Janssen Cilag GmbH

Statistical Analysis Plan – Study Part 3

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

TREMFYA® **(guselkumab)**

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Statistical Analysis Plan – Overall Safety Analysis

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

TREMFYA® **(guselkumab)**

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Janssen Cilag GmbH

Statistical Analysis Plan – Re-Treatment Phase

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

TREMFYA® **(guselkumab)**

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	27 Mar 2023	Not applicable	Initial release
1.1	16 Jun 2023	Choice of subgroups; Per-protocol analysis; additional analyses for subgroups; compute time to regain disease control for NRI instead of OC	Changes implemented as agreed at the Dry Run Meeting for the first interim analysis held on 14-Jun-2023 (see meeting minutes)
1.2	27 Jun 2023	Extend analysis window for week R8 to Day 85 (end date)	Changes implemented as agreed after the Dry Run Meeting for the first interim analysis
2.0	04 Jul 2023	Extend analysis window for week R8 to Day 20 (start date)	Changes implemented as agreed after the Dry Run Meeting for the first interim analysis
3.0	29 Oct 2024	Add analyses for single items of DLQI and PSSD; re-define the subgroups by time of entering the Re-treatment phase	Changes implemented before the final analysis to gain more information from the study data

1. INTRODUCTION

The statistical analysis plan (SAP) is a detailed technical extension to the Clinical Study Protocol (CSP) and follows the principles of the guideline ICH E9.

Statistical analyses of Janssen-Cilag GmbH CSP CNTO1959PSO3012 are performed for each of the three Study Parts (of which Parts 1 and 2 are already completed, and Part 3 is ongoing):

- The exploratory analysis of Study Part 1 ("Open-label treatment phase") occurred after all subjects had completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis included the safety analysis and all efficacy measures until the week 28 visit.
- The confirmatory analysis of this study was performed at the end of Study Part 2 ("Double-blind treatment phase"), ie, after all subjects had completed their visit at week 68 (ie, 40 weeks after randomization) or discontinued earlier. This analysis included 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 exploratory analyses of Study Part 3 ("Drug withdrawal phase") consist of two interim analyses and one final analysis: They occur after all subjects have completed, if not gone into re-treatment before, their visit at week 116 (ie, 48 weeks after inclusion in Study Part 3 at week 68), 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). Only subjects who started Study Part 3 in study groups 3a or 3b are included in these analyses for safety evaluations and all efficacy measures after week 68 covering the time until week 116/164/220, respectively.

For each of above analyses, a separate SAP is available. Final decisions about which subjects are included in the analyses of Study Parts 1, 2, or 3, are made during the Data Review or Dry Run Meetings.

Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or Study Part 3, and subjects with fluctuating disease (PASI score 3 to 5) at week 68 enter the re-treatment arms (study 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, "Re-treatment phase"). Duration of withdrawal from guselkumab differs among subjects. One specific endpoint has been formulated in the CSP for the re-treatment study data.

This current SAP describes the statistical analyses planned to be performed for the study data of the Re-treatment phase and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF). Only those subjects will be analyzed in the context of this SAP in whom open-label guselkumab was re-started after randomized treatment in Study Part 2 was stopped (group **2d**), completed (group **3c**) or in whom withdrawal of study treatment led to loss of disease control (PASI >5) in Study Part 3 (group **3c**). There will be up to three separate – cumulative – analyses:

- The first interim analysis includes all re-treatment assessments in subjects starting re-treatment at the latest at the week 116 visit,
- The second interim analysis includes all re-treatment assessments in subjects starting re-treatment at the latest at the week 164 visit (optional analysis),

- The final analysis includes all re-treatment assessments in subjects starting re-treatment at the latest at the week 220 visit.

This plan is the core document for all statistical programming planned for the analyses of study data referring to the Re-treatment phase of study protocol no. CNTO1959PSO3012. The statistical analyses will evaluate efficacy and safety endpoints assessed after re-treatment was started.

1.1. Objectives and Endpoints

1.1.1. 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.*

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:

- Disease duration (days) = Date of visit 1 - date of first symptoms +1.

Exploratory objectives

The exploratory objectives are to be explored in the mechanistic biomarker substudies. These objectives are out of scope of this SAP.

1.1.2. 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**)
  <u>Note:</u> Group 3c was added by mistake in the CSP and will be disregarded for analysis
- 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**)
  <u>Note:</u> Group 3c was added by mistake in the CSP and will be disregarded for analysis
- 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**)
  <u>Note:</u> Group 3c was added by mistake in the CSP and will be disregarded for analysis
- 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**).

1.2. 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. The study features the following structure and design:

<u>Study Part 1 (Open-label treatment phase) – Screening through week 28:</u>

Part 1 consists of a 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 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 (Double-blind treatment phase) – Week 28 through week 68:

Subjects with a PASI score = 0 at weeks 20 **and** 28 are 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 are equally distributed to either group by stratified randomization. Study visits of Study Part 2 are conducted every 8 weeks.

To blind the study, study treatment (guselkumab or Placebo) is administered q8w starting at week 28 until the end of study therapy (last administration in week 60). The q16w group receives 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), enter the re-treatment arm (group **2d**, see section Re-treatment phase below).

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

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

In case of PASI score >0 at weeks 20 and/or 28, the subjects 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**).

Study Part 3 (Drug withdrawal phase) – Week 68 through week 220:

Subjects of group 2a and 2b with a PASI score <3 at week 68 enter Study Part 3 (in study groups **3a** and **3b**, respectively); they are withdrawn from the study medication and followed-up until week 220. Study visits of Study Part 3 are 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) is 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 takes place at week 220.

Re-treatment phase – Week R0 through Week R28:

Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or 3 (ie, until week 220), enter the Re-treatment phase (study groups **2d** or **3c**) with three guselkumab 100 mg administrations starting at that visit (= re-treatment-week 0 (“R0 visit”), followed by administration at re-treatment-weeks 8 (“R8 visit”) and 16 (“R16 visit”)).

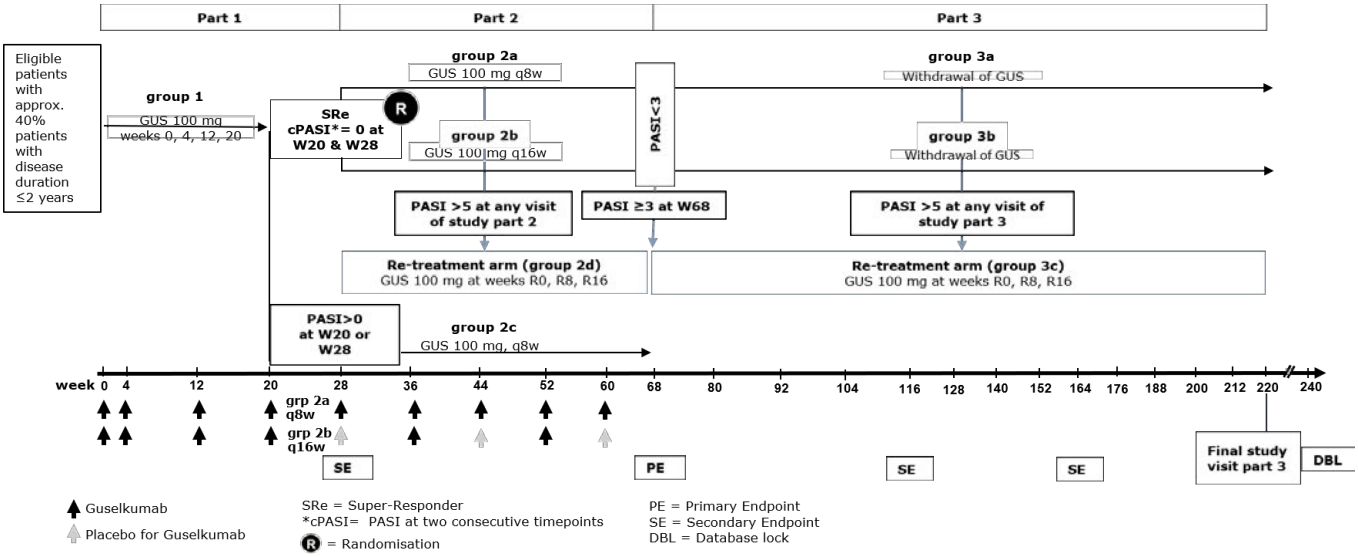
If re-treatment is started at a visit which would usually not require all patient-reported outcomes needed at the first re-treatment visit, those patient-reported outcomes are obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

The final efficacy assessment for all subjects in the re-treatment arms takes place 24 weeks after loss of control, and study termination is 28 weeks after loss of control (final study visit/safety follow-up, "R28 visit"). At visit week 24 of the Re-treatment phase ("R24 visit"), 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 also get the opportunity to enter the re-treatment arm (**3c**).

The last chance to start re-treatment is 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).

2. STATISTICAL HYPOTHESES

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 (*to be demonstrated in Study Part 2*) 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).

3. SAMPLE SIZE DETERMINATION

The sample size estimation using the power approach was performed for the per-protocol analysis set for Study Part 2 as described below. No formal adjustment of the significance level was 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 past trials, it is assumed that a rate of about 20% randomized subjects will not be evaluable for the per-protocol analysis in Study Part 2. Therefore, 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 were adjusted if necessary (without protocol amendment), to achieve 280 SRe at week 28. Ongoing subjects in Study Part 1 continued to Part 2 if eligible, irrespective of whether or not 280 SRe were already randomized. Only screenings were be closed.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS OF THE RE-TREATMENT PHASE

In the Re-treatment phase the following analysis sets will be defined for the efficacy and safety analyses.

4.1. All Enrolled Analysis Set

Not applicable for the Re-treatment phase (only applicable for Study Part 1). However, for the Re-treatment phase, the number of 'Subjects starting re-treatment' (irrespective of the time point of initiation, ie, before week 68 (study group **2d**), at week 68 or after week 68 (both study group **3c**)) will be reported and used for display of summary tables, if applicable.

Note: The All enrolled analysis set in Study Part 1 included all subjects who were enrolled and were scheduled to receive study agent.

4.2. Efficacy Analysis Set(s)

The exploratory efficacy analysis of the secondary endpoint variables will be performed for the Intent-to-treat analysis set (ITT). If decided at the Dry Run Meeting, also the Per-protocol analysis set (PP) will be evaluated.

Update after the Dry Run Meeting for the first interim analysis: The PP analysis will not be performed.

4.2.1. Intent-to-Treat Analysis Set (ITT)

For all analyses on efficacy data obtained during the Re-treatment phase, all subjects starting re-treatment (ie, received at least one dose at or after week R0) will be included in the Intent-to-treat (ITT) analysis set.

Note: In the current SAP template the term 'full analysis set' is used. In this SAP the term 'intent-to-treat analysis set' is used instead to match the Clinical Study Protocol. In terms of content, there is no difference between the two names.

4.3. Safety Analysis Set

For all safety analyses, all subjects who received at least one dose of re-started guselkumab will be included in the Safety analysis set; hence the Safety analysis set is identical to the ITT analysis set.

4.4. Pharmacokinetics Analysis Set

The PK analysis and the definition of the PK analysis set is out of scope for this SAP. There will be a separate SAP for this analysis.

5. STATISTICAL ANALYSES FOR THE RE-TREATMENT PHASE

For the planned statistical analyses of the Re-treatment phase, the following "analysis groups" are defined:

First interim analysis (re-treatment started the latest at the week 116 visit):

Analysis group I: Re-treatment started in Study Part 2, after week 28 and before week 68. These subjects had to show PASI >5 to enter the Re-treatment phase (study group 2d),

Analysis group II: Re-treatment started at the end of Study Part 2, at week 68. These subjects had to show PASI ≥3 to enter the Re-treatment phase (study group 3c),

Analysis group III: Re-treatment started during Study Part 3, after week 68 until week 116. These subjects had to show PASI >5 to enter the Re-treatment phase (study group 3c).

Second interim analysis (re-treatment started the latest at the week 164 visit – analysis was not performed):

Analysis group III: Re-treatment started after week 68 until week 116.

Analysis group IV: Re-treatment started after week 116 until week 164.

Final analysis (re-treatment started the latest at the week 220 visit):

Analysis group III: Re-treatment started after week 68 until week 116.

Analysis group IV: Re-treatment started after week 116 until week 164.

Analysis group V: Re-treatment started after week 164.

All summary tables will provide results by analysis group and for the total of the sample in the respective analysis set.

5.1. General Considerations

The following general analysis definitions refer only to the Re-treatment phase.

The statistical analysis of the Re-treatment phase will be exploratory. Inferential statistics (ie, confidence intervals) will be provided only for the visit R24 data of endpoints in the Re-treatment phase. With the exception of the secondary endpoint (PASI <3 at visit R24), all other summary tables will be purely descriptive (for comparison of subgroups see below).

Descriptive statistics will include counts and proportions for categorical data, and mean, SD, median, interquartile range, and range, for continuous data. Graphical data displays will also be used to summarize the data.

Time-to-event endpoints will be analyzed using the Kaplan-Meier product limit method to estimate the survival distributions and the median time-to-event.

For selected endpoints, subgroups will be analyzed to evaluate – among others – the effect of randomization to treatment frequency (performed for Study Part 2) and the effect of disease duration (assessed in Study Part 1 as stratification factor) on efficacy endpoints assessed after re-treatment was started; subgroups are defined in Section 5.8.8. Subgroups will exploratorily be compared using the two-sided unadjusted two-group Chi^2 test acc. to Wald (binary endpoints), the log-rank test (time-to-event endpoints) or a univariate analysis of covariance (ANCOVA) model with fixed effect for subgroup and baseline value as covariate (continuous endpoints).

Individual subject data listings will be presented parameter-wise and will be sorted by study site, subject's identification number and study visit, if applicable (without a preceding classification variable).

Note: Statistical analysis for safety of the Re-treatment phase will not include analyses of study data recorded before start of re-treatment, as safety for Study Parts 2 and 3 was already evaluated in previous analyses. However, the analysis for efficacy of the Re-treatment phase will include the preceding study visits before R0 (the start of the Re-treatment phase). For each subject, up to five pre-R0 visits will be selected based on the 12-week visit schedule, where visit R-1 is the regular visit before the R0 visit. Data of Study Parts 1, 2 and 3 will be included in the individual subject data listings.

A more detailed description of the planned statistical analyses is provided in the sections below.

5.1.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows for analysis and the target days for each visit. The reference day is Re-treatment Day 1 (for definition see section 5.1.3). If a subject has two or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. Additional or unscheduled visits will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If two actual visits are equidistant from the target day within a visit window, the later visit will be used.

Study visits of Study Parts 1, 2 and 3 taken place before re-treatment with guselkumab has been started will not be re-assigned to visit windows as they will not be included in tabulation; however, the (negative) relative day will be computed to be displayed in the individual data listings.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below in Table 2 are the visit windows and the target days for each visit of the Re-treatment phase.

Table 2 – Visit Windows for Analysis

Parameter	Analysis Period	Scheduled Visit	Time Interval (Label on output)	Time Interval (Day) *	Target Time Point (Day)
All	Re-trt	R0	Week R0	Not applicable #	1
	Re-trt	R8	Week R8	20 to 85	57
	Re-trt	R16	Week R16	86 to 127	113
	Re-trt	R24	Week R24	> 127	169
	Re-trt	R28	Week R28 (SFU)	Not applicable[&]	197

* Relative to Re-treatment Day 1. Time intervals for analysis are wider than the visit windows allowed per CSP.

\# In some subjects, the first re-treatment dose was given at an unscheduled visit after the R0 visit. For these, the R0 visit will have a negative relative day.

[&] No visit window is defined for the safety follow-up visit as no efficacy data are obtained at this visit.

If there are site visits outside of the defined windows above, final decisions on the allocation of the actual visit to an earlier or later planned visit or whether the data will not be included in the analysis will be made during the Data Review or Dry Run Meeting.

Table 2 above shows visit windows for visits during the Re-treatment phase only. In addition, for PASI, DLQI and BSA, up to five pre-R0 visits will be selected for tabulation according to the 12-week visit schedule: Visit R-1 ("R minus 1") is the regular visit before R0, R-2 is the regular visit before R-1, R-3 is the regular visit before R-2, R-4 is the regular visit before R-3, and R-5 is the regular visit before R-4. For analysis groups I and II, only visit R-1 (lying in Study Part 2) will be

used. For the analysis groups III to V, the earliest visit to be used is the week 68 visit (start of the Drug withdrawal phase). For this analysis, if a score value for a visit is missing it will not be imputed and the subject will not provide data for the respective R-x visit.

5.1.2. Pooling Algorithm for Analysis Centers

No pooling of centers will be performed.

5.1.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration within Study Part 1. However, for the analysis of the Re-treatment phase, the efficacy and safety assessments at all visits, including those of Study Parts 1, 2, and 3, will be assigned a day relative to the date re-treatment with guselkumab started (first dose of Re-treatment phase).

Hence, the relative day for a visit within the current analysis is defined as:

- Visit date – Date of Re-treatment Day 1 + 1, if visit date is ≥ start date of re-treatment
- Visit date – Date of Re-treatment Day 1, if visit date is < start date of re-treatment.

There is no 'Day 0'.

5.1.4. Baseline and Endpoint

Baseline for the Re-treatment phase is defined as the observation made at the R0 visit.

Endpoint for the Re-treatment phase is defined as the last available post-baseline result within the analysis period after the R0 visit. Results obtained at unscheduled visits are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last post-baseline result available within the analysis period for the Re-treatment phase.

5.1.5. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial onset dates of adverse events (AEs) will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - Day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - Day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same.
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the [study agent start date], if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the [study agent start date],
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

5.1.6. Treatment Failure Criteria

No treatment failure criteria are defined for the analysis of the Re-treatment phase.

5.1.7. Treatment Failure Rules

Not applicable as there are no treatment failure criteria.

5.1.8. Missing Data Imputation

Data of efficacy endpoints from subjects who started a protocol-prohibited medication/therapy during the study that could improve psoriasis will be set to 'missing' from that point onward. If the prohibited medication was stopped and the stop date is before the R0 visit, any efficacy data observed on or after the R0 visit will be used for analysis. The protocol-prohibited medications/therapies are listed in section 8.1 of the CSP. For the statistical analysis of the Re-treatment phase, protocol prohibited medication/therapy will be identified in the SDTM DV domain as DVDECOD='Received a disallowed concomitant treatment'.

After the rule for handling of protocol-prohibited medication/therapy is applied, missing data will be handled as follows:

- Non-responder imputation for binary efficacy endpoints will be applied for subjects with missing data within a given visit window.
- Last Observation Carried Forward (LOCF) imputation for continuous efficacy endpoints will be applied for subjects with missing data in the Re-treatment phase. Only the visits R8, R16, and R24, or any unscheduled visit after R0, will be considered as the LOCF value.
    - This approach implies that a separate "endpoint" visit will be calculated that gets the imputed value, thus leaving the observed value as it is, if data are summarized descriptively only.
- Time-to-event analyses of binary endpoints will be performed after the rule for handling of protocol-prohibited medication/therapy is applied (missing data will not be replaced for time-to-event analyses).

An 'observed cases analysis' for all binary and continuous endpoints in the Re-treatment phase without any imputation of missing data (ie, also not set to missing once protocol-prohibited medication/therapy is started) will also be done. These analyses will provide only descriptive statistical results (see section 5.6).

5.2. Participant Dispositions

The number of subjects in the following disposition categories will be summarized by analysis group (see Section 5.0) and overall:

- Subjects who started re-treatment #
- Subjects who completed the Re-treatment phase
- Subjects who discontinued the Re-treatment phase prematurely
- Reasons for termination of study within the Re-treatment phase.

The first interim analysis will include all subjects who started re-treatment at the latest by the week 116 visit, the second (optional) interim analysis all subjects who started re-treatment at the latest by the week 164 visit, and the final analysis all subjects who started re-treatment at the latest by the week 220 visit.

5.3. Primary Endpoint(s) Analysis

Not applicable for the re-treatment analysis.

5.3.1. Definition of Endpoint(s)

Not applicable for the re-treatment analysis.

5.3.2. Estimand

Not applicable for the re-treatment analysis.

5.3.3. Analysis Methods

Not applicable for the re-treatment analysis.

5.4. Major Secondary Endpoint(s) Analysis

Not applicable for the re-treatment analysis.

5.4.1. Definition of Endpoint(s)

Not applicable for the re-treatment analysis.

5.4.2. Estimand(s)

Not applicable for the re-treatment analysis.

5.4.3. Analysis Methods

Not applicable for the re-treatment analysis.

5.5. Other Secondary Endpoint(s)

Statistical analyses will be descriptive and exploratory only. They will be performed for the Intent-to-treat analysis set and, if requested, the Per-protocol analysis set. Details on handling of missing data are described in section 5.1.8.

Other secondary endpoints of this study to be evaluated for the Re-treatment phase are:

- 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.

5.5.1. Definition of Endpoint(s)

5.5.1.1. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is an instrument used for assessing and grading the severity of psoriatic lesions and their response to therapy. In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 (no psoriasis) to 72. A higher score indicates a more severe disease.

5.5.2. Estimand(s)

Not applicable for the re-treatment analysis.

5.5.3. Analysis Methods

5.5.3.1. Psoriasis Area and Severity Index (PASI)

- Proportion of subjects who regain control of disease (PASI <3) 24 weeks after start of re-treatment

The proportion of subjects showing a PASI value <3 within the R24 visit window will be displayed in a frequency table providing the number and percentage of subjects per analysis group and overall (NRI and OC analysis). For all proportions, unstratified two-sided 95% confidence intervals (CIs) according to Clopper-Pearson will be calculated. Graphical presentation will be done by means of bar charts.

Details on handling of missing data are described in section 5.1.8. For the analysis groups III to V (total only), subgroup analyses will be performed as specified in section 5.8.8. Subgroups will be compared exploratorily for the NRI analysis using the Chi-square test (without covariate) to test the difference between two subgroups. The 95% confidence interval for the difference will be calculated based on the Wald statistic. Counts and percentages for subjects responding to treatment, along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals and the nominal (not adjusted for multiplicity) p-value for the factor effect 'subgroup' will be provided. Graphical presentation will be done by means of bar charts.

5.6. Additional Analyses

New analyses that were not pre-planned in the CSP are introduced as follows:

5.6.1. PASI Assessments

Efficacy parameters related to the PASI score are defined below:

Time to regain disease control after start of re-treatment

The time to regain disease control is defined as time from the R0 visit (planned start of re-treatment) to first date PASI is <3 within the Re-treatment phase. In the absence of documented disease control the time to regain disease control will be censored at the date of the last PASI assessment until the week R24 visit. The time to regain disease control will be computed as:

- Date of PASI <3 – Date of week R0, if the subject regains disease control,
- Date of last PASI assessment – Date of week R0, if the subject does not regain disease control.

The following endpoints will be evaluated:

- Time to regain disease control (PASI <3) after start of re-treatment

The time to regain disease control will be analyzed using the Kaplan-Meier product limit method. Summary tables will provide counts and percentages by analysis group and overall, the median time-to-event with 95% CIs. The analysis will be performed on the observed cases only after the rule for handling of protocol-prohibited medication/therapy is applied. (ie, missing data will not be replaced for time-to-event analyses). Time to regain disease control will also be computed for subgroups (for the total only of analysis groups III to V), and subgroups will be compared using the log-rank test. The survival curves will also be displayed graphically: by analysis group and by subgroups.

Update after the Dry Run Meeting for the first interim analysis: The Kaplan-Meier analysis will not be performed on observed cases but as NRI analysis as PASI values under prohibited medication will not be used for analysis.

Update before start of programming for the final week 220 analysis: To harmonize with the statistical analysis for the Withdrawal phase, the Kaplan-Meier analysis will be performed on observed cases (OC) while PASI values under prohibited medication will not be used for analysis.

- Proportion of subjects who achieve a PASI value =0 over time
- Proportion of subjects who achieve a PASI value ≤1 over time
- Proportion of subjects who achieve a PASI value <3 over time
- Proportion of subjects who achieve a PASI value ≤5 over time

Per analysis group and overall, the proportion of subjects meeting the response criterion will be displayed in a frequency table providing the number and percentage of subjects (NRI analysis). No inferential statistics will be provided. Graphical presentation will be done by means of bar charts. For the analysis groups III to V (total only), subgroup analyses will be performed as specified in section 5.8.8.

- Proportion of subjects with PASI value =0 at 24 weeks after start of re-treatment
- Proportion of subjects with PASI value ≤1 at 24 weeks after start of re-treatment
- Proportion of subjects with PASI value ≤5 at 24 weeks after start of re-treatment

These endpoints will be analyzed for subgroups within analysis groups III to V (total only). The proportion of subjects showing response within the R24 visit window will be displayed in a frequency table providing the number and percentage of subjects per subgroup (NRI analysis). For all proportions, unstratified two-sided 95% confidence intervals (CIs) according to Clopper-Pearson will be calculated. Subgroups will be compared exploratorily for the NRI analysis using the Chi-square test (without covariate) to test the difference between two subgroups. The 95% confidence interval for the difference will be calculated based on the Wald statistic. Counts and percentages for subjects responding to treatment, along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals and the nominal (not adjusted for multiplicity) p-value for the factor effect 'subgroup' will be provided.

- PASI values over time

Per analysis group and overall, PASI values at scheduled study visits and changes from baseline (R0 visit) will be tabulated by descriptive statistics (OC analysis). No inferential statistics will be provided. For the analysis groups III to V (total only), subgroup analyses will be performed as specified in section 5.8.8.

- Change from baseline (R0 visit) in PASI value 24 weeks after start of re-treatment

The change from baseline (R0 visit) to week R24 will be tabulated for all subjects of analysis groups III to V (total only). A univariate ANCOVA model will be used to test the difference between subgroups; the change from baseline being the dependent variable, and subgroup and baseline as independent variables. A 95% confidence interval for the difference in Least Squares (LS) means and nominal (not adjusted for multiplicity) p-value will be calculated based on contrast test statistics. The LS means, the LS mean difference and the standardized mean difference (computed according to Hedges' g), together with the 95% CI and two-sided nominal p-value, will be provided from the ANCOVA model.

5.6.2. End of the Treatment-Free Period

- Time to end of the treatment-free period

The time to end of the treatment-free period is defined as time from the visit guselkumab was injected the last time in Study Part 2 to the date of the R0 visit at which re-treatment was to start, irrespective of PASI assessments. No censoring for subjects without re-treatment applies, as only subjects starting re-treatment are included in the analysis. The time to end of the treatment-free period will be computed as:

- Date of R0 visit – Date of last guselkumab injection in Study Part 2.

The time to end of the treatment-free period will be displayed for observed cases in a summary table providing the mean and median time-to-event, by analysis group and overall. No inferential statistics will be provided.

5.6.3. DLQI Assessments

The Dermatology Life Quality Index (DLQI) is a dermatology-specific quality of life instrument

designed to assess the impact of the disease on a subject's quality of life. It is a 10-item questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: 1) symptoms and feelings, 2) daily activities, 3) leisure, 4) work or school performance, 5) personal relationships, and 6) treatment.

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease. A score of ≤1 indicates no effect at all of disease on subject's health related quality of life.

For a partially answered questionnaire (eg, not all 10 answers in the DLQI questionnaire are available) the following rules will be applied:

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

Note: The answer "Not relevant" will be scored 0, as intended by the score developers.

The following endpoints will be evaluated:

- Proportion of subjects who achieve a DLQI score 0/1 and <5 over time

Per analysis group and overall, the proportion of subjects meeting the response criterion will be displayed in a frequency table providing the number and percentage of subjects (NRI analysis). No inferential statistics will be provided. Graphical presentation will be done by means of bar charts.

- Proportion of subjects with DLQI 0/1 or <5 response 24 weeks after start of re-treatment

Only subgroups within analysis groups III to V (total only) will be analyzed. The proportion of subjects showing response within the R24 visit window will be displayed in a frequency table providing the number and percentage of subjects per subgroup (NRI analysis). For all proportions, unstratified two-sided 95% confidence intervals (CIs) according to Clopper-Pearson will be calculated. Subgroups will be compared exploratorily for the NRI analysis using the Chi-square test (without covariate) to test the difference between two subgroups. The 95% confidence interval for the difference will be calculated based on the Wald statistic. Counts and percentages for subjects responding to treatment, along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals and the nominal p-value for the factor effect 'subgroup' will be provided.

- DLQI values over time

Per analysis group and overall, DLQI values at scheduled study visits and changes from baseline (R0 visit) will be tabulated by descriptive statistics (OC analysis). No inferential statistics will be provided.

Update after the Dry Run Meeting for the first interim analysis: DLQI values by study visit will also be displayed for selected subgroups according to Section 5.8.8.

Update before start of programming for the final week 220 analysis: Values by scheduled study visit and changes from baseline (R0 visit) will also be tabulated by descriptive statistics (OC analysis) for the DLQI item 1 ("Over the last week, how itchy, sore, painful or stinging has your skin been?") for all subjects and the analysis groups (no further subgroups).

5.6.4. BSA Assessments

One physical measure to define disease severity is to determine how much of the Body Surface Area (BSA) is affected by psoriasis. Involved BSA is calculated by using the palm of the subject's hand as equivalent to 1% of the BSA (rule of palm).

The following endpoint will be evaluated:

- Affected BSA over time

For analysis groups III to V (and overall) only, BSA values at scheduled study visits will be tabulated by descriptive statistics (OC analysis). Changes from baseline (R0 visit) cannot be computed since BSA was not documented at the R0 visit. No inferential statistics will be provided.

5.6.5. NAPPA Assessments

The Nail Assessment in Psoriasis and Psoriatic Arthritis (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). The NAPPA-QOL global score is computed by averaging all items. In case more than 25% of the items are missing (6 or more items missing), the score is not computed for the respective patient.
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. The weighted NAPPA-PBI global score is computed as follows: For score calculation, both "does not apply" and "question unanswered" will be treated as missing values. The global score will be calculated using all items pairs (importance + benefit) for which the patient has given a response other than "does not apply". 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). Only if more than 25% of items pairs are unanswered (=7 or more item pairs with missing values), no global score will be calculated.
3. NAPPA-CLIN has been developed from the Nail Psoriasis Severity Index (NAPSI) score, a nail psoriasis-specific score, which in its original version comprises the assessment of matrix and nail bed involvement in every finger and toe by 8 criteria for each nail. The NAPPA-CLIN is a simplified version of the NAPSI which only assesses the least and the worst involved nail of both hands, or both feet, respectively. Score (matrix or bed for hands or feet)) is 0 if the findings are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail:

   - thus, each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 individual scores (0-8) for hands or feet;

- sum of the total score of all involved nails is the total NAPPA-CLIN score for that patient at that time for hands or feet;
- thus, the NAPPA-CLIN scores for hands or feet range from 0 to 16 empirically;
- if a matrix score or a nail bed score is missing, the NAPPA-CLIN score is also missing.

The following endpoint will be evaluated:

- NAPPA score over time

For analysis groups III to V (and overall) only, the global scores of NAPPA-QOL, NAPPA-PBI, and NAPPA-CLIN at scheduled study visits and changes from baseline (R0 visit) will be tabulated by descriptive statistics (OC analysis). According to the definition of the global score of NAPPA-PBI, the post-baseline values are already the changes from baseline (there is no baseline value). No inferential statistics will be provided.

5.6.6. PSSD Assessments

The Psoriasis Symptom and Sign Diary (PSSD) is a patient-reported outcome (PRO) questionnaire designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit. The PSSD includes 11 items covering symptoms (itch, pain, stinging, burning and skin tightness) and subject observable signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) using 0 (=absent) to 10 (=worst imaginable) numerical rating scales for severity. Two subscores will be derived: the psoriasis symptom score and the psoriasis sign score. A higher score indicates more severe disease. Additionally, the single items itch, pain, and scaling and also the other single items will be evaluated. The subjects will complete the 7-day recall version of the PSSD as indicated in the Time and Events Schedule.

The calculations of PSSD symptom, and sign scores are listed below.

Symptom Score (0-100)

a) Symptom score includes itch (Q1), pain (Q11), stinging (Q10), burning (Q9) and skin tightness (Q4).
b) Averaging items on the symptom scores when at least 3 items (≥50% of 5 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Symptom score = average value x 10 with 0 representing the least severe and 100 the most severe. Otherwise, the symptom score will be set to missing.

Sign Score (0-100)

a) Sign score includes skin dryness (Q2), cracking (Q3), scaling (Q5), shedding or flaking (Q6), redness (Q7) and bleeding (Q8).
b) Averaging items on the sign scores when at least 3 items (≥50% of 6 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Sign score = average value x 10 with 0 representing the least severe and 100 the most severe. Otherwise, the sign score will be set to missing.

The following endpoints will be evaluated:

- PSSD Signs and Symptoms aggregate scores over time

For analysis groups III to V (and overall) only, the PSSD Signs and Symptom scores at scheduled study visits and changes from baseline (R0 visit) will be tabulated by descriptive statistics (OC analysis). No inferential statistics will be provided.

Update before start of programming for the final week 220 analysis: Values by scheduled study visit and changes from baseline (R0 visit) will also be tabulated by descriptive statistics (OC analysis) for the PSSD items 1, 9, 10 and 11, for all subjects and the analysis groups (no further subgroups).

- Change from baseline (R0 visit) in PSSD Signs and Symptoms scores 24 weeks after start of re-treatment

The change from baseline (R0 visit) to week R24 will be tabulated for all subjects of analysis groups III to V (total only). A univariate ANCOVA model will be used to test the difference between subgroups by disease duration; the change from baseline being the dependent variable, and disease duration and baseline as independent variables. A 95% confidence interval for the difference in LS means and nominal p-value will be calculated based on contrast test statistics. The LS means, the LS mean difference and the standardized mean difference (computed according to Hedges' g), together with the 95% CI and two-sided nominal p-value, will be provided from the ANCOVA model.

5.7. Safety Analyses

All safety analyses for the Re-treatment phase will be based on the Safety analysis set. Data from the safety follow-up at week R28 will be included in the analyses. Safety data, including but not limited to, adverse events (AEs), serious AEs, infections, serious infections, changes in laboratory assessments, and changes in vital signs, will be evaluated. Treatment-emergent AEs (TEAEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and Preferred Terms (PT).

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. All tables will provide results by analysis group and overall.

5.7.1. Extent of Exposure

The number and percentage of subjects who received study agent during the Re-treatment phase will be summarized by visit. Descriptive statistics will be presented for the number of study agent administrations.

5.7.2. Adverse Events

The verbatim terms used in the eCRF by investigators to describe adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the day of first re-treatment dose is considered to be treatment-emergent. If the onset date is recorded partially only or is completely missing, then the event is regarded as treatment-emergent unless it is known to be prior to the first dose of re-treatment based on partial onset date or

resolution date. All reported treatment-emergent adverse events (TEAEs) will be included in the detailed analysis.

For each adverse event (ie, Preferred Term) the number and percentage of subjects who experience at least one occurrence of the given event will be provided. Summary tabulation will also provide the number of events, if applicable.

Summary tables will be generated for:

- AEs
- TEAEs
- TEAEs by severity
- TEAEs by relationship to study agent
- TEAEs leading to discontinuation of study agent
- Infections
- Injection site reactions
- Serious TEAEs (TESAEs)
- Serious infections
- Serious injection site reactions.

In addition to the summary tables, listings will be provided for subjects who:

- Had (S)AEs
- Had AEs leading to discontinuation of study agent.

Deaths will be displayed by analysis group. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no) (yes includes the following eCRF items: possible, probable, very likely).

A listing of subjects who died will also be provided.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

All clinical laboratory tests recorded within the Re-treatment phase will be tabulated for the subjects included in the Safety analysis set.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points (weeks R0, R16, and R28).

Change from baseline (R0 visit) to postbaseline time points (weeks R16 and R28) will be summarized for chemistry and hematology tests.

The number and percentage of subjects with postbaseline clinically important laboratory values and/or markedly abnormal postbaseline values will be presented over time.

The clinically important laboratory findings to be reported are described below:

- [AST (U/L): 2x ULN]
- [ALT (U/L): 2x ULN]
- [Alkaline phosphatase (U/L): 2x ULN].

Markedly abnormal laboratory findings to be reported are described below:

- [AST (U/L): 3x ULN]
- [ALT (U/L): 5x ULN].

A listing of clinically important laboratory values will be provided.

Shift tables will be provided summarizing the shift in laboratory values from baseline (R0 visit) to post-baseline time points (weeks R16 and R28) with respect to abnormality criteria (low, normal, high).

Lab values given as borderline value only (eg <8 or >200) will be evaluated by ignoring the sign.

5.7.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, pulse, and blood pressure (systolic and diastolic), will be summarized at each assessment time point throughout the Re-treatment phase. Changes from baseline (R0 visit) will be summarized for all post-baseline visits within the Re-treatment phase. Descriptive statistics (mean, standard deviation, median, quartiles, minimum and maximum) will be presented. A listing of subjects with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Incidence of treatment-emergent clinically important vital signs while on treatment, as defined in Table 4, will be summarized for subjects who had a baseline assessment (R0 visit) and at least one post-baseline assessment for that vital sign.

Table 4 – Clinically Important / Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline (R0)
	<50 bpm and with >20 bpm decrease from baseline (R0)
Systolic blood pressure	>180 mmHg and with >40 mmHg increase from baseline (R0)
	<90 mmHg and with >30 mmHg decrease from baseline (R0)
Diastolic blood pressure	>105 mmHg and with >30 mmHg increase from baseline (R0)
	<50 mmHg and with >20 mmHg decrease from baseline (R0)

Abnormal findings in physical examination (additional to psoriasis findings) at baseline (R0 visit), week R24, and week R28, will be tabulated by the body systems given in the eCRF. Details on abnormal findings in verbatim terms will be displayed in individual data listings.

5.7.3.3. Electrocardiogram

Not applicable for this study.

5.7.3.4. Other Safety Parameters

Tuberculosis Evaluation

Categorical data on tuberculosis evaluation at each scheduled visit within the Re-treatment phase will be displayed in a frequency table providing the number and percentage of subjects per category.

Urine Pregnancy Test

Categorical data on urine pregnancy tests at each scheduled visit within the Re-treatment phase will be displayed in a frequency table providing the number and percentage of subjects per category.

5.8. Other Analyses

5.8.1. Pharmacokinetics

Not applicable for the re-treatment analysis.

5.8.2. Immunogenicity

Not applicable for the re-treatment analysis.

5.8.3. Pharmacodynamics

Not applicable for the re-treatment analysis.

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable for the re-treatment analysis.

5.8.5. Biomarkers

Not applicable for the re-treatment analysis.

5.8.6. Health Economics

Not applicable for this study.

5.8.7. Other Variables and/or Parameters

Not applicable for the re-treatment analysis.

5.8.8. Definition of Subgroups

Subgroup analyses are planned to be performed for the following endpoints:

- Proportion of subjects who regain control of disease (PASI <3) 24 weeks after start of re-treatment
- Time to regain disease control after start of re-treatment
- Proportion of subjects who achieve a PASI value =0 / ≤1 / <3 / ≤5 over time
- Proportion of subjects with PASI =0 / ≤1 / ≤5 at 24 weeks after start of re-treatment
- PASI values over time
- Change from baseline (R0 visit) in PASI score 24 weeks after start of re-treatment
- Proportion of subjects with DLQI 0/1 / <5 response 24 weeks after start of re-treatment

- Change from baseline (R0 visit) in PSSD scores 24 weeks after start of re-treatment.

The following subgroups will be defined:

- A: Study group according to randomization performed for Study Part 2
  - Guselkumab 100 mg q8w in Study Part 2 (group 2a)
  - Guselkumab 100 mg q16w in Study Part 2 (group 2b)
- B: Disease duration at week 0, assessed in Study Part 1 (ie, the factor used for stratification)
  - PSO duration ≤ 2 years
  - PSO duration > 2 years
- C: Disease duration and study group
  - PSO duration ≤ 2 years and guselkumab 100 mg q8w in Study Part 2 (group 3a)
  - PSO duration ≤ 2 years and guselkumab 100 mg q16w in Study Part 2 (group 3b)
  - PSO duration > 2 years and guselkumab 100 mg q8w in Study Part 2 (group 3a)
  - PSO duration > 2 years and guselkumab 100 mg q16w in Study Part 2 (group 3b)
- D: Time point of entering the Re-treatment phase
  - Re-treatment started between the week 68 visit and the week 92 visit
  - Re-treatment started later than the week 92 visit
- E: BMI at week 0
  - Subjects with normal BMI (≤ 25 kg/m²)
  - Subjects with overweight (> 25 – 30 kg/m²)
  - Obese subjects (> 30 kg/m²)
- F: Body weight at week 0
  - Body weight ≤ 90 kg
  - Body weight > 90 kg
- G: Disease duration and body weight
  - PSO duration ≤ 2 years and body weight ≤ 90 kg
  - PSO duration ≤ 2 years and body weight > 90 kg
  - PSO duration > 2 years and body weight ≤ 90 kg
  - PSO duration > 2 years and body weight > 90 kg
- H: PASI score at week 68 (nominal, not necessarily within the visit window)
  - PASI =0 at week 68
  - PASI >0 at week 68.

In case subgroups will be compared using inferential statistics, subgroups according to classification C and G will be excluded from analysis.

Subgroup analyses will be performed on both, the ITT and the PP analysis set (if evaluated), after the rule for handling of protocol-prohibited medication/therapy has been applied using non-responder imputation for binary endpoints and observed cases analyses for continuous endpoints. The decision whether the PP should be used for the subgroup analyses will be taken at the Data Review Meeting for the Re-treatment phase.

Note: At the Data Review Meeting and/or Dry Run Meeting for the Re-treatment phase it will be decided which subgroup analyses will actually be performed for the Re-treatment phase.

Update after the Dry Run Meeting for the first interim analysis: The PP analysis will not be done. The following subgroups will not be evaluated: C (by disease duration and study group), and G (by disease duration and body weight). The following subgroups will be evaluated for the display of DLQI values over time: B, D, and H. In addition, one new subgroup will be defined (without statistical comparison to another subgroup):

- I: Sex
    - Females of childbearing potential (as documented in the CRF).

It was further decided to display basic demographic and disease characteristics for each subgroup:

- Categoric variables: sex, body mass index, age class, disease duration (≤2 years, >2 years), prior psoriasis treatment includes biologics (yes, no)
- Numeric variables: age, weight, body mass index, disease duration, body surface area affected by psoriasis at week 0, PASI score at week 0.

Update before start of programming for the final week 220 analysis:

The subgroups by time point of entering the Re-treatment phase will be modified:

D: Time point of entering the Re-treatment phase
- Re-treatment started between the week 68 visit and the week 92 visit
- Re-treatment started later than the week 92 visit until the week 116 visit
- Re-treatment started later than the week 116 visit until the week 164 visit
- Re-treatment started later than the week 164 visit until the week 220 visit.

The following subgroups will be added:

- J: Age at week 0
    - Younger subjects (age < median age)
    - Older subjects (age ≥ median age)
- K: BMI at week 0 dichotomized
    - Thinner subjects (BMI < median BMI)
    - Thicker subjects (BMI ≥ median BMI)
- L: Sex
    - Female subjects
    - Male subjects
- M: Disease duration at week 0 (subjects with short disease duration only)
    - Disease duration < 15 months
    - Disease duration 15 to 24 months.

To obtain a comprehensive order, subgroups will be presented in the following sequence: A, B, M, D, J, E, K, F, L, I, H.

5.9. Interim Analyses

No formal confirmatory interim analysis is planned for this study. Statistical analyses are performed separately for each of the three Study Parts. The respective statistical analyses did not represent an interim analysis of the study, they rather evaluated disjoint study phases.

Study Part 3 was prolonged by a CSP amendment. In order to obtain early results for the Drug withdrawal phase and the subsequent Re-treatment phase, the data of Study Part 3 will be analyzed after all subjects still in study had their week 116 visit (here: completed re-treatment that was started at the latest by the week 116 visit), 164 visit (here: completed re-treatment that was started at the latest by the week 164 visit – optional analysis), or 220 visit (here: completed re-treatment that was started at the latest by the week 220 visit), or discontinued before. The week 116, week 116 re-treatment, week 164 and week 164 re-treatment analysis are regarded as explorative interim analyses for Study Part 3.

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

A data monitoring committee has not been employed for review of efficacy and/or safety data.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
BMI	Body mass index
bpm	beats per minute
BSA	Body surface area
CI	Confidence interval
CLIN	Clinical
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
eg	example given
FAE	Fumaric acid ester
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ie	that is
ITT	Intent-to-treat
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mmHg	Millimeter of mercury
MTX	Methotrexate
NAPPA	Nail Assessment in Psoriasis and Psoriatic Arthritis
NAPSI	Nail Psoriasis Severity Index
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PK	Pharmacokinetic(s)
PP	Per protocol
PSO	Psoriasis
PSSD	Psoriasis Symptoms and Signs Diary
PUVA	Psoralene plus ultraviolet A radiation
q8w/q16w	every 8/16 weeks
QoL	Quality of life
RD	Risk difference
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SDTM	Standard Data Tabulation Model
SFU	Safety Follow-up
SOC	System organ class
SRe	Super-Responder
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal range
UVB	Ultraviolet B radiation
vs.	versus
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

No important changes from the planned analyses specified in the protocol and its amendments were applied.

However, the time point of analyses is changed slightly. While the CSP states that "interim analyses 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)", it was decided to split the analyses of group 3a/3b subjects and the analyses of group 3c subjects (Re-treatment phase). By this, the results for the week 116/164/220 analyses of study groups 3a and 3b will be available as soon as possible. A separate SAP is written for the analysis of the analysis of Study Part 3 data obtained before re-treatment starts.

In addition, some new analyses have been added to the evaluation; see section 5.6 for details.

The initial SAP, prepared before the Dry-run meeting for the first interim analysis (re-treatment started until week 116), was updated several times during the course of the study:

- Changes introduced before the Week 116 re-treatment analysis:
  - The analysis window for week R8 was enlarged from Day 20 to Day 85 and for week R16 from Day 86 to Day 127.
  - The Kaplan-Meier analysis for the time to regain disease control is not performed on observed cases but as NRI analysis.
  - DLQI values by study visit are also displayed for selected subgroups according to Section 5.8.8.
  - Subgroups C and G are not evaluated.
  - DLQI values over time are displayed for subgroups B, D, and H.
  - Subgroup I is added.
  - Demographic data are displayed separately for each subgroup.
- Changes introduced before the Week 220 re-treatment analysis:
  - Single items of DLQI and PSSD are added for analysis.
  - The subgroups by time of entering the Re-treatment phase are re-defined.
  - New subgroups J, K, L and M are added to the analysis.
  - The Kaplan-Meier analysis for the time to regain disease control is regarded as OC analysis while PASI values under prohibited medication are not used for analysis.

6.3. Appendix 3 Demographics and Baseline Characteristics

Subjects' demographic data (eg, age, weight, BMI, height, sex, childbearing potential, and race) and baseline disease characteristics at week 0 (eg, age at diagnosis, BSA [%], baseline DLQI, PSSD, NAPPA-CIN (if applicable), PASI score, psoriasis arthritis, and nail assessment) will be summarized. In addition, summaries of subjects' medical history and current diagnoses will be provided (see section 6.6).

Table 5 presents a list of the demographic variables that will be summarized.

Table 5 – Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median, quartiles, and range [minimum and maximum]).
Weight (kg) Height (cm) BMI (kg/m²)	
Categorical Variables	
Age (< 45, >= 45 to 65, > 65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Childbearing potential (of childbearing potential, permanently sterilized, postmenopausal)	
BMI (normal ≤ 25, overweight > 25 – 30, obese > 30 kg/m²)	
Race[a] (White, Asian, Black, Multiple, Other, Unknown)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other: to be defined in the Major Protocol Deviation Criteria document.

The study selection criteria will also be grouped into the following 5 categories (psoriasis disease criteria, medication criteria, laboratory criteria, medical history criteria, and other), and will be summarized in a frequency table.

6.5. Appendix 5 Prior and Concomitant Medications

Subjects' prior psoriasis therapy history with topical therapy, phototherapy (PUVA, UVB), non-biologic systemic therapies (MTX, Cyclosporine, FAE, Acitretin, Apremilast, Tofacitinib, oral steroids, and other, if applicable), and biologic medications (Infliximab, Etanercept, Adalimumab, Efalizumab, Ustekinumab, Secukinumab, Ixekizumab, Brodalumab, Certolizumab, and other, if applicable) will be summarized. The allocation of medications to the four categories of therapy will be approved at the Data Review Meeting and/or Dry Run Meeting.

Subjects' last psoriasis therapy prior to participation in this study will be analyzed analogously. In addition, reasons for which subjects discontinued previous systemic therapies including PUVA, Methotrexate, FAE, Cyclosporine, Adalimumab, Ustekinumab, Secukinumab, Ixekinumab, Certolizumab (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized.

For analysis of psoriasis therapies by therapy regimen as described above, the patients will be counted in only one therapy regimen according to the following hierarchical derivation procedure:

Table 6 – Hierarchic Prior Psoriasis Therapy Regimen

Therapy regimen	Derivation
Topical therapy	All patients receiving at least one prior psoriasis medication of the type 'Topical' as defined above who did not receive a medication of another type.
Phototherapy	All patients receiving at least one prior psoriasis medication of the type 'Phototherapy' as defined above who did not receive a medication of another type except 'Topical'
Non-biologic systemic therapy	All patients receiving at least one prior psoriasis medication of the subtype 'Non-biologic systemic' as defined above who did not receive a medication of another type except 'Topical' or 'Phototherapy'.
Biologic therapy	All patients receiving at least one prior psoriasis medication of the subtype 'Biologics' as defined above who did not receive a medication of another type except 'Topical' (type), 'Phototherapy' (type), or 'Non-biologic systemic' (subtype).

In addition, the number of subjects who received concomitant treatment with a moisturizer for psoriasis will be summarized.

Prior and concomitant non-psoriasis therapies will be summarized descriptively.

Prior and Concomitant therapies (psoriasis and non-psoriasis) will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior therapies are defined as any therapy used before the day of first dose (partial or complete) of study agent at week 0. Concomitant therapies are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent, and regardless of whether the therapy was given during the Re-treatment phase.

Summaries of concomitant therapies will be presented by Anatomic Therapeutic Class (ATC) level 2 term and Preferred Name. The proportion of subjects who receive each concomitant therapy will be summarized as well as the proportion of subjects who receive at least one concomitant therapy. Prior therapies (incl. psoriasis therapies) will also be summarized by ATC level 2 term and Preferred Name.

The frequency table of subjects' prior psoriasis therapy history will be repeated by displaying Preferred Names by category used for hierarchization.

6.6. Appendix 6 Medical History

Categorical family history data will be summarized by means of a frequency table. The number and percentage of subjects with findings regarding the medical history terms of interest will be displayed in MedDRA system organ class (SOC) and Preferred Terms (PT). Summary tabulation will also consider whether the disease is ongoing or not at screening visit.

6.7. Appendix 7 Intervention Compliance

Study agent compliance within the Re-treatment phase will be summarized descriptively. Study agent compliance will be calculated as follows:

Study agent compliance (%) = 100 x number of actual administrations / number of planned administrations (3).

Study agent compliance during all Study Parts will also be assessed by protocol deviations related to study drug administration (ie, incorrect and missed administrations), if rated relevant for the Re-treatment phase analysis.

6.8. Appendix 8 Adverse Events of Special Interest

Not applicable for the re-treatment analysis.

6.9. Appendix 9 Medications of Special Interest

Not applicable for the re-treatment analysis.

6.10. Appendix 10 Laboratory Toxicity Grading

Not applicable for the re-treatment analysis.

7. REFERENCES

Protocol CNTO1959PSO3012; Phase 3b, AMENDMENT 5, Janssen-Cilag GmbH, Approved 14 June 2021

TABLE OF CONTENTS

VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	11-Apr-2025	Not applicable	Initial release

1. INTRODUCTION

The statistical analysis plan (SAP) is a detailed technical extension to the Clinical Study Protocol (CSP) and follows the principles of the guideline ICH E9.

Statistical analyses of Janssen-Cilag GmbH CSP CNTO1959PSO3012 are performed separately for each of the three Study Parts and the Re-treatment phase:

- The exploratory analysis of Study Part 1 ("Open-label treatment phase") was performed after all subjects had completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis included the safety analysis and all efficacy measures until the week 28 visit.
- The confirmatory analysis of this study was performed at the end of Study Part 2 ("Double-blind treatment phase"), ie, after all subjects had completed their visit at week 68 (ie, 40 weeks after randomization) or discontinued earlier. This analysis included 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 exploratory analyses of Study Part 3 ("Drug withdrawal phase") were performed after all subjects have completed, if not gone into re-treatment before, their visit at week 116 (ie, 48 weeks after inclusion in Study Part 3 at week 68), 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). Only subjects who started Study Part 3 in study groups 3a or 3b were considered in the analyses. These analyses included the safety evaluations and all efficacy measures after week 68 and covered the time until week 116/164/220, respectively. Thus, the statistical analysis for Study Part 3 consisted of two interim analyses and one final analysis.
- The exploratory analyses of the "Re-treatment phase" included subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or Study Part 3, and subjects with fluctuating disease (PASI score 3 to 5) at week 68 who started re-treatment at that visit. They were performed for all subjects starting re-treatment at the latest at the week 116 visit (interim analysis) and at the latest at the week 220 visit (final analysis).

For each above analysis, a respective SAP is available, accompanied by specific mock tables.

In addition to above analyses, safety aspects need to be evaluated using the adverse event (AE) data from the entire study period. This current SAP describes the statistical analyses planned to be performed for this purpose and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF).

This plan is the core document for all statistical programming planned for the Overall safety analysis of study protocol no. CNTO1959PSO3012. The statistical analysis will focus on the comparison of adverse event data in various subgroups.

1.1. Objectives and Endpoints

As the overall safety analysis was not planned at the time of protocol development, no objectives nor endpoints are defined in the protocol. The aim of this analysis is to gather information on the overall safety profile in long-term treatment with guselkumab, including long term withdrawal and possible re-treatment, in various patient subgroups.

1.2. 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. The study features the following structure and design:

Study Part 1: Screening through Week 28:

Part 1 consists of a 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 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 are 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 are equally distributed to either group by stratified randomization. Study visits of Study Part 2 are conducted every 8 weeks.

To blind the study, study treatment (guselkumab or Placebo) is administered q8w starting at week 28 until the end of study therapy (last administration in week 60). The q16w group receives 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), enter the Re-treatment arm (group **2d**, see section Re-treatment below).

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

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

In case of PASI score >0 at weeks 20 and/or 28 the subjects 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**).

Study Part 3: Week 68 through Week 220:

Subjects of group 2a and 2b with a PASI score <3 at week 68 enter Study Part 3 (in study groups **3a** and **3b**, respectively); they are withdrawn from the study medication and followed-up until week 220. Study visits of Study Part 3 are 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) is 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 takes 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), 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).

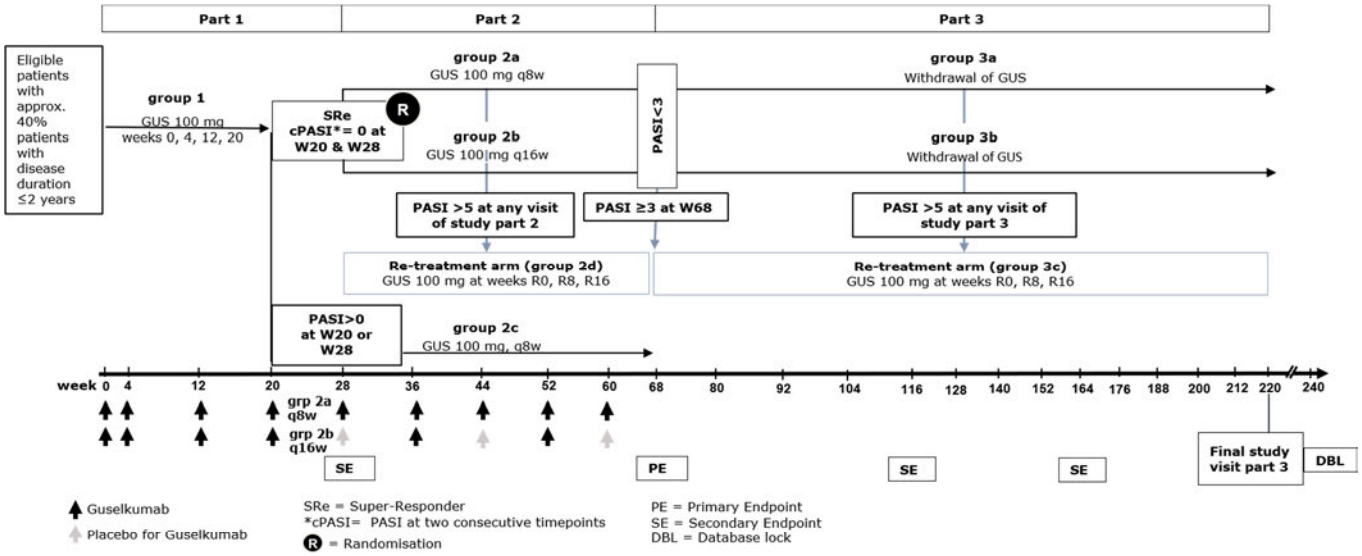
If re-treatment is started at a visit which would usually not require all patient-reported outcomes needed at the first re-treatment visit, those patient-reported outcomes are obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

The final efficacy assessment for all subjects in the re-treatment arms takes place 24 weeks after loss of control, and study termination is 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 also get the opportunity to enter the re-treatment-arm (**3c**).

The last chance to start re-treatment is 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).

2. STATISTICAL HYPOTHESES

There is no statistical hypothesis for the Overall safety analysis.

3. SAMPLE SIZE DETERMINATION

The sample size estimation using the power approach was performed for the per-protocol analysis set for Study Part 2. No formal adjustment of the significance level was 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 past trials, it is assumed that a rate of about 20% randomized subjects will not be evaluable for the per-protocol analysis in Study Part 2. Therefore, 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.

4. POPULATIONS (ANALYSIS SETS) FOR THE OVERALL SAFETY ANALYSIS

In the Overall safety analysis, the following analysis sets will be defined.

4.1. All Subjects Treated in Study Part 1

880 subjects started open-label guselkumab in Study Part 1 and received at least one dose (study group **1**). All 880 subjects are included in this analysis set to be evaluated for AEs in the study period from date of first dose (week 0) until the day before the date of the week 28 dose (start of randomized or open-label treatment within Study Part 2), or, in 58 subjects not starting Study Part 2, until the end of documentation.

4.2. All Subjects Treated in Study Part 2

From all 880 subjects who started open-label guselkumab in Study Part 1, 297 super-responders received randomized treatment in Study Part 2 (study groups **2a** and **2b**) and 525 non-super-responders continued open-label treatment (study group **2c**). So, 822 subjects are included in this analysis set and will be displayed separately to be evaluated for AEs in the study period from date

of the first verum dose (week 28 or week 36) until date of last verum dose (week 52 or week 60) in Study Part 2 plus 90 days (date of re-treatment and thereafter excluded, if at all).

4.3. All Subjects Randomized for Study Part 2

Among the 297 super-responders treated in Study Part 2 (study groups **2a** and **2b**), 148 were randomized to guselkumab q8w and 149 to guselkumab q16w. The 297 subjects included in this analysis set will be evaluated and displayed separately for AEs in the study period from date of randomization (week 28) until date of last verum dose (week 52 or week 60) in Part 2 plus 90 days (date of re-treatment and thereafter excluded, if at all).

4.4. All Subjects with a Withdrawal Phase Longer than 90 Days

From all 273 subjects starting the Withdrawal phase after the week 68 visit (randomized subjects only, study groups **3a** and **3b**), those subjects will be selected who stay in the Withdrawal phase for more than 90 days after the last randomized verum dose of guselkumab. The subjects included in this analysis set will be evaluated for AEs in the study period starting from the 91st day after last verum dose in Study Part 2 until the day before re-treatment is started (if at all).

4.5. All Subjects who Started Re-Treatment

From all 273 subjects starting the Withdrawal phase after the week 68 visit (randomized subjects only), those 227 subjects will be selected who started re-treatment with open-label guselkumab for additional up to 3 doses after showing PASI deterioration of > 5 until the week 220 visit. In addition, 9 subjects started re-treatment without a Withdrawal phase (among these, 3 subjects who started re-treatment during Study Part 2 (before the week 68 visit) with PASI > 5, and 6 subjects who started re-treatment at the week 68 visit with a PASI value of 3 to 5) and will be included as well. The 236 subjects included in this analysis set will be evaluated for AEs starting from the date of re-treatment until the end of documentation.

5. STATISTICAL ANALYSES FOR THE OVERALL SAFETY ANALYSIS

As no efficacy data will be evaluated in the Overall safety analysis, no inferential statistics (ie, exploratory p-values, confidence intervals, etc.) will be provided; the analysis is purely descriptive. The statistical analysis will be performed using the SAS® software.

5.1. General Considerations

Descriptive statistics will include counts and proportions for categorical data, and mean, standard deviation, median, interquartile range, and range, for continuous data (if at all). Graphical data displays will not be generated.

In general, summary tables will be displayed by analysis group as the main classification variable and for the total of the sample in the respective analysis set. Individual subject data listings will be presented parameter-wise and will be sorted by analysis group, study site, subject's identification number, and date of AE onset. A more detailed description of the planned statistical analyses is provided in the sections below.

5.1.1. Visit Windows

Visit windows are not applicable for this analysis.

5.1.2. Pooling Algorithm for Analysis Centers

No pooling of centers will be performed.

5.1.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration within Study Part 1. To all AEs a day relative to this date will be assigned.

Study day or relative day for the AE onset is defined as:

- AE start date – Date of Study Day 1 +1, if the AE start date is ≥ date of Day 1
- AE start date – Date of Study Day 1, if the AE start date is < date of Day 1.

There is no 'Day 0'.

5.1.4. Baseline and Endpoint

The terms “Baseline” and “Endpoint” are not defined in this analysis.

5.1.5. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial onset dates of AEs will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - Day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - Day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same.
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the [study agent start date], if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the [study agent start date],
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

- Completely missing resolution dates will not be imputed.

5.1.6. Treatment Failure Criteria

No treatment failure criteria are defined for this analysis.

5.1.7. Treatment Failure Rules

NA

5.1.8. Missing Data Imputation

There are no missing data in this analysis. All AEs documented will be considered for analysis.

5.2. Participant Dispositions

Data on subject disposition or demographic data will not be evaluated in this analysis.

5.3. Efficacy Analyses

Efficacy is not a topic of this analysis.

5.4. Safety Analyses

All safety analyses will be based on all five analysis sets introduced in chapter 4.

5.4.1. Adverse Events

The verbatim terms used in the eCRF by investigators to describe adverse events (AEs) are coded using the Medical Dictionary for Regulatory Activities (MedDRA). For analysis, AEs will be summarized by MedDRA system organ class (SOC) and Preferred Terms (PT) for each analysis group and overall.

For each analysis set, a separate time period will be considered for analysis:

Analysis set	Time period to be analyzed	Excluded time period
All subjects treated in Study Part 1 (N = 880)	Date of first dose (week 0) until study end	Date of week 28 dose and thereafter
All subjects treated in Study Part 2 (N = 822) #	Date of first verum dose (week 28 or week 36) until Date of last verum dose (week 52 or week 60) in Study Part 2 plus 90 days	Date of re-treatment and thereafter
All subjects randomized for Study Part 2 (N = 297) §	Date of randomization (week 28) until Date of last verum dose (week 52 or week 60) in Study Part 2 plus 90 days	Date of re-treatment and thereafter
All subjects with a Withdrawal phase longer than 90 days (N < 273)	91st day after last verum dose in Study Part 2 until the day before re-	Date of re-treatment and thereafter

Analysis set	Time period to be analyzed	Excluded time period
	treatment is started (or study end if no re-treatment was started)	
All subjects who started re-treatment (N = 236)	Date of first re-treatment dose (week R0) until study end	None

In this analysis, subjects will be evaluated as well by analysis groups (super responders and non-super-responders).

§ In this analysis, subjects will be evaluated only by analysis groups (treated q8w and treated q16w).

If the AE onset date is recorded partially only or is completely missing, then the event will be considered for analysis unless it is known to be prior to the respective time period based on partial onset date or resolution date. Rules to impute a partial or missing onset date are presented in Section 5.1.5. In case a subject missed the week 68 visit, the date of the week 68 visit will be estimated as 8 weeks (56 days) after the week 60 visit.

For each AE, the number and percentage of subjects who experience at least one occurrence of the given event (SOC, PT) will be summarized by analysis group and overall. Summary tabulation will also provide the number of events, if applicable.

Summary tables will be provided – separately for each analysis set – for:

- AEs
- AEs by highest relationship to study agent
- AEs by worst severity
- Infections
- Injection site reactions
- Serious AEs (SAEs)
- Serious infections.

In addition to the summary tables, listings will be provided for subjects who

- had AEs
- had SAEs.

Deaths will be displayed by analysis group. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no) (yes includes the following eCRF items: possible, probable, very likely).

A listing of subjects who died will also be provided.

5.4.2. Additional Safety Assessments

No other safety parameters will be analyzed in the Overall safety analysis.

5.4.3. Definition of Subgroups

No subgroup analyses are planned for the Overall safety analysis. For each analysis set, analysis groups are defined in Chapter 4.

5.5. Interim Analyses

There will be no interim analysis for the Overall safety analysis.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	Adverse event
CSP	Clinical Study Protocol
eCRF	electronic Case Report Form
FOIA	Freedom of Information Act
ICH	International Council for Harmonization
ie	that is
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PSO	Psoriasis
q8w/q16w	every 8/16 weeks
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SOC	System organ class
SRe	Super-Responder

6.2. Appendix 2 Changes to Protocol-Planned Analyses

This analysis was not pre-planned per study protocol, it is introduced by this SAP.

6.3. Appendix 3 Demographics and Baseline Characteristics

Demographic and baseline characteristics are not part of this analysis. Respective data have already been shown in previous analyses.

6.4. Appendix 4 Protocol Deviations

Protocol deviations will not be considered for this analysis.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and concomitant medications are not part of this analysis.

6.6. Appendix 6 Medical History

Medical history is not part of this analysis.

6.7. Appendix 7 Intervention Compliance

Exposure to study agent and study compliance are not part of this analysis..

6.8. Appendix 8 Adverse Events of Special Interest

Not applicable for this analysis.

6.9. Appendix 9 Medications of Special Interest

Not applicable for this analysis.

6.10. Appendix 10 Laboratory Toxicity Grading

Not applicable for this analysis.

7. REFERENCES

1. Protocol CNTO1959PSO3012; Phase 3b, AMENDMENT 5, Janssen-Cilag GmbH, Approved 14 June 2021

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	20 Oct 2022	Not applicable	Initial release
2.0	14 Feb 2023	See text "Update after the Dry Run Meeting" in the respective SAP sections	Release after Dry Run Meeting for the Week 116 analysis of Study Part 3
3.0	12 Oct 2023	Changes introduced as update after the Dry Run Meeting for the Week 116 analysis are incorporated in the main text of the respective SAP sections. In addition, demographic data will be displayed by subgroup.	Release before start of programming and the Dry Run Meeting for the Week 164 analysis of Study Part 3, to define all changes made for SAP version 2.0 as pre-planned analyses
4.0	04 Jul 2024	Some subgroup analyses are removed and some added; Efficacy scores by visit and changes from baseline are done only for OC modified subjects; QLQI categories are removed.	Changes implemented before the final analysis to gain more information from the study data and reduce the number of tables
5.0	31 Jan 2025	Analysis of NAPPA-CLIN (Hands) and NAPPA-CLIN (Feet) is restricted to subjects with NAPPA-CLIN (Hands) or NAPPA-CLIN (Feet) ≥ 1 at Baseline	To avoid number of subjects at post-baseline visits is higher than number of subjects evaluated for baseline

1. INTRODUCTION

The statistical analysis plan (SAP) is a detailed technical extension to the Clinical Study Protocol (CSP) and follows the principles of the guideline ICH E9.

Statistical analyses of Janssen-Cilag GmbH CSP CNTO1959PSO3012 are performed for each of the three Study Parts (of which Parts 1 and 2 are already completed:

- The exploratory analysis of Study Part 1 ("Open-label treatment phase") occurred after all subjects had completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis included the safety analysis and all efficacy measures until the week 28 visit.
- The confirmatory analysis of this study was performed at the end of Study Part 2 ("Double-blind treatment phase"), ie, after all subjects had completed their visit at week 68 (ie, 40 weeks after randomization) or discontinued earlier. This analysis included 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 3 ("Drug withdrawal phase") will be exploratory and will occur after all subjects have completed, if not gone into re-treatment before, their visit at week 116 (ie, 48 weeks after inclusion in Study Part 3 at week 68), 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). Only subjects who started Study Part 3 in study groups 3a or 3b will be included in the analyses. These analyses will include the safety evaluations and all efficacy measures after week 68 and will cover the time until week 116/164/220, respectively. Thus, the statistical analysis for Study Part 3 will consist of two interim analyses and one final analysis. All three analyses are described in the current SAP.

Final decisions about which subjects are to be included in the analyses of the Study Parts 1, 2, or 3, are made during the Data Review or Dry Run Meetings.

This current SAP describes the statistical analyses planned to be performed for Study Part 3 and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF). Statistical analyses of study data recorded before week 68 have been specified in separate SAPs, if not otherwise specified.

This plan is the core document for all statistical programming planned for the analyses of Study Part 3 of study protocol no. CNTO1959PSO3012. The statistical analyses will focus on the comparison of the two groups which were randomized for double-blind treatment in Study Part 2, ie, group **3a** (guselkumab 100 mg q8w in Study Part 2 but no treatment in Study Part 3) vs. group **3b** (guselkumab 100 mg q16w in Study Part 2 but no treatment in Study Part 3).

Note: Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 (ie, until week 68) or Study Part 3 (ie, until weeks 116, 164, or 220), and subjects with fluctuating disease (PASI score 3 to 5) at week 68 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). Statistical analyses of re-treatment study data will be specified in a separate SAP. Evaluating the endpoint related to the re-treatment phase in a separate analysis allows an earlier analysis of the endpoints measured in study groups 3a and 3b.

1.1. Objectives and Endpoints

1.1.1. 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.*

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:

- Disease duration (days) = Date of visit 1 – date of first symptoms +1.

Exploratory objectives

The exploratory objectives are to be explored in the mechanistic biomarker substudies. These objectives are out of scope of this SAP.

1.1.2. 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**).

1.2. 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. The study features the following structure and design:

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

Part 1 consists of a 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 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 are 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 are equally distributed to either group by stratified randomization. Study visits of Study Part 2 are conducted every 8 weeks.

To blind the study, study treatment (guselkumab or Placebo) is administered q8w starting at week 28 until the end of study therapy (last administration in week 60). The q16w group receives 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), enter the Re-treatment arm (group **2d**, see section Re-treatment below).

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

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

In case of PASI score >0 at weeks 20 and/or 28 the subjects 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**).

Study Part 3: Week 68 through Week 220:

Subjects of group 2a and 2b with a PASI score <3 at week 68 enter Study Part 3 (in study groups **3a** and **3b**, respectively); they are withdrawn from the study medication and followed-up until week 220. Study visits of Study Part 3 are 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) is 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 takes 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), 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 patient-reported outcomes needed at the first re-treatment visit, those patient-reported outcomes are obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

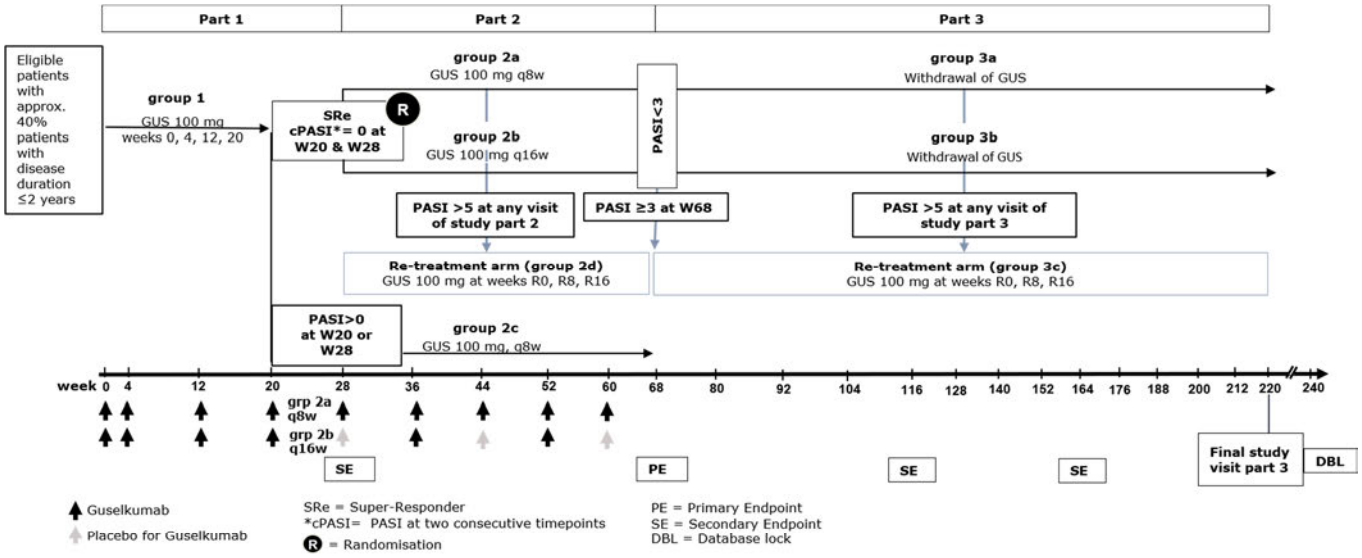
The final efficacy assessment for all subjects in the re-treatment arms takes place 24 weeks after loss of control, and study termination is 28 weeks after loss of control (final study visit/safety follow-up). At visit week 24 of the re-treatment, the investigator may continue actual treatment

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 also get the opportunity to enter the re-treatment-arm (**3c**).

The last chance to start re-treatment is 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).

2. STATISTICAL HYPOTHESES

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 (*to be demonstrated in Study Part 2*) 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).

3. SAMPLE SIZE DETERMINATION

The sample size estimation using the power approach was performed for the per-protocol analysis set as described below. No formal adjustment of the significance level was 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 past trials, it is assumed that a rate of about 20% randomized subjects will not be evaluable for the per-protocol analysis in Study Part 2. Therefore, 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS OF STUDY PART 3

In Study Part 3 the following analysis sets will be defined for the efficacy and safety analyses.

4.1. All Enrolled Analysis Set

Not applicable for Study Part 3 (only applicable for Study Part 1). However, for Study Part 3 the number of 'Subjects starting Study Part 3 in groups 3a or 3b' will be reported and used for display of summary tables, if applicable.

Note: The All enrolled analysis set in Study Part 1 included all subjects who were enrolled and were scheduled to receive study agent.

4.2. Efficacy Analysis Set(s)

The exploratory efficacy analysis of the secondary endpoint variables will be performed for the Intent-to-treat analysis set (ITT). It was decided at the Dry Run Meeting for the Week 116 analysis that the PP analysis will not be performed.

4.2.1. Intent-to-Treat Analysis Set (ITT)

For all efficacy analyses to compare study groups **3a** and **3b** in Study Part 3, all subjects entering Study Part 3 (either group 3a or 3b) will be included in the Intent-to-treat analysis set (ITT).

Note1: Subjects entering study group 3c, ie, the re-treatment arm, will be evaluated separately. Analysis is not covered by the present SAP.

Note 2: In the current SAP template the term 'full analysis set' is used. In this SAP the term 'intent-to-treat analysis set' is used instead to match the Clinical Study Protocol. In terms of content, there is no difference between the two names.

4.2.2. Per-protocol Analysis Set (PP)

The Per-protocol analysis set (PP) will consist of all subjects in the Intent-to-treat analysis set (ITT) without any major deviation of the protocol and its procedures until the week 116/164/220 visit. Subjects with major protocol deviations (except those not effecting the secondary endpoints) will be excluded from the per-protocol analysis.

4.2.3. Nail Psoriasis Analysis Set

The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at the respective scheduled week will be evaluated among subjects with nail psoriasis at baseline (week 0). Nail psoriasis at baseline (week 0) will be defined as follows:

- eCRF question 'Was Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) performed?' is answered with 'Yes'
    - if 'Yes', patient has nail psoriasis if NAPPA-CLIN ≥ 1 at baseline (week 0).

These analyses will be performed for the ITT set and, if requested, the PP set.

Update before the final analysis:
For the analysis of NAPPA-CLIN (hands), only those subjects who have a NAPPA-CLIN (hands) score ≥ 1 at Baseline (Week 0) will be included.
For the analysis of NAPPA- CLIN (feet), only those subjects who have a NAPPA-CLIN (feet) score ≥ 1 at Baseline (Week 0) will be included.

4.2.4. Safety Analysis Set

For all safety analyses, all subjects who entered groups **3a** or **3b** of Study Part 3 will be included in the Safety analysis set; hence the Safety analysis set is identical to the ITT analysis set.

Note: For study groups 3a and 3b there is no administration of study agent in Study Part 3; if treatment was started in Study Part 3 the subject is evaluated in study group **3c** for the analysis of re-treatment phase which is not covered by this SAP.

4.2.5. Pharmacokinetics Analysis Set

The PK analysis and the definition of the PK analysis set is out of scope for this SAP.

5. STATISTICAL ANALYSES FOR STUDY PART 3

Description of planned statistical analyses in Study Part 3 will focus on the comparison of the two study groups 3a and 3b which are without administration of study agent in Study Part 3 (ie, group **3a**: randomized to guselkumab 100 mg q8w in Study Part 2 vs. group **3b**: randomized to guselkumab 100 mg q16w in Study Part 2). Inferential statistics (ie, exploratory p-values, confidence intervals, etc.) will be provided only for the week 116/164/220 data of endpoints in Study Part 3.

Note 1: Statistical analysis of Study Part 3 will also include analyses of study data recorded before week 68. Data of Study Parts 1 and 2 will be summarized by descriptive statistics only. No exploratory inferential statistics (ie, p-values, confidence intervals, etc.) will be provided for the data of Study Parts 1 and 2.

Note 2: Subjects of group 3a and 3b who start re-treatment with guselkumab within Study Part 3 (up to week 116) will be evaluated only up to the study visit R0 at which PASI >5 is shown. If PASI was ≥3 already at week 68 the subject will not be evaluated for Study Part 3 in the scope of this SAP; a separate SAP will describe the analysis of the re-treatment phase.

5.1. General Considerations

The following general analysis definitions refer only to Study Part 3.

The statistical analysis of Study Part 3 will be exploratory. All inferential statistical testing (including calculation of confidence intervals) is to be interpreted in the exploratory sense only. There are no multiplicity adjustments, all p-values are nominal.

Descriptive statistics will include counts and proportions for categorical data, and mean, SD, median, interquartile range, and range, for continuous data. Graphical data displays will 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 still maintain control of disease. Continuous response parameters will be compared using a univariate analysis of covariance model with fixed effects for study group, and disease duration and baseline value as covariates. Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event.

In general, summary tables will be displayed by study group as the main classification variable and for the total of the sample (not for efficacy analyses) in the respective analysis set; ie, results will be provided for group **3a**, group **3b**, and total of group **3a** and group **3b (**not for efficacy

analyses). Additional classification variables are explicitly mentioned in the following text. Individual subject data listings will be presented parameter-wise and will be sorted by study group, study site, subject's identification number and study visit, if applicable. A more detailed description of the planned statistical analyses is provided in the sections below.

5.1.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1 (for definition see section 5.1.3). If a subject has two or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If two actual visits are equidistant from the target day within a visit window, the later visit will be used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the visit windows and the target days for each visit defined in the protocol.

Table 2 – Visit Windows

Parameter	Analysis Period	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
All	1	Scr	Screening	-35 to -1	
	1	W0	Baseline	-14 to 6	1
	1	W4	Week 4	15 to 43	29
	1	W12	Week 12	71 to 99	85
	1	W16	Week 16	100 to 126	113
	1	W20 %	Week 20	127 to 182	141
	1	W28 §	Week 28	183 to 238	197
	2	W36	Week 36	239 to 267	253
	2	W44	Week 44	295 to 323	309
	2	W52	Week 52	351 to 379	365
	2	W60	Week 60	407 to 435	421
	2	W68 §	Week 68	463 to 532	477
	3	W80	Week 80	533 to 589	561
	3	W92	Week 92	617 to 673	645
	3	W104	Week 104	701 to 757	729
	3	W116 # §	Week 116	758 to 868	813
	3	W128	Week 128	869 to 925	897
	3	W140	Week 140	953 to 1009	981
	3	W152	Week 152	1037 to 1093	1065
	3	W164 # §	Week 164	1094 to 1204	1149
	3	W176	Week 176	1205 to 1261	1233
	3	W188	Week 188	1289 to 1345	1317
	3	W200	Week 200	1373 to 1429	1401
	3	W212	Week 212	1457 to 1513	1485
	3	W220 #	Week 220	1513 to 1569	1541

* Relative to Study Day 1

W116, W164 and W220 are the final visits for the interim or final analyses of Study Part 3 – for these no upper border of the visit window will be applied (ie, all W116/W164/W220 visits later than the upper border will be used for analysis of the respective evaluation).

% Visit window for week 20 has been expanded after completion of the Week 116analysis.

§ Visit windows for flagged scheduled weeks have been expanded after the Dry Run Meeting for the Week 116 analysis.

Telephone visits scheduled at weeks 74, 86, 98, 110, 122, 134, 146, 158, 170, 182, 194, and 206, will not be re-assigned, as no endpoint data are assessed at these visits.

If there are site visits outside of the defined windows above, final decisions on the allocation of the actual visit to an earlier or later planned visit or whether the data will not be included in the analysis will be made during the Data Review or Dry Run Meeting.

5.1.2. Pooling Algorithm for Analysis Centers

No pooling of centers will be performed.

5.1.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration within Study Part 1. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date – (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date – Date of Day 1, if visit date < date of Day 1.

There is no 'Day 0'.

5.1.4. Baseline and Endpoint

Baseline for Study Part 3 is defined as the last observation (ie, value, measurement) prior to the start of the first study agent administration at baseline (week 0) in Study Part 1.

Endpoint for Study Part 3 is defined as the last available post-baseline result within the analysis period from week 68 until week 116/164/220. Results obtained at unscheduled visits are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last post-baseline result available within the analysis period from week 68 until week 116/164/220.

5.1.5. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial onset dates of adverse events (AEs) will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - Day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - Day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same.

- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the [study agent start date], if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the [study agent start date],
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

5.1.6. Treatment Failure Criteria

No treatment failure criteria are defined for Study Part 3 analysis.

5.1.7. Treatment Failure Rules

NA

5.1.8. Missing Data Imputation

Data of study endpoints from subjects who started a protocol-prohibited medication/therapy during the study period that could improve psoriasis will be set to 'missing' from that point onward. The protocol-prohibited medications/therapies are listed in section 8.1 of the CSP. For the statistical analysis of Study Part 3, protocol prohibited medication/therapy will be identified in the SDTM DV domain as DVDECOD='RECEIVED DISALLOWED CONCOMITANT TREATMENT'.

After the rule for handling of protocol-prohibited medication/therapy is applied, missing data will be handled as follows:

- Non-responder imputation for binary efficacy endpoints will be applied for subjects with missing data at any study visit.
- Last Observation Carried Forward (LOCF) imputation for continuous efficacy endpoints will be applied for subjects with missing data in Study Part 3.
  - This approach implies that a separate "endpoint" visit will be calculated that gets the imputed value, thus leaving the observed value as it is, if data are summarized descriptively only.
  - The earliest visit used for LOCF approach is the week 68 visit; no data from Parts 1 and 2 will be used as LOCF value for the week 116/164/220 visit.

- Time-to-event analyses of binary endpoints will be performed after the rule for handling of protocol-prohibited medication/therapy is applied (missing data will not be replaced for time-to-event analyses).

An 'observed cases analysis' for all binary and continuous endpoints in Study Part 3 without any imputation of missing data (ie, also not set to missing once protocol-prohibited medication/therapy is started) will also be done. These analyses will provide only descriptive statistical results and will also include by-visit data of Study Parts 1 and 2 (see section 5.6).

5.2. Participant Dispositions

The number of subjects in the following disposition categories will be summarized throughout the study for Study Part 3 by study groups (ie, groups **3a**, **3b**) and the total of group **3a** and **3b**:

- Subjects who entered groups 3a or 3b of Study Part 3
  (without those subjects who started re-treatment already at the week 68 visit)
- Subjects of groups 3a and 3b who completed Study Part 3 until the week 116/164/220 visit
- Subjects of groups 3a and 3b who discontinued Study Part 3 prematurely until the week 116/164/220 visit, respectively
- Subjects of groups 3a and 3b who started re-treatment at the week 116 visit
- Subjects of groups 3a and 3b who were still in the Withdrawal period at the week 116 visit
- Subjects of groups 3a and 3b who terminated Study Part 3 at the week 116 visit according to the unamended study protocol **
- Subjects of groups 3a and 3b who continued the Withdrawal phase beyond the week 116 visit
- Reasons for termination of study within Study Part 3 (subjects of groups 3a and 3b).

** For this subset of subjects, summary and frequency tables will be created showing age at baseline, sex, disease duration, as well as PASI and DLQI values at week 116.

5.3. Primary Endpoint(s) Analysis

Not applicable for the Study Part 3 analysis.

5.3.1. Definition of Endpoint(s)

Not applicable for the Study Part 3 analysis.

5.3.2. Estimand

Not applicable for the Study Part 3 analysis.

5.3.3. Analysis Methods

Not applicable for the Study Part 3 analysis.

5.4. Major Secondary Endpoint(s) Analysis

Statistical analyses will be descriptive and exploratory only. They will be performed for the Intent-to-treat analysis set and, if requested, the Per-protocol analysis set.

Major secondary endpoints of this study in Study Part 3 are:

- 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 116, 164, and 220, per study group
- 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.

5.4.1. Definition of Endpoint(s)

5.4.1.1. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is an instrument used for assessing and grading the severity of psoriatic lesions and their response to therapy. In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

5.4.2. Estimand(s)

NA

5.4.3. Analysis Methods

- Proportion of subjects who achieve an absolute PASI score of 0, ≤1 and <3 at weeks 116, 164, and 220
- Proportion of subjects who retain disease control from week 68 through week 116, from week 68 through week 164, and from week 68 through week 220

The proportion of subjects responding to treatment or maintaining disease control will be displayed in frequency tables providing the number and percentage of subjects per study group (NRI and OC analysis) along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 95% confidence intervals (95% CIs) stratified by 'disease duration'. For single proportions within each study group, unstratified two-sided 95% CIs according to Clopper-Pearson will be calculated. Graphical presentation will be presented by means of bar charts.

The two-group large-sample normal approximation Wald Z-test with Mantel-Haenszel stratum weights for 'disease duration' will be used to compare the respective proportion of subjects among the study groups. The Mantel-Haenszel estimate, the two-sided Wald-type 95% confidence limits, and the test for the difference of proportions will be computed by using Mantel-Haenszel stratum weights (Mantel & Haenszel, 1959) and the Sato variance estimator (Sato 1989).

The respective proportion of subjects will also be given by disease duration category (assessed at baseline, ie, ≤2 years, >2 years, and additionally only for ≤2 years: <15 months, 15 to 24 months) and overall, providing exploratory p-values (unadjusted Chi² test) for the difference between disease duration categories.

Details on handling of missing data are described in section 5.1.8. Subgroup analyses will be performed unstratified for the subgroups as specified in section 5.8.8.

Results will also be given for the entire population. In addition, in a modified OC analysis all subjects fulfilling the criteria for re-treatment within the week 116 visit window (ie, PASI>5) will be disregarded.

5.5. Other Secondary Endpoint(s)

Statistical analyses will be descriptive and exploratory only. They will be performed for the Intent-to-treat analysis set and, if requested, the Per-protocol analysis set. Details on handling of missing data are described in section 5.1.8.

Other secondary endpoints of this study to be evaluated in Study Part 3 are:

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 116, 164, and 220, per study group
- Time to loss of disease control (absolute PASI score >5 at any visit) after treatment withdrawal beyond week 68 per study group
- Change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at weeks 116, 164, and 220, per study group
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at weeks 116, 164, and 220, per study group
- Change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 80, 104, 116, 140, 164, 188, 212, and 220
- Change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at weeks 116, 164, and 220, among subjects with nail psoriasis at baseline (week 0)
- Change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at weeks 116, 164, and 220.

5.5.1. Definition of Endpoint(s)

5.5.1.1. Psoriasis Area and Severity Index (PASI)

Efficacy endpoints related to the PASI score are defined below:

PASI 75 Responder

Subjects with ≥75% improvement in PASI from baseline will be considered PASI 75 responders.

PASI 90 Responder

Subjects with ≥90% improvement in PASI from baseline will be considered PASI 90 responders.

PASI 100 Responder

Subjects with a PASI score of 0 will be considered PASI 100 responders.

Time to loss of disease control

The time to loss of disease control is defined as time from the week 68 visit (start of withdrawal phase) to first date PASI is >5 within Study Part 3. In the absence of documented disease control, the time to loss of disease control will be censored at the date of the last PASI assessment until the week 116/164/220 visit. The time to loss of disease control will be computed as:

- Date of PASI >5 – Date of week 68, if the subject loses disease control,
- Date of last PASI assessment – Date of week 68, if the subject maintains disease control.
- In case the subject missed the week 68 visit, the start date of the withdrawal phase will be estimated as 8 weeks (56 days) after the week 60 visit.

5.5.1.2. Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is a 10-item questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: 1) symptoms and feelings, 2) daily activities, 3) leisure, 4) work or school performance, 5) personal relationships, and 6) treatment.

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease. A score of ≤1 indicates no effect at all of disease on subject's health related quality of life.

For a partially answered questionnaire (eg, not all 10 answers in the DLQI questionnaire are available) the following rules will be applied:

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

Note: The answer "Not relevant" will be scored 0, as intended by the score developers.

5.5.1.3. Body Surface Area (BSA%)

One physical measure to define disease severity is to determine how much of the Body Surface Area (BSA) is affected by psoriasis. Involved BSA is calculated by using the palm of the subject's hand as equivalent to 1% of the BSA (rule of palm).

5.5.1.4. Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA)

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). The NAPPA-QOL global score is computed by averaging all items. In case more than 25% of the items are missing (6 or more items missing), the score is not computed for the respective patient.
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. The weighted NAPPA-PBI global score is computed as follows: For score calculation, both "does not apply" and "question unanswered" will be treated as missing values. The global score will be calculated using all items pairs (importance + benefit) for which the patient has given a response other than "does not apply". 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). Only if more than 25% of items pairs are unanswered (=7 or more item pairs with missing values), no global score will be calculated.

3. NAPPA-CLIN has been developed from the Nail Psoriasis Severity Index (NAPSI) score, a nail psoriasis-specific score, which in its original version comprises the assessment of matrix and nail bed involvement in every finger and toe by 8 criteria for each nail. The NAPPA-CLIN is a simplified version of the NAPSI which only assesses the least and the worst involved nail of both hands, or both feet, respectively. Score (matrix or bed for hands or feet)) is 0 if the findings are not present, 1 if they are present in 1 quadrant of the nail, 2 if present in 2 quadrants of a nail, 3 if present in 3 quadrants of a nail, and 4 if present in 4 quadrants of a nail:

   - thus, each nail has a matrix score (0-4) and a nail bed score (0-4), and the total nail score is the sum of those 2 individual scores (0-8) for hands or feet;

   - sum of the total score of all involved nails is the total NAPPA-CLIN score for that patient at that time for hands or feet;

   - thus, the NAPPA-CLIN scores for hands or feet range from 0 to 16 empirically;

   - if a matrix score or a nail bed score is missing, the NAPPA-CLIN score is also missing.

5.5.1.5. Psoriasis Symptom and Sign Diary (PSSD)

The Psoriasis Symptom and Sign Diary (PSSD) is a patient-reported outcome (PRO) questionnaire designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit. The PSSD includes 11 items covering symptoms (itch, pain, stinging, burning and skin tightness) and subject observable signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) using 0 (=absent) to 10 (=worst imaginable) numerical rating scales for severity. Two subscores will be derived: the psoriasis symptom score and the psoriasis sign score. A higher score indicates more severe disease. Additionally, the single items itch, pain, and scaling and also the other single items will be evaluated. The subjects will complete the 7-day recall version of the PSSD as indicated in the Time and Events Schedule.

The calculations of PSSD symptom, and sign scores are listed below.

Symptom Score (0-100)

a) Symptom score includes itch (Q1), pain (Q11), stinging (Q10), burning (Q9) and skin tightness (Q4).
b) Averaging items on the symptom scores when at least 3 items (≥50% of 5 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Symptom score = average value x 10 with 0 representing the least severe and 100 the most severe. Otherwise, the symptom score will be set to missing.

Sign Score (0-100)

a) Sign score includes skin dryness (Q2), cracking (Q3), scaling (Q5), shedding or flaking (Q6), redness (Q7) and bleeding (Q8).
b) Averaging items on the sign scores when at least 3 items (≥50% of 6 items) on this scale are answered. Then, the average value is converted into 0-100 scoring such that Sign score = average value x 10 with 0 representing the least severe and 100 the most severe. Otherwise, the sign score will be set to missing.

5.5.2. Estimand(s)

NA

5.5.3. Analysis Methods

5.5.3.1. Psoriasis Area and Severity Index (PASI)

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 116, 164, and 220

The proportion of subjects still meeting the response criteria will be displayed in frequency tables providing the number and percentage of subjects per study group (NRI and OC analysis) along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 95% confidence intervals (95% CIs) stratified by 'disease duration'. For single proportions within each study group, unstratified two-sided 95% CIs according to Clopper-Pearson will be calculated. Graphical presentation will be presented by means of bar charts.

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 responding subjects among the study groups. The Mantel-Haenszel estimate, the two-sided Wald-type 95% confidence limits, and the test for the difference of proportions will be computed by using Mantel-Haenszel stratum weights (Mantel & Haenszel, 1959) and the Sato variance estimator (Sato 1989).

Results will also be given for the entire population. In addition, in a modified OC analysis all subjects fulfilling the criteria for re-treatment within the week 116 visit window (ie, PASI>5) will be disregarded.

- Time to loss of disease control after treatment withdrawal beyond week 68

Time-to-event endpoints will be analyzed using the Kaplan-Meier product limit method and Cox proportional hazards model. Summary tables will provide counts and percentages by study group, the median time-to-event with 95% confidence intervals (CI), and the hazard ratio (including 95% CI and the p-value calculated from Cox-regression with the factors 'study group' and 'disease duration'). The survival curves will also be displayed graphically. Time-to-event analyses of binary endpoints will be performed on the observed cases only after the rule for handling of protocol-prohibited medication/therapy is applied. (ie, missing data will not be replaced for time-to-event analyses).

Time to loss of disease control will also be evaluated by disease duration category (assessed at baseline, ie, ≤2 years, >2 years, <15 months, 15 to 24 months) and overall, providing exploratory p-values (unadjusted log-rank test) for the difference between disease duration categories. This analysis will be repeated for the subgroups presented in Section 5.8.8.

5.5.3.2. Dermatology Life Quality Index (DLQI)

- Change from baseline (week 0) in DLQI score at weeks 116, 164, and 220

The change from baseline in DLQI will be summarized by descriptive statistics using appropriate tabulation. The baseline value, the week 116/164/220 value, and the respective change from baseline value, will be displayed.

A univariate analysis of covariance (ANCOVA) model will be used to test the difference in change from baseline between study groups; the change from baseline being the dependent variable, and former treatment, disease duration, and baseline value of endpoint, as independent variables. A

95% confidence interval for the difference in Least Squares (LS) means and p-value will be calculated based on contrast test statistics. The LS means, the LS mean difference and the standardized mean difference (computed according to Hedges' g), together with the 95% CI and two-sided p-value, will be provided from the ANCOVA model.

- Proportion of subjects who achieve a DLQI score 0/1 and <5 at weeks 116, 164, and 220

The proportion of subjects meeting the response criteria will be displayed in a frequency table providing the number and percentage of subjects per study group (NRI and OC analysis) along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 95% confidence intervals (95% CIs) stratified by 'disease duration'. For single proportions within each study group, unstratified two-sided 95% CIs according to Clopper-Pearson will be calculated. Graphical presentation will be presented by means of bar charts.

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 responding subjects among the study groups. The Mantel-Haenszel estimate, the two-sided Wald-type 95% confidence limits, and the test for the difference of proportions will be computed by using Mantel-Haenszel stratum weights (Mantel & Haenszel, 1959) and the Sato variance estimator (Sato 1989).

The respective proportion of subjects will also be given by disease duration category (assessed at baseline, ie, ≤2 years, >2 years) and overall, providing exploratory p-values (unadjusted Chi^2 test) for the difference between disease duration categories.

Results will also be given for the entire population. In addition, in a modified OC analysis all subjects fulfilling the criteria for re-treatment within the week 116 visit window (ie, PASI>5) will be disregarded. Moreover, the statistical comparison of disease duration categories will be repeated for OC.

5.5.3.3. Body Surface Area (BSA%)

- Change from baseline (week 0) in affected BSA at weeks 80, 104, 116, 140, 164, 188, 212, and 220

The change from baseline in BSA affected by psoriasis will be summarized by descriptive statistics using appropriate tabulation. The baseline value, the values for the respective weeks, and the respective changes from baseline, will be displayed.

A univariate analysis of covariance (ANCOVA) model will be used to test the difference in change from baseline between study groups; the change from baseline being the dependent variable, and former treatment, disease duration, and baseline value of endpoint, as independent variables. A 95% confidence interval for the difference in Least Squares (LS) means and p-value will be calculated based on contrast test statistics. The LS means, the LS mean difference and the standardized mean difference (computed according to Hedges' g), together with the 95% CI and two-sided p-value, will be provided from the ANCOVA model.

5.5.3.4. Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA)

- Change from baseline (week 0) in the NAPPA score at weeks 116, 164, and 220, among subjects with nail psoriasis at baseline (week 0)

The change from baseline in the global scores of NAPPA-QOL, NAPPA-PBI, and NAPPA-CLIN will be summarized by descriptive statistics using appropriate tabulation. The baseline value, the

value for the endpoint week of the respective analysis, and the respective change from the baseline value, will be displayed. According to the definition of the global score of NAPPA-PBI, the post-baseline values are already the changes from baseline (there is no baseline value).

No inferential statistical analyses will be performed for global scores of NAPPA-QOL, NAPPA-PBI, and NAPPA-CLIN.

5.5.3.5. Psoriasis Symptom and Sign Diary (PSSD)

- Change from baseline (week 0) in the PSSD Signs and Symptoms aggregate scores at weeks 116, 164, and 220

The change from baseline in the respective PSSD score will be summarized by descriptive statistics using appropriate tabulation. The baseline value, the value for the endpoint week of the respective analysis, and the respective change from the baseline value, will be displayed.

A univariate analysis of covariance (ANCOVA) model will be used to test the difference in change from baseline between study groups; the change from baseline being the dependent variable, and former treatment, disease duration, and baseline value of endpoint, as independent variables. A 95% confidence interval for the difference in Least Squares (LS) means and p-value will be calculated based on contrast test statistics. The LS means, the LS mean difference and the standardized mean difference (computed according to Hedges' g), together with the 95% CI and two-sided p-value, will be provided from the ANCOVA model.

5.6. Additional Analyses

In addition to the efficacy analyses of the study endpoints described above, continuous and binary endpoints related to PASI, DLQI, PSSD, affected BSA, NAPPA, and PSSD, at all scheduled study visits during Study Parts 1, 2 and 3 (Week 0 until Week 116/164/220) will be summarized descriptively (observed cases analysis for continuous endpoints; observed cases analysis and non-responder imputation (after the rule for handling of protocol-prohibited medication/therapy is applied) for binary endpoints). For binary endpoints and the PASI score by visit, data will be presented for the overall population as well.

New analyses that were not pre-planned in the CSP are introduced as follows:

- Proportion of subjects with short (≤2 years) and longer (>2 years) disease duration who achieve an absolute PASI score of ≤5 at weeks 116, 164, and 220, per study group

The proportion of subjects responding to treatment will be displayed in frequency tables providing the number and percentage of subjects per study group (NRI and OC analysis) along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 95% confidence intervals (95% CIs) stratified by 'disease duration'. For single proportions within each study group, unstratified two-sided 95% CIs according to Clopper-Pearson will be calculated. Graphical presentation will be presented by means of bar charts.

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 with PASI ≤5 among the study groups. The Mantel-Haenszel estimate, the two-sided Wald-type 95% confidence limits, and the test for the difference of proportions will be computed by using Mantel-Haenszel stratum weights (Mantel & Haenszel, 1959) and the Sato variance estimator (Sato 1989).

The proportion of subjects who achieve an absolute PASI score of ≤5 will also be given by disease duration category (assessed at baseline, ie, ≤2 years, >2 years, <15 months, 15 to 24 months) and overall, providing exploratory p-values (unadjusted Chi² test) for the difference between disease duration categories.

Results will also be given for the entire population. In addition, in a modified OC analysis all subjects fulfilling the criteria for re-treatment within the week 116 visit window (ie, PASI>5) will be disregarded.

- Proportion of subjects with PASI ≤5 over time

For each scheduled study visit during Study Parts 1, 2 and 3, the proportion of subjects meeting the response criterion will be displayed in a frequency table providing the number and percentage of subjects, per study group and disease duration category (≤2 years, >2 years), and overall. No inferential statistics will be provided.

- PASI values over time in subjects with PASI >0 and ≤5 at week 116

For each scheduled study visit during Study Parts 1, 2 and 3, summary statistics for observed values will be provided, restricted to only those subjects who show PASI >0 and ≤5 at week 116. Results will be given per study group and disease duration category (≤2 years, >2 years), and overall. No inferential statistics will be provided.

- PASI values over time in subjects with PASI ≥0 and ≤5 at week 116

For each scheduled study visit during Study Parts 1, 2 and 3, summary statistics for observed values will be provided, restricted to only those subjects who show PASI ≥0 and ≤5 at week 116. Results will be given per study group and disease duration category (≤2 years, >2 years), and overall. No inferential statistics will be provided.

- Time to end of the treatment-free period

The time to end of the treatment-free period is defined as time from the visit guselkumab was injected the last time in Study Part 2 to the date of the R0 visit at which re-treatment started, irrespective of PASI assessments. For subjects without re-treatment until the week 116/164/220 visit, the time to end of the treatment-free period will be censored at the date of the week 116/164/220 visit or the date of study termination, whatever comes first. The time to end of the treatment-free period will be computed as:

- Date of R0 visit – Date of last guselkumab injection in Study Part 2, if the subject started re-treatment,
- First date of (week 116/164/220 visit or study termination) – Date of last guselkumab injection in Study Part 2, if the subject did not start re-treatment.

The time to end of the treatment-free period will be analyzed using the Kaplan-Meier product limit method and Cox proportional hazards model. Summary tables will provide counts and percentages by study group and total, the median time-to-event with 95% confidence intervals (CI), and the hazard ratio (including 95% CI and the p-value calculated from Cox-regression with the factors 'study group' and 'disease duration'). The survival curves will also be displayed graphically (for all subjects, and additionally only for subjects previously treated with guselkumab q8w). Time-to-event analyses of binary endpoints will be performed on the observed cases only after the rule for

handling of protocol-prohibited medication/therapy is applied. (ie, missing data will not be replaced for time-to-event analyses).

Time to end of the treatment-free period will also be evaluated by disease duration category (assessed at baseline, ie, <15 months, 15 to 24 months, ≤2 years, >2 years) and overall, providing exploratory p-values (unadjusted log-rank test) for the difference between disease duration categories. A Kaplan-Meier graphic will show the time to end of the treatment-free period for categories <15 months, 15 to 24 months, and >2 years.

The analyses will be repeated for the subgroups presented in Section 5.8.8.

- Proportion of subjects with DLQI values falling in quality-of-life categories

DLQI values, if available within a visit window and if not after start of a prohibited medication, will be assigned to one of the categories presented in the following table:

Table 3 – DLQI Categories

DLQI Score	Meaning of Category
0 to 1	Psoriasis has no effect on quality of life
2 to 5	Psoriasis has a mild effect on quality of life
6 to 10	Psoriasis has a moderate effect on quality of life
11 to 20	Psoriasis has a severe effect on quality of life
21 to 30	Psoriasis has a very severe effect on quality of life

For selected study visit during Study Parts 1 (baseline, week 28), 2 (weeks 52 and 68) and 3 (weeks 80, 92, 104, 116, 140, 164, and 220), the proportion of subjects in each category will be displayed in a frequency table providing the number and percentage of subjects, per study group and disease duration category (≤2 years, >2 years), and overall. No inferential statistics will be provided. Percentages will be based on the available number of subjects with non-missing data per visit.

Update before the final analysis:

- An additional frequency table will be provided for the number and proportion of subjects starting re-treatment after week 68 to week 116, after week 116 to week 164, and after week 164 to week 220; proportions will also be broken down by disease duration subgroups.
- The proportion of subjects with PASI or DLQI response by visit will be evaluated twice, first using the NRI approach and second the OC modified approach (applied to all visits after week 68).
- In addition, all efficacy scores (PASI, DLQI, PSSD, BSA, and NAPPA) by visit and changes from baseline will be presented only for visits with PASI < 5 (OC modified, applied to all visits after week 68), with subgroups A and B (see Section 5.8.8).
- The endpoints PASI values over time in subjects with PASI >0 and ≤5 at week 116 and PASI values over time in subjects with PASI ≥0 and ≤5 at week 116 will not be evaluated for the Week 220 analysis.
- Proportions of subjects with DLQI response (0/1; < 5) by visit will be given by subgroups A and B only.
- DLQI categories will not be evaluated for the Week 220 analysis.

5.7. Safety Analyses

All safety analyses in Study Part 3 will be based on the Safety analysis set. Data from the safety follow-up at week 72 (study groups 2c and 3c) will not be included in the Study Part 3 analyses; last visit to be included for the Study Part 3 analyses is week 116/164/220 or R0 visit in case re-treatment was started. Safety data, including but not limited to, adverse events (AEs), serious AEs, infections, serious infections, and changes in vital signs, will be summarized by study group and overall. AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and Preferred Terms (PT) for each study group and overall.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

5.7.1. Extent of Exposure

The number and percentage of subjects who received study agent during Study Parts 1 and 2 will be summarized. Descriptive statistics will be presented for the number of study agent administrations.

5.7.2. Adverse Events

The verbatim terms used in the eCRF by investigators to describe adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring after the day of the week 68 visit until the day of the week 116/164/220 visit (or the R0 visit, if applicable) in Study Part 3 will be included in the analysis. If the onset date is recorded partially only or is completely missing, then the event will be considered for analysis unless it is known to be prior to the week 68 visit based on partial onset date or resolution date. In case a subject missed the week 68 visit, the date of the week 68 visit will be estimated as 8 weeks (56 days) after the week 60 visit.

For each adverse event, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized by study group and overall. Summary tabulation will also provide the number of events, if applicable.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs by severity
- AEs by relationship to study agent
- Infections
- Serious infections
- Injection site reactions.

In addition to the summary tables, listings will be provided for subjects who:

- Had (S)AEs.

Deaths will be displayed by study group. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no) (yes includes the following eCRF items: possible, probable, very likely).

A listing of subjects who died will also be provided.

Any AE occurring after the day of the week 68 visit until the day of the week 116/164/220 visit (or the day before the R0 visit, if applicable, ie, the day of the R0 visit is excluded) in Study Part 3 will be included in the analysis.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

Laboratory assessments were not done in Study Part 3 (except for single cases in an unscheduled visit), these were only planned for the re-treatment phase (study group 3c, see separate SAP). Therefore, no analysis of laboratory parameters will be done for study groups 3a and 3b.

5.7.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, pulse, and blood pressure (systolic and diastolic), will be summarized at each assessment time point throughout Study Parts 1, 2, and 3. Changes from baseline (week 0) will be summarized for all post-baseline visits from week 4 until week 116/164/220. Descriptive statistics (mean, standard deviation, median, quartiles, minimum and maximum) will be presented. A listing of subjects with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Incidence of treatment-emergent clinically important vital signs while on treatment, as defined in Table 4, will be summarized for subjects who had a baseline assessment and at least 1 post-baseline assessment for that vital sign.

Table 4 – Clinically Important / Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>180 mmHg and with >40 mmHg increase from baseline
	<90 mmHg and with >30 mmHg decrease from baseline
Diastolic blood pressure	>105 mmHg and with >30 mmHg increase from baseline
	<50 mmHg and with >20 mmHg decrease from baseline

Physical examinations were not done in Study Part 3, these were only planned for the re-treatment phase (study group 3c, see separate SAP). Therefore, no analysis of physical examinations will be done for study groups 3a and 3b.

5.7.3.3. Electrocardiogram

Not applicable for this study.

5.7.3.4. Other Safety Parameters

Tuberculosis Evaluation

Tuberculosis evaluations were not done in Study Part 3, these were only planned for the re-treatment phase (study group 3c, see separate SAP). Therefore, no analysis of tuberculosis evaluations will be done for study groups 3a and 3b.

Urine Pregnancy Test

Urine pregnancy tests were not done in Study Part 3, these were only planned for the re-treatment phase (study group 3c, see separate SAP). Therefore, no analysis of urine pregnancy tests will be done for study groups 3a and 3b.

5.8. Other Analyses

5.8.1. Pharmacokinetics

Not applicable for Study Part 3 analysis.

5.8.2. Immunogenicity

Not applicable for Study Part 3 analysis.

5.8.3. Pharmacodynamics

Not applicable for Study Part 3 analysis.

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable for Study Part 3 analysis.

5.8.5. Biomarkers

Not applicable for Study Part 3 analysis.

5.8.6. Health Economics

Not applicable for Study Part 3 analysis.

5.8.7. Other Variables and/or Parameters

Not applicable for Study Part 3 analysis.

5.8.8. Definition of Subgroups

Subgroup analyses are planned to be performed for the major secondary endpoints in study groups **3a** and **3b** as well as for other endpoints:

- Proportion of subjects who achieve an absolute PASI score of 0, ≤1 and <3 at week 116/164/220
- Proportion of subjects who retain disease control (PASI <3) from week 68 on
- PASI values over time
- Time to end of the treatment-free period
- Proportion of subjects who achieve a DLQI score 0/1 or <5 over time.

All subgroup analysis will be performed unstratified, ie, without use of 'disease duration' as stratification factor in the exploratory inferential statistical analysis. The following subgroups will be defined:

- A: Disease duration at baseline
  - ≤ 2 years
  - > 2 years
- B: Disease duration at baseline for subjects with short disease duration (SDD; ≤ 2 years) only
  - < 15 months
  - 15 to 24 months
- C: Age at baseline
  - < 45 years
  - ≥ 45 to 65 years
  - > 65 years
- D: BMI at baseline
  - normal (≤ 25 kg/m²)
  - overweight (> 25 – 30 kg/m²)
  - obese (> 30 kg/m²)
- E: Body weight at baseline
  - ≤ 90 kg
  - > 90 kg
- F: PSO-pretreatment (for hierarchical categorization see section 6.5)
  - No prior therapy
  - Topical therapy
  - Phototherapy
  - Non-biologic systemic therapy
  - Biologic therapy
- G: PSO-pretreatment with biologics
  - Biologic naïve (including subjects without PSO-pretreatment)
  - 1 or more biologics.

Based on the week 68 visit (nominal, not necessarily within the visit window), the following subgroups will be defined, if PASI was assessed:

- H: PASI score at week 68
  - PASI =0 at week 68
  - PASI >0 at week 68.

For these subgroups the following endpoints will be analyzed:

- Proportion of subjects who achieve an absolute PASI score of 0, ≤1 and <3 at week 116/164/220
- Proportion of subjects who achieve an absolute PASI score <3 and ≤5 by visit
- PASI values over time

- Time to end of the treatment-free period
- Proportion of subjects who achieve a DLQI score 0/1 and <5 over time
- Proportion of subjects with DLQI values falling in quality-of-life categories.

Subgroup analyses will be performed on both, the ITT and the PP analysis set (if evaluated), after the rule for handling of protocol-prohibited medication/therapy has been applied using non-responder imputation for binary endpoints (for the proportion of subjects with DLQI values falling in quality-of-life categories: observed cases analysis) and observed cases analyses for time-to-event endpoints. The decision whether the PP should be used for the subgroup analyses was taken at the Data Review Meeting for the Week 116 analysis of Study Part 3: No PP analysis will be performed.

For each subgroup category the subgroups will be compared by statistical testing for the total of subjects (not separately for group 3a and 3b); the only exception where this will not be done are the subgroups created based on the prior psoriasis therapy regimen. Figures to display subgroups will be generated for the time to end of the treatment-free period.

Update before the final analysis:
The subgroups C to H will not be evaluated for the Week 220 analysis of PASI response (PASI = 0, <= 1, < 3, Retain disease control).
In contrast, for the time-to-event endpoints Loss of disease control and End of the treatment-free period, the following subgroups will be evaluated in addition to previous defined subgroups A to H:

- I: Age at baseline
  - Younger subjects (age < median age)
  - Older subjects (age >= median age)
- J: BMI at baseline
  - Thinner subjects (BMI < median BMI)
  - Thicker subjects (BMI >= median BMI)
- K: Sex
  - Female subjects
  - Male subjects.

5.9. Interim Analyses

No formal confirmatory interim analysis is planned for this study. Statistical analyses are performed separately for each of the three Study Parts. The statistical analysis of Study Parts 1 and 2 did not represent an interim analysis of the study, they rather evaluated disjoint study phases.

Study Part 3 was prolonged by a CSP amendment. In order to obtain early results for the Drug withdrawal phase, the data of Study Part 3 will be analyzed after all subjects still in study had their week 116, 164, or 220 visit (or discontinued before). The week 116 and week 164 analysis are regarded as explorative interim analyses for Study Part 3.

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

A data monitoring committee has not been employed for review of efficacy and/or safety data.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
BMI	Body mass index
bpm	beats per minute
BSA	Body surface area
CI	Confidence interval
CLIN	Clinical
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
eg	example given
FAE	Fumaric acid ester
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ie	that is
ITT	Intent-to-treat
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mmHg	Millimeter of mercury
MTX	Methotrexate
NAPPA	Nail Assessment in Psoriasis and Psoriatic Arthritis
NAPSI	Nail Psoriasis Severity Index
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PK	Pharmacokinetic(s)
PP	Per protocol
PSO	Psoriasis
PSSD	Psoriasis Symptoms and Signs Diary
PUVA	Psoralene plus ultraviolet A radiation
q8w/q16w	every 8/16 weeks
QoL	Quality of life
RD	Risk difference
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SDTM	Standard Data Tabulation Model
SOC	System organ class
SRe	Super-Responder
ULN	Upper limit of normal range
UVB	Ultraviolet B radiation
vs.	versus
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

No important changes from the planned analyses specified in the protocol and its amendments were applied.

However, the time point of analyses is changed slightly. While the CSP states that "interim analyses 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)", it was decided to split the analyses of group 3a/3b subjects and the analyses of group 3c subjects (re-treatment phase). By this, the results for the week 116/164/220 analyses of study groups 3a and 3b will be available as soon as possible. A separate SAP will be written for the analysis of the re-treatment phase that will include – beneath the group 3c – also the analysis of study group 2d (subjects who entered the re-treatment phase already in study part 2).

In addition, some new analyses have been added to the evaluation; see section 5.6 for details.

The initial SAP, prepared before the Dry-run meeting for the first interim analysis (week 116), was updated several times during the course of the study:

- Changes introduced before the Week 116 analysis:
  - The windows for the week 28, 68, 116, 164 and week 220 visits are expanded.
  - For LOCF, the earliest visit used for carrying forward is the week 68 visit.
  - Statistical testing for binary endpoints is also performed for the OC analysis.
  - For binary endpoints, a modified OC analysis is done to exclude visits with PASI>5.
  - Subgroups are compared by statistical testing.
  - The analysis of adverse events excluded AEs starting on the day of the R0 visit.
- Change introduced before the Week 164 analysis:
  - Demographic data are displayed separately for each subgroup.
- Changes introduced before the Week 220 analysis:
  - The subgroups C to H are not evaluated for the analysis of PASI and DLQI response.
  - For the time-to-event endpoints, subgroups I to H are added.
  - All efficacy endpoints (PASI, DLQI, PSSD, BSA, and NAPPA scores and changes from baseline) by visit are presented only for visits with PASI < 5 (OC modified), with subgroups A and B.
  - PASI and DLQI response by visit are evaluated for NRI and OC modified.
  - The number of subjects starting re-treatment in defined time periods are added.
  - Some tables for PASI values over time are removed.
  - DLQI categories are not evaluated.

6.3. Appendix 3 Demographics and Baseline Characteristics

Subjects' demographic data (eg, age, weight, BMI, height, sex, childbearing potential, and race) and baseline disease characteristics (eg, age at diagnosis, BSA [%], baseline DLQI, PSSD, NAPPA-CIN (if applicable), PASI score, psoriasis arthritis, and nail assessment) will be summarized. In addition, summaries of subjects' medical history and current diagnoses will be provided (see section 6.6).

Table 5 presents a list of the demographic variables that will be summarized.

Table 5 – Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median, quartiles, and range [minimum and maximum]).
Weight (kg) Height (cm) BMI (kg/m²)	
Categorical Variables	
Age (< 45, >= 45 to 65, > 65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Childbearing potential (of childbearing potential, permanently sterilized, postmenopausal)	
BMI (normal ≤ 25, overweight > 25 – 30, obese > 30 kg/m²)	
Race[a] (White, Asian, Black, Multiple, Other, Unknown)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

In addition, the following basic demographic and disease characteristics will be displayed for each subgroup:

- Categoric variables: sex, body mass index, age class, disease duration (≤2 years, >2 years), prior psoriasis treatment includes biologics (yes, no)
- Numeric variables: age, weight, body mass index, disease duration, body surface area affected by psoriasis at week 0, PASI score at week 0.

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other: to be defined in the Major Protocol Deviation Criteria document.

The study selection criteria will also be grouped into the following 5 categories (psoriasis disease criteria, medication criteria, laboratory criteria, medical history criteria, and other), and will be summarized in a frequency table.

6.5. Appendix 5 Prior and Concomitant Medications

Subjects' prior psoriasis therapy history with topical therapy, phototherapy (PUVA, UVB), non-biologic systemic therapies (MTX, Cyclosporine, FAE, Acitretin, Apremilast, Tofacitinib, oral steroids, and other, if applicable), and biologic medications (Infliximab, Etanercept, Adalimumab, Efalizumab, Ustekinumab, Secukinumab, Ixekizumab, Brodalumab, Certolizumab, and other, if

applicable) will be summarized. The allocation of medications to the four categories of therapy will be approved at the Data Review Meeting and/or Dry Run Meeting.

Subjects' last psoriasis therapy prior to participation in this study will be analyzed analogously. In addition, reasons for which subjects discontinued previous systemic therapies including PUVA, Methotrexate, FAE, Cyclosporine, Adalimumab, Ustekinumab, Secukinumab, Ixekinumab, Certolizumab (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized.

For analysis of psoriasis therapies by therapy regimen as described above, the patients will be counted in only one therapy regimen according to the following hierarchical derivation procedure:

Table 6 – Hierarchic Prior Psoriasis Therapy Regimen

Therapy regimen	Derivation
Topical therapy	All patients receiving at least one prior psoriasis medication of the type 'Topical' as defined above who did not receive a medication of another type.
Phototherapy	All patients receiving at least one prior psoriasis medication of the type 'Phototherapy' as defined above who did not receive a medication of another type except 'Topical'
Non-biologic systemic therapy	All patients receiving at least one prior psoriasis medication of the subtype 'Non-biologic systemic' as defined above who did not receive a medication of another type except 'Topical' or 'Phototherapy'.
Biologic therapy	All patients receiving at least one prior psoriasis medication of the subtype 'Biologics' as defined above who did not receive a medication of another type except 'Topical' (type), 'Phototherapy' (type), or 'Non-biologic systemic' (subtype).

In addition, the number of subjects who received concomitant treatment with a moisturizer for psoriasis will be summarized.

Prior and concomitant non-psoriasis therapies will be summarized descriptively.

Prior and Concomitant therapies (psoriasis and non-psoriasis) will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior therapies are defined as any therapy used before the day of first dose (partial or complete) of study agent at week 0. Concomitant therapies are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent. In the statistical analysis only therapies will be counted as ‘concomitant' for Study Part 3 analysis, which started before or at the date of the week 116/164/220 visit (stop of the respective Study Part 3 analysis window).

Summaries of concomitant therapies will be presented by Anatomic Therapeutic Class (ATC) level 2 term and Preferred Name. The proportion of subjects who receive each concomitant therapy will be summarized as well as the proportion of subjects who receive at least one concomitant therapy. Prior therapies (incl. psoriasis therapies) will also be summarized by ATC level 2 term and Preferred Name.

The frequency table of subjects' prior psoriasis therapy history will be repeated by displaying Preferred Names by category used for hierarchization.

6.6. Appendix 6 Medical History

Categorical family history data will be summarized by means of a frequency table. The number and percentage of subjects with findings regarding the medical history terms of interest will be displayed in MedDRA system organ class (SOC) and Preferred Terms (PT). Summary tabulation will also consider whether the disease is ongoing or not at screening visit.

6.7. Appendix 7 Intervention Compliance

Study agent compliance within Study Part 2 will be summarized descriptively. Study agent compliance will be calculated as follows:

Study agent compliance (%) = 100 x number of actual administrations / number of planned administrations).

Study agent compliance during Study Parts 1 and 2 will also be assessed by protocol deviations related to study drug administration (ie, incorrect and missed administrations), if rated relevant for Study Part 3.

6.8. Appendix 8 Adverse Events of Special Interest

Not applicable for Study Part 3 analysis.

6.9. Appendix 9 Medications of Special Interest

Not applicable for Study Part 3 analysis.

6.10. Appendix 10 Laboratory Toxicity Grading

Not applicable for Study Part 3 analysis.

7. REFERENCES

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