Janssen-Cilag GmbH*

Clinical Protocol

A Phase 3b, Randomized, Double-blind, Parallel Group, Multicenter Study to Evaluate Further Therapeutic Strategies with Guselkumab in Patients with Moderate-to-Severe Plaque-Type Psoriasis

GUIDE

Protocol CNTO1959PSO3012; Phase 3b
AMENDMENT 5

TREMFYA® (guselkumab)

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	5 July 2018
Amendment 1	06 December 2018
Amendment 2	29 May 2019
Amendment 3	15 April 2020 (COVID-19 amendment)
Amendment 4	15 June 2020
Amendment 5	10 June 2021

Key changes in Amendment 5 are summarized below; minor changes of language and editorial items are not listed.

Amendment 5 (10 June 2021)

Overall Rationale for the Amendment: The overall reason for the amendment is the prolongation of study part 3 by two years (ie, 104 weeks) for all subjects regularly and successfully enrolled at study beginning.

Section Number / Name	Description of Changes and Brief Rationale
Synopsis, 2.1.1 Objectives	**Description of Change:** Two new secondary objectives were defined to evaluate whether super responders (SRe) will show sustained remission, continued loss of response, or stabilization of disease worsening over two additional years of observation.
	Rationale: To determine additional objectives for the prolonged study part 3
Synopsis, 2.7 Endpoints	**Description of Change:** Various endpoints were adapted to include week 164 (~2 years after drug withdrawal) and week 220 (~3 years after drug withdrawal, final study visit), respectively, including the whole period from week 68 to week 220.
	Rationale: To allow evaluation of the prolonged study part 3
Synopsis, 3.1 Study Design, 7 Treatment Compliance, 9.1.5 Study Evaluations - Study Part 3, Time and Events Schedule	**Description of Change:** Text, study design diagram and time and events schedule were adapted to include the prolonged study part 3. Additional on-site visits will occur every 3 months, i.e. at weeks 128, 140, 152, 164, 176, 188, 200, 212 and 220. In between there will be a telephone-visit 6 weeks after each visit (ie, telephone visits at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206.
	Rationale: To display prolongation of study part 3
Synopsis, 3.1 Study Design: Substudies	**Description of Change:** The novel measure tape stripping will be performed for all participants in part 3 (SRe). It is a less invasive collection method to allow measurements of gene expression and levels of proteins or other biomarkers in the stratum corneum.
	Rationale: To implement a novel investigational method to the prolonged study part 3
Synopsis, 11.9 Statistical Analyses per Study Part	**Description of Change:** Two interim analyses of study part 3 were added. They are planned after all subjects have completed their visit at week 116 (or at week 144 in case of subjects entering the re-treatment arm in week 116) and at week 164 (or at week 192 in case of subjects entering re-treatment arm in week 164). The final analysis will be performed after all subjects have completed their visit at week 220 (or at week 248 in case of subjects entering the re-treatment arm in week 220).
	Rationale: To allow two interim analyses of study part 3
10.2 Discontinuation of Study Treatment, 12.3.2. Serious Adverse Events, Appendix	**Description of Change:** Section 10.2 was adapted to include that study treatment must be discontinued in case of abnormal liver tests. Corresponding appendices (8A and 8B) were added to provide liver stopping criteria and guidance for follow-up assessments. Section 12.3.2 was adapted to emphasize that any possible Hy's law case (AST or ALT ≥ 3x ULN together with bilirubin ≥ 2X ULN or INR >1.5) has to be reported to the sponsor in an expedited manner using the Serious Adverse Event form.
	Rationale: To incorporate Hy's law language into the protocol

SYNOPSIS

A Phase 3b, Randomized, Double-blind, Parallel Group, Multicenter Study to Evaluate Further Therapeutic Strategies with Guselkumab in Patients with Moderate-to-Severe Plaque-Type Psoriasis (GUIDE).

Protocol Number: CNTO1959PSO3012

EudraCT NUMBER: 2018-001238-16

Study drug: CNTO 1959 (guselkumab;) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The 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 Th17 (IL-17 producing T helper cell), Tc17 (IL-17 producing cytotoxic T cell) and Th22 cell proliferation, cytokine production, and survival. In July 2017, guselkumab has been approved for the treatment of moderate-to-severe psoriasis by the Food and Drug Administration (FDA) and in November 2017 by the European Medicines Agency (EMA).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary objective

The primary objective of the study is to demonstrate that Super-Responders (SRe; defined as psoriasis subjects who receive on-label guselkumab treatment until week 20 and respond with a Psoriasis Area and Severity Index [PASI] score=0 at weeks 20 **and** 28) maintain control of disease until week 68 with prolonged treatment intervals of 16 weeks (100 mg q16w). *To be demonstrated in Study Part 2 (see Section 3.1 for study design)*.

Secondary objectives

Secondary objectives are to evaluate,

- whether subjects with short disease duration (≤2 years) show a more rapid and better guselkumab response compared to subjects with longer disease duration and whether subjects with shorter disease are more likely to maintain drug-free control of disease after guselkumab withdrawal. *To be evaluated in Study Parts 1, 2, and 3.*
- whether SRe with short disease duration and PASI=0 at week 116 (ie, remission for one year after withdrawal) will show sustained remission (ie, PASI=0) over two additional years compared to subjects with longer disease duration. *To be evaluated in Study Part 3.*
- whether SRe with short disease duration and PASI>0 to ≤5 at week 116 (ie, partial relapse for one year after withdrawal) will show continued loss of response or stabilization of disease worsening over two additional years compared to subjects with longer disease duration. *To be evaluated in Study Part 3.*
- whether different treatment intervals (weeks 28 to 60: guselkumab 100 mg q8w vs. guselkumab 100 mg q16w) affect the maintenance of drug-free control of disease after 68 weeks of guselkumab treatment. *To be evaluated in Study Part 3.*
- the safety and tolerability of guselkumab in subjects with moderate-to-severe plaque-type psoriasis.

Note: disease duration will be calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit.

Exploratory objectives

The following objectives are to be explored in the mechanistic biomarker substudies:

- characterization of the immune cellular and molecular composition at baseline (week 0) and changes (quantitative and qualitative characterization) in the lesional skin of subjects during treatment with guselkumab as determined by fluorescence activated cell sorting (FACS)-based analysis. *To be explored in substudy 1*
- characterization of the immune cellular changes (quantitative and qualitative characterization) in the blood of subjects at baseline (week 0), during and after treatment with guselkumab as determined by FACS-based analysis. *To be explored in substudy 1*
- characterization of molecular (gene expression) changes during treatment with guselkumab in the skin of subjects treated with guselkumab as determined by RNA sequencing (RNAseq) and quantitative polymerase chain reaction (qPCR)**.** *To be explored in substudies 2 and 3*
- characterization of the tissue immunopathological changes in the skin of subjects during and after treatment with guselkumab as determined by immunohistochemistry (IHC)/ immunofluorescence (IF)/ in situ hybridization (ISH). *To be explored in substudy 2*
- characterization of the effects of guselkumab treatment on serum biomarkers as determined by immunoassays. *To be explored in substudy 3*
- characterization of the association between changes in the various exploratory biomarker endpoints and 1) efficacy of guselkumab, 2) duration of psoriasis, 3) maintenance of response after stopping guselkumab treatment, and 4) ability to achieve a PASI 100 response at weeks 20 and 28 (super responder status). *To be explored in all substudies*

Endpoints

For the endpoints, the following terms were defined:

- Control of disease: PASI score <3
- Fluctuating disease: PASI score 3 to 5
- Loss of disease control: PASI score >5.

Study groups are defined as follows:

- **1**: All participating subjects who are enrolled and are scheduled to receive guselkumab 100 mg at weeks 0, 4, q8w until week 28 (Study Part 1)
- **2a**: SRe (PASI score=0 at weeks 20 **and** 28) randomized to guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)
- **2b**: SRe randomized to guselkumab 100 mg q16w at weeks 28 to 60 (Study Part 2)
- **2c**: non-SRe with a PASI score >0 at week 20 and/or 28 who will receive guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)
- **2d**: SRe with loss of disease control between week 28 and 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8, and 16 calculated from the date of loss of disease control (Study Part 2)
- **3a**: SRe randomized to guselkumab 100 mg q8w in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)
- **3b**: SRe randomized to guselkumab 100 mg q16w in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)
- **3c**: SRe with fluctuating disease at week 68 or loss of disease control at any other visit after week 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8, and 16 calculated from the date of loss of disease control (Study Part 3).

Endpoints of the main study

Primary endpoint

The primary endpoint of the main study is the proportion of subjects in study groups **2a** and **2b** who achieve an absolute PASI score <3 at week 68.

Major secondary endpoints

Major secondary endpoints of this study are:

- Time to improvement from baseline (week 0) in PASI (PASI 75/90/100 response and absolute PASI score=0) for subjects with short (≤ 2 years) and longer (>2 years) disease duration per study group (**1**, **2a, 2b,** and **2c**)
- Proportion of subjects with short (≤2 years) and longer (>2 years) disease duration who achieve an absolute PASI score of 0, ≤1 and <3 at weeks 20, 28, 68, 116, 164, and 220 per study group (**1, 2a, 2b, 2c, 3a,** and **3b**)
- Proportion of subjects who retain disease control (ie, absolute PASI score <3 at all visits) from week 68 through week 116, from week 68 through week 164, and from week 68 through week 220 for subjects with short (≤ 2 years) and longer (>2 years) disease duration per study group (**3a** and **3b**).

Other secondary endpoints of this study are:

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 20, 28, 68, 116, 164, and 220 per study group (**1, 2a, 2b, 2c, 3a,** and **3b**)
- Time to loss of disease control (absolute PASI score >5 at any visit) after treatment withdrawal beyond week 68 per study group (**3a** and **3b**)
- Proportion of subjects with an absolute PASI score=0 at all of the following visits: weeks 12, 16, 20, and 28 (**study group 1**)
- Change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at weeks 28, 68, 116, 164, and 220 per study group (**1**, **2a**, **2b, 2c, 3a, 3b, and 3c**)
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at weeks 28, 68, 116, 164, and 220 per study group (**1**, **2a**, **2b, 2c, 3a, 3b, and 3c**)
- Change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 12, 28, 52, 68, 80, 104, 116, 140, 164, 188, 212, and 220 (**all study groups**)
- Change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at weeks 28, 68, 116, 164, and 220 among subjects with nail psoriasis at baseline (week 0; **1, 2a, 2b, 2c, 3a,** and **3b**).
- Change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at weeks 28, 68, 116, 164, and 220 (**1, 2a, 2b, 2c, 3a,** and **3b**)
- Proportion of subjects who achieve a PSSD sign score=0 at week 68 among subjects with a PSSD sign score ≥1 at week 28 per study group (**2a, 2b,** and **2c**).
- Association between trough serum guselkumab concentration and efficacy or serum biomarker level
- Association between trough serum guselkumab levels at weeks 20, 28, 36, and 68 and achieving a PASI score <3 at week 68 per study group (**2a** and **2b**)
- Proportion of subjects who were re-treated due to loss of disease control (PASI >5) and regain control of disease (PASI <3) 24 weeks after start of re-treatment (study groups **2d** and **3c**)
- Safety and tolerability with regard to adverse events (AEs) and abnormal laboratory results (**all study groups**).

Hypothesis

In this study, Super-Responders (SRe) are defined as psoriasis subjects achieving clear skin (measured as absolute PASI score=0) at weeks 20 **and** 28 of treatment. Subjects with shorter disease duration (≤2 years calculated from date at which first symptoms [plaque] were reported by subject to date of screening visit) are expected to have a higher likelihood to be SRe.

In Super-Responders, guselkumab treatment might have stronger modifying effects on immunopathological mechanisms of the disease than in non-SRe. Therefore, it is hypothesized that this subpopulation might not lose control of disease even with a longer dosing interval (q16w instead of q8w) and that this subpopulation will have higher probability of drug-free remission after 60 weeks of treatment.

The hypothesis of this study is that guselkumab q16w treatment is non-inferior to guselkumab q8w treatment in SRe as assessed by the proportion of subjects with an absolute PASI score <3 at week 68 (alternative hypothesis in a statistical sense). If the hypothesis is accepted, the study will be considered positive.

OVERVIEW OF STUDY DESIGN

The present trial is designed as a phase 3b, randomized, double-blind, parallel-group, multicenter, comparison study in subjects of at least 18 years of age with moderate to severe plaque-type psoriasis.

It is planned to achieve about 280 subjects categorized as Super-Responders (SRe, ie PASI score=0 at weeks 20 **and** 28) for randomization in Study Part 2 (140 subjects in study group **2a** and 140 subjects in study group **2b**). It is assumed that 900-1000 subjects are therefore needed to be screened at up to 90 German study sites and 10 French study sites and that 888 subjects are needed to be enrolled (based on a SRe rate of 30-35% of enrolled subjects). Screenings and enrollments will be adjusted if necessary (without protocol amendment) to achieve 280 SRe at week 28. Ongoing subjects in Study Part I will continue to Part II if eligible, irrespective of whether or not 280 SRe are already randomized. Only screenings will be closed.

Of the enrolled subjects approximately 40% must have a disease duration of ≤2 years calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit. Subjects with a disease duration of ≤2 years are expected to have a higher likelihood to be SRe. At randomization two stratification criteria apply: (i) SRe with a disease duration of ≤2 years will be stratified equally to study group **2a** and **2b**. Further, (ii) SRe who are participating in the mechanistical substudy 1 will be stratified equally to study group **2a** and **2b**.

The study will feature the following structure and design:

Study Part 1: Screening through Week 28:

This will be screening phase lasting up to four weeks (+ 7 calendar days) prior to first administration of guselkumab (week 0) followed by a 28-week run-in period with visits and administration of 100 mg guselkumab at weeks 4, 12, and 20. In case of a PASI score=0 at weeks 20 **and** 28 subjects are qualified to be randomized either to study group **2a** or **2b** of Study Part 2. In case of PASI score >0 at weeks 20 and/or 28 the subjects will continue to receive guselkumab 100 mg q8w until week 60 (last administration at week 60 visit) with final study assessments at week 68 and final safety follow-up visit at week 72 (defined as study group **2c**).

Study Part 2: Week 28 through Week 68:

Subjects with a PASI score=0 at weeks 20 **and** 28 will be defined as SRe and randomly assigned to the following two treatment groups: **2a**) guselkumab 100 mg q8w or **2b**) guselkumab 100 mg q16w. In addition, subjects with disease duration ≤2 years will be equally distributed to either group. Study visits of Study Part 2 will be conducted every 8 weeks.

To blind the study, study treatment (guselkumab or Placebo) will be administered q8w starting at week 28 until the end of study therapy (last administration in week 60). The q16w group will receive Placebo at weeks 28, 44 and 60. Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 (ie, until week 60), will enter the Re-treatment arm (group 2d, see section Re-treatment below).

The assessment for the primary endpoint (EP) will be at week 68 for both study groups (**2a** and **2b**).

In case of PASI <3 at week 68 the subject will not receive any study medication and enter the drug withdrawal part (Study Part 3). In case of PASI ≥ 3 at visit week 68 the subject will enter the re-treatment arm **3c** (see section Re-treatment below).

In case of PASI score >0 at weeks 20 and/or 28 the subjects will continue to receive guselkumab 100 mg q8w until week 60 (last administration of study treatment) with final study assessments at week 68 and final safety follow-up visit at week 72 (defined as study group **2c**). At visit week 68 (for group **2c**), the investigator may continue treatment with commercially available guselkumab (ie, not provided by Sponsor) to maintain a q8w interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period (ie, 12 weeks after last dose). If the investigator feels strongly that additional therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

Study Part 3: Week 68 through Week 220:

Subjects of group 2a and 2b with a PASI score <3 at week 68 will enter Study Part 3 and be withdrawn from the study medication and followed-up until week 220. Study visits of Study Part 3 will be conducted every 12 weeks (ie, at weeks 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, and 212; ± 14 days). In between the 12-weekly on-site visits, a telephone-visit 6 weeks (± 7 days) will be done after each on-site visit (ie, telephone visits at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206) to assess whether the subject notices a worsening of his/her psoriasis. If so, the subject must attend an on-site visit for efficacy assessment by the assessor as soon as possible but not later than 2 weeks after the phone call. For patients not starting re-treatment, the final visit will take place at week 220.

Re-treatment

Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or 3 (ie, until week 220), will enter the re-treatment-arms (**2d** or **3c**) with three guselkumab 100 mg administrations starting at that visit (= re-treatment-week 0, followed by administration at re-treatment-weeks 8 and 16).

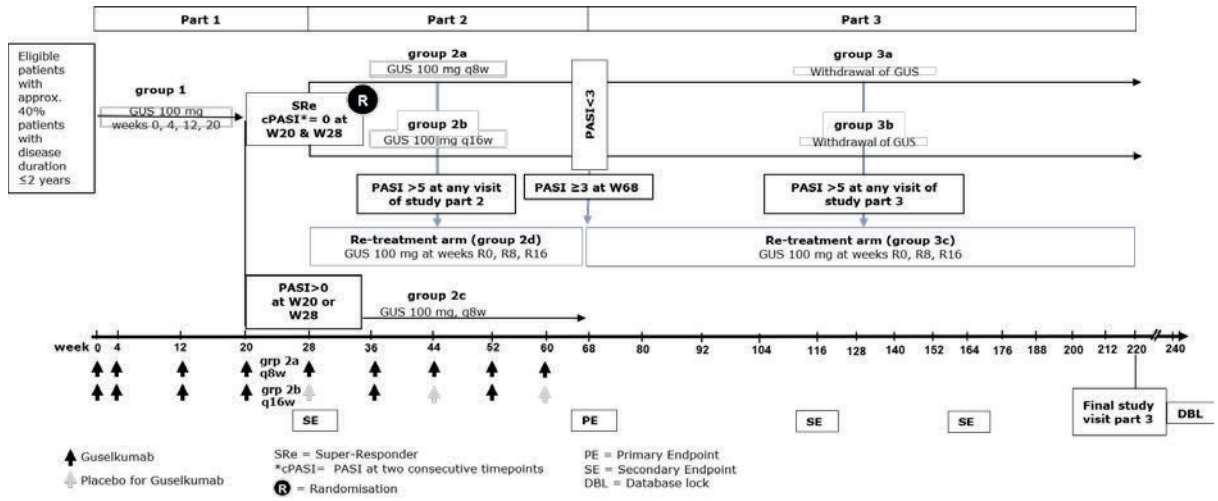
If re-treatment is started at a visit which would usually not require all PROs needed at the first re-treatment visit, those PROs will be obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

The final efficacy assessment for all subjects in the re-treatment-arms will take place 24 weeks after loss of control and study termination will be 28 weeks after loss of control (final study visit/safety follow-up). At visit week 24 of the re-treatment, the investigator may continue actual treatment with commercially available guselkumab (ie, not supplied by Sponsor) to maintain a q8w interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period (ie, 12 weeks after last dose). If the investigator feels strongly that an additional therapy is needed, this should be discussed with the Sponsor before initiation of the new therapy.

Subjects with fluctuating disease (ie, PASI score 3 to 5) at the week 68 visit will also get the opportunity to enter the re-treatment-arm (**3c**).

The last chance to start re-treatment will be the visit week 220 (ie, final efficacy assessment at week 244 with final study visit/safety follow-up at week 248).

A schematic diagram of the study design is provided below:



Study groups:

1: All participating subjects who are enrolled and scheduled to receive guselkumab 100 mg at weeks 0, 4, q8w until week 28 (Study Part 1)

2a: SRe (PASI score = 0 at weeks 20 and 28) randomized to guselkumab 100 mg **q8w** at weeks 28 to 60 (Study Part 2)

2b: SRe randomized to guselkumab 100 mg **q16w** at weeks 28 to 60 (Study Part 2)

2c: non-SRe with a PASI score >0 at week 20 and/or 28 who will receive guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)

2d: SRe with loss of disease control between week 28 and 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8 and 16 calculated from the date of loss of disease control (Study Part 2)

3a: SRe randomized to guselkumab 100 mg **q8w** in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)

3b: SRe randomized to guselkumab 100 mg **q16w** in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)

3c: SRe with fluctuating disease at week 68 or loss of disease control at any other visit after week 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8 and 16 calculated from the date of loss of disease control (Study Part 3).

Treatment compliance

Week 0 can be done once all screening activities are completed, results are available, and the subject is eligible, but latest 4 weeks (+7 calendar days) after screening visit. From weeks 4 to 68 it is expected that all subjects will attend visits within a range of ±7 calendar days. Visits during the re-treatment period (study groups 2d and 3c) are also expected to occur within a range of ±7 days. Visits from week 68 through week 220 are to be conducted within ±14 calendar days of the anticipated visit date. The week 220 visit should be conducted at least 160 weeks after the last study agent injection.

Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd 7-day version of PSSD, 3rd NAPPA-QoL and 4th NAPPA-PBI), and subsequently by the investigator (PASI, BSA and NAPPA-CLIN).
An exception to this order is the entrance into a re-treatment arm at a visit which would normally not require all PROs needed at the first visit of the re-treatment arm (R0). In this case, PROs will be obtained immediately after efficacy assessments (which are the basis for re-treatment-decision) and prior to drug administration at that visit.
Safety evaluations will include the monitoring of adverse events (AEs; including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry and pregnancy testing), physical examinations, vital signs, concomitant medication review, and early detection of tuberculosis (TB). Venous blood samples will be collected for the determination of serum guselkumab concentrations (pharmacokinetics).

The first study drug injection will be administered at week 0, and the last regular injection will be given at week 60. For subjects entering the re-treatment arm the last possible drug injection will be week 84 (arm 2d) and week 236 respectively (please refer to re-treatment section).
Including a 4-week screening phase and a 12-week safety follow-up, the minimum duration of a subject's regular participation in this study will be 75 weeks and the maximum duration will be 252 weeks.

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final visit at that study site, in the time frame specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 84 months (start in Q4 2018, stop in Q1 2025). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

Substudies:

Four substudies are planned to further evaluate pharmacologic effects of guselkumab and evaluate various pharmacologic/clinical response relationships allowing assessment of inter-individual variability in clinical outcomes and possible identification of subject population groups that may respond differently to guselkumab. The substudies will also aim to further define the mechanism of action (MoA) of guselkumab at the molecular and cellular levels during and after treatment. Changes in gene expression as well as quantitative and qualitative changes in different types of immune cells will be evaluated in skin biopsies and blood.

Substudy 1 (Cellular MoA substudy):

Few sites will be identified that have expertise to conduct fluorescence activated cell sorting (FACS)-based cellular immunophenotypic characterization of freshly isolated skin biopsies. Participation in this study is optional. Subjects recruited to the selected sites will be asked to agree to the cellular MoA substudy (target n=60). 6 mm skin biopsy samples will be collected as follows: 1 non-lesional (NL) and 1 lesional (L) biopsy at weeks 0 and 116 (only SRe), and 1 L biopsy at weeks 4, 28, 68, and 220. In addition, when subjects lose control of disease (PASI >5) in Study Parts 2 or 3 and go into re-treatment, an additional biopsy will be taken from a lesional plaque that shows disease activity. Biopsies will be dissociated into single cell suspension and subjected to FACS-based immunophenotyping analyses. Whole blood samples for the isolation of peripheral blood mononuclear cells (PBMCs) will also be collected from consenting subjects for subsequent immunophenotyping analyses by FACS (according to TES at weeks 0, 4, 28, 68, 80, 116, and 220).

Substudy 2 (Gene expression substudy):

Skin biopsies will be collected in a subset of subjects (target n=100) at selected sites (capable of performing the skin biopsy collection and processing procedure) to evaluate gene and protein expression profiles and cellular content. Participation in this skin biopsy substudy is optional. 6 mm skin biopsy samples will be collected as follows: 1 NL and 1 L biopsy at weeks 0 and 116 (only SRe), and 1 L biopsy at weeks 4, 28, 68, and 220. In addition, when subjects lose control of disease (PASI >5) in Study Part 2 or 3, and go into re-treatment, an additional biopsy will be taken from a lesional plaque that shows disease activity. Each biopsy will be split in two parts; one part will be stored in RNA later preservative for RNA gene expression analysis, while the other part will be stored frozen in optimal cutting temperature (OCT) media for hematoxylin and eosin stain (H&E), immunohistochemistry (IHC) and immunofluorescence (IF) analysis. Two 3 mm biopsies may be taken instead of the 6 mm biopsy if preferred by the investigator and consented by the patient. The splitting step is not applicable in that case.

In addition to the biopsy collection for the selected patients taking part in the substudy 2, the novel method tape stripping (non-invasive) will be done for all participants in part 3 (SRe). Tape stripping is a less invasive collection method that may allow measurement of gene expression as well as levels of proteins or other biomarkers in the stratum corneum. The tape strip approach will be done to gain epidermal cells for biomarker analysis (transcriptomics via RNA seq; proteomics) and to validate tape stripping results by comparison with available skin biopsies. Tape stripping will be performed, where feasible, at week 116 for all participants, and at R0 visit or week 220 visit for those, who do or do not relapse. Tape strip samples will be collected from both lesional and adjacent non-lesional areas during the sampling period starting at week 116.

The samples will be shipped to the central lab and will be analyzed later.

Substudy 3 (Serum analysis):

Participation in this substudy is mandatory. Serum samples will be collected from all subjects to assess PD markers associated with the response to guselkumab as well as markers related to psoriasis. Measurements may include but are not limited to serum IL-17A, IL-17F, IL-22 levels and beta defensin-2 (BD-2). The samples) will be collected according to the TES at weeks 0, 4, 28, 68, 80, 116, 164, and 220 (and R0, if applicable) and analyzed by immunoassays.

Substudy 4 (Genetic analyses):

It is recognized that genetic variation can be an important contributing factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Genetic (DNA) analysis may help to identify population subgroups that respond differently to a drug. The goal of the genetic (DNA) analysis is to collect a single DNA sample at week 0 as specified in the TES to search for genetic factors that may influence molecular effects, clinical efficacy, or tolerability of guselkumab and to identify genetic factors associated with psoriasis. Participation in this study is optional. Only subjects who sign the consent form to participate in the genetic assessment will have whole blood DNA samples collected.

Note: One additional blood sample for biomarker assessments will be taken at the time when the subject loses control of disease (defined as PASI >5 at any visit during Study Part 2 or 3 = R0).

Altogether, these substudies will provide crucial information about possible subject-optimized guselkumab treatment algorithms and may relate immunopathological mechanisms to clinical course and characteristics of plaque psoriasis.

SUBJECT POPULATION

The target population comprises adults with a diagnosis of plaque-type psoriasis (approximately 40% subjects with disease duration ≤2 years calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit). Subjects must have moderate-to-severe plaque-type psoriasis defined by PASI >10 or affected body surface area (BSA) >10% and additionally a DLQI >10. Subjects must be candidates for systemic therapy for psoriasis. Subjects with a clinical active psoriasis arthritis (PsA) which needs treatment beyond NSAIDs, non-plaque forms of psoriasis (eg, erythrodermic, guttate or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) will be excluded.

DOSAGE AND ADMINISTRATION

A guselkumab-prefilled syringe assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) device, designed to deliver a single, fixed dose of 100 mg and a matched PFS-U containing Placebo will be used. Products will be labeled in a blinded manner; it will not be possible to differentiate between active and Placebo-prefilled syringes.

For **Study Part 1** all enrolled subjects will receive one injection of guselkumab according to the TES, ie at weeks 0, 4, 12, and 20.

Subjects with a PASI score=0 at weeks 20 and 28 are qualified for randomization in Study Part 2. In case of PASI score >0 at weeks 20 or/and 28, subjects will continue to get guselkumab 100 mg q8w with last administration in week 60 (study group 2c).

Randomized subjects of **Study Part 2** (study groups 2a and 2b) will receive one injection of either guselkumab or matching Placebo solution for injection (ie, identical to guselkumab in color, smell, and shape) according to the following schemes:

- Study group 2a: guselkumab 100 mg q8w, ie at weeks 28/36/44/52/60
- Study group 2b: guselkumab 100 mg q16w, ie guselkumab at weeks 36 and 52; Placebo at weeks 28/44/60 (guselkumab and placebo will be provided blinded, IWRS will assure correct assignment).

Subjects (from groups 2a and 2b) with a PASI score <3 at week 68 are qualified for entering **Study Part 3** and will be withdrawn from the study medication.

Subjects (from groups 2a, 2b, 3a and 3b) losing control of disease, defined as PASI score >5 at any visit of Study Parts 2 or 3 (ie, until week 220), will enter the re-treatment-arm with guselkumab 100 mg q8w for further 3 administrations (starting at that visit = re-treatment week 0, followed by administration at re-treatment-weeks 8 and 16). The final efficacy assessment for all subjects in the re-treatment arm will take place 24 weeks after loss of control and study termination will be 28 weeks after loss of control (final study visit). Subjects with fluctuating disease (ie, PASI score 3 to 5) or PASI >5 (subjects losing control of disease) at week 68 will also get the opportunity to enter the re-treatment-arm.

All study procedures should be completed prior to administering the study drug. Sub-cutaneous injections should be administered by qualified study site staff during the study visit, if possible. However, in cases where a site visit is not possible, subjects who have appropriate experience or have received required training may self-administer study drug at the times instructed by the investigator. Study site staff must ensure that those subjects have the appropriate experience or have received the required training to perform self-administration of SC injections.

Self-administration at home is only allowed subsequent to performance of a phone or video visit. Application of study drug at home can also be performed by a Home Health Care service provider if agreed by the sponsor, investigator and subject. Self-administration cannot take place on 2 consecutive visits.

Site personnel and subjects will remain blinded to the treatment assignments until the last subject completes week 220 evaluations and the database has been locked.

EFFICACY EVALUATIONS

Efficacy evaluations chosen for this study are consistent with those used to evaluate other therapies for psoriasis and include:

- Psoriasis Area and Severity Index (PASI)
- Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA-CLIN)
- Psoriasis-affected Body Surface Area (BSA)
- Dermatology Life Quality Index (DLQI) [PRO]
- Psoriasis Symptom and Sign Diary (PSSD, 7-day version) [PRO]
- Nail associated quality of life (NAPPA-QoL) and patient- relevant treatment benefit (NAPPA-PBI) [PRO]
- Target Lesion Severity Scores (TLSS; only for subjects participating in substudies 1 and 2).

The efficacy assessments PASI, affected BSA and NAPPA-CLIN will be performed at the site by an efficacy assessor (preferably a dermatologist) trained by the Sponsor and at the appropriate visits as outlined in the TES.

PHARMACOKINETIC EVALUATIONS

Venous blood samples will be collected at the points in time shown in the TES for the determination of serum guselkumab concentrations. Each sample will be divided into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as back-up sample). Samples must be collected before study drug administration at visits when a study drug administration is scheduled. The exact dates and times of blood sampling must be recorded in the laboratory requisition form. The samples will be shipped to the central laboratory and will be analyzed later.

Please refer to the Laboratory Manual for further information regarding collection, handling, and shipment of biological samples. The Sponsor, or its designee, will assay these samples using a validated, specific, and sensitive immunoassay method under conditions in which the subjects' identity remains blinded.

Note: One additional blood sample for PK assessments will be taken at the time when the subject loses control of disease (PASI score >5 at any visit during Study Parts 2 or 3, or PASI ≥3 at week 68). However at R0, PK-samples will only be taken for Study Part 2d (ie, not for Study Part 3c).

SAFETY EVALUATIONS

Safety and tolerability of guselkumab will be monitored until 12 weeks after last administration of study drug by collecting information on AEs (including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry and pregnancy testing), physical examinations, vital signs, concomitant medication review, and early detection of tuberculosis (TB). Subjects participating in Study Part 3 and not treated in the re-treatment arm will be monitored through week 220 by collecting information on AEs (including injection site and allergic reactions), vital signs, weight, and concomitant medication review.

STATISTICAL METHODS

The statistical analyses in this study will be performed separately for each Study Part and will focus on the comparison of the two randomized treatment groups (ie, **2a**: guselkumab 100 mg q8w vs. **2b**: guselkumab 100 mg q16w) in Study Part 2. The analyses will be confirmatory for the primary endpoint, and exploratory for the major secondary endpoints and for all other secondary endpoints.

Descriptive statistics will include counts and proportions for categorical data, and mean, standard deviation, median, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data. The two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used to compare the proportion of subjects responding to treatment. Continuous response parameters will be compared using an analysis of variance model with fixed effects for treatment group and disease duration and baseline (week 0) value as a covariate. Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event. The confirmatory significance level for non-inferiority testing is fixed to a one-sided α=0.05. Besides the confirmatory testing of the primary endpoint all other inferential statistical testing (including calculation of confidence intervals) is to be interpreted in the exploratory sense only.

Sample Size Determination

The present trial is designed to demonstrate that guselkumab 100 mg q16w treatment is non-inferior to guselkumab 100 mg q8w treatment in SRe as assessed by the proportion of subjects with an absolute PASI score <3 at week 68. A non-inferiority margin of 10% was chosen based on a minimally clinically meaningful difference. Based on data from CNTO1959PSO3002 (IB, Section 4.3.1.5) the proportion of subjects with an absolute PASI score <3 at week 68 is assumed to be 90% for guselkumab 100 mg q8w. The expected difference in proportions between the treatment groups is 0%.

The sample size estimation using the power approach is performed for the per-protocol analysis set as described below. No formal adjustment of the significance level is necessary.

When the sample size in each group is 112, a two-group large-sample normal approximation Wald Z-test of proportions with a one-sided 0.05 significance level will have 80% power to reject the null hypothesis that the guselkumab 100 mg q16w treatment is inferior to the guselkumab 100 mg q8w treatment (the difference in proportions, $P_{\text{guselkumab 100mg q16w}} - P_{\text{guselkumab 100mg q8w}}$, is $\leq$ -10%) in favor of the alternative hypothesis that the guselkumab 100 mg q16w treatment is non-inferior to the guselkumab 100 mg q8w treatment (the difference in proportions is > -10%), assuming that the expected difference in proportions is 0 and the proportion in the guselkumab 100 mg q8w treatment group is 90% (nQuery Advisor® 7.0).

Considering the frequency of drop-out rates and protocol violations from previous trials, it is assumed that about 20% randomized subjects will not be evaluable for the per-protocol analysis in Study Part 2. Hence, 280 subjects (140 subjects per treatment group) are planned to be randomized in a ratio of 1:1 to meet the required sample size of 224 subjects (112 subjects per treatment group) for the per-protocol analysis.

Based on data from CNTO1959PSO3001 and CNTO1959PSO3002, it is anticipated that approximately 35% of enrolled subjects in Study Part 1 will be eligible for randomization at week 28 in Study Part 2. Thus, a total of 800 subjects should be enrolled in Study Part 1 to ensure that at least 280 subjects are eligible for randomization in Study Part 2. Accounting for a 10% drop-out rate of subjects ineligible for randomization at week 28 because of study discontinuation prior to week 28, it is therefore planned to enroll a total of 888 subjects in Study Part 1.

Note: Screenings and enrollments will be adjusted if necessary (without protocol amendment) to achieve 280 SRe at week 28. Ongoing subjects in Study Part I will continue to Part 2 if eligible, irrespective of whether or not 280 SRe are already randomized. Only screenings will be closed.

Efficacy Analyses

The efficacy analyses will be performed separately for each Study Part. For all efficacy analyses to compare guselkumab 100 mg q8w vs. guselkumab 100 mg q16w in Study Part 2, all randomized subjects at week 28 will be included. In Study Part 2 subjects will be analyzed according to the group to which they were randomized regardless of the treatment they actually received (intent-to-treat analysis set).

The per-protocol analysis set will consist of all subjects in the intent-to-treat analysis set terminating the study without any major deviation of the protocol and its procedures. Subjects with major protocol deviations will be excluded from the per-protocol analysis.

The confirmatory analysis of the primary endpoint variable will be performed both for the intent-to-treat analysis set and the per-protocol analysis set. In Study Part 1 and Study Part 3 all subjects treated with at least one dose of study drug will be included in the efficacy analyses. For all efficacy analyses in Study Part 1 and Study Part 3, subjects will be analyzed according to the treatment they actually received.

All analyses as described in detail in the statistical analysis plan (SAP) will be performed after DBL.

Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs (TEAEs) will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

Pharmacokinetic Analyses

Serum guselkumab concentrations at specified visits will be summarized by efficacy response status for each treatment group. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each sampling time. All concentrations below the lowest quantifiable sample concentration of the assay (below the quantifiable limit; BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset. The BQL concentrations will be treated as zero in the summary statistics.

Biomarker Analyses

Biomarker samples will be used to define serum markers, skin gene expression and cellular profiles, and genetic (DNA) data for correlative analyses to better understand the molecular effects of guselkumab on the pathogenesis of psoriasis including the differences between >2 years and ≤2 years disease duration and to understand why people may respond differently to guselkumab. These analyses are considered exploratory and will be summarized in a separate technical manual.

Statistical Analyses per Study Part

Statistical analyses will be performed for each Study Part.

The confirmatory analysis is planned to be performed at the end of Study Part 2, ie, after all subjects have completed their visit at week 68 (ie, 40 weeks after randomization) or discontinued earlier. This analysis will include the confirmatory analysis of the primary endpoint, and the exploratory analyses of the major secondary endpoints and all other predefined efficacy and safety analyses from week 28 until week 68.

The analyses of Study Part 1 and Study Part 3 will be exploratory. The exploratory analysis of Study Part 1 will occur after all subjects have completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis will include the safety analysis and all efficacy measures after Week 0 and will cover the time until the week 28 visit. The exploratory analysis of Study Part 3 will occur after all subjects have completed their visits at week 116 (ie, 48 weeks after inclusion in Study Part 3 at week 68) or week 144 in case of subjects entering the re-treatment arm in week 116, at week 164 (ie, 96 weeks after inclusion in Study Part 3 at week 68) or week 192 in case of subjects entering the re-treatment arm in week 164, and at week 220 (ie, 152 weeks after inclusion in Study Part 3 at week 68) or week 248 in case of subjects entering the re-treatment arm in week 220 or discontinued earlier. These analyses will include the safety analyses and all efficacy measurements after week 68 and will cover the time until week 116/164/220 and week 144/192/248, respectively.

TIME AND EVENTS SCHEDULE

Schedule of Study Conduct: Part 1 and 2

Study Period	Screening[b]	Part 1 (Therapy Initiation, group 1)					Part 2* for SRe (Blinded Treatment, groups 2a and 2b)						Part 2** for non-SRe (q8w Treatment, group 2c)							ETV ****
Week		0	4	12	16	20	28	36	44	52	60	68	28	36	44	52	60	68	72 (SFU) *****	
Study Procedures[a]																				
Screening/Administrative																				
Informed consent[c]	X																			
Medical history and demographics	X																			
Eligibility criteria	X	X																		
Study Drug Administration																				
Randomization[d]							X													
Stratification							X													
Study drug administration[e]		X	X	X		X	X	X	X	X	X		X	X	X	X	X			
Study drug accountability		X	X	X		X	X	X	X	X	X		X	X	X	X	X			
Safety Assessments																				
Physical examination	X	X				X	X				X	X	X				X	X	X	X
Vital signs		X----------X																		
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph[p]	X																			
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																		
Weight		X					X					X	X					X	X	X
Concomitant therapy	X----------X																			
Adverse events	X----------X																			

Study Period	Screening[b]	Part 1 (Therapy Initiation, group 1)					Part 2* for SRe (Blinded Treatment, groups 2a and 2b)						Part 2** for non-SRe (q8w Treatment, group 2c)							ETV ****
Week		0	4	12	16	20	28	36	44	52	60	68	28	36	44	52	60	68	72 (SFU) *****	
Efficacy Assessments																				
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
NAPPA		X					X			X		X	X			X		X		X
BSA		X		X	X		X			X		X	X			X		X		
DLQI[g]	X	X			X	X	X			X		X	X			X		X		X
PSSD[g]	X	X			X	X	X			X		X	X			X		X		X
TLSS[h]		X	X				X					X	X					X		
Photo documentation[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Clinical Laboratory[j]																				
QuantiFERON-TB test	X																			
Hepatitis B & C serology	X																			
HIV serology	X																			
Hematology[k]	X	X		X		X		X		X		X		X		X		X	X	X
Chemistry[k]	X	X		X		X		X		X		X		X		X		X	X	X
Pharmacokinetics																				
Serum guselkumab concentration[l]						X	X	X				X	X							
Biomarkers																				
Serum biomarkers (3)[l]		X	X				X					X	X					X		
Skin biopsy for cellular substudy (1)[m] (optional)		X	X				X					X	X					X		
Skin biopsy for gene expression substudy (2)[m] (optional)		X	X				X					X	X					X		
Whole blood (PBMC) for cellular substudy (1)[n] (optional)		X	X				X					X	X					X		
Genetic (DNA) evaluations(4)[o] (optional)		X																		

Schedule of Study Conduct: Part 3														
Study Period	**Part 3*** (Withdrawal, groups 3a and 3b)**													
Week	**80**	**92**	**104**	**116**	**128**	**140**	**152**	**164**	**176**	**188**	**200**	**212**	**220 (FSV)**	**ETV ******
Study Procedures[a]														
Safety Assessments														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight				X				X					X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPPA	X		X	X				X					X	X
BSA	X		X	X		X		X		X		X	X	
DLQI[g]	X	X	X	X		X		X					X	X
PSSD[g]				X		X		X					X	X
Photo documentation[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers														
Serum biomarkers (3)[l]	X			X				X					X	
Skin biopsy for cellular substudy (1)[m] (optional)				X									X	
Whole blood (PBMC) for cellular substudy (1)[n] (optional)	X			X									X	
Skin biopsy for gene expression substudy (2)[m] (optional)				X									X	
Non-invasive novel method 'tape stripping'				X									X	

BSA = body surface area; DLQI = Dermatology Life Quality Index; ETV = Early Termination Visit; FSV = Final Study Visit; NAPPA = Nail Assessment in Psoriasis and Psoriatic Arthritis (CLIN, PBI and QoL); PASI = Psoriasis Area and Severity Index; PBMC = peripheral blood mononuclear cells; PSSD = Psoriasis Symptom and Sign Diary 7-day version; SFU = Safety-Follow-up visit; TLSS = Target Lesion Severity Scores

Visits through week 68 are to be conducted within ±7 calendar days and visits after week 68 are to be conducted within ±14 calendar days; please prospectively contact the Sponsor for further instructions if it is anticipated that a visit may fall outside this window. In the event of early discontinuation of study agent, the assessments should be conducted at the time of discontinuation of study agent (ETV). After ETV, safety follow-up should be conducted for 12 weeks after the last administration of study drug. Subjects who discontinue study agent may or may not continue in the study depending on the reason for discontinuation of study agent; refer to Section 10.2 for further details.

***):** Only for subjects reaching a PASI score=0 at weeks 20 **and** 28
****):** Subjects who will not reach a PASI score=0 at week 20 or week 28 will receive further q8w guselkumab 100 mg treatment until week 60 (last guselkumab administration), with final study assessment at week 68 and final Safety Follow-Up Visit at week 72.
*****):** Study Part 3 will last about 152 weeks until week 220 (Final Study Visit) and will not require any administrations of guselkumab. In between the 12-weekly on-site visits, telephone-visits will be done 6 weeks (± 7 days) after each on-site visit (ie, telephone visits at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206) to notice a possible worsening of psoriasis.
******):** For subjects, who withdraw from study participation, every effort should be made to conduct the ETV.

*******):** For all subjects (part 1 and part 2) who discontinue study treatment prematurely, every effort should be made to conduct the **SFU** 12 weeks **after the last study drug administration**.

a. All study procedures and evaluations are to be completed before study drug injection. Assessments for subjects who discontinue study agent administration or withdraw from the study are described in Section 10.2 and 10.3, respectively.
b. To occur within 4 weeks prior to week 0.
c. Informed consent form must be signed before any study-related activity
d. All subjects reaching a PASI=0 at week 20 **and** 28 will be determined as Super-Responders (SRe) and will be randomized at week 28 in Study Part 2.
e. Subjects will receive guselkumab 100 mg at the weeks 0, 4, 12 and 20 (Study Part 1), and guselkumab or Placebo q8w at the weeks 28 to 60 (Study Part 2).
f. Women of childbearing potential must have a negative urine pregnancy test result at all study visits before study treatment drug administration.
g. Performed by the subject (PRO) before any tests, procedures, or other evaluations (eg, PASI, affected BSA or NAPPA-CLIN) are performed for that visit.
h. TLSS for the selected target lesion will be recorded at each biopsy collection time.
i. Photo-documentation will be done standardized and professionally at few selected sites equipped with an appropriate photography laboratory (described in photo-documentation manual).
j. All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled. Details will be provided in the Laboratory Manual.
k. Laboratory assessments can be non-fasting and are listed in Section 9.6.
l. One additional blood sample for pharmacokinetic and serum biomarker assessments will be taken at the time when the subject loses control of disease (defined as PASI score >5 at any visit during Study Parts 2 or 3, or PASI ≥3 at week 68).
m. Biopsy samples for molecular and cellular analyses will be collected only from subjects who consent to participate in the optional biopsy substudy. A total of six 6 mm biopsy samples (or twelve 3 mm biopsy samples in substudy 2, if applicable; refer to Section 3.1) will be collected (1 NL at week 0, 1 L at weeks 0, 4, 28, and 68, and where feasible, 1 biopsy from a relapsing plaque at the time a subject in Study Part 2 or 3 requires re-treatment (see l). For further details regarding these evaluations, refer to Section 9.4. The target lesion will be photo-documented in a standardized manner (described in the Biopsy manual) if the subject agrees to photo-documentation.
n. Blood samples to isolate PBMC for immunophenotyping analyses will be collected only from subjects who consent to participate in the optional substudy 1. For further details regarding these evaluations, refer to Section 9.4.
o. Blood samples for genetic (DNA) analyses will be collected only from subjects who sign a separate consent form to participate in the genetic (DNA) evaluations. For further details regarding these evaluations, refer to Section 9.4.
p. Only if no chest radiograph done within the last 3 months before administration of first study drug.

Schedule of Study Conduct - Part 2 and 3: Re-treatment for subjects with loss of disease control (groups 2d and 3c)*					
Re-treatment Week	**R0**	**R8**	**R16**	**R24**	**R28 (SFU)**
Study Procedures[a]					
Study Drug Administration					
Study drug administration[b]	X	X	X		
Study drug accountability	X	X	X		
Safety Assessments					
Physical examination	X			X	X
Vital signs	X----------				----------X
Tuberculosis evaluation	X----------				----------X
Urine pregnancy test[c]	X----------				----------X
Weight				X	
Concomitant therapy	X----------				----------X
Adverse events	X----------				----------X
Efficacy Assessments					
PASI	X	X	X	X	
NAPPA	X			X	
BSA				X	
DLQI[d]	X		X	X	
PSSD[d]	X			X	
TLSS[e]	X				
Photo documentation[f]	X	X	X	X	
Clinical Laboratory[g]					
Hematology[h]	X		X		X
Chemistry[h]	X		X		X
Pharmacokinetics					
Serum guselkumab concentration[i]	X				
Biomarkers					
Serum biomarkers (3)[i]	X				
Skin biopsy and blood sample for PBMC for cellular substudy (1)[j k] (optional)	X				
Skin biopsy for gene expression substudy (2) (optional)[j]	X				
Non-invasive novel method 'tape stripping'	X				

BSA = body surface area; DLQI = Dermatology Life Quality Index; NAPPA = Nail Assessment in Psoriasis and Psoriatic Arthritis (CLIN, PBI and QoL); PASI = Psoriasis Area and Severity Index; PSSD = Psoriasis Symptom and Sign Diary 7-day version; SFU = Safety-Follow-up visit; TLSS = Target Lesion Severity Scores

Re-treatment visits are to be conducted within ±7 calendar days; please prospectively contact the Sponsor for further instructions if it is anticipated that a visit may fall outside this window. In the event of early discontinuation of study agent, these assessments should be conducted at the time of discontinuation of study agent (ETV). After ETV, safety follow-up should be conducted for 12 weeks after the last administration of study drug. Subjects who discontinue study agent may or may not continue in the study depending on the reason for discontinuation of study agent; refer to Section 10.2 for further details.

***):** Subjects (SRe) with PASI score >5 at any visit in Study Part 2 or 3, or a PASI score ≥3 at week 68 will receive guselkumab 100 mg q8w for further 3 administrations (at that visit = re-treatment weeks 0, 8 and 16) and study termination after 28 weeks (Safety-Follow Up visit)

a. All study procedures and evaluations are to be completed before study drug injection. Assessments for subjects who discontinue study agent administration or withdraw from the study are described in Section 10.2 and 10.3, respectively.
b. Subjects will receive guselkumab 100 mg q8w for further 3 administrations (re-treatment weeks 0, 8 and 16).
c. Women of childbearing potential must have a negative urine pregnancy test result at all study visits before study treatment drug administration.
d. Performed by the subject (PRO) before any tests, procedures, or other evaluations (eg, PASI, affected BSA or NAPPA-CLIN) are performed for that visit.
e. TLSS for the selected target lesion will be recorded at each biopsy collection time.
f. Photo-documentation will be done standardized and professionally at few selected sites equipped with an appropriate photography laboratory (described in Photo-documentation manual).
g. All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled. Details will be provided in the Laboratory Manual.
h. Laboratory assessments can be non-fasting and are listed in Section 9.6.
i. One additional blood sample for pharmacokinetic and serum biomarker assessments will be taken at the time when the subject loses control of disease (defined as PASI score >5 at any visit during Study Parts 2 or 3, or PASI ≥3 at week 68). However at R0, PK-samples will only be taken for Study Part 2d (ie, not for Study Part 3c).
j. Biopsy samples for molecular and cellular analyses will be collected only from subjects who consent to participate in the optional biopsy substudy. A total of six 6 mm biopsy samples (or twelve 3 mm biopsy samples in sub 2 if appl., refer to Section 3.1). will be collected (1 NL at week 0, 1 L at weeks 0, 4, 28, and 68, and where feasible, 1 biopsy from a relapsing plaque at the time a subject in Study Part 2 or 3 requires re-treatment (see l). For further details regarding these evaluations, refer to Section 9.4. The target lesion will be photo-documented in a standardized manner (described in the Biopsy manual), if the subject agrees to photo-documentation.
k. Blood samples to isolate PBMC for immunophenotyping analyses will be collected only from subjects who consent to participate in the optional substudy 1. For further details regarding these evaluations, refer to Section 9.4.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APC	antigen presenting cell
AST	aspartate aminotransferase
BSA	body surface area
CLIN	Clinical
CRF	case report form(s)
DBL	database lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
eDC	electronic data capture
eg	example given
FSV	Final study visit
GCP	Good Clinical Practice
HBV/HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	human immunodeficiency virus
IB	Investigators Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ie	that is
IEC	Independent Ethics Committee
IGRA	interferon-gamma-release-assay
IL	Interleukin
IL-23-R	interleukin-23 receptor
IRB	Institutional Review Board
ISR	injection site reaction
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAPPA	Nail Assessment in Psoriasis and Psoriatic Arthritis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PFS-U	Prefilled Syringe assembled with the UltraSafe PLUS™ Passive Needle Guard
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PSSD	Psoriasis Symptom and Sign Diary
QoL	quality of life
q8w/q16w	every 8/16 weeks
RNA	ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SRe	Super-Responder(s)
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
Tc17 cell	IL-17 producing cytotoxic T cell
TES	Time and Events Schedule
Th17 cell	IL-17 producing T helper cell
TLSS	Total Lesion Severity Score
ULN	upper limit normal

DEFINITIONS OF TERMS

PASI < 3: controlled disease
PASI 3 to 5: fluctuating disease
PASI >5: loss of control/re-treatment

1. INTRODUCTION

1.1. Background

Psoriasis is a chronic inflammatory immune-mediated disease characterized by patches of inflamed skin covered with silvery-white scaly skin. Psoriasis pathogenesis involves the dysregulation of interleukin (IL)-23 mediated immune responses (Kollipara, et al. 2015). IL-23 is a key regulatory cytokine produced by macrophages and dendritic cells (DCs), which directs the differentiation, expansion and maintenance of CD4+ IL-17 producing T helper (Th17) cells, CD8+ IL-17 producing cytotoxic T (Tc17) cells, and CD4+ Th22 cells. It is probably also involved in the pathological differentiation and survival of tissue resident memory T cells (TRMs) (Cheuk, Wikén, et al. 2014).

Th17 cells secrete several inflammatory mediators including IL-17A, IL-17F, and IL-22. In addition to being produced by Th17 cells, IL-17A is also generated by CD8+ Tc17 cells and various other immune cells, which are also to some extent regulated by IL-23 (Ness-Schwickerath, Jin und Morita 2010). The numbers of Th17 and Tc17 cells have been shown to be increased in psoriatic plaques (Cheuk, Wikèn, et al. 2014, Cheuk, Martini, et al. 2017) , and blockage of either IL-23 or IL-17 has demonstrated clinical benefit in psoriasis (Blauvelt, Lebwohl und Bissonnette 2015). Inhibition of IL-23 has shown to normalize transcriptional signatures associated with Th17, and to normalize the levels of IL17A, IL17F and IL22 in psoriatic patients' serum (Branigan et al., 2016 SID; Liu et al., 2017, Gene to Clinic). In 2014, IL-23 inhibition was shown to result in clinical efficacy that was superior to that seen after TNF-α inhibition (Sofen, et al. 2014, Blauvelt, Papp, et al. 2017, Reich, et al. 2017).

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds selectively to human IL-23 with high specificity and affinity. In in vitro models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signaling, activation and cytokine cascades and subsequent Th17, Tc17 and Th22 cell proliferation, cytokine production and survival. Other cells likely affected by guselkumab treatment include innate lymphoid cells type 3 (ILC3s) which also produce IL17 and IL22, are activated by IL-1 and IL-23 and are thought to be involved in psoriasis pathogenesis particularly during initiation of disease (Villanova, et al. 2014, Teunissen, et al. 2014).

Clinical studies with guselkumab have shown clearance rates that exceeded those afforded by other non-biologic and most biologic systemic psoriasis treatments, with ~30-45% of patients reaching complete clearance (Psoriasis Area and Severity Index [PASI] score=0) and approximately 70% of patients reaching nearly complete clearance (PASI score ≤1) 24 weeks after start of guselkumab treatment (Blauvelt, Papp, et al. 2017, Reich, et al. 2017, Papp, et al. 2018).

Additionally, blocking of IL-23 may have the potential to achieve a profound effect in the pathophysiology of the disease that goes beyond temporary clearance of psoriatic skin lesions. The induction of a sustained response with longer dosing intervals in a subset of patients will be investigated in this study.

1.2. Overall Rationale for the Study

Previous guselkumab studies suggest that after achieving a PASI 90 response some patients were still able to keep their responses for months after stopping the treatment. Several parameters including shorter disease duration, absolute PASI of 0 at week 28 and inflammatory cytokine serum levels at baseline (week 0) might be associated with higher drug-free remission rates.

Indeed, in exploratory analyses (unpublished data from CNTO1959PSO3001 and CNTO1959PSO3002), subjects with shorter disease duration (≤2 years) seem to have a higher maintenance of response rate after drug withdrawal than subjects with a longer history of disease (ie, >10 years) and achieving an absolute PASI of 0 at week 28 was associated with long-term maintenance of PASI 90 response (45.8% of subjects who achieved an absolute PASI of 0 at week 28 achieved long-term maintenance of PASI 90 response; compared to 24% of subjects who didn't achieve an absolute PASI of 0 at week 28 achieved long-term maintenance of PASI 90 response odds ratio of 2.66, $p<0.005$, Fisher's exact test).

Whether there is a distinct subset of subjects, here termed Super Responders (SRe), who are more likely to show a more profound response of guselkumab on the pathophysiology of disease establishment, maintenance and relapse shall be investigated in this study.

More precisely, the present study aims to define the subset of SRe (ie, subjects who achieve an absolute PASI score=0 at weeks 20 **and** 28) and is intended to evaluate whether these subjects maintain disease control during extended dosing intervals as well as after drug withdrawal.

To evaluate these points one after the other the study is divided into three parts:

Part 1 – Identification of SRe

- SRe are defined by an absolute PASI score=0 at weeks 20 **and** 28

Part 2 – Comparison of treatment algorithms for SRe

- Non-inferiority of q16w vs. q8w dosing of guselkumab

Part 3 – Maintenance of drug-free remission

- Evaluation of drug-free maintenance of response following drug withdrawal in SRe.

All parts of the study are accompanied by investigations (4 substudies) on whether changes in clinical response are associated with distinct molecular or cellular changes in serum or skin biopsies.

To better understand the underlying immunological mechanisms of the profound effect of IL-23 inhibition on disease establishment and chronicity of plaque psoriasis, a significant proportion (approximately 40%) of the subjects to be included in the study will have a disease history of ≤2 years.

The following points were considered for design and conduct of the present clinical study:

- Specific therapeutic algorithms/regimens are to be established to achieve subject-optimized guselkumab treatment: A dose regimen of 100 mg guselkumab at weeks 0, 4, and q8w thereafter has been shown to be most suitable regarding efficacy and safety for the overall population of subjects suffering from moderate-to-severe plaque psoriasis and was therefore approved by EMA and FDA (SmPC Tremfya® 2017). This regimen will also be used for Study Part 1 (lasting 28 weeks) and as comparative dosing regimen in Study Part 2.
- As described above, SRe are presumed to respond better to guselkumab treatment even with extended dosing intervals and to show more profound changes in immunopathophysiology of the disease. Therefore, the primary objective of this study is to demonstrate non-inferiority of q16w treatment to q8w treatment in SRe in Study Part 2.

1.3. Benefit/Risk Assessment

A large global Phase 3 program consisting of 3 studies (CNT1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003) has been conducted to investigate the efficacy and safety of sc guselkumab in adult patients with moderate to severe plaque psoriasis. The longer-term efficacy and safety of guselkumab is being assessed in 4-year extensions of studies CNTO1959PSO3001 and CNTO1959PSO3002 (ie, both studies will have an overall study duration of 5 years). In the EU, approval was obtained for the use of Tremfya® in adults with moderate to severe plaque psoriasis on 10 November 2017. As such, the benefit-risk profile for guselkumab in the treatment of plaque psoriasis is considered to be favorable.

Extensive clinical development is also ongoing in other inflammatory diseases such as psoriatic arthritis (PsA), Crohn's disease, generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis, as summarized in the latest version of the IB.

Dosing in the current study is either at the approved dosing regimen for guselkumab in psoriasis (100 mg sc at Week 0 and Week 4, and then q8w) or at an extended interval (100 mg sc q16w). Details about the design and rationale of the study are provided in Section 3.

Potential risks of the study, including those of serious infection and malignancy, are being addressed via judicious inclusion/exclusion criteria, guidelines for subject management (including for discontinuation of study treatment), prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the trial. Further details about the safety evaluations that will be utilized in the study are provided in Section 9.6.

Based on the available data and the proposed safety measures, the potential risks for subjects in the current study appear to be acceptable relative to the potential benefits of the study.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary objective

The primary objective of the study is to demonstrate that Super-Responders (SRe; defined as psoriasis subjects who receive on-label guselkumab treatment until week 20 and respond with a Psoriasis Area and Severity Index [PASI] score=0 at weeks 20 **and** 28) maintain control of disease until week 68 with prolonged treatment intervals of 16 weeks (100 mg q16w). *To be demonstrated in Study Part 2 (see Section 3.1 for study design).*

Secondary objectives

Secondary objectives are to evaluate

- whether subjects with short disease duration (≤2 years) show a more rapid and better guselkumab response compared to subjects with longer disease duration and whether subjects with shorter disease are more likely to maintain drug-free control of disease after guselkumab withdrawal. *To be evaluated in Study Parts 1, 2, and 3.*
- whether SRe with short disease duration and PASI=0 at week 116 (ie, remission for one year after withdrawal) will show sustained remission (ie, PASI=0) over two additional years compared to subjects with longer disease duration. *To be evaluated in Study Part 3.*
- whether SRe with short disease duration and PASI>0 to ≤5 at week 116 (ie, partial relapse for one year after withdrawal) will show continued loss of response or stabilization of disease worsening over two additional years compared to subjects with longer disease duration. *To be evaluated in Study Part 3.*
- whether different treatment intervals (weeks 28 to 60: guselkumab 100 mg q8w vs. guselkumab 100 mg q16w) affect the maintenance of drug-free control of disease after 68 weeks of guselkumab treatment. *To be evaluated in Study Part 3.*
- the safety and tolerability of guselkumab in subjects with moderate-to-severe plaque-type psoriasis.

Note: disease duration will be calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit.

Exploratory objectives

The following objectives are to be explored in the mechanistic biomarker substudies:

- characterization of the immune cellular and molecular composition at baseline (week 0) and changes (quantitative and qualitative characterization) in the lesional skin of subjects during treatment with guselkumab as determined by fluorescence activated cell sorting (FACS)-based analysis. *To be explored in substudy 1*
- characterization of the immune cellular changes (quantitative and qualitative characterization) in the blood of subjects at baseline (week 0), during and after treatment with guselkumab as determined by FACS-based analysis. *To be explored in substudy 1*

- characterization of molecular (gene expression) changes during treatment with guselkumab in the skin of subjects treated with guselkumab as determined by RNA sequencing (RNAseq) and quantitative polymerase chain reaction (qPCR)**.** *To be explored in substudy 2*
- characterization of the tissue immunopathological changes in the skin of subjects during and after treatment with guselkumab as determined by immunohistochemistry (IHC)/ immunofluorescence (IF)/ in situ hybridization (ISH). *To be explored in substudy 2*
- characterization of the effects of guselkumab treatment on serum biomarkers as determined by immunoassays. *To be explored in substudy 3*
- characterization of the association between changes in the various exploratory biomarker endpoints and 1) efficacy of guselkumab, 2) duration of psoriasis, 3) maintenance of response after stopping guselkumab treatment, and 4) ability to achieve a PASI 100 response at weeks 20 and 28 (super responder status). *To be explored in all substudies*

2.1.2. Endpoints

For the endpoints, the following terms were defined:

- Control of disease: PASI score <3
- Fluctuating disease: PASI score 3 to 5
- Loss of disease control: PASI score >5.

Study groups are defined as follows:

- **1**: All participating subjects who are enrolled and are scheduled to receive guselkumab 100 mg at weeks 0, 4, q8w until week 28 (Study Part 1)
- **2a**: SRe (PASI score=0 at weeks 20 **and** 28) randomized to guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)
- **2b**: SRe randomized to guselkumab 100 mg q16w at weeks 28 to 60 (Study Part 2)
- **2c**: non-SRe with a PASI score >0 at week 20 and/or 28 who will receive guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)
- **2d**: SRe with loss of disease control between week 28 and 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8, and 16 calculated from the date of loss of disease control (Study Part 2)
- **3a**: SRe randomized to guselkumab 100 mg q8w in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)
- **3b**: SRe randomized to guselkumab 100 mg q16w in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)
- **3c**: SRe with fluctuating disease at week 68 or loss of disease control at any other visit after week 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8 and 16 calculated from the date of loss of disease control (Study Part 3).

Primary endpoint

The primary endpoint of the main study is the proportion of subjects in study groups **2a** and **2b** who achieve an absolute PASI score <3 at week 68.

Major secondary endpoints

Major secondary endpoints of this study are:

- Time to improvement from baseline (week 0) in PASI (PASI 75/90/100 response and absolute PASI score=0) for subjects with short (≤ 2 years) and longer (>2 years) disease duration per study group (**1**, **2a, 2b,** and **2c**)
- Proportion of subjects with short (≤2 years) and longer (>2 years) disease duration who achieve an absolute PASI score of 0, ≤1 and <3 at weeks 20, 28, 68, 116, 164, and 220 per study group (**1, 2a, 2b, 2c, 3a,** and **3b**)
- Proportion of subjects who retain disease control (ie, absolute PASI score <3 at all visits) from week 68 through week 116, from week 68 through week 164, and from week 68 through week 220 for subjects with short (≤ 2 years) and longer (>2 years) disease duration per study group (**3a** and **3b**)

Other secondary endpoints of this study are:

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 20, 28, 68, 116, 164, and 220 per study group (**1, 2a, 2b, 2c, 3a,** and **3b**)
- Time to loss of disease control (absolute PASI score >5 at any visit) after treatment withdrawal beyond week 68 per study group (**3a** and **3b**)
- Proportion of subjects with an absolute PASI score=0 at <u>all</u> of the following visits: weeks 12, 16, 20, and 28 (**study group 1**)
- Change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at weeks 28, 68, 116, 164, and 220 per study group (**1**, **2a**, **2b, 2c, 3a, 3b, and 3c**)
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at weeks 28, 68, 116, 164, and 220 per study group (**1**, **2a**, **2b, 2c, 3a, 3b, and 3c**)
- Change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 12, 28, 52, 68, 80, 104, 116, 140, 164, 188, 212, and 220 (**all study groups**)
- Change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at weeks 28, 68, 116, 164, and 220 among subjects with nail psoriasis at baseline (week 0; **1, 2a, 2b, 2c, 3a,** and **3b**).
- Change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at weeks 28, 68, 116, 164, and 220 (**1, 2a, 2b, 2c, 3a** and **3b**)
- Proportion of subjects who achieve a PSSD sign score=0 at week 68 among subjects with a PSSD sign score ≥1 at week 28 per study group (**2a**, **2b,** and **2c**).
- Association between trough serum guselkumab concentration and efficacy or serum biomarker level
- Association between trough serum guselkumab levels at weeks 20, 28, 36, and 68 and achieving a PASI score <3 at week 68 per study group (**2a** and **2b**)
- Proportion of subjects who were re-treated due to loss of disease control (PASI >5) and regain control of disease (PASI <3) 24 weeks after start of re-treatment (study groups **2d** and **3c**)
- Safety and tolerability with regard to adverse events (AEs) and abnormal laboratory results (**all study groups**).

Refer to Section 9 for evaluations related to these endpoints.

2.2. Hypothesis

In this study, Super-Responders (SRe) are defined as psoriasis subjects achieving clear skin (measured as absolute PASI score=0) at weeks 20 **and** 28 of treatment. Subjects with shorter disease duration (≤2 years calculated from date at which first symptoms [plaque] were reported by subject to date of screening visit) are expected to have a higher likelihood to be SRe.

In Super-Responders, guselkumab treatment might have stronger modifying effects on immunopathological mechanisms of the disease than in non-SRe. Therefore, it is hypothesized that this subpopulation might not lose control of disease even with a longer dosing interval (q16w instead of q8w) and that this subpopulation will have higher probability of drug-free remission after 60 weeks of treatment.

The hypothesis of this study is that guselkumab q16w treatment is non-inferior to guselkumab q8w treatment in SRe as assessed by the proportion of subjects with an absolute PASI score <3 at week 68 (alternative hypothesis in a statistical sense).

If the hypothesis is accepted, the study will be considered positive.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

The present trial is designed as a phase 3b, randomized, double-blind, parallel-group, multicenter, comparison study in subjects of at least 18 years of age with moderate to severe plaque-type psoriasis.

It is planned to achieve about 280 subjects categorized as Super-Responders (SRe, ie, PASI score=0 at weeks 20 **and** 28) for randomization in Study Part 2 (140 subjects in study group **2a** and 140 subjects in study group **2b**). It is assumed that 900-1000 subjects are therefore needed to be screened at up to 90 German study sites and 10 French study sites and that 888 subjects are needed to be enrolled (based on a SRe rate of 30-35% of enrolled subjects). Screenings and enrollments will be adjusted if necessary (without protocol amendment) to achieve 280 SRe at week 28. Ongoing subjects in Study Part I will continue to Part II if eligible, irrespective of whether or not 280 SRe are already randomized. Only screenings will be closed.

Of the enrolled subjects approximately 40% must have a disease duration of ≤2 years calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit. Subjects with disease duration of ≤2 years are expected to have a higher likelihood to be SRe. At randomization two stratification criteria apply: (i) SRe with disease duration of ≤2 years will be stratified equally to study group **2a** and **2b**. Further, (ii) SRe who are participating in the mechanistical substudy 1 will be stratified equally to study group **2a** and **2b**.

The study will feature the following structure and design:

<u>Study Part 1: Screening through Week 28:</u>

This screening phase will last up to four weeks (+ 7 calendar days) prior to first administration of guselkumab (week 0) followed by a 28-week run-in period with visits and administration of 100 mg guselkumab at weeks 4, 12, and 20. In case of a PASI score=0 at weeks 20 **and** 28 subjects are qualified to be randomized either to study group **2a** or **2b** of Study Part 2.

In case of PASI score >0 at the weeks 20 and/or 28 the subjects will continue to receive guselkumab 100 mg q8w until week 60 (last administration at week 60 visit) with final study assessments at week 68 and final safety follow-up visit at week 72 (defined as study group **2c**).

Study Part 2: Week 28 through Week 68:

Subjects with a PASI score=0 at weeks 20 and 28 will be defined as SRe and randomly assigned to the following two treatment groups: 2a) guselkumab 100 mg q8w or 2b) guselkumab 100 mg q16w. In addition, subjects with disease duration ≤2 years will be equally distributed to either group. Study visits of Study Part 2 will be conducted every 8 weeks.

To blind the study, study treatment (guselkumab or Placebo) will be administered q8w starting at week 28 until the end of study therapy (last administration in week 60). The q16w group will receive Placebo at weeks 28, 44 and 60. Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 (ie, until week 60), will enter the Re-treatment arm (group 2d, see section Re-treatment below).

The assessment for the primary endpoint (EP) will be at week 68 for both study groups.

In case of PASI <3 at week 68 the subject will not receive any study medication and enter the drug withdrawal part (Study Part 3). In case of PASI ≥ 3 at visit week 68 the subject will enter the re-treatment arm **3c** (see section Re-treatment below).

In case of PASI score >0 at the weeks 20 and/or 28 the subjects will continue to receive guselkumab 100 mg q8w until week 60 (last administration at week 60 visit) with final study assessments at week 68 and final safety follow-up visit at week 72 (defined as study group **2c**). At visit week 68 (for group **2c**), the investigator may continue treatment with commercially available guselkumab (ie, not provided by the Sponsor) to maintain a q8w interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period (ie, 12 weeks after last dose). If the investigator feels strongly that an additional therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

Study Part 3: Week 68 through Week 220:

Subjects of group 2a and 2b with a PASI score <3 at week 68 will enter Study Part 3 and be withdrawn from the study medication and followed-up until week 220. Study visits of Study Part 3 will be conducted every 12 weeks (ie, at weeks 80, 92, 104, 116, 128, 140, 152, 164, 176, 188, 200, and 212; ± 14 days). In between the 12-weekly on-site visits, a telephone-visit 6 weeks (± 7 days) will be done after each on-site visit (ie, telephone visits at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206) to assess whether the subject notices a worsening of his/her psoriasis. If so, the subject must attend an on-site visit for efficacy assessment by the assessor as soon as possible but not later than 2 weeks after the phone call. For patients not starting re-treatment, the final visit will take place at week 220.

Re-treatment

Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or 3 (ie, until week 220), will enter the re-treatment-arms (**2d** or **3c**) with three guselkumab 100 mg administrations starting at that visit (= re-treatment-week 0, followed by administration at re-treatment-weeks 8 and 16).

If re-treatment is started at a visit which would usually not require all PROs needed at the first re-treatment visit, those PROs will be obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

The final efficacy assessment for all subjects in the re-treatment-arms will take place 24 weeks after loss of control and study termination will be 28 weeks after loss of control (final study visit/safety follow-up). At visit week 24 of the re-treatment, the investigator may continue actual treatment with commercially available guselkumab (ie, not supplied by Sponsor) to maintain a q8w interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period (ie, 12 weeks after last dose). If the investigator feels strongly that an additional therapy is needed, this should be discussed with the Sponsor before initiation of the new therapy.

Subjects with fluctuating disease (ie, PASI score 3 to 5) at the week 68 visit will also get the opportunity to enter the re-treatment-arm (**3c**).

The last chance to start re-treatment will be the visit week 220 (ie, final efficacy assessment at week 244 with final study visit/safety follow-up at week 248).

Photo-documentation

At few selected sites equipped with professional photo-documentation laboratory, photos of affected body areas and their changes will be performed after efficacy assessments (PASI, BSA, NAPPA-CLIN) are completed and if the subject agrees to photo-documentation. More details are described in a photo-documentation manual.

TLSS

For substudy 1 and 2, the TLSS for the selected target lesion will be recorded at each biopsy collection time. The target lesion will be photo-documented in a standardized manner (described in the Biopsy manual) if the subject agrees to photo-documentation.

Treatment compliance

Week 0 can be done once all screening activities are completed, results are available, and the subject is eligible, but latest 4 weeks after screening visit (+ 7 calendar days). From weeks 4 to 68 it is expected that all subjects will attend visits within a range of ±7 calendar days. Visits from week 68 through week 220 are to be conducted within ±14 calendar days of the anticipated visit date. The week 220 visit should be conducted at least 160 weeks after the last study agent injection. Visits during the re-treatment period (study groups **2d** and **3c**) are also expected to occur within a range of ±7 days.

Efficacy measurements

Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd 7-day version of PSSD, NAPPA-QoL and NAPPA-PBI), and subsequently by the investigator (PASI, BSA and NAPPA-CLIN).
An exception to this order is the start of re-treatment at a visit, which would usually not require all PROs needed at the visit week 0 of the re-treatment arm. In this case, PROs will be obtained immediately after efficacy assessments (which are the basis for re-treatment-decision) and prior to drug administration at that visit.

Safety measurements

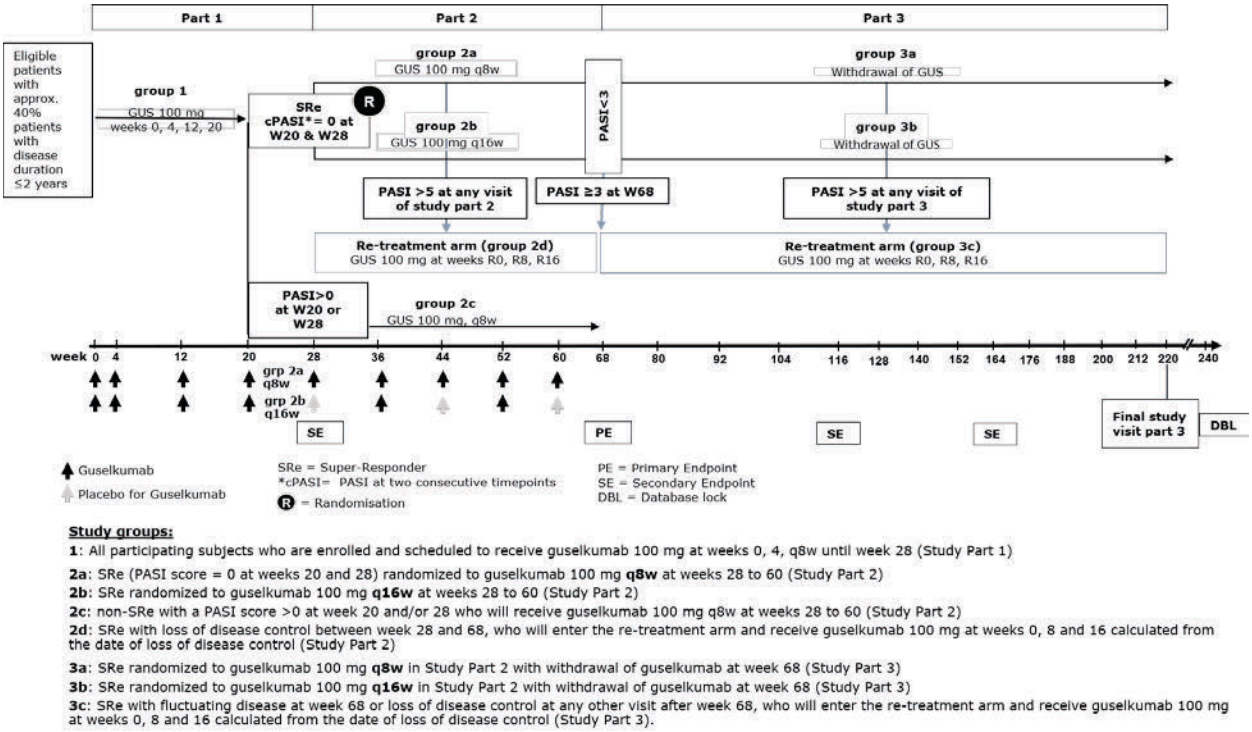
Safety evaluations will include the monitoring of adverse events (AEs, including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry and pregnancy testing), physical examinations, vital signs, concomitant medication review, and early detection of tuberculosis (TB). Venous blood samples will be collected for the determination of serum guselkumab concentrations (pharmacokinetics).

Study duration

The first study drug injection will be administered at week 0, and the last regular injection will be given at week 60. For subjects entering the re-treatment arm last possible drug injection will be week 84 (group **2d**) and week 236 (group **3c**) respectively (please refer to re-treatment section). Including a 4-week screening phase and a 12-week safety follow-up, the minimum duration of a subject's regular participation in this study will be 75 weeks and the maximum duration will be 252 weeks.

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final visit at that study site, in the time frame specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 84 months (start in Q4 2018, stop in Q1 2025). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

A schematic diagram of the study design is provided below:



Study groups:

1: All participating subjects who are enrolled and scheduled to receive guselkumab 100 mg at weeks 0, 4, q8w until week 28 (Study Part 1)

2a: SRe (PASI score = 0 at weeks 20 and 28) randomized to guselkumab 100 mg **q8w** at weeks 28 to 60 (Study Part 2)

2b: SRe randomized to guselkumab 100 mg **q16w** at weeks 28 to 60 (Study Part 2)

2c: non-SRe with a PASI score >0 at week 20 and/or 28 who will receive guselkumab 100 mg q8w at weeks 28 to 60 (Study Part 2)

2d: SRe with loss of disease control between week 28 and 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8 and 16 calculated from the date of loss of disease control (Study Part 2)

3a: SRe randomized to guselkumab 100 mg **q8w** in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)

3b: SRe randomized to guselkumab 100 mg **q16w** in Study Part 2 with withdrawal of guselkumab at week 68 (Study Part 3)

3c: SRe with fluctuating disease at week 68 or loss of disease control at any other visit after week 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks 0, 8 and 16 calculated from the date of loss of disease control (Study Part 3).

Figure 3.1-1: Overview of Study Design

Substudies

Four substudies are planned to further evaluate pharmacologic effects of guselkumab and evaluate various pharmacologic/clinical response relationships allowing assessment of inter-individual variability in clinical outcomes and possible identification of subject population groups that may respond differently to guselkumab. The substudies will also aim to further define the mechanism of action (MoA) of guselkumab at the molecular and cellular levels during and after treatment. Changes in gene expression as well as quantitative and qualitative changes in different immune cells will be evaluated in skin biopsies and blood.

Substudy 1 (Cellular MoA substudy):

Few sites will be identified that have expertise to conduct fluorescence activated cell sorting (FACS)-based cellular immunophenotypic characterization of freshly isolated skin biopsies. Participation in this study is optional. Subjects recruited to the selected sites will be asked to agree to the cellular MoA substudy (target n=60). 6 mm skin biopsy samples will be collected as follows: 1 non-lesional (NL) and 1 lesional (L) biopsy at weeks 0 and 116 (only SRe), and 1 L biopsy at weeks 4, 28, 68, and 220. In addition, when subjects lose control of disease (PASI >5) in Study Parts 2 or 3 and go into re-treatment, an additional biopsy will be taken from a lesional plaque that shows disease activity. Biopsies will be dissociated into single cell suspension and subjected to FACS-based immunophenotyping analyses. Whole blood samples for the isolation of peripheral blood mononuclear cells (PBMCs) will also be collected from consenting subjects for subsequent immunophenotyping analyses by FACS (according to TES at weeks 0, 4, 28, 68, 80, 116, and 220).

Substudy 2 (Gene expression substudy):

Skin biopsies will be collected in a subset of subjects (target n=100) at selected sites (capable of performing the skin biopsy collection and processing procedure) to evaluate gene and protein expression profiles and cellular content. Participation in this skin biopsy substudy is optional. 6 mm skin biopsy samples will be collected as follows: 1 NL and 1 L biopsy at weeks 0 and 116 (only SRe), and 1 L biopsy at weeks 4, 28, 68, and 220. In addition, when subjects lose control of disease (PASI >5) in Study Part 2 or 3, and go into re-treatment, an additional biopsy will be taken from a lesional plaque that shows disease activity. Each biopsy will be split in two parts; one part will be stored in RNA later preservative for RNA gene expression analysis, while the other part will be stored frozen in optimal cutting temperature (OCT) media for hematoxylin and eosin stain (H&E), immunohistochemistry (IHC) and immunofluorescence (IF) analysis. Two 3 mm biopsies may be taken instead of the 6 mm biopsy if preferred by the investigator and consented by the patient. The splitting step is not applicable in that case.

In addition to the biopsy collection for the selected patients taking part in the substudy 2, the novel method tape stripping (non-invasive) will be done for all participants in part 3 (SRe). Tape stripping is a less invasive collection method that may allow measurement of gene expression as well as levels of proteins or other biomarkers in the stratum corneum. The tape strip approach will be done to gain epidermal cells for biomarker analysis (transcriptomics via RNA seq; proteomics) and to validate tape stripping results by comparison with available skin biopsies. Tape stripping will be performed, where feasible, at week 116 for all participants, and at R0 visit or week 220 visit for those, who do or do not relapse. Tape strip samples will be collected from both lesional and adjacent non-lesional areas during the sampling period starting at week 116.

The samples will be shipped to the central lab and will be analyzed later.

Substudy 3 (Serum analysis):
Participation in this substudy is mandatory. Serum samples will be collected from all subjects to assess PD markers associated with the response to guselkumab as well as markers related to psoriasis. Measurements may include but are not limited to serum IL-17A, IL-17F, IL-22 levels and beta defensin-2 (BD-2). The samples) will be collected according to the TES at weeks 0, 4, 28, 68, 80, 116, 164, and 220 (and R0, if applicable), and analyzed by immunoassays.

Substudy 4 (Genetic analyses):
It is recognized that genetic variation can be an important contributing factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Genetic (DNA) analysis may help to identify population subgroups that respond differently to a drug. The goal of the genetic (DNA) analysis is to collect a single DNA sample at week 0 as specified in the TES to search for genetic factors that may influence molecular effects, clinical efficacy, or tolerability of guselkumab and to identify genetic factors associated with psoriasis. Participation in this study is optional. Only subjects who sign the consent form to participate in the genetic assessment will have whole blood DNA samples collected.

Note: One additional blood sample for biomarker assessments will be taken at the time when the subject loses control of disease (defined as PASI >5 at any visit during Study Part 2 or 3 = R0).

Altogether, these substudies will provide crucial information about possible subject-optimized guselkumab treatment algorithms and may relate immunopathological mechanisms to clinical course and characteristics of plaque psoriasis.

3.2. Study Design Rationale

Dose rationale
A dose regimen of guselkumab 100 mg at weeks 0, 4 and q8w thereafter was selected for Study Part 1. This is the dose regimen, which is known to result in clinically meaningful improvement of the disease (SmPC TREMFYA®). In Study Part 2, subjects with a PASI score=0 at weeks 20 **and** 28 will be randomly assigned to either guselkumab 100 mg q8w or q16w to evaluate if these subjects maintain their disease control (absolute PASI score <3 at week 68) under extended dosing intervals. A larger dosing interval would provide higher comfort and better economy for subjects and physicians.

Duration of treatment period and whole study period
This study will have a 4-week screening phase, a 60-week treatment phase and a 12- to 160-week safety follow-up phase (depending on whether subjects are participating in Study Part 3). The duration of the regular subject's participation allows for an adequate treatment period and provides sufficient time to perform follow-up on safety and maintenance of response.

Blinding and randomization
Randomization will be used to minimize bias in the assignment of subjects to guselkumab 100 mg q8w or q16w (Study Part 2), to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Double-blinded treatment (Placebo treatment at weeks 28, 44 and 60 for subjects assigned to guselkumab 100 mg q16w) will be used to reduce potential bias during data collection and evaluation of the endpoints. Week 28 was chosen as the time for randomization because it allows subjects to reach steady-state

guselkumab concentrations with a q8w dosing regimen as well as steady-state clinical response. Randomization will be stratified by disease duration at baseline (≤2 years vs. >2 years) and by participation in the mechanistical substudy 1 to allow for evaluation of similarities or differences regarding the response rates.

Biomarker and DNA collection

Besides assessing clinical parameters, biomarker and DNA samples will be collected to further evaluate i) the MoA and molecular effects of guselkumab, ii) psoriasis pathogenesis including differences between >2 years and ≤2 years disease duration, and iii) inter-individual variability in clinical outcomes. Furthermore, population subgroups may be identified who respond differently to guselkumab (iv).

Serum samples will be collected in all subjects (mandatory) to assess pharmacodynamic markers associated with the response to guselkumab (substudy 3). Skin biopsies and blood for immunophenotyping of PBMCs will be only collected in a subgroup of subjects who consent to participate in the optional biomarker substudies 1 or 2. The goal of these biopsy substudies is to analyze immunological parameters and biomarkers, and to compare the results between subjects with long and short disease duration before starting, during and after withdrawal of the treatment with guselkumab.

Whole blood samples will be collected for genetic analyses in those subjects who sign the consent form to participate in the genetic (DNA) assessment. It is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain inter-individual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect DNA to allow identification of genetic factors that may influence the pharmacodynamics, efficacy, or tolerability of guselkumab and to find genetic factors associated with psoriasis.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 4 weeks before administration of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following two subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.1.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female with at least 18 years of age.
2. Has a disease duration of plaque psoriasis of either ≤2 years or >2 years calculated from date at which first symptoms [plaque] were reported by subject to date of screening visit at screening; approximately 40% subjects must have a disease duration ≤2 years.
3. Has moderate-to-severe plaque-psoriasis defined by a) a PASI score >10 or affected BSA >10%

   and b) additionally a DLQI score >10 at baseline (week 0).
4. Is a candidate for systemic treatment for psoriasis.

Reproduction-related inclusion criteria

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 subjects in clinical studies.

5. Before first administration of study drug, a woman must be (as defined in Attachment 5):
   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 agrees to remain on a highly effective method method while receiving study treatment and until 12 weeks after last dose - the end of relevant systemic exposure. Examples of highly effective methods of contraception are located in Attachment 5.
6. A woman of childbearing potential must have a negative urine pregnancy test at baseline and agree to urine pregnancy testing before receiving injections and at safety follow-up.
7. 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.
8. A male subject must wear a condom when engaging in any activity that allows for passage of ejaculate to another person.

9. A male subject 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 study treatment.

10. **TB-related inclusion criteria:**

    Subjects are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB before screening.
       - an exception is made for subjects 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 study drug,
         - or have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study drug.

       Note: It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and to provide appropriate documentation.

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

    c. Have 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 drug.

    d. Within 2 months before baseline, have a negative QuantiFERON®-TB Gold test result, or have 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 baseline. Within 2 months before baseline, a negative tuberculin skin test, or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before baseline, is additionally required if the QuantiFERON-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

       Note: The QuantiFERON-TB Gold test and the tuberculin skin test are not required at baseline for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; subjects with a documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

    e. Have a chest radiograph (posterior-anterior and lateral views, or per country regulations where applicable), taken within 3 months before the first administration of study drug and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

11. Agrees not to receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study drug.

12. Agrees not to receive a BCG vaccination during the study, or within 12 months after the last administration of study drug.

13. **Clinical laboratory-related inclusion criteria:**
Has screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:
    a. Hemoglobin ≥10 g/dL (SI: ≥100 g/L)
    b. White blood cells ≥3.5 x 10^3/μL (SI: ≥3.5 GI/L)
    c. Neutrophils ≥1.5 x 10^3/μL (SI: ≥1.5 GI/L)
    d. Platelets ≥100 x 10^3/μL (SI: ≥100 GI/L)
    e. Serum creatinine ≤1.5 mg/dL (SI: ≤137 μmol/L)
    f. Aspartate aminotransferase ≤2 × upper limit of normal (ULN)
    g. Alanine aminotransferase ≤2 × ULN
    h. Alkaline phosphatase ≤2 × ULN

Other inclusion criteria:

14. Agrees to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources during study.
15. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
16. 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.
17. Must sign a separate ICF if he or she agrees to provide an optional DNA sample or skin biopsy samples for research (where local regulations permit). Refusal to give consent for the optional substudies does not exclude a subject from participation in the main study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from study participation:

Medical history-related exclusion criteria:

1. Has a clinically active psoriasis arthritis (PsA) which needs systemic therapy beyond NSAIDs at baseline (week 0).
2. Has a diagnosed or reported history or current signs or symptoms indicating severe, progressive, or uncontrolled hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances, which are detected at screening assessments (i.e., laboratory testing, physical examination, vital signs) or reported by the subject.
3. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) or a cardiac hospitalization within the last 3 months, diagnosed or reported by the subject.
4. Has a transplanted organ (exception: a corneal transplant >3 months before first study drug).
5. 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.

6. Is pregnant, nursing, or planning a pregnancy (both men and women) while enrolled in this study and within 16 weeks following the last administration of study drug.
7. Has a non-plaque form of psoriasis (eg, erythrodermic, guttate, or pustular).
8. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
9. Had major surgery, (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or will not have fully recovered from surgery at baseline, or has surgery planned during the time the subject is expected to participate in the study.

   Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
10. Had a substance abuse (drug or alcohol) problem within the previous 12 months.
11. Had a known allergy or sensitivity to products containing latex.

Concomitant or previous medical therapies-related exclusion criteria:

12. Has previously received any therapeutic agent directly targeted to IL-23 (including but not limited to guselkumab, tildrakizumab [MK3222], risankizumab [BI-655066])
13. Has received any anti-TNF-α biologic therapy within 3 months before the first administration of study drug.
14. Has received any therapeutic agent directly targeted to IL-12/23, IL-17A or IL-17R within 3 months of the first administration of study drug (including but not limited to ustekinumab, ixekizumab [LY2439821], brodalumab [AMG 827], or secukinumab).
15. 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 study drug.
16. Has received any systemic immunosuppressant (eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus, fumaric acid esters), or anakinra within 4 weeks of the first administration of study drug.
17. 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 and analogues, psoralens, sulfasalazine, hydroxyurea, apremilast, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study drug.
18. Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study drug.

19. Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or has received lithium, antimalarials, or IM gold within 4 weeks of the first study drug administration.
20. 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 first study drug administration or is currently enrolled in another study using an investigational agent or procedure.
21. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug.
22. Has had a BCG vaccination within 12 months of screening.
23. 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.
24. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure).

Infections or predisposition to infections-related exclusion criteria:

25. 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 non-remitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.
26. Has a history of active granulomatous infection before study start, including histoplasmosis or coccidioidomycosis. Refer to Inclusion Criterion 10 for information regarding eligibility with a history of latent TB.
27. Has a chest radiograph within 3 months before the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB.
28. Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis). Subjects with a history of esophageal candidiasis or thrush would also be exceptions to this criterion.
29. Has persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB® Gold test results. Indeterminate results should be handled as described in Section 9.1.2.1.
30. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody).
31. Tests positive for hepatitis B virus (HBV) infection or who are seropositive for antibodies to hepatitis C virus (HCV), unless they have 2 negative HCV RNA test results 6 months apart after completing antiviral treatment and prior to baseline and have a third negative HCV RNA test result at baseline.
32. Has or has had a serious infection (eg, sepsis, pneumonia, pyelonephritis), was hospitalized or received intravenous antibiotics for an infection during 2 months before baseline.
33. Has or has had herpes zoster within the 2 months before baseline.

Malignancy or increased potential for malignancy-related exclusion criteria:

34. Currently has a known malignance or has a history of malignancy within 5 years before study start (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study drug administration).
35. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

Other exclusion criteria:

36. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
37. Lives in an institution on court or authority order.
38. Has a condition that, in the opinion of the investigator, would participation not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
39. 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.
40. **Criterion added per Amendment 4:**
    Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:

    o During the 6 weeks prior to baseline, 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, patients may be included with a documented negative result for a validated SARS-CoV-2 test (direct detection methods)

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

    AND

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

    NOTES on COVID-related exclusion:

    Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during study participation

NOTES:
Investigators should ensure that all study enrollment criteria have been met at baseline. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Prior to randomization at week 28 and again prior to entering Study Part 3 at week 68 exclusion criterion 1 (subject has a clinically active psoriasis arthritis which needs systemic therapy beyond NSAIDs) has to be re-evaluated and subjects with diagnosed PsA who need systemic therapy beyond NSAIDs are to be excluded from further participation in the trial.

SRe who already had their regular final study visit at week 116 before Study Amendment 5 was implemented and have not yet completed the study for more than 12 weeks, will be asked by the investigator if they want to participate in the long-term extension (LTE) follow-up phase defined by Amendment 5. All SRe with PASI ≤5 at week 116 are allowed to enter LTE with the first visit in week 128 (12 weeks after last study visit). In case of PASI >5 at week 128, it will be possible to start re-treatment according to protocol. Subjects who have previously used an antipsoriatic medication prohibited by the protocol are not allowed to continue after week 116.

Section 17.4 describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the entire course of the study to be eligible for participation:

1. Refer to Section 8 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. Subjects must 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 baseline until the last dose of study drug.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation/ Procedures for Randomization

Central randomization will be implemented in Study Part 2. Eligible subjects (confirmation by physician needed that the subject achieved a PASI score=0 at weeks 20 and 28) will be randomly assigned to one of two guselkumab treatment groups (ratio 1:1) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. The randomization will be balanced by using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

Subjects will be equally stratified in study group 2a and 2b during randomization for i) disease duration of ≤2 or >2 years (note: disease duration will be calculated from date at which first

symptoms (plaque) were reported by subject to date of screening visit) and ii) for participation in substudy 1. Definitions when to stop/pause recruitment of subjects with longer disease duration will be provided in a separate document.

It is expected that about 280 of the subjects included in Study Part 1will be categorized as SRe and thus be eligible for central randomization in Study Part 2. However, this number is not fixed but can be slightly exceeded if potential SRe are still in Part 1. To limit the number of subjects in Study Part 2 recruitment might be stopped before the limit of 900-1000 subjects in Study Part 1 has been reached but might also be extended if less than 280 subjects are likely to be defined as SRe.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (eg, treatment allocation, study drug preparation/accountability data and administration of study drug) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock (DBL) and unblinding. Under normal circumstances, the blind should not be broken for subjects, investigators, or site personnel until the end of the study and database lock.

In Study Part 3 starting at week 68 throughout week 220, subjects, investigators and site personnel will remain blinded towards their injection interval (q8w or q16w) in Study Part 2. The sponsor will be unblinded after DBL at week 68 to conduct the analysis of the primary endpoint.

Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the treatment code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these subjects will be based upon consultation of the investigator with the medical monitor.

In general, randomization codes will be disclosed fully only if the study is completed, and the clinical database is closed. However, since analyses are planned for each study part, the randomization codes and, if required, the translation of randomization codes into treatment groups will be disclosed to those authorized and only for those subjects included in the different analyses.

6. DOSAGE AND ADMINISTRATION

A guselkumab-prefilled syringe assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) device, designed to deliver a single, fixed dose of 100 mg and a matched PFS-U containing Placebo will be used. Products will be labeled in a blinded manner; it will not be possible to differentiate between active and Placebo-prefilled syringes.

For **Study Part 1** all enrolled subjects will receive one injection of guselkumab according to the TES, ie at weeks 0, 4, 12, and 20.
Subjects with a PASI score=0 at weeks 20 and 28 are qualified for randomization in Study Part 2. In case of PASI score >0 at weeks 20 or/and 28, subjects will continue to get guselkumab 100 mg q8w with last administration in week 60.

Randomized subjects of **Study Part 2** (study group 2a and 2b) will receive one injection of either guselkumab or matching Placebo solution for injection (ie, identical to guselkumab in color, smell, and shape) according to the following schemes:

- Study group 2a: guselkumab 100 mg q8w, ie at weeks 28/36/44/52/60
- Study group 2b: guselkumab 100 mg q16w, ie guselkumab at weeks 36 and 52; Placebo at weeks 28/44/60 (guselkumab and placebo will be provided blinded, IWRS will assure correct assignment).

Subjects of groups 2a and 2b with a PASI score <3 at week 68 are qualified for entering **Study Part 3** and will be withdrawn from the study medication.

Subjects of groups 2a,2b, 3a and 3b losing control of disease, defined as PASI score >5 at any visit of Study Parts 2 or 3 (ie, until week 220), will enter the re-treatment arm with guselkumab 100 mg q8w for further 3 administrations (starting at that visit = re-treatment week 0, followed by administration at re-treatment-weeks 8 and 16). The final efficacy assessment for all subjects in the re-treatment arms will take place 24 weeks after loss of control and study termination will be 28 weeks after loss of control (final study visit). Subjects with fluctuating disease (ie, PASI score 3 to 5) or PASI >5 (subjects losing control of disease) at week 68 will also get the opportunity to enter the re-treatment-arm.

All study procedures should be completed prior to administering the study drug. Sub-cutaneous injections should be administered by qualified study site staff during the study visit, if possible. However, in cases where a site visit is not possible, subjects who have appropriate experience or have received required training may self-administer study drug at the times instructed by the investigator. Study site staff must ensure that those subjects have the appropriate experience or have received the required training to perform self-administration of SC injections.

Self-administration at home is only allowed subsequent to performance of a phone or video visit. Application of study drug at home can also be performed by a Home Health Care service provider if agreed by the sponsor, investigator and subject.
During this virtual visit, site staff will perform safety evaluations according to protocol, ensure assessment of PRO instruments and efficacy assessments (video/photo assessment of applicable lesions) as far as possible, prior to (self-)administration of the investigational product.

Randomization to part 2a/b is only possible (in case of Super-Responder) if week 20 and week 28 efficacy assessments have been done on-site, otherwise the subjects will enter part 2c.

If laboratory tests are to be performed at this scheduled visit, the blood draw for safety monitoring (hematology and chemistry) can be postponed to the next visit or, if the investigator deems it medically necessary, performed in a local certified laboratory.

For women of childbearing potential, a negative pregnancy test must be available. The patient should confirm self-administration to the site in a timely manner and will be asked by the site personnel for administration-related and injection site reactions. Self-administration cannot take place on 2 consecutive visits.
Site personnel and subjects will remain blinded to the treatment assignments until the last subject completes week 220 evaluations and the database has been locked.

During the safety follow-up period (week 68 through Week 72 for group 2 c, week R24 through week R28 of the re-treatment arm or in case of prematurely stop of study treatment 12 weeks after the last application of study drug), concomitant treatments for psoriasis may be administered at the investigator's discretion as follows:
The Investigator may continue treatment with guselkumab or switch to another commercially available treatment. Due to the half-life of guselkumab, it is recommended not to start a new therapy other than commercially available guselkumab during safety follow-up period. If the investigator feels strongly that another therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

7. TREATMENT COMPLIANCE

Each administration of study drug performed at a study visit will be recorded in the subject's source documents, with the assistance of a staff member at the study site who will be supervising study drug administration at these visits. For any study drug administration performed by the subject outside of a study site, subjects will keep the syringe carton and return the empty carton to the study site at their next visit. The subject will record the corresponding date and time of the administration in the study drug application card. Study site personnel will utilize subject's documentation to ensure compliance and record at-home study drug administrations in the eCRF.

Week 0 can be done once all screening activities are completed, results are available, and the subject is eligible, but latest 4 weeks after screening visit (+ 7 calendar days). From weeks 4 through week 68 it is expected that all visits will occur within a range of ±7 days. Any visits outside of these ranges should be discussed with the Sponsor. If a study visit occurs outside the specified visit window, the subject should then resume his or her normal dose schedule relative to the baseline visit (week 0) as soon as possible. Study visits in Study Part 3 should occur within ±14 days of the scheduled study visit. Visits during the re-treatment period (study groups 2d and 3c) are also expected to occur within a range of ±7 days. Any out-of-range visit should be documented in the subject's source notes and discussed with the sponsor.

Study-site personnel will maintain a log of all study drug administered. Drug supplies for each subject will be inventoried and accounted for. Information regarding study drug administrations that are administered outside of the scheduled windows or missed will be recorded. Subject charts and worksheets may be reviewed and compared with the data entries on the eCRF and IWRS to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

8. CONCOMITANT THERAPY

Concomitant therapies will be recorded until week 220 for subjects participating in all three study parts. For subjects of the re-treatment arm concomitant therapies will be recorded until 12 weeks after the last dose of study drug. For subjects not participating in Study Part 3, concomitant therapies should be recorded beyond week 72 only in conjunction with related serious adverse events (SAEs) that meet the criteria outlined in Section 12.3.2. All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from study drug, as well as all shampoos, moisturizers or emollients used to treat psoriasis, must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

If a prohibited therapy is administered during the (blinded) active treatment phase (ie, week 0 to week 68 – all subjects, whether SRe or not and re-treatment arms), discontinuation should be discussed with the Sponsor. If a prohibited therapy is initiated during weeks 68 to 220 (only SRe), the subject should still complete the final visit at week 220, and the medication should be recorded as a concomitant medication.

For non-SRe: If a prohibited therapy is initiated after the final efficacy assessments at week 68 and until the end of the safety follow-up at week 72, the subject should still complete the final safety follow-up visit at week 72 and the medication should be recorded as a concomitant medication.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Concomitant Medications for Treatment of Psoriasis

Topical Therapy

Topical therapies that could affect psoriasis or the efficacy evaluation (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methotrexat [MTX], pimecrolimus, tacrolimus, and traditional Taiwanese, Korean, or Chinese medicines) are not permitted at any time during the study until week 220 and during re-treatment to not confound the efficacy data (incl. Study Part 3). The only allowable concomitant treatments for psoriasis throughout the study are shampoos (containing tar or salicylic acid only) and topical moisturizers. The subject should not use these topical agents (shampoos, moisturizers) on the day of a study visit. Non-medicated shampoos may be used on the day of the study visit.

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 tumor necrosis factor α (including but not limited to infliximab, adalimumab, or etanercept), drugs targeted for reducing IL-12, IL-17A, IL-17R, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], ixekizumab [LY2439821], or brodalumab [AMG827]), JAK-inhibitors, alpha-4 integrin antagonists (including but not limited to natalizumab), apremilast, steroids, any conventional systemic therapy that could affect psoriasis or the efficacy evaluation (including but not limited to MTX, fumaric acid esters, cyclosporine, acitretin), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or systemic medication that could affect psoriasis or efficacy evaluation.

8.2. Concomitant Medications for Conditions other than Psoriasis

Every effort is to be made to keep subjects on stable concomitant medications if medically justified. If the medication is temporarily discontinued due to 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 medical records. 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. Lithium and antimalarial agents may not be used. 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, no longer than 2 weeks (cumulative) within six months. Longer use of corticosteroids should be discussed with the Sponsor and may require discontinuation of study drug. Inhaled, otitic, ocular, nasal, or other topical routes of mucosal delivery for corticosteroids are allowed throughout the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TES summarizes the frequency and timing of efficacy, immunogenicity, biomarker, pharmacogenomic and safety measurements applicable to this study. All subjects will be asked to sign the consent forms (main study and optional substudies) before any study-related procedures are conducted.

All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions (1st DLQI, 2nd PSSD, 3rd NAPPA-QoL, 4th NAPPA-PBI). The other efficacy assessment (PASI, BSA and NAPPA-CLIN) should be completed after the PROs but before any study drug administrations. Further general instructions see Attachment 4. An exception to this order is the start of a re-treatment arm at a visit, which does not require all PRO's needed at the visit week 0 of the re-treatment arm. In this case, PRO's will be obtained immediately after efficacy assessments (which is the basis for re-treatment-decision) and prior to drug administration at that visit.

Urine, blood and biopsy collections should be kept as close to the specified time as possible. Actual dates of assessments will be recorded in the source documentation and CRF. A urine pregnancy test will be performed to confirm the absence of pregnancy at every study drug administration visit. 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 subject's study participation.

The total blood volume for the study is approximately 230-330 mL (80-130 mL for safety, 30-40 mL for pharmacokinetics, 6 mL for pharmacogenomics, and 125-135 mL for biomarkers). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Details on required blood volume are provided below.

Table 9.1-1: Required Blood Volume per Subject

	average			incl. re-treatment arm		
Safety (including screening and posttreatment assessments)	**Volume per Sample (ml)**	**No. of Samples per subject**	**Total Volume of Blood (mL)**	**Volume per Sample (ml)**	**No. of Samples per subject**	**Total Volume of Blood (mL)**
Hematology	2	7	14	2	10	20
Chemistry	6	7	42	6	10	60
Serology (HBV, HCV, HIV)	6	1	6	6	1	6
HBV DNA testing[a]	3	1	3	3	1	3
TB testing	4	1	4	4	1	4
Pharmacokinetic/ Immunogenicity samples	7.5	4	30	7.5	5	37.5
Biomarkers (PBMCs)	16	5	80	16	5	80
Serum biomarkers[f]	8.5	5	42.5	8.5	6	51
Genetic (DNA) sample[b]	6	1	6	6	1	6
SUM Safety			**69**			**93**
Approximate Total[c,d,e]			**221.5**			
Approximate Total incl. Re-treatment[c, d, e]						**261.5**

Calculated as number of samples multiplied by amount of blood per sample.
a. Performed only in subjects who test positive for core HBV antibody.
b. Blood samples will be collected only from subjects who have consented to provide optional DNA samples for research.
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
d. Total blood increases by appx. 6 ml for subjects who consent to participate in the optional genetic substudy.
e. Total sum calculated for patients taking part in substudy 1 and 2.
f. For SRe, a maximum of 3 additional samples are planned between week 116 and 220.

The recording of AEs and concomitant medications will start after the signing of the informed consent and will continue until the last study-related procedure has been completed. Concomitant therapies will be recorded until week 220 for subjects participating in all three study parts. For subjects not participating in Study Part 3 concomitant therapies will be recorded beyond week 72 (or 12 weeks after last administration of study drug in case of early discontinuation) only if they are in conjunction with SAEs that meet the criteria outlined in Section 12.3.2.

Throughout the study, it is important to monitor subjects for TB. Instructions for screening for TB are provided in Section 9.1.2.1; instructions for early detection of active TB are provided in Section 9.6.

9.1.2. Screening Phase

All subjects will have a screening visit that will occur approximately 4 weeks before their week 0 visit. The screening phase is designed to assess inclusion/exclusion criteria and to establish baseline characteristics for a subject's psoriasis. Subjects will undergo screening for TB (see Section 9.1.2.1), HBV (see Attachment 3) and antibodies to HCV and HIV. Each subject will be asked to sign the consent form(s) at screening before any study-related procedures are conducted.

9.1.2.1. TB screening

As outlined in the eligibility criteria, all subjects must be questioned about a history of TB or other personal exposure to individuals with active TB. Potential subjects should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. With the exception of subjects with a history of appropriately treated latent TB within 5 years before the first administration of study drug (Inclusion Criterion 10), subjects must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. Interferon-gamma-release-assay (IGRA) TB-testing, i.e. QuantiFERON®-TB Gold test (Manuel und Kumar 2008) will generally be performed by the central laboratory. However, if available, test results from local laboratory can be accepted.

Investigators should screen for latent TB if they believe, based on their judgment, that the use of the test is clinically indicated in order to evaluate a subject who has high risk of having latent TB. If the QuantiFERON-TB Gold test is positive, the subject is considered to have latent TB infection for the purposes of eligibility for this study.

Subjects with a negative QuantiFERON-TB Gold test result are eligible for study participation. Subjects with a newly identified positive QuantiFERON-TB Gold test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects.

A subject 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 subject should be excluded from the study.

9.1.2.2. Screening Failure/Rescreening

If the subject has not met all inclusion criteria or met any exclusion criteria during the screening phase or is unable or unwilling to adhere to the prohibitions and restrictions of the study, the subject is considered to be a screening failure and is not eligible for study participation at that time.

Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once. Eligibility may be reassessed using a single unscheduled visit during screening.

In general, if a subject is a screening failure but at some point in the future meets all of the eligibility criteria, the subject may be re-screened after a new informed consent has been obtained. Subjects who are re-screened will be assigned a new subject number and will restart a new screening phase. Re-screening will be permitted once.

9.1.3. Study Part 1: Open-label Treatment Phase

Study Part 1 will be a 28-week open-label, run-in period. All visit procedures will be performed as specified in the TES. All study procedures and evaluations are to be completed before administration of study drug. From weeks 0 to 28 it is expected that all visits will occur within a range of ±7 days.

All subjects who prematurely stop taking the study drug should complete the early termination visit (ETV) as listed in the TES. After ETV, safety follow-up should be conducted for 12 weeks after the last administration of study drug. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety evaluations as listed in the TES.

9.1.4. Study Part 2: Double-blind Treatment Phase

Subjects with a PASI score=0 at weeks 20 and 28 will be defined as SRe and are qualified for randomization in study group 2a or 2b. Following randomization via IWRS at week 28, eligible subjects will continue into the double-blind treatment period, with visits to be conducted every 8 weeks. The final study agent injection will take place at week 60, final assessments will be made at week 68.
Subjects starting a prohibited psoriasis treatment do have to complete a safety follow up visit at week 72 visit or 12 weeks after last dose of guselkumab, whichever comes first. It is expected that all visits in the double-blind treatment phase will occur within a range of ±7 days. All study procedures and evaluations are to be conducted before administration of study drug. For further details on study agent administration, refer to Section 6.

Subjects not eligible for participation in the double-blind treatment period will continue to receive guselkumab 100 mg q8w until week 60 (last administration at week 60 visit) with final study assessments at week 68 and final safety follow-up visit at week 72.

All subjects who prematurely stop taking the study drug should complete the ETV and 12 weeks later the safety follow-up. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety evaluations.

9.1.5. Study Part 3: Drug Withdrawal phase

Study Part 3 starts for subjects from group 2a and 2b after the assessments at week 68 which qualify the subject for this part. No study treatment is applied during the drug withdrawal phase. Topical therapies that could affect psoriasis, phototherapies or systemic antipsoriatic medications are not permitted at any time during the study until week 220 or week 248 (in case of re-treatment starting at week 220). Subjects starting a prohibited psoriasis treatment will still have to complete the week 220 visit.
Visits are to be conducted every 12 weeks within ±14 calendar days of the anticipated visit date. In between the 12-weekly on-site visits, a telephone-visit 6 weeks (± 7 days) will be done after each on-site visit (ie, telephone visits at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206) to assess whether the subject notices a worsening of his/her psoriasis. If so, the subject must attend an on-site visit for efficacy assessment by the assessor as soon as possibly but not later than 2 weeks after the phone call. The week 220 visit should be conducted at least 160 weeks following the last study agent injection.

9.1.6. Re-treatment Phase

Subjects losing control of disease, defined as PASI score >5 at any visit during Study Parts 2 or 3 (ie, until week 220), will enter the re-treatment arms (groups **2d** or **3c**) with three guselkumab 100 mg administrations starting at that visit (= re-treatment week 0, followed by administration at re-treatment weeks 8 and 16).

If re-treatment is started at a visit, which would usually not require all PROs needed at the re-treatment visit week 0, those PROs will be obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

The final efficacy assessment for all subjects in the re-treatment arms will take place 24 weeks after loss of disease control and study termination will be 28 weeks after loss of disease control (final study visit/safety follow-up). At visit week 24 of the re-treatment, the investigator may continue actual treatment with commercially available guselkumab (ie, not provided by the Sponsor) to maintain a q8w interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period (ie, 12 weeks after last dose). If the investigator feels strongly that an additional therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

Subjects with fluctuating disease (ie, PASI score 3 to 5) at the week 68 visit will also get the opportunity to enter the re-treatment-arm (**3c**). The last chance to start re-treatment will be the visit week 220.

9.2. Efficacy Evaluations

Efficacy evaluations chosen for this study are consistent with those utilized to evaluate other therapies for psoriasis. Efficacy evaluations include:

- Psoriasis Area and Severity Index (PASI)
- Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA-CLIN)
- Psoriasis-affected Body Surface Area (BSA)
- Dermatology Life Quality Index (DLQI) [PRO]
- Psoriasis Symptom and Sign Diary (PSSD, 7-day version) [PRO]
- Nail associated quality of life and patient- relevant treatment benefit (NAPPA-QoL/-PBI) [PRO]
- Target Lesion Severity Score (TLSS; only for subjects participating in substudies 1 and 2).

9.2.1. Efficacy Assessor Assessments

The efficacy assessor assessments (PASI, NAPPA-CLIN, BSA) will be performed at the site by an efficacy assessor trained by the Sponsor and at the appropriate visits as outlined by the TES.

Efficacy assessments should preferably be done by a dermatologist but if a dermatologist is not available, a health care provider with at least 1 year of experience in performing the efficacy assessments (PASI, NAPPA-CLIN, BSA) may serve as efficacy assessor. Health care providers with less than 1 year of experience may serve as an efficacy assessor based upon the discretion and approval of the Sponsor.

The Sponsor will provide PASI, NAPPA, BSA training prior to the screening of the first subject at each site. If the efficacy assessor was trained by the Sponsor in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study. However, repeat training prior to start of the study is encouraged. Training documentation of each efficacy assessor should be maintained at the study site. All efficacy assessors at a site must be listed on the delegation log.

9.2.1.1. 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 (Feldman, et al. 1996). In the PASI system, the body is divided into four 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 from 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.

9.2.1.2. Nail Assessment in Psoriasis and Psoriatic Arthritis

The NAPPA is an instrument for assessing clinical and patient-reported outcomes in nail psoriasis (Augustin, et al. 2014). It comprises three components:

1. NAPPA-QOL is a 20-item nail-specific quality of life (QoL) questionnaire covering the past week. Signs, stigma and everyday life are rated on a scale from 0 (no suffering) to 4 (high suffering). A global score is computed by averaging all items.
2. NAPPA-PBI is a 24-item questionnaire to assess patient-defined needs before and patient-rated benefits after treatment. The answers are given on a scale from 0 to 4, and a global score is calculated as follows: Each benefit item is multiplied with the respective importance item, and the product is divided by the sum of all importance items. The results are summed up over all items. The resulting global score ranges from 0 (no benefit) to 4 (highest possible benefit).
3. NAPPA-CLIN is an instrument used by the physician to assess the least and the worst involved nail of both hands or both feet with scores ranging from 0 to 16.

9.2.1.3. Psoriasis-affected Body Surface Area

The percentage of the psoriasis-affected body surface area (BSA %) is a system used for assessing the severity of psoriasis (Ramsay und Lawrence 1991). The plaque coverage is estimated using the rule of palm (1 palm of the hand = 1% BSA).

9.2.1.4. Target Lesion Severity Score

The target lesion severity score (TLSS), also known as target plaque severity score (TPSS), documents the physician's assessment of a subject's target psoriasis lesion according to the following categories: induration, scaling, and erythema. Every effort should be made to ensure that the physician or designee who performed the TLSS evaluations for a subject at randomization performs the TLSS for that subject at all subsequent visits. A description of the TLSS is provided in Attachment 1.

9.2.2. Patient-reported Outcomes

PROs will be assessed in the following order: 1st DLQI, 2nd 7-day version of PSSD, 3rd NAPPA-QoL and 4th NAPPA-PBI), The questionnaires will be completed on paper sheets at the site by subjects at the appropriate visits as outlined by the TES. Data collected on the paper sheets will be handled as source data and will be transferred into the eCRF by the site staff.

9.2.2.1. Dermatology Life Quality Index

The DLQI is a dermatology specific QoL instrument designed to assess the impact of the disease on a patient's QoL. It is a 10-item questionnaire that, in addition to evaluating overall QoL, can be used to assess six different aspects that may affect QoL: 1) symptoms and feelings, 2) daily activities, 3) leisure, 4) work or school performance, 5) personal relationships, and 6) treatment (Finlay und Khan 1994). Each question is scored from 0 to 3, giving a possible score range from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL).

9.2.2.2. Psoriasis Symptom and Sign Diary

The PSSD is a questionnaire designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit (Feldmann, et al. 2016). The PSSD is a patient self-administered outcomes instrument that includes 11 items covering symptoms (itch, pain, stinging, burning and skin tightness) and patient observable signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) using 0 to 10 numerical rating scales for severity. Two subscores each ranging from 0 to 100 will be derived: the psoriasis symptom score and the psoriasis sign score. A higher score indicates more severe disease.

A change of ≥40 points in PSSD symptom score or sign score, and a ≥3-point change in individual PSSD item scale scores will be defined as clinically meaningful change (response). In this study, the 7-day-version of the PSSD will be used.

9.3. Pharmacokinetics (PK)

Venous blood samples will be collected at the points in time shown in the TES for the determination of serum guselkumab concentrations. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

Each sample will be divided into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as back-up sample). Samples must be collected before study drug administration. The exact dates and times of blood sampling must be recorded in the laboratory requisition form. The samples will be shipped to the central lab and analyzed (i) after the completion of Study Part 1 (after week 28 visit) and (ii) after completion of the study including the re-treatment arm for analysis of the respective secondary endpoints.

Subject confidentiality will be maintained. See the Laboratory Manual for further information regarding collection, handling, and shipment of biological samples. The sponsor, or its designee, will assay these samples using a validated, specific, and sensitive immunoassay method under conditions in which the subjects' identity remains blinded.

Note: One additional blood sample for PK assessments will be taken at the time when the subject loses control of disease (PASI score >5 at any visit of Study Parts 2 or 3, or PASI ≥3 at week 68). However at R0, PK-samples will only be taken for Study Part 2d (ie, not for Study Part 3c).

9.4. Biomarkers

The samples will be collected according to the points in time specified in the TES. Guidelines and specifications for sample collection and shipment information are provided in the Laboratory Manual.

Immunophenotyping of PBMCs

Whole blood samples will be collected from subjects who are enrolled by the sites selected for **substudy 1**. Measurements include the quantity of different PBMCs. Immunophenotyping of PBMCs will be performed using flow cytometry by sites with expertise to conduct FACS-based cellular immunophenotypic characterization of freshly isolated blood cells. Subjects' identity will remain blinded.

Immunophenotyping of skin biopsies

6 mm biopsies will be collected from subjects who are enrolled by the sites selected for **substudy 1**. Measurements include the quantity of Th17, Tc17 non-TRM T cells, TRM T cells, Tregs and antigen presenting cells. Immunophenotyping of skin biopsies will be performed using flow cytometry by sites with expertise to conduct FACS-based cellular immunophenotypic characterization of freshly isolated biopsies. Subjects' identity will remain blinded.

Gene expression analysis of skin biopsies

Skin biopsy samples will be collected according to the Time and Events Schedule from a subset of subjects who consent to participate in **substudy 2**. Each 6 mm biopsy will be split in two parts; one part will be stored for RNA gene expression analysis, while the other part will be frozen in OCT and stored for H&E, IHC and IF analyses. If two 3 mm biopsies have been taken instead of the 6 mm biopsy, one 3 mm biopsy will be stored in RNAlater for RNA preparation and gene expression analysis, while the other 3 mm biopsy will be frozen in OCT and stored for H&E, IHC and IF analyses.

The samples will be shipped to the central lab and analyzed later under conditions in which the subjects' identity remains blinded.

Serum biomarkers

Serum samples of approximately 8.5 mL will be collected from all subjects to assess PD markers associated with the response to guselkumab as well as markers related to psoriasis (**substudy 3**). Measurements will include but are not limited to serum IL-17A, IL-17F, IL-22 levels and beta defensin. Detection and characterization of cytokines will be done using various immune assays.

9.5. Pharmacogenomic (DNA) Evaluations

At week 0, a single whole blood sample of approximately 6 mL will be collected from a subset of subjects who consent to participate in **substudy 4**. The goal of the pharmacogenomic (DNA) analysis is to search for genetic factors that may influence molecular effects, clinical efficacy, or tolerability of guselkumab and to identify genetic factors associated with psoriasis. They will be performed using validated assay methods by or under the supervision of the Sponsor.

DNA samples will be used for research related to guselkumab. They may also be used to develop tests/assays related to guselkumab. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome in relation to guselkumab.

9.6. Safety Evaluations

Safety and tolerability of guselkumab will be monitored until 12 weeks after last administration of study drug by collecting information on AEs, including injection site and allergic reactions, clinical laboratory tests (hematology, chemistry and pregnancy testing), physical examinations, vital signs, concomitant medication review, and early detection of tuberculosis (TB), as specified in the TES. Subjects participating in Study Part 3 and not treated in the re-treatment arm will be monitored through week 220 by collecting information on AEs, including injection site and allergic reactions, vital signs, weight, and concomitant medication review. 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 endpoint is reached.

In cases of self-administration of SC study intervention at home, subjects are requested to contact their treating physician as soon as possible to consider reporting of an adverse event.

Clinical laboratory safety monitoring may be performed at a certified local laboratory identified by the study site rather than at the central laboratory; for selected measures (eg, urine pregnancy), home testing may be employed.

The study will include the following safety evaluations:

Adverse Events
AEs will be reported by the subject for the duration of the study. AEs will be followed by the investigator as specified in Section 12.

Injection Site Reactions
An injection site reaction (ISR) is any unfavorable or unintended sign that occurs at the study drug injection site. After administration of study drug at week 0, all subjects will be carefully observed at the study site for at least 30 minutes after the SC injection of study drug for symptoms of an ISR. If an ISR is observed, the subject should be treated at the investigator's discretion. Any adverse reaction (eg, pain, erythema, induration) should be noted on the AE page of the eCRF.

Allergic Reactions
Subjects must be observed carefully for symptoms of an allergic reaction (e.g., rash, urticaria, itching, shortness of breath, or drop in blood pressure) for at least 30 minutes after the study drug injection. If an allergic reaction is observed, treatment should be administered according to standard practice. Any allergic reaction should be noted on the AE page of the eCRF.

Clinical Laboratory Tests

Blood samples for hematology, serum chemistry and serology will be collected. The investigator must review the results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory values should be followed as clinically appropriate or until they return to normal or are otherwise explained by the investigator. Laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory:

- **Hematology Panel**:
  - hemoglobin
  - hematocrit
  - red blood cell (RBC) count
  - platelet count
  - white blood cell (WBC) count
    - lymphocytes (%, absolute)*
    - monocytes (%, absolute)*
    - neutrophils (%, absolute)*
    - eosinophils (%, absolute)*
    - basophils (%, absolute)*
- **Serum Chemistry Panel**:
  - sodium
  - potassium
  - chloride
  - blood urea nitrogen (BUN)
  - creatinine
  - glucose
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - gamma-glutamyltransferase (GGT)
  - total bilirubin
  - magnesium
  - alkaline phosphatase (AP)
  - creatine phosphokinase (CPK)
  - lactic acid dehydrogenase (LDH)
  - uric acid
  - calcium
  - phosphate
  - albumin
  - total protein
  - cholesterol
  - triglycerides
- **Serology**: Samples for HIV antibody, hepatitis B (see Attachment 3) and hepatitis C virus antibodies will be obtained at screening.
- **Urine Pregnancy Testing** for women of childbearing potential will be done at screening and at the times shown in the TES. Pregnancy tests must be completed and negative at the study visit prior to administration of study drug. All pregnancy test results must be recorded in study source documents.

Vital Signs

Blood pressure and heart rate measurements will be assessed as specified in the TES. If any clinically significant changes in vital signs are noted, they must be reported as AEs and followed to resolution, or until reaching a clinically stable endpoint.

Physical Examination

Physical examinations will be performed by body systems, eg, eyes, ears/nose/throat, head/neck/thyroid, heart, lung, chest, abdomen etc., by the investigator or designated physician, nurse practitioner or physician assistant as specified in the TES. Total body skin examination will be performed to determine the presence of any suspected malignant skin lesions including basal cell carcinoma, squamous cell carcinoma, and melanoma. In addition, the study agent injection site is to be evaluated. Any new, clinically significant finding must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Body height and weight
Body height and weight will be measured as specified in the TES. Subjects will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

Concomitant Medication Review
Concomitant medications will be reviewed and reported at each visit. A list of restricted and prohibited concomitant medications is provided in Section 8.

Early Detection of Active Tuberculosis
To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits. 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 subject 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 subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects 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 (a repeat tuberculin skin test in countries in which the QuantiFERON-TB Gold test is not approved/ registered or the tuberculin skin test is mandated by local health authorities) and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during the investigation. 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. The QuantiFERON-TB Gold test will generally be performed by the central laboratory. However, if available, test results from local laboratory can be accepted.

If recommended, treatment for latent TB must be initiated prior to or simultaneously with the administration of further study agent. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and be encouraged to return for all subsequent scheduled study visits according to the TES.

9.7. Sample Collection and Handling

Actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the TES 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.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed Study Part 1 if he or she has completed assessments at the week 28 visit. A subject will be considered to have completed Study Part 2 if he or she has completed the assessments of week 68. A subject will be considered to have completed Study Part 3 if he or she has completed assessments at week 220 or re-treatment (week 24/28 SFU). Subjects entering the re-treatment arms (2d or 3c) will be considered to have completed the re-treatment arm if he or she has completed assessments at week 24 visit after start of re-treatment.

10.2. Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment before the end of the treatment regimen.

A subject's study treatment must be permanently discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject shows no response to study treatment at week 28, defined as no change or worsening of PASI score at week 28 in comparison to week 0.
- The subject becomes pregnant.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject 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.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result and/or an indeterminate QuantiFERON-TB Gold test result on repeat testing (refer to Section 9.6) (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities). Indeterminate QuantiFERON-TB Gold test results should be handled as described in Section 9.6.

  - A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The subject initiates a protocol-prohibited medication, eg, for a worsening of his or her psoriasis (unless agreed to by the medical monitor).
- The subject withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements.
- The subject develops an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study drug administration.
- The subject 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 study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Discontinuation of study treatment should be considered for subjects who develop a serious or opportunistic infection. Discussion of such subjects with the medical monitor or designee should also be considered.
- Discontinuation of study treatment for abnormal liver tests is required by the investigator when a subject meets one of the conditions outlined in Appendix 8A or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the subject.

  Refer to Appendix 8B for follow-up assessments (and study treatment restart guidelines) following abnormal liver test results. Study Sponsor must provide written approval before study intervention is restarted.

Subjects who decide to discontinue study drug administration must be interviewed by the investigator to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the possible contribution of AEs to their decision to discontinue study drug; investigators should confirm that any AE information elicited has been documented. If a subject elects to discontinue study drug due to an AE, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the AE would not require study drug discontinuation. The reason for study drug discontinuation must be documented in the eCRF and in source documents. Study drug assigned to a subject who discontinues may not be assigned to another subject.

If a subject discontinues study treatment for any reason before his or her last scheduled injection, he or she should return for the remaining regularly scheduled study visits for at least 12 weeks after receiving the last administration of study drug.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death.

To ensure access for subject follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from subjects (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the subject at study start.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good subject relationships to avoid withdrawals of consent. For subjects who truly request withdrawal of consent, it is recommended that the subject withdraw consent in writing; if the subject or the subject's representative refuses to do so or is physically unavailable, the study site should document the reason for the subject's failure to withdraw consent in writing, sign the documentation, and maintain it with the subject's source records.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of week 68 early termination visit (ETV) assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the subject's original separate informed consent for optional research samples.
- The subject may withdraw consent for optional research samples in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the Sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the substudy representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5). In that case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

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 (SAP). The SAP may be divided in three separate documents describing the analyses for the three study parts.

The statistical analyses in this study will be performed separately for each Study Part and will focus on the comparison of the two randomized treatment groups (ie, **2a**: guselkumab 100 mg q8w vs. **2b**: guselkumab 100 mg q16w) in Study Part 2. The analyses will be confirmatory for the primary endpoint, and exploratory for the major secondary endpoints and for all other secondary endpoints.

Descriptive statistics will include counts and proportions for categorical data, and mean, SD, median, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data. The two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used to compare the proportion of subjects responding to treatment. Continuous response parameters will be compared using an analysis of variance model with fixed effects for treatment group and disease duration and baseline value as a covariate. Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event. The confirmatory significance level for non-inferiority testing is fixed to a one-sided α=0.05. Besides the confirmatory testing of the primary endpoint all other inferential statistical testing (including calculation of confidence intervals) are to be interpreted in the exploratory sense only.

11.1. Subject Information

Descriptive statistics by treatment group will be provided for subject dispositions, demographics, baseline disease characteristics, and prior and concomitant medications. Details will be provided in the SAP.

11.2. Sample Size Determination

This randomized, double-blind, parallel-group, multicenter phase 3b trial is designed to demonstrate that guselkumab 100 mg q16w treatment is non-inferior to guselkumab 100 mg q8w treatment in SRe as assessed by the proportion of subjects with an absolute PASI score <3 at week 68. A non-inferiority margin of 10% was chosen based on a minimally clinically meaningful difference. This margin was also used in CNTO1959PSO3009 (ECLIPSE) study and is therefore considered a valid approach for evaluating non-inferiority of a new treatment.

The null hypothesis H_0 and the alternative hypothesis H_A are formulated as follows:

- H_0: $P_T - P_S \leq -10\%$ ('inferiority')
- H_1: $P_T - P_S > -10\%$ ('non-inferiority')

where P_T and P_S denote the proportions of subjects with an absolute PASI score <3 at week 68 in the guselkumab 100 mg q16w treatment arm (P_T = proportion test treatment) and the guselkumab 100 mg q8w treatment arm (P_S = proportion standard treatment).

Based on data from CNTO1959PSO3002 the proportion of subjects with an absolute PASI score <3 at week 68 is assumed to be 90% for guselkumab 100 mg q8w. The expected difference in proportions between the treatment groups (guselkumab 100 mg q16w minus guselkumab 100 mg q8w) is 0%.

According to current international guidance documents (CPMP, Points to consider on switching between superiority and non-inferiority 2001) the intent-to-treat analysis set and the per-protocol analysis set should have equal importance in a non-inferiority trial and their use should lead to similar conclusions for a robust interpretation.

Therefore, the sample size estimation using the power approach is performed for the per-protocol analysis set as described below. No formal adjustment of the significance level is necessary (CPMP, Points to Consider on Multiplicity Issues in Clinical Trials 2002).

When the sample size in each group is 112, a two-group large-sample normal approximation Wald Z-test of proportions with a one-sided 0.05 significance level will have 80% power to reject the null hypothesis that the guselkumab 100 mg q16w treatment is inferior to the guselkumab 100 mg q8w treatment (the difference in proportions, $P_T - P_S$, is $\leq -10\%$) in favor of the alternative hypothesis that the guselkumab 100 mg q16w treatment is non-inferior to the guselkumab 100 mg q8w treatment (the difference in proportions is > -10%), assuming that the expected difference in proportions is 0 and the proportion in the guselkumab 100 mg q8w treatment group is 90% (nQuery Advisor® 7.0).

Considering routine clinical conditions it is assumed that a rate of about 20% randomized subjects will not be evaluable for the per-protocol analysis in Study Part 2. Thus, 280 subjects (140 subjects per treatment group) are planned to be randomized in a ratio of 1:1 to meet the required sample size of 224 subjects (112 subjects per treatment group) for the per-protocol analysis.

Based on data from CNTO1959PSO3001 and CNTO1959PSO3002, it is anticipated that approximately 35% of enrolled subjects in Study Part 1 will be eligible for randomization at week 28 in Study Part 2. Thus, a total of 800 subjects should be enrolled in Study Part 1 to ensure that at least 280 subjects are eligible for randomization in Study Part 2. Accounting for a 10% drop-out rate of subjects ineligible for randomization at week 28 because of study discontinuation prior to week 28, it is therefore planned to enroll a total of 888 subjects in Study Part 1.

Note: Screenings and enrollments will be adjusted if necessary (without protocol amendment) to achieve 280 SRe at week 28. Ongoing subjects in Study Part I will continue to Part II if eligible, irrespective of whether or not 280 SRe are already randomized. Only screenings will be closed.

11.3. Efficacy Analyses

Analysis Data Set

The efficacy analyses will be performed separately for each Study Part. For all efficacy analyses to compare guselkumab 100 mg q16w vs. guselkumab 100 mg q8w in Study Part 2, all randomized subjects at week 28 will be included.

In Study Part 2 subjects will be analyzed according to the treatment group to which they were randomized regardless of the treatment they actually received (intent-to-treat analysis set).

The per-protocol analysis set will consist of all subjects in the intent-to-treat analysis set terminating the study without any major deviation of the protocol and its procedures. Subjects with major protocol deviations will be excluded from the per-protocol analysis.
The confirmatory analysis of the primary endpoint variable will be performed both for the intent-to-treat analysis set and the per-protocol analysis set.

In Study Part 1 and Study Part 3 all subjects treated with at least one dose of study drug will be included in the efficacy analyses. For all efficacy analyses in Study Part 1 and Study Part 3, subjects will be analyzed according to the treatment they actually received.

Primary Endpoint

The proportion of subjects with an absolute PASI score <3 at week 68 will be displayed in a frequency table providing the number and percentage of subjects. Graphical presentation will be presented by means of a bar chart.

To test the non-inferiority of guselkumab 100 mg q16w to guselkumab 100 mg q8w with a non-inferiority margin of 10% in Study Part 2, a one-sided (α=0.05) two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used. The Mantel-Haenszel estimate, the two-sided 90% Wald-type confidence limits, and the test for the difference of proportions will be computed by using Mantel-Haenszel stratum weights (Mantel und Haenszel 1959) and the Sato variance estimator (Sato 1989). Non-inferiority will be accomplished when the lower limit of the two-sided 90% confidence interval for the difference in response rates (guselkumab 100 mg q16w minus guselkumab 100 mg q8w) will be > -10% both for the intent-to-treat analysis and the per-protocol analysis.

Non-responder imputation will be applied for subjects with missing data for the primary endpoint as described in Section 11.11.

Major Secondary Endpoints

The major secondary endpoints will comprise the endpoints as defined in Section 2.1.2. Statistical analyses will be descriptive and exploratory only.

The proportion of subjects responding to treatment will be displayed in frequency tables providing the number and percentage of subjects. Graphical presentation will be presented by means of bar charts. In Study Part 2 the two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used to compare the proportion of subjects responding to treatment. The Mantel-Haenszel estimate, the two-sided Wald-type 90% confidence limits, and the test for the difference of proportions in Study Part 2 will be computed by using Mantel-Haenszel stratum weights (Mantel und Haenszel 1959) and the Sato variance

estimator (Sato 1989). Exploratory statistical analyses of response parameters in Study Part 1 and Study Part 3 will be performed analogously, as appropriate.

Non-responder imputation will be applied for subjects with missing data for the major secondary endpoints as described in Section 11.11. Details will be provided in the SAP.

Other Secondary Endpoints

The other secondary endpoints will comprise the endpoints as defined in Section 2.1.2. Statistical analyses will be descriptive and exploratory only.

The proportion of subjects responding to treatment will be displayed in frequency tables providing the number and percentage of subjects. Graphical presentation will be presented by means of bar charts. For continuous response parameters absolute values and changes from baseline will be summarized by descriptive statistics and box and whisker plots.

In Study Part 2 the two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used to compare the proportion of subjects responding to treatment. The Mantel-Haenszel estimate, the two-sided 90% Wald-type confidence limits, and the test for the difference of proportions in Study Part 2 will be computed by using Mantel-Haenszel stratum weights (Mantel und Haenszel 1959) and the Sato variance estimator (Sato 1989). Continuous response parameters in Study Part 2 will be compared using an analysis of variance model with fixed effects for treatment group and disease duration and baseline value as covariate. Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event. Exploratory statistical analyses of response parameters in Study Part 1 and Study Part 3 will be performed analogously, as appropriate. Details will be provided in the SAP.

Non-responder imputation (for binary endpoints) or Last Observation Carried Forward (LOCF) imputation (for continuous endpoints) will be applied for subjects with missing data for the other secondary endpoints as described in Section 11.11.

Criteria for Endpoints

Treatment failure: Subjects who discontinue study agent due to lack of efficacy, an AE, worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study period that could improve psoriasis are considered treatment failures. Treatment failure rules (TFR) will be applied after week 68 for a separate analysis. The treatment failure rules will be documented in detail in the SAP.

PASI 75 Responders:	Subjects with ≥75% improvement in PASI from baseline at week 28
PASI 90 Responders:	Subjects with ≥90% improvement in PASI from baseline at week 28
PASI 100 Responders	Subjects with 100% improvement in PASI from baseline at week 28
Maintenance of control of disease	Subjects with a PASI score <3
Fluctuating disease:	absolute PASI score 3 to 5
Loss of disease control	absolute PASI score >5

11.4. Pharmacokinetic Analyses

Serum guselkumab concentrations at specified visits will be summarized by efficacy response status.

Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each sampling time. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system dataset. The BQL concentrations will be treated as zero in the summary statistics.

If data permit, the relationships between serum guselkumab concentration and efficacy or serum biomarker level may be analyzed graphically.

11.5. Biomarker Analyses

Biomarker samples outlined in Section 9.4 will be used to define serum markers, skin gene expression and cellular profiles for correlation analyses to better understand:

1.) The mechanism of action and the molecular effects of guselkumab

2.) The pathogenesis of psoriasis including the differences between >2 years and ≤2 years disease duration

3.) Inter-individual variability in clinical outcomes

Furthermore, population subgroups may be identified who respond differently to guselkumab.

These analyses are considered exploratory and will be summarized in a separate technical report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.6. Pharmacogenomic Analyses

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response, maintenance of response, relapse, and non-response.

These analyses are considered exploratory. Details of the analysis plan and summary of results from pharmacogenomics analyses will be reported separately.

11.7. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs (TEAEs) will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred terms (PT).

Analysis Data Set

The safety analyses will be performed separately for each Study Part. For all safety analyses, all subjects treated with at least one dose of study drug will be included. For all the safety analyses, subjects will be analyzed according to the treatment they actually received.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using MedDRA. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious AE.

The following analyses will be used to assess the safety of subjects in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of infections.
- The incidence and type of reasonably related AEs.
- The incidence and type of injection site reactions.
- The laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. In addition, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades will be used in the summary of laboratory data. A listing of subjects with postbaseline abnormal laboratory results based on NCI-CTCAE grades will also be provided. Descriptive statistics will be calculated for each laboratory item at baseline and for observed values and changes from baseline at each scheduled point in time. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges) at selected points in time. Listings of subjects with any laboratory results outside the reference ranges or any markedly abnormal laboratory results will be provided.

Vital Signs

Descriptive statistics of pulse/heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits (specified in the SAP) will be summarized.

Physical Examination

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.8. Other Analyses

Stratified Newcombe confidence limits for the common proportion difference with respect to the primary endpoint will also be provided by using the method of Yan and Su (Yan und Su 2010).

In addition, the primary endpoint will also be analyzed without adjustment for disease duration ('unadjusted analysis'). The two-group large-sample normal approximation Z-test ('asymptotic

Wald test of noninferiority') along with the two-sided 90% Wald type and Newcombe confidence interval will be computed.

For binary endpoints in Study Part 2 counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), two-sided 90% confidence intervals and p-values for treatment comparison based on Mantel-Haenszel weights adjusted for disease duration will be provided.

The change from baseline of continuous endpoints in Study Part 2 will be analyzed by an analysis of covariance model (ANCOVA) with the fixed effect factors for treatment group and disease duration and the baseline value as covariate. The Least-Squares means (LS means), the LS mean difference and the standardized mean difference (computed according to Hedges' g) with the two-sided 90% CI will be provided from the ANCOVA model.

Statistical analyses for time to event endpoints in Study Part 2 will provide the median time-to-even estimates per treatment group with two-sided 90% confidence intervals and the hazard ratio (including two-sided 90% confidence interval) calculated from Cox-regression with the factors treatment group and disease duration as covariate.

Exploration of possible heterogeneity of treatment effects across centers for the primary endpoint will be performed by descriptive frequency statistics including graphical display of the results of the individual centers, as appropriate. No pooling of centers will be performed.

11.9. Statistical Analyses per Study Part

Statistical analyses will be performed for each Study Part.

The confirmatory analysis is planned to be performed at the end of Study Part 2, ie, after all subjects have completed their visit at week 68 (ie, 40 weeks after randomization) or discontinued earlier. This analysis will include the confirmatory analysis of the primary endpoint, and the exploratory analyses of the major secondary endpoints and all other predefined efficacy and safety analyses from week 28 until week 68.

The analyses of Study Part 1 and Study Part 3 will be exploratory. The exploratory analysis of Study Part 1 will occur after all subjects have completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis will include the safety analysis and all efficacy measures after week 0 and will cover the time until the week 28 visit. The exploratory analyses of Study Part 3 will occur after all subjects have completed their visit at week 116 (ie, 48 weeks after inclusion in Study Part 3 at week 68) or week 144 in case of subjects entering the re-treatment arm in week 116, at week 164 (ie, 96 weeks after inclusion in Study Part 3 at week 68) and at week 220 (ie, 152 weeks after inclusion in Study Part 3 at week 68), or week 248 in case of subjects entering the re-treatment arm in week 220 or discontinued earlier.

These analyses will include the safety evaluations and all efficacy measures after week 68, and will cover the time until week 116/164/220 and until week 144/192/248, respectively.

11.10. Subgroup and Sensitivity Analyses

Subgroup analyses are planned to be performed according to disease duration (≤2 and >2 years) and pre-treatment (systemic naïve/experienced, biologic naïve/experienced) for all endpoints.

Sensitivity analyses are planned to be performed with respect to the applied statistical procedure (see Section 11.9) and by applying different imputation rules for missing data (see Section 11.11).

Additional subgroup analyses, eg. age, gender, baseline PASI, and sensitivity analyses may be performed and will be specified in the SAP. Multiple logistic regression analysis may be used to investigate the relationship between potential prognostic or risk factors and a single binary outcome variable (eg, influence of age or PK-level on SRe in Study Part 1).

11.11. Handling of Missing Data

All available data will be included in the analyses and will be summarized as far as possible. If not otherwise specified, there will be no substitution of missing data, ie, missing data will not be replaced, missing data will be handled as ‘missing’ in the statistical evaluation (‘observed cases analysis’).

Non-responder imputation will be applied for subjects with missing data for the primary endpoint at week 68 as described below:

Subjects who do not maintain control of disease (absolute PASI score ≥ 3) or subjects who discontinue study treatment during the study before week 68 will be considered non-responders for the primary endpoint at week 68. In addition, subjects who do not return for evaluation at week 68 will be considered non-responders at week 68.

Non-responder imputation for the other binary endpoints will be performed analogously.

For continuous response parameters, the last available observation after baseline will be calculated and used for analysis in case of premature termination (Last Observation Carried Forward approach; LOCF).

LOCF may also be used as sensitivity analysis for binary response parameters. Treatment failure rules (TFR) will be applied after week 68 for a separate analysis. Additional sensitivity analyses may be done by applying different imputation rules for missing data (eg, 'multiple imputation'). An 'observed cases analysis' for all binary and continuous endpoints without substitution of missing data may also be used. A more detailed description of the handling of missing data will be provided in the SAP.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures (SOPs) 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational-) product. An AE does not necessarily have a causal relationship with the treatment. An AE 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 Council for Harmonization- [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 Section 12.3.1 for time of last AE recording).

Serious Adverse Event

A serious AE (SAE) 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 subject 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 subject or may require intervention to prevent any of the other SAE outcomes listed above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug 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).

Unlisted (Unexpected) Adverse Event/Reference Safety Information
An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics (SmPC TREMFYA®).

Adverse Event Associated With the Use of the Drug
An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related
An AE that is not related to the use of the drug.

Doubtful
An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely
An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by de-challenge and re-challenge).

12.1.3. 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 subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Accidental or occupational exposure to a Sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a Sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject exposure to product)
- Exposure to a Sponsor study drug from breastfeeding.

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. 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 subject's last study-related procedure, which may include contact for follow-up of safety. SAEs, including those spontaneously reported to the investigator within 12 weeks after the last dose of study drug, must be reported using the SAE Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, 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 on relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

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. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Subjects 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 subject 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 staff only)
- Site number and subject number
- Any other information that is required to do an emergency breaking of the blind.

12.3.2. 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 SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject'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 study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject 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 an SAE.

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.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study within 12 weeks of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects 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 SAE Form. Any subject who becomes pregnant during the study must be promptly discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study agent in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3. 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 an SAE.

12.5. 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.

13. 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 subjects, 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.

13.1. 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 an SAE, the study-site personnel must report the PQC to the Sponsor according to the SAE reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The guselkumab supplied for this study is sterile liquid for SC injection in a single-use PFS assembled with the PFS-U. Each single-use PFS-U contains 100 mg (1 mL fill of liquid) guselkumab in a 1 mL glass syringe with a 27-gauge, 1/2 inch fixed needle and a latex-free rigid needle shield. No preservatives are present. The guselkumab solution should be essentially free of visible particulate matter. Guselkumab will be manufactured and provided under the responsibility of the Sponsor. Refer to the Investigator's Brochure for a list of excipients.

Placebo is supplied as a sterile liquid for SC injection at a fill volume of 1 mL in a single-use PFS assembled with the PFS-U. Each PFS-U contains 10 mM L-histidine, 8.5% (w/v) sucrose, and 0.055% (w/v) polysorbate 80 at pH 5.8.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Guselkumab and Placebo will be supplied to the study sites. All study drug must be stored at controlled temperatures ranging from 2°C to 8°C (36°F to 46°F) and protected from exposure to light. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during dose preparation or administration of guselkumab.

Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Study drug in PFS will be ready to use. Aseptic procedures must be used during the preparation and administration of the study material. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

Study drug 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. Any study subject who will be self-administering study drug at home will receive detailed instructions on how to store study drug, disposal of used syringes, and handling of unused study material. Subjects will receive a sharps container to dispose of used syringes and will be instructed to return cartons to the study site. Subjects will record the time and date of study drug administration in the study drug application card.

Unused study drug must be available for verification by the Sponsor's study site monitor during on-site monitoring visits. The return to the Sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense study drug from, nor store it at, any site other than the study sites agreed upon with the Sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- SmPC for guselkumab
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- PRO questionnaires
- IWRS Manual
- eDC Manual
- Sample ICF (including substudy ICFs and Photo-documentation ICF)
- Sample genetic research for ICF, as applicable
- Biopsy Manual (for biopsy substudy sites only)
- Photo-documentation manual.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects 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 (228 - 268 mL) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study. As scheduled, the phlebotomy is highly unlikely to induce anemia or other blood volume-related complications.

16.2. Regulatory Ethics Compliance

16.2.1. 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. 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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure 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 drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct).

At the end of the study, the investigator (or Sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICFs (main and optional substudies) must be signed before performance of any study-related activity. The ICFs that are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the subject 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 subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 subject will receive for the treatment of his or her disease. Subjects 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 subject 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 subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject 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 subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

At some sites, subjects 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 subject 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 subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 subjects confidential.

The informed consent obtained from the subject 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 subject 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.

Exploratory DNA, PD, and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, 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 subjects 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 data.

16.2.5. 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 psoriasis, to understand differential drug responders, and to develop tests/assays related to guselkumab and 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. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 subjects, 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) involves 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. Data recorded in the CRF and source documents will reflect any departure from the protocol, and source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the Sponsor before shipment of study drug to a 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, subject 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 subject:

- 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, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness. The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify participating subjects by an anonymized subject identification number and the age at initial informed consent.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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: subject 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; drug receipt/ dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug 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 minimum source documentation requirements for Section 4.1 and Section 4.2 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 subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the Sponsor for each subject in electronic format. 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.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements will be completed by the same individual who made the initial baseline determinations whenever possible.

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.

17.6. 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.

17.7. 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 subject, 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 administration in an ICH region and until there are no pending or contemplated marketing administrations 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.

17.8. Monitoring

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). 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 study progress at the site.

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the Sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. 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 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 subjects by the investigator
- Discontinuation of further study drug development.

17.10. 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. Subject 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding guselkumab or the Sponsor's operations (eg, patent administration, 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 pharmacogenomic or 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 as 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 subject 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 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 administration. 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 substudy 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, 18 months after 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 conception or to the 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 and the results of clinical studies as required by law.

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Attachment 1: Assessment of Induration. Erythema and Scaling for Target Lesion Severity Score (TLSS) and Investigator's Global Assessment (IGA)

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

TLSS and IGA 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 $\leq$1.49, score = 1; if total $\geq$ 1.50, score = 2.

Attachment 2: 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. 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, trunk, upper extremities, and lower extremities, 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) are: 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:

- The neck is considered part of the head
- The axillae and groin are part of the trunk
- 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, A = area, h = head, t = trunk, u = upper extremities, and l = lower extremities

Attachment 3: Hepatitis B Virus (HBV) Screening with HBV DNA

Subjects must undergo screening for hepatitis B virus (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):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Subjects 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.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects 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 subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For subjects 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.			

Attachment 4: Instructions for the Completion of PRO Assessments

The following instructions are intended to assist investigators, study coordinators, and those with monitoring responsibilities with the accurate completion of all the PRO questionnaires. It is important for sites to be familiar with the TES to ensure subjects complete the PROs at the correct setting and visit. Please refer to the PRO Completion Guide for further information.

SITE RESPONSIBILITIES (GENERAL)

- For this study, we expect that it will take approximately 15 minutes for the subjects to be trained and complete the PROs that are intended to be completed during site visits.
- Never copy PROs from other sources (eg, websites); use only the PROs provided.
- Ensure subject completes the PROs before any clinical assessments are done or results are provided in the following order: 1st DLQI, 2nd 7-day version of PSSD, 3rd NAPPA-QoL and 4th NAPPA-PBI
- Please have the subject complete the PROs in the same order each time.

PREPARING THE SUBJECT

- Instruct subjects to complete all PRO questionnaires using a blue or black ballpoint pen.
- Explain that all the information on the PROs is confidential, and that someone from the study staff will only check for completeness and not share the results with other clinical staff.
- Explain to subjects the reasons why they are being asked to complete the PROs, ie, they are part of the overall medical assessment and are designed to find out more information about how having their disease has affected their life.
- Allow as much time as the subject needs to orient themselves and complete all PROs.
- Instruct the subjects to:
  - Read the instructions for each questionnaire carefully.
  - Note the recall period for each questionnaire.
  - Complete all PROs; Instruct the subject not to skip any questions/or questionnaires.
- Subjects must interpret questions and complete the PROs without input from anyone. If asked for help interpreting or completing the PROs by the subject, please simply reply that there are no right or wrong answers and he/she should use his/her best judgment to complete each question (based on what the subject thinks the question is asking).
- Do not attempt to interpret or explain the instructions, questions, or response options.
- If the subject has difficulty choosing between 2 response options, simply state "choose the answer that most closely matches your experience."
- Provide a quiet, private or semi-private location for the subject to complete the PROs.
- Ensure subjects have access to study staff for questions.

QUALITY CONTROL

- Complete the subject number, visit date and time on every PRO questionnaire.
- Before the subject leaves:
  - Check for any questions that might have been skipped/left blank.
  - If an item has been skipped, point this out to the subject and ask them to complete.
  - If an item has more than one response, ask the subject to reconsider the question and try to choose the answer that most closely matches their experience.

SPECIAL ISSUES

- Subjects should be instructed to complete the PROs without input from anyone. However, if a subject cannot read the PROs or complete it/them independently (eg, due to visual impairment, limited literacy, or difficulty with pens), then a designated person can read the items and response choices aloud and mark the appropriate response choices as verbally stated by the subject.
- The designated person should read each question in its entirety in a neutral voice, avoiding any cues, even if interrupted by the subject with an answer. The designated person should repeat each of the subject's answers, eg, "A little bit." The subject should not be prompted by the designated person in any other way. No help should be offered to the subject in interpreting the questionnaire.
- If a person is designated to assist the subject with the PROs, this person should remain consistent across assessment questionnaires and across assessment periods.
- If a designated person assists the subject with the PROs, this should be noted in the Footer section on the first page of each PRO assessment instrument.

Attachment 5: Contraception

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.
- **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.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT (**PREFERRED** METHOD) **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) or Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(provided that the partner is the sole sexual partner and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is ~ 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –Oral / intravaginal / transdermal / injectables
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] –Oral / injectable
• Sexual abstinence *(only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated.)*
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 subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Attachment 6: Guidance on Study Conduct during the COVID-19 Pandemic

BACKGROUND

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

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If at any time a subject's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely, virtually, or will be delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes will be communicated to the sites and health authorities according to local guidance.

If a subject has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer or designee to discuss plans for study intervention and follow-up.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Study Interventions and Assessments

Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak; therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

Administration of Study Medication

In cases where a site visit is not possible under restrictions and limitations due to the COVID-19 pandemic, subjects may self-administer subcutaneous (SC) injections of study intervention outside a study site (eg, at home). Those subjects will receive instructions on compliance, storage, disposal of used syringes, handling of unused study material, and adverse event reporting. Self-administration on site under supervision of site personal is also allowed.

Notes on Shipment of Study Intervention to Subjects

If it is necessary to ship the study drug directly to study subjects, shipment by the study site itself is preferred under this exception due to the COVID-19 pandemic. Shipment should be made in a manner that allows tracking of both transport and delivery. The subject 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 drug), direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider as trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymization and, if necessary, blinding of subjects to the sponsor using appropriate measures. Both the transport and handover conditions for study drug should be part of the contractual arrangements, so that pharmaceutical drug safety of study drug as well as protection of the privacy and personal data of subjects are adequately safeguarded. The study drug must be delivered directly to the subject or a person authorized by the subject 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 drug to subjects, written instructions on storage and return of used and unused study drug should be provided to subjects. When shipped by study sites, the receipt, consumption and return of study drug supplies 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.

Study Assessments and Analyses

Missed Assessments

Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study drug and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

Other relevant study data elements impacted by the COVID-19 pandemic should also be documented/labeled as "COVID-19-related" 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.

Study Analyses

The Sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in the statistical analysis plan(s).

Attachment 7: Protocol Amendment History

This is the fourth global amendment. The summary of changes table for the current amendment is located after the Table of Contents (TOC). The summary of changes tables for the previous amendments are presented below:

Amendment 4 (15 June 2020)

Overall Rationale for the Amendment: To add an additional exclusion criterion for patients with confirmed or potential SARS-CoV-2 infection. Changes from COVID-19 related Amendment 3 were included in the full protocol.

Section Number and Name	Description of Changes and Brief Rationale
Synopsis; 6. Dosing and Administration	**Description of Change:** Added text to allow subcutaneous injections of study drug to be self-administered outside a study site, in cases where a study site visit is not possible, provided those subjects have appropriate experience or have received adequate training to perform self-administration of SC injections.
	Rationale: To provide flexibility of dose administration in cases where a study site visit is not possible.
5.2 Exclusion Criteria	**Description of Change:** Added exclusion criterion 40, to document exclusion of patients with confirmed or suspected SARS-CoV-2 infection or who have had close contact with a person with confirmed or suspected SARS-CoV-2 infection within 6 weeks before baseline and to provide COVID-19-related guidance on study participation and exclusion.
	Rationale: To exclude patients with confirmed or potential SARS-CoV-2 Infection.
7. Treatment Compliance; 14.5. Drug Accountability	**Description of Change:** Clarified documentation requirements for self-administration of study drug. Added text on documentation requirements and on storage, disposal of used syringes, and handling of unused study material for subjects who will be self-administering study drug at home.
	Rationale: To provide details on handling of study materials and documentation for self-administration of study drug by subjects in cases where a study site visit is not possible.
9.6 Safety Evaluations	**Description of Change:** Clarified adverse event reporting procedure for subjects who will be self-administering study drug at home.
	Rationale: To document adverse events for subjects in cases where a study site visit is not possible.
Attachment 6 - Guidance on Study Conduct During the COVID-19 Pandemic	**Description of Change:** Added attachment as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.
	Rationale: To provide guidance on study conduct and assessments during the COVID-19 pandemic

Amendment 3 (COVID-19 amendment) from 15 April 2020

Overall Rationale for the Amendment: To allow for self-administration of subcutaneous study intervention outside a study site (eg, at home), in cases where a study site visit is not possible under restrictions and limitations during the COVID-19 pandemic. Guidance on other aspects of study conduct during the COVID-19 pandemic is also included.

Section Number and Name	Description of Changes and Brief Rationale
Added Attachment 6-Guidance on Study Conduct During the COVID-19 Pandemic	**Description of Change:** Added attachment as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.
	Rationale: To provide guidance on study conduct and assessments during the COVID-19 pandemic.

Amendment 2 from 29 May 2019

Overall Reason: The overall reason for the amendment is the extension of study sites from only Germany to Germany and France.

Applicable Section(s)	Description of Change(s)
Rationale: Extension of study sites to France.	
Front page	*Janssen-Cilag is a regional organization that operates through different legal entities in **various countries** ~~Germany~~.
Synopsis-SUBJECT POPULATION	…Subjects must have moderate-to-severe plaque-type psoriasis defined by PASI >10 or affected body surface area (BSA) >10% and additionally a DLQI >10 ~~according to German S3 guidelines~~….
Synopsis-OVERVIEW of study design 3.1 Overview of study design	… subjects are therefore needed to be screened at up to ~~120~~ **90** German study sites **and 10 French study sites**…
Rationale: Clarification of allowed psoriasis treatment during the safety follow-up period	
Synopsis-Study Part 2: Week 28 through Week 68 3.1 Overview of study design	… **At visit week 68 (for group 2c), the investigator may continue treatment with commercially available guselkumab (ie. not provided by the sponsor) to maintain a q8 interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period. If the investigator feels strongly that an additional therapy is needed, this should be discussed with the sponsor before initiation of the new therapy**.

Applicable Section(s)	Description of Change(s)
6. Dosage and Administration	**During the safety follow-up period (Week 68 through Week 72 for group 2c, week R24 through week R28 of the re-treatment arm or in case of prematurely stop of study treatment 12 weeks after the last application of study drug), concomitant treatments for psoriasis may be administered at the investigator´s discretion as follows:** **The Investigator may continue treatment with commercially available guselkumab (ie. not provided by the sponsor) to maintain a q8 interval. Due to the half-life of guselkumab, it is recommended not to start a new therapy during safety follow-up period. If the investigator feels strongly that an additional therapy is needed, this should be discussed with the sponsor before initiation of the new therapy**.
Rationale: Two 3 mm biopsies may be taken instead of the 6 mm biopsy.	
Synopsis-Study Part 2: Week 28 through Week 68 3.1 Overview of study design	Substudy 2 (Gene expression substudy): … **Two 3 mm biopsies may be taken instead of the 6 mm biopsy if preferred by the investigator and consented by the patient. The splitting step is not applicable in that case.** …
Time and event schedule- Biomarker	Footnote m: …A total of **six** 6 **mm** biopsy samples **(or twelve 3 mm biopsy samples in sub 2 if appl., refer to Section 3.1)**. will be collected ….
9.4 Biomarkers	…. Each **6 mm** biopsy will be split in two parts; one part will be stored for RNA gene expression analysis, while the other part will be **frozen** ~~stored for~~ **in** OCT **and stored for** H&E, IHC and IF analyses. **If two 3 mm biopsies have been taken instead of the 6 mm biopsy, one 3 mm biopsy will be stored in RNAlater for RNA preparation and gene expression analysis, while the other 3 mm biopsy will be frozen in OCT and stored for H&E, IHC and IF analyses.** …
Rationale: A footnote is added to the Time and Event Schedule to improve clarity of the protocol.	
Time and event schedule- safety assessments	Footnote added to chest radiograph: **p: Only if no chest radiograph taken within the last 3 months before administration of first study drug is available.**
Rationale: Fumaric acid esters are added to exclusion criterion 16.	
4.2 Exclusion criteria	16. Has received any systemic immunosuppressant (eg, methotrexate, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus**, fumaric acid esters**), …

Applicable Section(s)	Description of Change(s)
Rationale: Definition added to be consistent with exclusion criterium 1	
4.2 Exclusion criteria Note	Prior to randomization at week 28 and again prior to entering Study Part 3 at week 68 exclusion criterion 1 (subject has a clinically active psoriasis arthritis **which needs systemic therapy beyond NSAIDs)** has to be re-evaluated and subjects with diagnosed PsA **who need systemic therapy beyond NSAIDs** are to be excluded from further participation in the trial.

Amendment 1 06 December 2018

The overall reason for the amendment: The overall reason for the amendment is the request of the responsible Health Authority (HA) to add a discontinuation criterium for patients showing no response to study treatment by week 28.

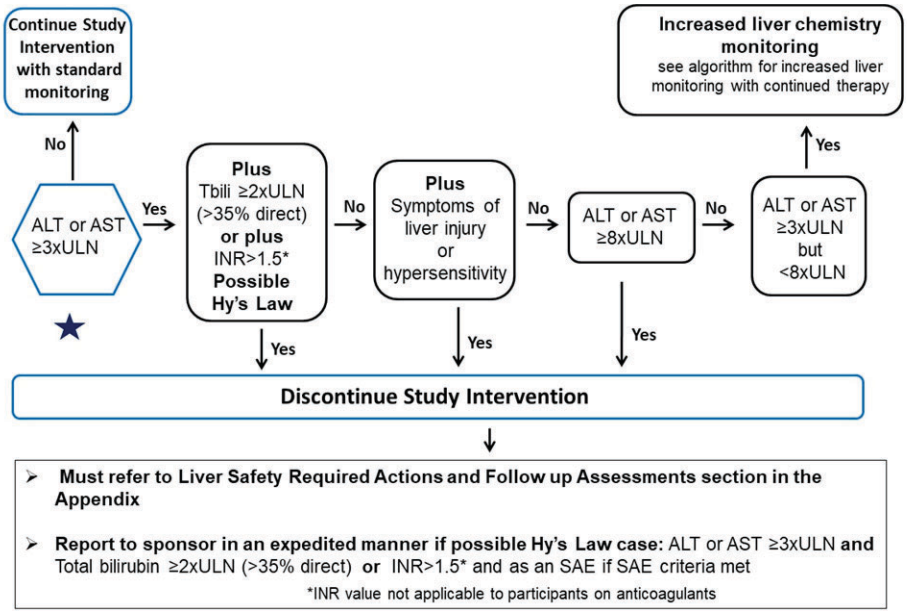
Applicable Section(s)	Description of Change(s)
Rationale: Addition of a discontinuation criterium for patients showing no response to study treatment by week 28 as requested by HA.	
10.2. Discontinuation of Study treatment	A subject´s study treatment must be permanently discontinued if: …. • **The subject shows no response to study treatment at week 28, defined as no change or worsening of PASI score at week 28 in comparison to week 0.** …..
Rationale: Inconsistencies are corrected in the Time and Event Schedule to improve clarity of the protocol.	
Time and event schedule	- Safety Assessments: Added missing **X** for Physical Examination at week 28 for SRe - Biomarkers: "**optional**" relocated from the header to substudy **1**,**2** and **4** - Week 72 (SFU): footnote added: *******: For all subjects (part 1 and part 2), who discontinue study treatment prematurely, every effort should be made to conduct the SFU visit 12 weeks after the last study drug administration.** - TES Re-Treatment: Skin biopsy **and blood sample for PBMC** for cellular substudy **(1)**[k] **(optional)** - To occur within **4** ~~3~~ weeks prior to week 0.

Attachment 8: Liver Stopping Criteria and Follow-up Assessments

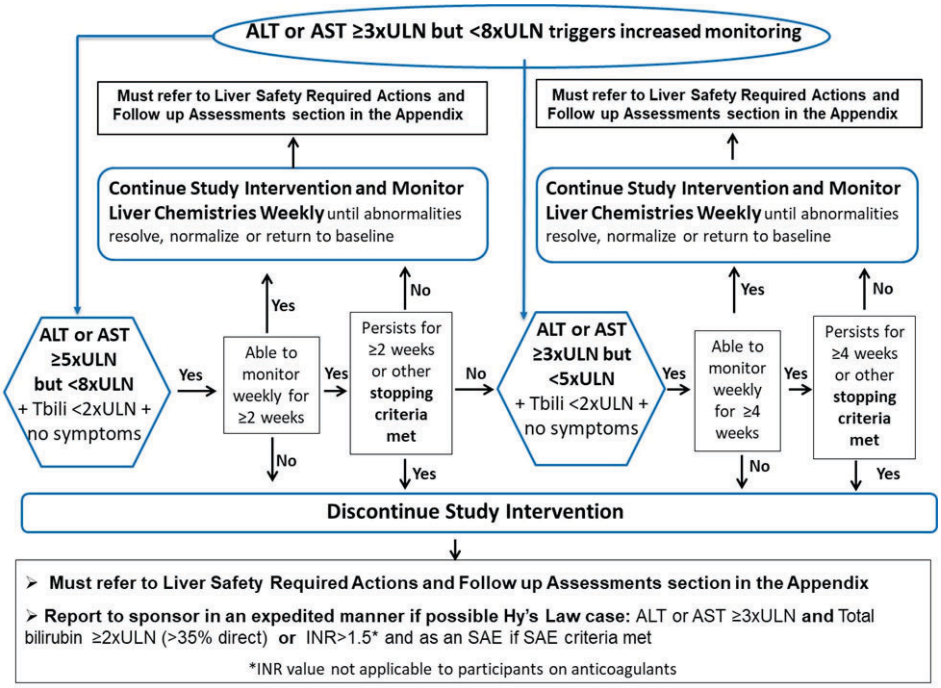
A: Liver chemistry stopping criteria and increased monitoring algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT or AST ≥3xULN but <8xULN



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 8 B: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines.

B: Liver chemistry stopping criteria and follow-up assessments

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Liver Chemistry Stopping Criteria and Follow-Up assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ≥8xULN
ALT or AST-Increase	ALT or AST ≥5xULN but <8xULN persists for ≥2 weeks ALT or AST ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT or AST ≥3xULN **and** international normalized ratio (INR) >1.5
Cannot Monitor	ALT or AST ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT or AST ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT or AST ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring, and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention • Report the event to the sponsor within **24 hours** • Complete the liver event reporting form and complete an SAE CRF if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline **MONITORING:** **If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT or AST≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and sponsor approval is granted	• Viral hepatitis serology[4] • Obtain blood sample for PK-analysis as quick as possible after the most recent dose[4] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], and glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event reporting form • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications) • Record alcohol use on the liver event alcohol intake form **If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week

• If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments	• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete the liver imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: – In patients when serology raises the possibility of autoimmune hepatitis (AIH) – In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In patients with acute or chronic atypical presentation • If liver biopsy conducted complete the liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT or AST ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are included in the pertinent Study Reference Manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT or AST ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR<1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR ALT or AST≥3xULN and <5xULN **and** total bilirubin <2xULN or INR<1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline • If at any time the participant meets liver chemistry stopping criteria proceed as described in the pertinent manual • If ALT or AST decreases from ALT or AST≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly • If, after 4 weeks of monitoring, ALT or AST<3xULN and total bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

References:

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology 2019; 70 (6):1222-1261.

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 drug, 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-Cilag GmbH, Neuss/ Germany

Signature: PPD Date: 14.06.2021

(Day Month Year)

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

Janssen-Cilag GmbH*

Clinical Protocol
Appendix - Guidance on Study Conduct during the COVID-19 Pandemic

Protocol Title
A Phase 3b, Randomized, Double-blind, Parallel Group, Multicenter Study to Evaluate Further Therapeutic Strategies with Guselkumab in Patients with Moderate-to-Severe Plaque-Type Psoriasis
GUIDE

Protocol CNTO1959PSO3012; Phase 3b
Amendment 3

TREMFYA® (guselkumab)

*Janssen-Cilag is a regional organization that operates through different legal entities in various countries. The legal entity acting as the Sponsor for Janssen-Cilag studies may vary, such as, but not limited to Janssen-Cilag International NV or Janssen Pharmaceuticals NV. The term "Sponsor" is used throughout the protocol to represent these various legal entities. The Sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2018-001238-16

Status: Approved
Date: 15 April 2020
Prepared by: Janssen-Cilag GmbH
EDMS number: EDMS-ERI-165008226

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 3 (COVID-19 Attachment)	15 April 2020
Amendment 2	29 May 2019
Amendment 1	06 December 2018
Original Protocol	05 July 2018

Amendment 3, 15 April 2020

Overall Rationale for the Amendment: To allow for self-administration of subcutaneous study drug outside a study site (eg, at home), in cases where a study site visit is not possible under restrictions and limitations during the COVID-19 pandemic. Guidance on other aspects of study conduct during the COVID-19 pandemic is also included.

Section Number and Name	**Description of Changes and Brief Rationale**
Added Attachment 6-Guidance on Study Conduct During the COVID-19 Pandemic	**Description of Change:** Added attachment as guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.
	Rationale: To provide guidance on study conduct and assessments during the COVID-19 pandemic.

BACKGROUND

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

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If at any time a subject's safety is considered to be at unacceptable risk, study drug will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely, virtually, or will be delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study drug, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes will be communicated to the sites and health authorities according to local guidance.

GUIDANCE SPECIFIC TO THIS PROTOCOL

If a subject has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer or designee to discuss plans for study drug and follow-up.

Study Medications and Assessments

Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak; therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

Administration of Study Medication

In cases where a site visit is not possible under restrictions and limitations due to the COVID-19 pandemic, subjects may self-administer subcutaneous (SC) injections of study drug outside a study site (eg, at home). Those subjects will receive instructions on compliance, storage, disposal of used syringes, handling of unused study material, and adverse event reporting. The specific protocol changes are documented below:

Dosage and Administration (Protocol Section 6.)

Sub-cutaneous injections should be administered by qualified study site staff during the study visit, if possible. To limit contact with the site, personal self-administration on site is also allowed. However, in cases where a site visit is not possible, subjects who have appropriate experience or have received required training may self-administer study drug at the times instructed by the investigator. Study site staff must ensure that those subjects have the appropriate experience or have received the required training to perform self-administration of SC injections.

Self-administration at home is only allowed subsequent to performance of a phone or video visit. Application of study drug at home can also be performed by a Home Health Care service provider if agreed by the sponsor, investigator and subject.

During this virtual visit, site staff will perform safety evaluations according to protocol, ensure assessment of PRO instruments and efficacy assessments (video/photo assessment of applicable lesions) as far as possible.

Randomization to part 2a/b is only possible (in case of Super-Responder) if week 20 and week 28 efficacy assessments have been done on-site, otherwise the subjects will enter part 2c.

If laboratory tests are to be performed at this scheduled visit, the blood draw for safety monitoring (hematology and chemistry) can be postponed to the next visit or, if the investigator deems it medically necessary, performed in a local certified laboratory.

For women of childbearing potential, a negative pregnancy test must be available. The patient should confirm self-administration to the site in a timely manner and will be asked by the site

personnel for administration-related and injection site reactions. Self-administration cannot take place on 2 consecutive visits.

Treatment Compliance and Drug Accountability (Protocol Sections 6.2.7 and 14.5.4)

Each administration of study drug performed at a study visit will be recorded in the subject's source documents, with the assistance of a staff member at the study site who will be supervising study drug administration at these visits. For any study drug administration performed by the subject outside of a study site, subjects will keep the syringe carton and return the empty carton to the study site at their next visit. The subject will record the corresponding date and time of the administration in the study drug application card. Study site personnel will utilize subject's documentation to ensure compliance and record at-home study drug administrations in the eCRF.

Any study subject who will be self-administering study drug at home will receive detailed instructions on how to store study drug, disposal of used syringes, and handling of unused study material. Subjects will receive a sharps container to dispose of used syringes and will be instructed to return cartons to the study site. Subjects will record the time and date of study drug administration in the study drug application card.

Notes on Shipment of Study Medications to Subjects

If it is necessary to ship the study drug directly to study subjects, shipment by the study site itself is preferred under this exception due to the COVID-19 pandemic. Shipment should be made in a manner that allows tracking of both transport and delivery. The subject 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 drug), direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider as trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymization and, if necessary, blinding of subjects to the sponsor using appropriate measures. Both the transport and handover conditions for study drug should be part of the contractual arrangements, so that pharmaceutical drug safety of study drug as well as protection of the privacy and personal data of subjects are adequately safeguarded. The study drug must be delivered directly to the subject or a person authorized by the subject, 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 drug to subjects, written instructions on storage and return of used and unused study drug should be provided to subjects. When shipped by study sites, the receipt, consumption and return of study drug supplies 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.

Study Assessments and Analyses

Safety Assessments (Protocol Section 9.6)

In cases of self-administration of SC study drug at home, subjects are requested to contact their treating physician as soon as possible to consider reporting of an adverse event.

Clinical laboratory safety monitoring may be performed at a certified local laboratory identified by the study site rather than at the central laboratory; for selected measures (eg, urine pregnancy), home testing may be employed.

Missed Assessments

Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study drug and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

Other relevant study data elements impacted by the COVID-19 pandemic should also be documented/labeled as "COVID-19-related" 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.

Study Analyses

The Sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in the statistical analysis plan(s).

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 interventions, 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-Cilag Germany

Signature: PPD Date: (See signature stamp)
(Day Month Year)

Note: If t nges during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.