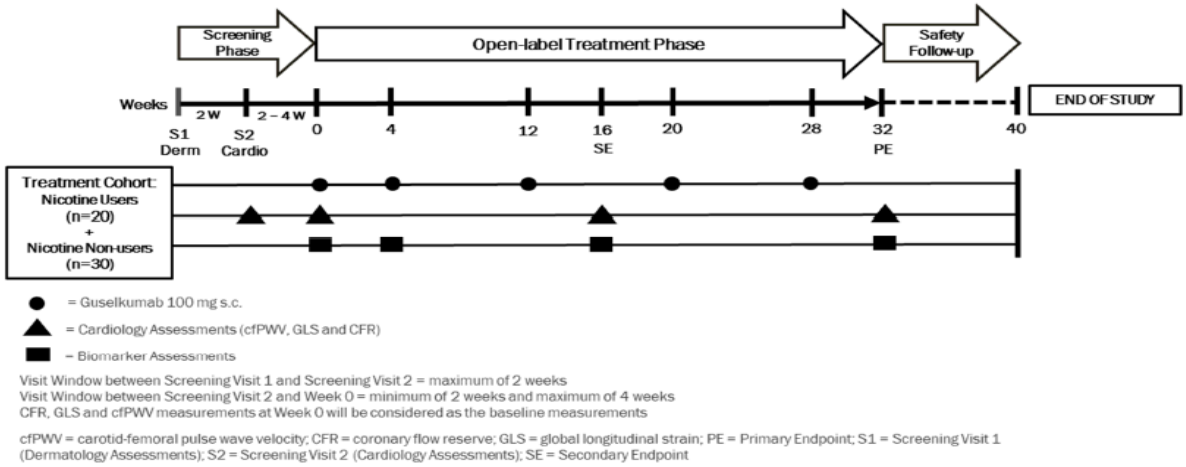
- To evaluate the correlation between skin improvement and cardiovascular risk surrogate markers in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk.
- To evaluate the effect of guselkumab on disease-related quality-of-life in participants with moderate-to-severe psoriasis 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.

1.2. Study 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 psoriatic arthritis [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.

An overview of the intervention study is presented in Figure 1 below:

Figure 1: Schematic Overview of Study Design



The study is prematurely discontinued on 31st of May 2023,

- All data collected will be analyzed and therefore, all data will need to go through data cleaning process.
- Before the 31st of May 2023, per protocol visits can be scheduled, this allows sites to decide for continued patient treatment, either on commercial guselkumab or any other treatment
- After the 31st of May 2023 only the Final Efficacy visits, and Final Safety visits are to be scheduled.
- There are instances where the sponsor recommends not to do the per-protocol visits prior to 31st of May in case this results in too much patient burden in terms of assessments e.g., 2 cardiovascular assessments in a short timeframe.

2. STATISTICAL HYPOTHESES

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 of CFR measurement at Week 32 (i.e., change from baseline of CFR measurement at Week 32 is positive).

3. SAMPLE SIZE DETERMINATION

The initial sample size calculation was 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 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.

After the decision to prematurely terminate the study, this sample size calculation was no longer relevant.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Set	Description
Screened	All participants who signed the informed consent form (ICF).
Full Analysis Set (FAS)	The FAS includes all participants who received at least 1 dose of guselkumab.
Safety Analysis Set	The safety analysis set includes all participants who received at least 1 dose of adenosine and guselkumab.

5. STATISTICAL ANALYSES

5.1. General Considerations

Descriptive statistics (eg, mean, median, standard deviation (SD), minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphic data displays may also be used to summarize the data. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize the data.

The summarized data will be presented by Nicotine-user, non-Nicotine user and total group.

Baseline Value: For all endpoints the last non-missing measurement prior to or on the day of the first administration of the study treatment (guselkumab) will be the Baseline value in the study (i.e., at 'Week 0, Baseline' analysis visit, following assignment of the actual visits using visit windows, as indicated in Table 2).

Level of Significance: In general, all tests will be performed at a 2-sided significance level of 0.05, unless otherwise specified. All interval estimations will be reported using 2-sided 95%CI. Nominal p-values will be presented.

Change from Baseline:
For the continuous variables pertaining to the cardiology outcomes, skin related outcomes, or paper PRO outcomes the determination of change from baseline will be determined only when both, baseline and the measurement for the particular visit is available.

$$Change\ from\ Baseline\ at\ visit\ x = Measurement\ from the\ visit\ x - Baseline\ value\ of\ the\ parmeter$$

The number of patients with missing change from baseline values will be also presented in the statistical outputs.

For continuous or ordinal efficacy endpoints, a Mixed-effect Model for Repeated Measures (MMRM) will be used. Covariates such as Nicotine use, body mass index (BMI), presence, or absence of PsA, age, gender, and visit will be incorporated into these models.

For binary efficacy endpoints, 95% confidence interval [CI] for binomial proportions will be provided using exact methods, such as Clopper-Pearson or Chan-Zhang.

5.1.1. Visit Windows

Baseline will be defined as the last non-missing measurement prior to or on the day of the first dose of study treatment (guselkumab).

Study day will be calculated as follows:

- Days prior to first dose: Study Day = date – treatment first dose date.
- Days on or after first dose: Study Day = date – treatment first dose date + 1.

First dose refers to guselkumab.

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

The Time Interval (label on output), Time Interval (Day) and the Target Time Point (Day) are indicated in Table 2. If an assessment is not scheduled for every visit, windows will be combined so that the interval between targeted study days is split evenly and consistently between visits.

Table 2: Visit Windows

Scheduled Visit Number	Time Interval (label on output)	Planned Time Point	Target Time Point (Interval for tests)	Time Interval (Day) *	Target Time Point (Day) *
S1	Screening Visit S1	Screening Visit S1 (Dermatology) (Maximum of 2 weeks prior to Screening Visit S2)	-42 – -28 (Only for pregnancy test)	-42 – -28	-
			-42 – -14 (Only for clinical laboratory tests and vital signs [blood pressure, pulse/heart rate and temperature])	-42 – -14 (Prior to Screening Visit S2)	-
			-56 – -1 (Only for QuantiFERON-TB Gold test) (Within 2 months before Week 0)	-56 – -1	-
			-84 – -1	-84 – -1	-

Scheduled Visit Number	Time Interval (label on output)	Planned Time Point	Target Time Point (Interval for tests)	Time Interval (Day) *	Target Time Point (Day) *
			(Only for Chest radiograph) (Within 3 months before Week 0)		
			-42 – -14	-42 – -14	-
S2	Screening Visit S2	Screening Visit S2 (Cardiology) (Minimum of 2 weeks and maximum of 4 weeks prior to Week 0)	-27 – -14 (Only for pregnancy test, urine nicotine test, cfPWV, GLS and CFR)	-27 – -14	-
1	Week 0, Baseline	Treatment Phase: Week 0	1 (Pre-dose)	≤ 1 (Pre-dose based on the time of the assessment if applicable) [a]	1
				-13 – 1 (Pre-dose based on the time of the assessment if applicable) [a] (For cfPWV, GLS and CFR)	1
2	Week 4	Treatment Phase: Week 4 (±7 days)	22 – 36 (Pre-dose)	2 – 57 (Pre-dose based on the time of the assessment if applicable)	29
3	Week 12	Treatment Phase: Week 12 (±7 days)	78 – 92 (Pre-dose)	58– 99 (Pre-dose based on the time of the assessment if applicable)	85
4	Week 16	Treatment Phase: Week 16 (-7 to +7 or +14 days) [b]	106 – 120 (Pre-dose)	100 – 125	113
			106 – 127 (Pre-dose) (Only for CFR)	100 – 129	113
5	Week 20	Treatment Phase: Week 20 (±7 days)	134 – 148 (Pre-dose)	126 – 169 (Pre-dose based on the time of the assessment if applicable)	141
				130 – 169 (Pre-dose based on the time of the	141

Scheduled Visit Number	Time Interval (label on output)	Planned Time Point	Target Time Point (Interval for tests)	Time Interval (Day) *	Target Time Point (Day) *
				assessment if applicable) (Only for CFR)	
6	Week 28	Treatment Phase: Week 28 (±7 days)	190 – 204 (Pre-dose)	170 – 210 (Pre-dose based on the time of the assessment if applicable)	197
7	Final Efficacy Visit (Week 32)	Final Efficacy Visit: Week 32 (-7 to +7 or +14 days) [b]	218 – 232	211 - 252 [c]	225
			218 – 239 (Only for CFR)	211 - 256 [c]	225
8	Final Safety Visit (Week 40)	Final Safety Visit: 12 Weeks (±7 days) after the last dose of guselkumab within the treatment phase	77 – 91 ** (after the last dose of guselkumab within the treatment phase)	253 – 287 [d e] or 77 – 91 ** (after the last dose of guselkumab within the treatment phase) [e]	281 or 85 **

* Relative to the day of first administration of the study treatment (guselkumab).
** Relative to the day of last administration of the study treatment (guselkumab) within the treatment phase.
[a] Baseline
[b] If CFR measurement is unsuccessful, 2 attempts to measure a CFR can be made on different days. In such cases, at Weeks 16 and 32 the visit window for the CFR parameter can be extended by 7 additional days (CFR visit window = -7 / +14 days).
[c] For participants, who do have a Week 28 assessment, 4 weeks after the last dose of the guselkumab within the treatment phase. For participants who permanently discontinue guselkumab before Week 28, the date of discontinuation. Following the premature termination of the study 4 to 8 weeks after the last dose of guselkumab within the treatment phase.
[d] Only for participants, who do have a Week 28 assessment.
[e] For participants who receive guselkumab after the treatment phase, the date of the first dose of guselkumab outside of the treatment phase.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by Nicotine-user, non-Nicotine user groups and overall:

- Participants enrolled (e.g., Participants who fulfilled eligibility criteria at Screening Visit S1 and with CFR ≥2 and ≤3.5 both at Screening Visit S2, and at Week 0.).

- Participants who received study intervention (guselkumab).
- Participants who completed the study.
- Participants who discontinued study intervention (guselkumab).
  - Reasons for discontinuation of study intervention (guselkumab).
- Participants who terminated study prematurely along with primary reasons.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention (guselkumab).
- Participants who terminated study prematurely
- Participants who were enrolled yet did not receive study intervention (guselkumab).

5.3. Primary Endpoint Analysis

The efficacy analysis of the primary endpoint will be based on the FAS.

5.3.1. Definition of Endpoint

5.3.1.1. Coronary flow reserve (CFR)

Coronary flow reserve will be measured non-invasively using transthoracic doppler echocardiography, 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.

The primary endpoint for the study is the change from baseline in CFR at Final Efficacy Visit (Week 32) based on FAS.

Data Handling of Primary Efficacy Endpoint

For most of the secondary efficacy analyses (eg, over time summaries), after the treatment failures are applied, no imputation will be performed for missing data (eg, lost to follow-up, missed study visit) and the values will remain as missing and as observed data will be used for the analysis.

5.3.2. Estimand

Primary Trial Objective: To evaluate the effect of guselkumab on CFR measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk. Intermediate cardiovascular risk is defined by CFR ≥2 and ≤3.5 at Screening Visit S2.

Estimand Scientific Question of Interest: What level of change from baseline of CFR considered to have benefited from guselkumab for the pre-specified duration (32 weeks).

Study intervention:

- Guselkumab (100 mg SC [Subcutaneous] injections at Week 0, 4, 12, 20 and 28)

Population: Participants with moderate to severe plaque psoriasis (with or without PsA) for at least 6 months prior to study entry. The target population consists of men or women aged 18 years and above with moderate to severe plaque psoriasis of at least 6 months' duration, defined as psoriasis area and severity index (PASI) ≥ 12, and involved body surface area (BSA) ≥ 10% at Screening Visit S1 and CFR with ≥ 2 to ≤ 3.5 at Screening Visit S2. Participants should not be with CFR of <2 or >3.5 at both Screening Visit S2 and Week 0.

Variable: Change from baseline in the CFR measurement at Final Efficacy Visit (Week 32). The CFR measurement at Week 0, Baseline will be considered as baseline value. Participants who had adequate primary endpoint measurements will be assessed at Final Efficacy Visit (Week 32) considering as observed for the analysis.

Summary measure (Population-level summary): Least squares means (LSmeans), together with the 95% CI and p-values based on the MMRM.

Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Usage of disallowed cardiac medication* (as listed in Table 1 of the protocol) during the treatment phase	**Composite Strategy:** A participant with this intercurrent event will be excluded from the analysis.

* List of concomitant medications from ADaM datasets will be shared with the clinical team after the receipt of SDTM data by the programming team for each data cut. The clinical team will review the list and flag the appropriate disallowed medications. This list will be used for the intercurrent events.

5.3.3. Analysis Methods

5.3.3.1. Main Estimator (Analysis) for the Primary Estimand

A MMRM will be used to determine the change from baseline in Cardiovascular measurement at Week 32 or Week 16 in the open label phase to compare the participant groups of nicotine users vs non-nicotine users, will be analyzed using a MMRM based on observed case data. The models will include baseline CFR measurement at Week 0, Baseline before first administration of guselkumab as a covariate, and Nicotine use, BMI, presence or absence of PsA, age, gender, and visit.

The estimates for the primary estimand of the treatment effect of guselkumab will be provided by the difference of change from baseline at Week 32 in the LSmeans. The 95% CI for the differences in LSmeans and p-values will be calculated based on the MMRM. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and autoregressive order 1 (AR[1]) with separate subject random effect.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Confirmatory Secondary Endpoint(s)

The key secondary endpoints include the following at Week 16 and Week 32:

- Change from baseline in CFR at Week 16
- Change from baseline in absolute GLS at Week 16 and Week 32.
- Change from baseline in carotid-femoral pulse wave velocity (cfPWV) at Week 16.
- Change from baseline in cfPWV at Week 32.
- Change from baseline in CFR at Week 16 and Week 32 among participants with CFR in the ranges of 2 to >2.75 and ≤ 2.75 to 3.5 at baseline.
- Change from baseline in CFR at Week 16 and Week 32 among nicotine users and non-users.
- Change from baseline in absolute 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.
- Rate of Adverse Events (AEs) among participants treated with guselkumab at Week 16 and Week 32.

5.4.1.1. Definition of Endpoint(s)

Refer to Section 5.3.1 for Definition of CFR Endpoint

The secondary endpoint for the study is the change from baseline in CFR at Week 16 or GLS/cf-PWV at Week 16 and Week 32 are based on FAS.

5.4.1.1.1. Global Longitudinal Strain (GLS) 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.

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

5.4.1.1.2. Carotid-femoral Pulse Wave Velocity (cf-PWV)

The measurement of cfPWV is accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness.28 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). Average of triplicate cfPWV measurements will be derived and used for the analysis at each of the treatment time point.

Data Handling Rules for Efficacy Analyses

The secondary efficacy analyses (eg, over time summaries), after the treatment failures are applied, no imputation will be performed for missing data (eg, lost to follow-up, missed study visit) and the values will remain as missing and as observed data will be used for the analysis.

5.4.1.2 Estimand

Secondary Trial Objective: To evaluate the effect of guselkumab on CFR/GLS/cf-PWV measured by transthoracic doppler-echocardiography, in participants with moderate-to-severe psoriasis and intermediate cardiovascular risk. Intermediate cardiovascular risk is defined by CFR $\geq$2 and $\leq$3.5 at Screening Visit S2.

Estimand Scientific Question of Interest: What level of change from baseline of CFR/GLS/cf-PWV considered to have benefited from guselkumab for the pre-specified duration (16 weeks).

Study intervention:

- Guselkumab (100 mg SC [Subcutaneous] injections at Week 0, 4, 12, 20 and 28)

Population: Participants with moderate to severe plaque psoriasis (with or without PsA) for at least 6 months prior to study entry. The target population consists of men or women aged 18 years and above with moderate to severe plaque psoriasis of at least 6 months' duration, defined as PASI ≥ 12, and involved BSA ≥ 10% at Screening Visit S1 and CFR with ≥ 2 to ≤ 3.5 at Screening Visit S2. Participants should not be with CFR of <2 or >3.5 at both Screening Visit S2 and Week 0.

Variable: Change from baseline in the CFR measurement at Week 16. The CFR measurement at Week 0, Baseline will be considered as baseline value. Similarly, for other secondary endpoints of GLS/cf-PWV at Week 16 and Week 32. Participants who had adequate secondary endpoint measurements will be assessed at Week 16 as per Table 2 and Final Efficacy Visit (Week 32) considering as observed for the analysis.

Secondary Estimand:
Summary measure (Population-level summary): LSmeans, together with the 95% CI and p-values based on the MMRM.

Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Usage of disallowed cardiac medication (as listed in Table 1 of the protocol) during the treatment phase	**Composite Strategy:** A participant with this intercurrent event will be excluded from the analysis.

5.4.1.3 Analysis Methods

Main Estimator (Analysis) for the Primary Estimand

A MMRM will be used to determine the change from baseline in Cardiovascular measurement at Week 16 or Week 32 in the open label phase to compare the participant groups of nicotine users vs non-nicotine users, will be analyzed using a MMRM based on observed case data. The models will include baseline CFR/GLS/cf-PWV measurement at Week 0, Baseline before first administration of guselkumab as a covariate, and Nicotine use, BMI, presence, or absence of PsA, age, gender, and visit.

The estimates for the primary estimand of the treatment effect of guselkumab will be provided by the difference of change from baseline at Week 32 in the LSmeans. The 95% CI for the differences in LSmeans and p-values will be calculated based on the MMRM. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect.

5.5. Tertiary/Exploratory Endpoint(s) Analysis:

As the study was prematurely terminated all exploratory endpoints will be presented by listing only with change from baseline where applicable.

5.5.1. Psoriasis Area and Severity Index

The psoriasis area and severity index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. 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 the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90%-100% involvement), and 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 (no psoriasis) to 72. A higher score indicates more severe disease.

The Scoring system of PASI:

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:

$$PASI = 0.1(\mathrm{Eh} + \mathrm{Ih} + \mathrm{Sh}) * \mathrm{Ah} + 0.3\ (\mathrm{Et} + \mathrm{It} + \mathrm{St}) * At + 0.2\ (Eu + Iu + Su) * Au + 0.4 * (El + Il + Sl) * Al$$

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

Listing of PASI will be presented with change from baseline at each of the scheduled timepoints.

5.5.2. Body Surface Area

The body surface area (BSA) score 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 is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The formula of BSA calculation is provided below:

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)

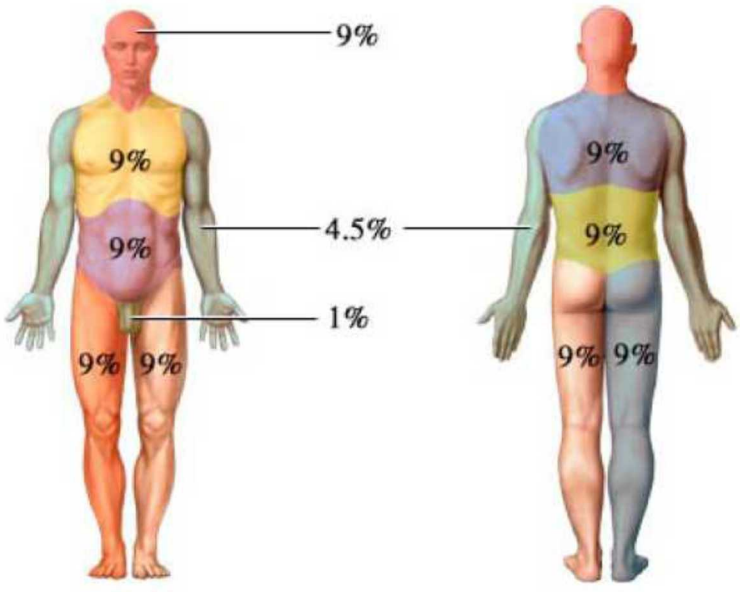
9% for the anterior and 9% posterior side of each leg (=36)

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



Listing of BSA will be presented with change from baseline at each of the scheduled timepoints.

5.5.3. Dermatology Life Quality Index

The dermatology life quality index (DLQI) is a dermatology-specific quality-of-life instrument designed to assess the impact of the disease on a participant's quality-of-life It is a 10 item PRO questionnaire that, in addition to evaluating total 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.

Listing of DLQI will be presented with change from baseline at each of the scheduled timepoints.

5.5.4. Investigator's Global Assessment

The investigator's global assessment (IGA) documents the investigator's assessment of the participant's psoriasis at a given timepoint. Total 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). The IGA mod 2011 scale is static, i.e., it referred exclusively to the participant's disease at the time of the assessment and did not compare with any of the participant's previous disease states at previous visits. The scores are: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe.

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, > 1 mm

Erythema (E) (averaged over all lesions)

0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration

Scaling (S) (averaged over all lesions)

0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = severe; thick, scale predominates

$$Total\ Average = (I + E + S) / 3$$

Average will be calculated in the device but not displayed. Numeric result will be included in data transfer.

Investigator's Global Assessment based upon above Total Average
0 = Cleared, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1
2 = Mild- majority of lesions have individual scores for I + E + S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3
4 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 4

Note: Scores should be rounded to the nearest whole number.
If total ≤ 1.49, score = 1;
if total ≥ 1.50, score = 2.

Listing of IGA will be presented with change from baseline at each of the timepoints scheduled.

5.5.5. Pittsburg Sleep Quality Index

The pittsburg sleep quality index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in the older adult. 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.

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.

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

PSQIDURAT	**DURATION OF SLEEP**
	IF Q4 ≥ 7, THEN set value to 0
	IF Q4 < 7 and ≥ 6, THEN set value to 1
	IF Q4 < 6 and ≥ 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) > 1 and < 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 < 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 ≥ 0 and ≤ 15, THEN set value of Q2new to 0

IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1

IF Q2 > 30 and ≤ 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 ≥ 1 and ≤ 2, THEN set value to 1

IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2

IF Q5a + Q2new ≥ 5 and ≤ 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 **TOTALSLEEP 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

Listing of PSQI will be presented with change from baseline at each of the timepoints.

5.5.6. Alcohol Use Disorders Identification Test

The alcohol use disorders identification test (AUDIT) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems. Both a clinician-administered version and a self-report version of the AUDIT 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.

Score of AUDIT:

Scores for each question range from 0 to 4, with the first response for each question (e.g., never) scoring 0, the second (e.g., less than monthly) scoring 1, the third (e.g., monthly) scoring 2, the fourth (e.g., weekly) scoring 3, and the last response (e.g., daily or almost daily) scoring 4. For questions 9 and 10m 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.

Listing of AUDIT will be presented with change from baseline at each of the timepoints.

5.5.7. The Hospital Anxiety and Depression Scale

The hospital anxiety and depression scale (HADS) measures anxiety and depression which commonly coexist in a general medical population of participants.[1] 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.

Listing of HADS will be presented with change from baseline at each of the timepoints.

5.6. Other Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified.

Missing safety data will generally not be imputed. Safety assessment values of the form of "<x" / "≤ x" (ie, below the lower limit of quantification) or "> x" / "≥ x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" / "≤ x" or ">x" / "≥ x" in the listings.

For all continuous safety variables, descriptive statistics by Nicotine use, non-Nicotine use and Total group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by Nicotine use, non-Nicotine use and Total group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention (guselkumab) will be summarized. The number and percentage of participants will also be summarized by visit of week.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range (minimum, maximum)) will be summarized. Participant-years of intervention are calculated as days of intervention/365.25. Participant-years will be presented by Nicotine use, non-Nicotine use and Total group.

Duration of intervention will be summarized in the following duration categories:

- <4 weeks,
- 4-<12 weeks,

- 12-<16 weeks,
- 16-<20 weeks,
- 20-<28 weeks within a study intervention

Cumulative duration of intervention >= 4 weeks, >=12 weeks, >= 16 weeks, >=20 weeks, >=28 weeks will be summarized.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

Total dosing days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention).

The number (%) of participants with a dose not administered will be summarized by Nicotine use, non-Nicotine use and Total group and visit of week. Reasons for doses not administered will also be summarized by visit of week.

The number (%) of participants with a study intervention modification prior to injection will be summarized by Nicotine use, non-Nicotine use and Total group and week of visit. A similar summary will be presented for study intervention modification during the injection.

Descriptive statistics will be presented for the following parameters:

- Number of injections
- Cumulative total dose
- Mean daily dose

The mean daily dose of study intervention is calculated as (sum of total daily dose during the intervention phase)/total dosing days of intervention.

Study intervention compliance will be summarized descriptively. See Appendix 7 for further details.

5.6.2. Adverse Events

The verbatim terms used in the case report form (CRF) by investigators to identify adverse events (AEs) will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) (System Organ Class and Preferred Term).

Any AE occurring at or after administration of adenosine or the initial administration of study intervention (guselkumab) through the day of last dose within the study phase plus 12 weeks or the date of the Final Safety visit, whichever is the latest, is considered to be treatment emergent adverse event (TEAE). If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be TEAE. If the event date is recorded as partial or completely missing, then the event

will be considered to be TEAE unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported TEAEs will be included in the analysis.

For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by Nicotine use, non-Nicotine use and Total group.

Any usual pharmacodynamic actions and expected effects of adenosine administration (refer to Appendix 6.11) of CFR assessment are not considered as AEs

Summary tables will be provided for TEAEs.

The incidence of other TEAEs of special interest will be summarized. See Appendix 8 for list of adverse events in each category.

Listing of all serious adverse events (SAEs) will be provided along with abnormalities of laboratory, vital signs, and other physical observations.

Deaths will be displayed by actual intervention received. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- Relationship to study intervention (yes/no)

A listing of participants who died will be provided.

5.6.2.1. Imputation Rules for Missing Adverse Event Date/Time of Onset

5.6.2.1.1. Treatment-emergent AEs

AEs with completely missing onset dates will be considered as treatment-emergent (avoiding under reporting of treatment-emergent AEs). AEs with partially missing onset dates will also be included as treatment-emergent when the month (if it exists) and the year occur on or later than the month and year of the initial study treatment date.

5.6.2.1.2. Imputation Rules

The date value is split into day, month, and year parts as outlined below:

	Day	Month	Year
Partial AE Start Date	Not used (missing and will be imputed)	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

Completely missing start dates will not be imputed. Partial AE start dates are imputed with reference to the treatment start date (TRTSDT) as outlined in the matrix of start year (YYYY) vs start month (MON) below.

The ***Italic bold*** font indicates the imputed values.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	Do not impute	Do not impute	Do not impute	Do not impute
YYYY < TRTY	(D) = ***31DEC***YYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start
YYYY = TRTY	(B) = min(***TRTSDT, AE resolution)*** Uncertain	(C) = ***01***MONYYYY Before Treatment Start	(B) = min(***TRTSDT, AE resolution)*** Uncertain	(A) = ***01***MONYYYY After Treatment Start
YYYY > TRTY	(E) = ***01JAN***YYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start

The following table is the legend to the matrix above.

Relationship	
Before Treatment Start	Partial date indicates AE start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE start date after Treatment Start Date
Uncertain	Partial date insufficient to determine the sequence of AE start date and Treatment Start Date
Imputation Calculation	
(A) After Treatment Start	**01**MONYYYY (The closest date to the treatment start date for imputation)
(B) Uncertain	min**(TRTSDT, AE resolution)** (AE happed just after the treatment start)
(C) Before Treatment Start	**01**MONYYYY (Start-month point will be used for imputation)
(D) Before Treatment Start	**31DEC**YYYY (End-year point will be used for imputation)
(E) After Treatment Start	**01JAN**YYYY (The closest date to the treatment start date for imputation)

Note: Imputation rules for concomitant medications follow the same approach as for AEs. In the case where prior or concomitant medication start/end dates are partial but is required in the calculation of time to first dose (see prior medication under section 6.5) temporary imputed variable(s) will be set earliest/latest possible date for medication start/end dates respectively.

The imputed dates will be used in the calculation of time to first dose but displayed as those were recorded in the listings.

5.6.3. Additional Safety Assessments (if applicable)

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics and graphical displays will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points. Week 0 is the Baseline visit for the Clinical Laboratory tests.

Hematology: Platelet Count, Reb blood cell count, Hemoglobin, Hematocrit, RBC Indices: MCV, MCH, %Reticulocytes, White Blood Cell (WBC) count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils.

Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Blood urea nitrogen (BUN), Creatinine, Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic, Alanine aminotransferase (ALT)/ Serum glutamic-oxaloacetic, Gamma- glutamyltransferase (GGT), Bilirubin, Alkaline phosphatase (AP), Creatinine phosphokinase (CP), Lactic acid dehydrogenase (LDH), Uric acid, Calcium, Phosphate, Albumin, Total protein, Cholesterol, HbA1C, hsCRP, Lipid and Metabolic Panel: Triglycerides, Magnesium, Low-density lipoproteins (LDL), High-density lipoproteins (HDL), Very-Low-density lipoproteins (VLDL) (calculated), Non-HDL (calculated), Serum glucose, Serum insulin

Urinalysis: Specific gravity, pH, Glucose, Protein, Blood, Ketones, Bilirubin, Urobilinogen, Nitrite, Leukocytes esterase, Red Blood Cells, White Blood Cells, Epithelial cells, Crystals, Casts, Bacteria, (8-Oxo-7,8-dihyd’o2'-desoxyguanosine) Concentration of oxidative lipid damage [8-Isoprostane] and Malondialdehyde in plasma Concentration of antioxidants (Vitamins C, E).

Screening: 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)

Change from baseline to week of visit will be summarized for chemistry, hematology, and urinalysis (pH, and specific gravity) tests and displayed by week of visit.

Abnormality criteria normal ranges will be applied to baseline and postbaseline values as per the lab reference ranges which will be obtained as an external document.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the

postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).

- For abnormalities based on observed values: If the postbaseline value is observed as abnormal and baseline value is normal (eg., Normal to Abnormal), then the postbaseline abnormality will be considered TE. If the postbaseline value is normal and the baseline value is abnormal (eg., Abnormal to Normal) then the postbaseline abnormality will not be considered TE.
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Number and percentage of participants with treatment-emergent clinically important laboratory values and markedly abnormal treatment emergent values will be presented based on the standard reference ranges provided by the Central Laboratory. A listing of clinically important laboratory values will be provided.

All abnormal laboratory values (out of standard reference range values) will be shared with the clinical team to obtain the flagging for markedly abnormal treatment emergent values.

The clinically important laboratory findings to be reported are described below during any post-baseline visits and not necessarily at the same visits:

- AST (U/L): 3 x ULN
- ALT (U/L): 3 x ULN
- Bilirubin > 2 x ULN or INR > 1.5 x ULN

Descriptive statistics and change from baseline analyses of clinical laboratory results will be presented.

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature (axillary, tympanic or forehead), height, weight, waist circumference, pulse/heart rate, blood pressure (systolic and diastolic), and BMI will be summarized at each assessment time point. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at Screening Visit S1 will be used in the calculation. Change from baseline will be summarized for the visit of week. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented. Week 0 is the Baseline visit for the Vital Signs and Physical Examination Findings (for Waist Circumference).

5.6.3.3. Electrocardiogram

Electrocardiogram (ECG) is collected only at Screening Visit S1. Listings will be produced for all ECG data including unscheduled visit data.

5.6.3.4. Other Safety Parameters

Not Applicable

5.7. Other Analyses

5.7.1. Pharmacokinetics

Pharmacokinetics analysis will not be evaluated for this study.

5.7.2. Immunogenicity

Not Applicable.

5.7.3. Pharmacodynamics

All Primary and Secondary endpoints in Section 5.3 and Section 5.4 are analyzed for the Pharmacodynamics endpoint.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not Applicable.

5.7.5. Biomarkers

Not Applicable.

5.7.6. Health Economics

Not Applicable.

5.7.7. Other Variables and/or Parameters

Coronary Flow Reserve (CFR) screening and screening failure analysis in this study include but not limited to:

1. Baseline characteristics of CRF Screening failure vs Included Participants.
2. Screening Visit S2 vs Week 0 analysis for:
    a. Coronary Flow Reserve (CFR).
    b. Global Longitudinal Strain (GLS).
    c. carotid-femoral Pulse Wave Velocity (cfPWV).

5.7.8. Definition of Subgroups

The study will be conducted with a subgroup of nicotine users vs. non-nicotine users.

5.8. Interim Analyses

No Interim Analyses will be performed for the study since it terminated prematurely.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

No DMC will be performed for the study.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
AR[1]	First order auto-regression correlation
ATC	anatomic and therapeutic class
AUDIT	Alcohol use disorders identification Test
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
CV	Cardiovascular
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DPS	Data Presentation Specifications.
ECG	Electrocardiogram
FAS	Full Analysis Set
GLS	Global longitudinal strain
HADS	Hospital anxiety and depression scale
HLT	High level term
IA	Interim Analysis
ICF	Informed Consent Form
IGA	Investigator's Global Assessment
IQ	Interquartile
LOCF	last observation carried forward
LSmeans	Least Square Means
MACE	Major Adverse Cardiovascular Events
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model for repeated measures
NRI	Non-responder imputation
PASI	Psoriasis area and severity index
PSQI	Pittsburg sleep quality index
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event
TRTSDT	Treatment Start Date
ULN	upper limit of normal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

The Safety Analysis Set is different in the Protocol.
Safety analysis set defined in the protocol as “All enrolled participants who receive at least 1 dose of guselkumab.” Whereas in SAP we have modified the definition as “The safety analysis set includes all participants who received at least 1 dose of adenosine and guselkumab”.

The Safety Analysis Set will likely contain more participants than the FAS. It would not be appropriate to define the safety analysis set as participants receiving at least one dose of guselkumab. It is necessary to also capture possible safety related information starting with the first assessment of the Coronary Flow Reserve at visit S2, because it involves use of intravenous Adenosine.

All enrolled participants who receive at least 1 dose of guselkumab, while it is “The full analysis set (FAS) includes all participants who received at least 1 dose of guselkumab." in the current SAP.

In Protocol the primary and secondary efficacy endpoints are performed at Week 32 for CFR, GLS and cfPWV, while in SAP it is appropriately defined to be completed at Final Efficacy Visit (Week 32) as per Table 2. The primary and secondary efficacy endpoints will be analyzed at Final Efficacy Visit (Week 32) with the definition applied as per Table 2 for the last dose after premature termination of the study.

In the protocol The Final Efficacy Visit (Week 32) should occur 4 weeks after the last dose of the guselkumab within the study. Whereas in SAP, following the premature termination of the study 4 to 8 weeks after the last dose of guselkumab within the treatment phase will be used.

In the protocol for participants who prematurely discontinues guselkumab before Week 28, the Final Efficacy Visit (Week 32) should take place at the time of discontinuation, or as soon as possible, and all assessments scheduled for the Final Efficacy Visit (Week 32) should be performed, whereas in the SAP for participants who permanently discontinue guselkumab before Week 28, the date of discontinuation will be used.

In the protocol for a Final Safety Visit (Week 40), the 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 (Week 40). Whereas in the SAP for Final Safety Visit (Week 40) for participants who receive guselkumab after the treatment phase, the date of the first dose of guselkumab outside of the treatment phase will be used.

The secondary endpoint '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' in the protocol, however a different range of 2 to 2.74 and 2.75 to 3.5 will be used for the final analysis. For the final analysis the study had a low number of participants after premature termination of the study. The ranges were updated accordingly.

Since the study was terminated prematurely the exploratory objectives and endpoints are removed from the corresponding SAP section.

No interim analysis will be performed per the protocol since the study prematurely terminated.

Biomarker analysis will not be performed due to the low number of participants after premature termination of the study.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by Nicotine user, Non-nicotine user and overall. In addition, the distribution of participants by country, and site ID will be presented unless otherwise noted.

Table 3 presents a list of the demographic variables that will be summarized by Nicotine user, Non-nicotine user and total for the FAS.

Similarly, baseline characteristics, including Years of Plaque Type Psoriasis Diagnosis, IGA Score, PASI Score, PsA and Cardiologic Family History, Psoriatic arthritis present, Prior nonbiologic systemic therapy, Prior biologic systemic therapy, Dyslipidemia/hyperlipidemia, hypertension, and Nicotine use status ([Never, Former, and Current]). will be summarized by Nicotine user, non-nicotine user and total for the FAS. Years of Psoriasis Plaque Type Diagnosis is defined as Year of baseline assessment – Year of first onset of plaque type psoriasis, as collected in the CRF.

Table 3: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
Waist circumference (cm)	
BSA (%)	
Baseline PASI	
Time since plaque type psoriasis diagnosis in years	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Age ([<45 years and >= 45 years])	
Sex (male, female, undifferentiated)	
Race (White, Black, Asian, Other)	
BMI ([underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2])	
Psoriatic arthritis present	
PsA family history	
Cardiologic family history	
Dyslipidemia/hyperlipidemia	
Baseline IGA score (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe.)	
Hypertension	
Nicotine use status ([Never, Former, Current])	
Prior nonbiologic systemic therapy	
Prior biologic systemic therapy	

A listing of prior topical therapy and phototherapy or systemic therapy for Psoriasis will be provided.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category. Details and definitions will be defined in the major protocol deviations criteria form (TV-FRM-04718).

- Missed Assessment/Visit
- Not Meeting the Inclusion or Meeting the Exclusion criteria
- Intake of Prohibited Concomitant Medication

Eligibility criteria deviations are deviations from Section 5.1 and 5.2 of the Protocol inclusion and exclusion criteria.

Post-entry deviations are deviations from the protocol that occurred after the patient was assigned to the study.

All major protocol deviation criteria will be listed by coded term and verbatim term.

Major PDs will be listed for patients with at least one corona virus disease 2019 (COVID-19) related PD, without any COVID-19 related PD being recorded and regardless of COVID-19 related PDs.

Additionally, listings for patients with major protocol deviations will be provided.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. If the stop date is missing or partial and it cannot be determined whether the participant stopped the medication before the start of study intervention (guselkumab), the medication will be considered as concomitant.

Concomitant medications are defined as any therapy used on or after 12 weeks after last dose of guselkumab or 8 weeks if the patient switches to commercial guselkumab or any other drug, the same day as the first dose of study injection, including those that started before and continue on after the first dose of study intervention. If the start or stop date is missing or partial and cannot be determined, the medication will be considered as concomitant.

Summaries of concomitant medications will be presented by Anatomical Therapeutic Chemical (ATC) level terms (Level 2 and Level 4) and standardized medication name. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. The proportion of participants receiving a medication will be summarized for Nicotine and Non-nicotine users and across the study (total). If participants receive a medication more than once within the treatment phase, they will be counted only once.

In addition, concomitant medications of special interest will be presented with at least ≥ 80% of the total column. These include [special interest categories] and standardized medication name. See Appendix 9 for list of medications in each category.

Prior medications will be summarized by ATC term.

The concomitant medication data listing will be displayed on the Safety analysis set.

Percentages will be calculated relative to the number of participants in the Safety analysis set.

6.6. Appendix 6 Medical History

Investigators should document all significant medical conditions that the participant has experienced in the past. Any medical condition present at the time informed consent is given is to be regarded as concomitant. A condition first occurring or detected on or after the day of the Baseline visit and/or worsening of a concomitant condition on or after the day of the baseline visit is to be documented as an AE on the CRF.

All conditions will be coded using latest version of MedDRA.

- A summary of medical history will be provided.
- A listing of medical history will be provided.

6.7. Appendix 7 Intervention Compliance

All guselkumab discontinuations, and the primary reasons for the discontinuation will be recorded in the Electronic case report form (eCRF).

Compliance to guselkumab will be summarized up to Week 28 only.

Compliance will be summarized descriptively.

The number and percentage of participants who have at least 80% compliance through the time of visit will be summarized.

Compliance will be calculated as follows:

Compliance (%) = 100 x Completed injections/total possible injections

Compliance will be summarized by Nicotine use, non-Nicotine use and Total group, descriptive statistics will be provided with N, mean, SD, median, and range (minimum, maximum).
In addition, the number (%) of participants in each compliance categories will be presented.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are categorized preferred terms. Adverse events of special interest will be programmatically derived from a predefined list of preferred terms (as mentioned in section 8.3.6 of the study protocol) from an external data from the clinical team.

6.9. Appendix 9 Medications of Special Interest

A listing of concomitant medications (excel file) will be provided by the ClinChoice programming team with treatment start date, study day, and duration to the sponsor clinical team to identify the disallowed medication and medication of special interest in the study. During the study the spreadsheet will be updated for every data cut and the list with flagging will be updated accordingly.

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g., grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e., worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic;* *120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
					assigned to grade 3, grade 2 not used.
Renal and urinary disorders					

Proteinuria	1+ proteinuria;
	urinary protein ≥ULN - <1.0 g/24 hrs;
	urinary protein ≥ULN - <1000 mg/day
		Adult:
		2+ and 3+ proteinuria;
		urinary protein 1.0 - <3.5 g/24 hrs;
		urinary protein 1000 - <3500 mg/day
		
		Pediatric:
		Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9;
		Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol
			Adult:
			4+ proteinuria;
			urinary protein >=3.5 g/24 hrs;
			urinary protein >=3500 mg/day;
			
			Pediatric:
			Urine P/C (Protein/Creatinine) ratio >1.9;
			Urine P/C (Protein/Creatinine) >214.7 g/mol
				-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine collection take precedence over dipstick.
					Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol).
					Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

***** Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

6.11. Appendix 11 Potential Risks due to Study Procedure (Adenosine Injection).

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	Stopping Adenosine and/or further medical intervention is at the discretion of the cardiology investigator and should be considered in case of:	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.
• Thoracic related: dyspnea (shortness of breath), chest discomfort	• Severe hypotension: Systolic pressure <80 mm Hg or 20 mmHg fall which persists	• Stop infusion –most effects resolve within 30- 60 seconds post infusion
• Nervous system related: Headache, dizziness, lightheadedness, paresthesia	• ST depression: >3 mm beyond baseline ECG without angina or >2 mm with angina	• 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.
• Gastrointestinal related: Nausea	• Persistent 2nd or 3rd degree heart block	Note: Adverse events (AEs) should be reported if medical intervention beyond stopping adenosine infusion is necessary. Please refer Appendix 13 of protocol for further information.
• Cardiac related: bradycardia, sinus pause, skipped beats, atrial extrasystoles, Atrio- Ventricular block, ventricular excitability disorders such as ventricular extrasystoles, non-sustained ventricular tachycardia	• Severe chest discomfort, dizziness, dyspnea, headache, nausea, syncope or dysrhythmia	

7. REFERENCES

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