Janssen Cilag GmbH

Statistical Analysis Plan – Study Part 1
Amendment 1

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)**

Status:	Final
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Prepared by:	Janssen-Cilag GmbH, Germany
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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

This SAP was originally finalized early on 16-Jul-2020, leaving open some decisions to be taken at the Data Review Meeting. However, statistical issues were not discussed at the Data Review Meeting but at the Dry Run Meeting, which was held on 21-Jun-2021 (meeting minutes are available). All decisions taken in the Dry Run Meeting that require an SAP update are described in this SAP update in a fashion that the original text is still visible: in each respective section a new paragraph is added that introduces and explains the changes. This updated SAP is finalized and signed before database lock for Study Part 1.

Table 1 – SAP Version History Summary

SAP Version	Version Date	Change	Rationale
Final	16 July 2020	Not Applicable	Initial release
Amendment 1	06 July 2021	see text 'update after dry run meeting' in the respective SAP sections	Release after dry-run meeting for Study Part 1

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
DBL	Database lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
eg	example given
EP	Endpoint
FAE	Fumaric acid ester
FAS	Full analysis set
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ie	that is
IQ	Interquartile range
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAPPA	Nail Assessment in Psoriasis and Psoriatic Arthritis
nSR	Non-Super-Responder
OR	Odds ratio
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PK	Pharmacokinetic(s)
PP	Per protocol
PROs	Patient reported outcomes
PSSD	Psoriasis Symptoms and Signs Diary
PT	Preferred terms
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
SD	Standard deviation
SOC	System organ class
SRe	Super-Responder
TEAE	Treatment-emergent adverse event
TES	Time and Events Schedule
ULN	Upper limit normal
UVB	Ultra violet B radiation
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

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 Clinical Study Protocol CNTO1959PSO3012 will be performed for each of the three Study Parts.

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

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

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

This plan describes the statistical analyses planned to be performed for the analysis of Study Part 1 (open-label treatment phase) and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF). Statistical analyses of study data recorded after week 28 will be specified in separate SAPs.

This SAP is the core document for all statistical programming planned to be performed for the analysis of Study Part 1 of study protocol no. CNTO1959PSO3012.

1.1. Trial 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 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 not part 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 and 116 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 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 and 116 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**)
- The change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at weeks 28 and 68 per study group (**1**, **2a**, **2b,** and **2c**)
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at weeks 28 and 68 per study group (**1**, **2a**, **2b,** and **2c**)
- The change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 12, 28, 52, 68, 80, and 104 (**all study groups**)
- The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at weeks 28, 68 and 116 among subjects with nail psoriasis at baseline (week 0) (**1, 2a, 2b, 2c, 3a** and **3b**).
- The change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at weeks 28, 68 and 116 (**1, 2a, 2b, 2c, 3a** and **3b**)
- The 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**).
- The association between trough serum concentration and efficacy or serum biomarker level
- The 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. Trial 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 will feature the following structure and design:

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

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

Study Part 2: Week 28 through Week 68:

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

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

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

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

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

Study Part 3: Week 68 through Week 116:

Subjects of group **2a** and **2b** with a PASI score <3 at week 68 will enter Study Part 3 and be withdrawn from the study medication and followed-up until week 116. Study visits of Study Part 3 will be conducted every 12 weeks (ie, at weeks 80, 92, 104, and 116; ± 14 days). In between the 12-weekly on-site visits, there will be a telephone-visit 6 weeks (± 7 days) after each visit (ie, telephone visits at weeks 74, 86, 98, and 110) 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.

Re-treatment

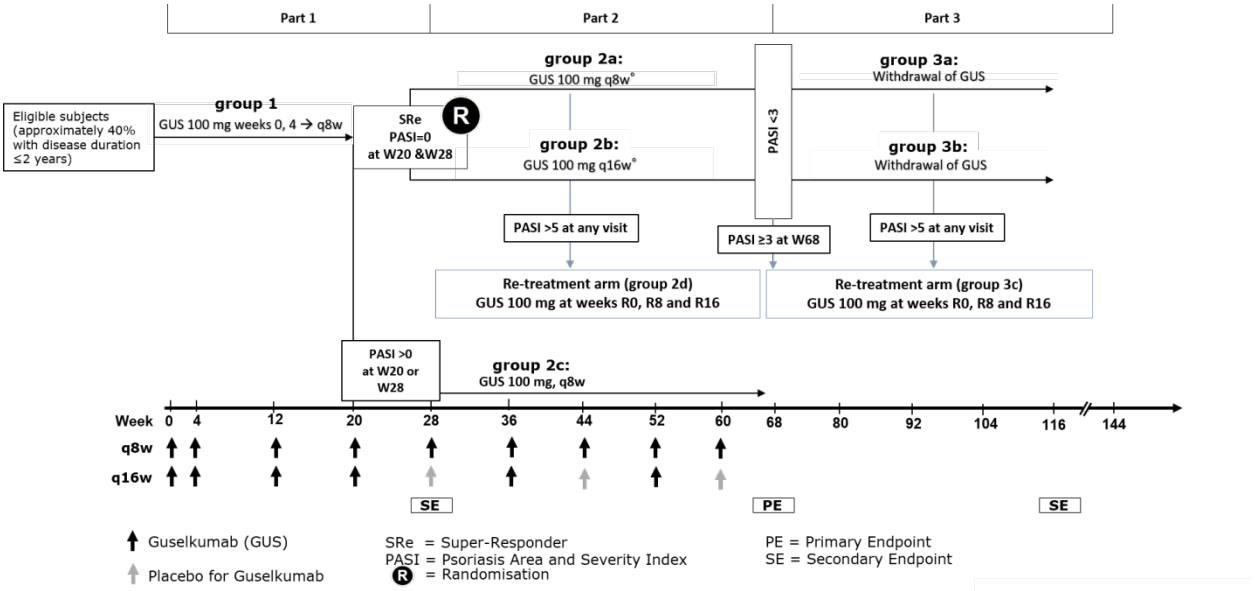
Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or 3 (ie, until week 116), will enter the re-treatment-arms (**2d** or **3c**) with three guselkumab 100 mg administrations starting at that visit (= re-treatment-week 0, followed by administration at re-treatment-weeks 8 and 16).

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

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

Subjects with fluctuating disease (ie, PASI score 3 to 5) at the week 68 visit will also get the opportunity to enter the re-treatment-arm (**3c**). The last chance to start re-treatment will be the visit week 116.

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 R0, R8 and R16 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 (PASI score 3 to 5) at week 68 or loss of disease control (PASI score >5) at any other visit after week 68, who will enter the re-treatment arm and receive guselkumab 100 mg at weeks R0, R8 and R16 calculated from the date of loss of disease control (Study Part 3)

1.3. Statistical Hypotheses for Trial Objectives

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

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

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

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

1.4. Sample Size Justification

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.

1.5. Randomization and Blinding

Treatment Allocation/ Procedures for Randomization

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

Subjects will be equally stratified in study group 2a and 2b during randomization for i) disease duration of ≤2 or >2 years (note: disease duration will be calculated from date at which first symptoms (plaque) were reported by subject to date of screening visit) and ii) for participation in substudy 1. Definitions when to stop/pause recruitment of subjects with longer disease duration will be provided in a separate document.

Blinding

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

Data that may potentially unblind the treatment assignment (eg, treatment allocation, study drug preparation/accountability data and administration of study drug) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock (DBL) and unblinding.

Under normal circumstances, the blind should not be broken for subjects, investigators, or site personnel until the end of the study and database lock.

In Study Part 3 (drug withdrawal) starting at week 68 throughout week 116, subjects, investigators and site personnel will remain blinded towards their injection interval (q8w or q16w) in Study Part 2. The sponsor will be unblinded after DBL at week 68 to conduct the analysis of the primary endpoint.

2. GENERAL ANALYSIS DEFINITIONS FOR STUDY PART 1

The following general analysis definitions refer only to Study Part 1.

2.1. 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 2.5). If a subject has 2 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 2 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 1) are the visit windows and the target days for each visit defined in the protocol.

Table 1 – 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	W20	Week 20	127 to 155	141
	1	W28	Week 28	183 to 211	197

*Relative to Study Day 1

If there are visits outside of the defined windows, final decisions on the allocation of the actual visit to an earlier or later planned visit or if the data will not be included in the analysis will be made during the Data Review Meeting. Since at Week 16 neither IP is administrated nor decisive assessments are conducted, deviations from the visit window will not constitute a major protocol deviation.

Update after the Dry Run Meeting: A visit window for week 16 is introduced to allocate PASI values at study days 100 to 126 to an analysis window. Also, the week 28 window was expanded. All values made at visits outside of defined windows will not be taken into account for by-visit analyses.

Table 1 – 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 155	141
	1	W28	Week 28	183 or higher	197

*Relative to Study Day 1

2.2. Pooling Algorithm for Analysis Centers

No pooling of centers will be performed.

2.3. Analysis Sets

In Study Part 1 all subjects treated with at least one dose of study agent will be included in the efficacy and safety analyses.

2.3.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who were enrolled and were scheduled to receive study agent.

2.3.2. All Randomized Analysis Set

Not applicable for Study Part 1 analysis.

2.3.3. Efficacy Analysis Set(s)

In Study Part 1 all subjects treated with at least one dose of study agent will be included in the efficacy analyses (intent-to-treat (ITT) analysis set).

The per-protocol (PP) analysis set will consist of all subjects in the ITT analysis set completing or terminating the Study Part 1 without any major deviation of the protocol and its procedures until the week 28 visit. Subjects with major protocol deviations (if not administrative) will be excluded from the per-protocol analysis.

Note: At the Data Review Meeting for Study Part 1 it will be decided whether a per-protocol analysis will be performed for Study Part 1.

Update after the Dry Run Meeting: It was decided not to perform a PP analysis for Study Part 1.

The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at week 28 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 BL

2.3.3.1. Primary Efficacy Analysis Set

The ITT analysis set will be used as the primary efficacy analysis set.

2.3.3.2. Secondary Efficacy Analysis Set

The PP analysis will be used as the secondary efficacy analysis set, if applicable.

2.3.4. Safety Analysis Set

For all safety analyses, all subjects treated with at least one dose of study agent will be included (intent-to-treat (ITT) analysis set).

2.3.5. Pharmacokinetics Analysis Set

The PK analysis and the definition of the PK analysis set will be provided in a separate SAP.

2.4. Definition of Subgroups

In general, summary tabulation for Study Part 1 data will be provided by disease duration (≤2 and >2 years) and overall.

Subgroup analyses are planned to be performed for demographics and selected baseline characteristics for the following subgroups.

- Country
  - Germany
  - France
- Response Status (defined at week 20/28)
  - Super-Responder (SR)
  - Non-Super-Responder (nSR)

Summary tabulation for these subgroup analyses will provide subgroup results by disease duration and overall where the subgroup factor is nested within the main group factor 'disease duration', ie., the following display will be used for the subgroup factor 'country' and analogously for the subgroup factor 'response status':

PSO duration <= 2 years, N = xxx		PSO duration > 2 years, N = xxx		Total, N = xxx	
Germany, N = xxx	France, N = xxx	Germany, N = xxx	France, N = xxx	Germany, N = xxx	France, N = xxx

Selected baseline characteristics planned to be used for the subgroup analyses will include the following variables:

- Age at Diagnosis
- BSA (affected by psoriasis)
- DLQI
- PSSD
- NAPPA-CLIN (hands and feet)
- PASI
- Prior Psoriasis Therapies
- Last Psoriasis Therapy
- Prior Non-Psoriasis Medication
- Concomitant Non-Psoriasis Medication

Subgroup analyses are also planned to be performed for the proportion of Super-Responders and for the major secondary endpoints for the following subgroups.

- Gender
  - male
  - female
- Age at baseline in years
  - < 45
  - ≥ 45 to 65
  - > 65
- BMI
  - normal ≤ 25
  - overweight > 25 – 30
  - obese > 30
- Weight in kg
  - ≤ 90
  - > 90
- Disease duration in years
  - > 2 to 10
  - > 10
- PASI at baseline
  - < 20
  - ≥ 20
- PSO-pretreatment (for hierarchical categorization see Section 4.6):
  - Topical therapy
  - Phototherapy
  - Non-biologic systemic therapy
  - Biologic therapy

- PSO-pretreatment with biologics:
    - 1 biologic
    - 2 biologics or more biologics
- PSO-pretreatment: IL-17 inhibitors (Ixekizumab, Secukinumab or Brodalumab)
    - ever used
    - never used

Results of the major secondary endpoints 'time to improvement from baseline (week 0) in PASI (PASI 75/90/100 response and absolute PASI score = 0)' will also be displayed for the subgroup 'Response Status' as defined above.

Additionally to the primary and the major secondary endpoints, DLQI will also be analyzed by response status.

Summary tabulation for these subgroup analyses will provide subgroup results for the total sample within each subgroup category but NOT by disease duration, ie., the following display will be used for the subgroup factor 'gender' and analogously for the other subgroup factors

Male, N = xxx	Female, N = xxx

Subgroup analyses for the proportion of Super-Responders and for the major secondary endpoints will be performed for the ITT analysis set using non-responder imputation (for binary endpoints) or Last Observation Carried Forward (LOCF) imputation (for continuous endpoints). An 'observed cases analysis' without imputation of missing data will also be done. Subgroup analysis may also be performed for the PP analysis set, if decided at the Data Review Meeting for Study Part 1.

No exploratory inferential statistical methods will be used to compare the results between subgroup categories within each subgroup, eg, no p-values will be calculated to compare the results between the subgroups 'male' and 'female'.

Note: At the Data Review Meeting for Study Part 1 it will be decided which subgroup analyses will actually be performed for Study Part 1.

Update after the Dry Run Meeting: For the analysis of baseline parameters, the following subgroups will not be evaluated:

- Country (Germany, France).

For the analysis of efficacy parameters, the following subgroups will not be evaluated:

- Gender (male, female)

- PASI at baseline (< 20, ≥ 20)
- PSO-pretreatment: IL-17 inhibitors (ever used, never used).

For the analysis of efficacy parameters, the subgroups by PSO-pretreatment with biologics will be set up as:

  - 0 biologics
  - 1 biologic
  - 2 or more biologics

2.5. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. 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'.

2.6. Baseline and Endpoint

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

Endpoint is defined as the last available postbaseline result within the analysis period until week 28. Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period.

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

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event 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
  - The 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
  - The 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 adverse event 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.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Statistical analyses will be performed separately for each of the three Study Parts. No formal confirmatory interim analysis is planned for this study.

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

4. SUBJECT INFORMATION

If not otherwise specified, the ITT analysis set will be used for all tabulations of subject information data. Summary tabulation will be provided by disease duration (≤2 and >2 years) and overall.

The number of subjects in each analysis set will be summarized and listed. In addition, the distribution of subjects by country, and site ID will be presented.

Update after the Dry Run Meeting: The distribution table by site ID will be skipped.

4.1. Demographics and Baseline Characteristics

Subjects' demographic data (eg, age, weight, BMI, height, sex, child bearing 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. Subgroup analyses of subjects' demographic data and selected baseline disease characteristics will be performed for the subgroups 'country' (Germany/France) and 'response

status' (super-responder/non-super-responder). Tabulation of demographic data by 'response status' will be repeated for the subgroup 'country´. In addition, summaries of subjects' medical history and current diagnoses will be provided.

Table 2 presents a list of the demographic variables that will be summarized.

Table 2: Demographic Variables

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

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

Update after the Dry Run Meeting: For age and BMI, cumulative distribution curves by disease duration and overall will be done. In addition, a summary table will tabulate the disease duration in years and months. Here, one year is set to 365 days, and one month is set to 30.5 days. A frequency table for disease duration will provide counts and percentages for the following categories:

- ≤ 6 months
- > 6 to ≤ 12 months
- > 12 to ≤ 18 months
- > 18 to ≤ 24 months
- > 2 years to ≤ 5 years
- > 5 to ≤ 8 years
- > 8 to ≤ 12 years
- > 12 to ≤ 15 years
- More than 15 years.

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized.

The number of subjects in the following disposition categories will be summarized throughout the study for Study Part 1:

- Subjects receiving study agent
- Subjects completing Study Part 1
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

Pertinent disposition information results will also be displayed by country and center.

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely

4.3. Treatment Compliance

Study agent compliance 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 will also be assessed by protocol deviations related to study drug administration (ie, incorrect and missed administrations).

4.4. Extent of Exposure

The number and percentage of subjects who receive study agent will be summarized. Descriptive statistics will be presented for number of study agent administrations.

4.5. 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.

4.6. Prior and Concomitant Therapies

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 was approved at the Dry Run Meeting.

Subjects' last psoriasis therapy prior to participation in this study will be analyzed analogously. Subgroup analyses will be performed for the subgroups 'country' (Germany/France) and 'response status' (super-responder/non-super-responder). 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.

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. Subgroup analyses will be performed for the subgroups 'country' (Germany/France) and 'response status' (super-responder/non-super-responder).

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. 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 1, which started before the date of randomization (start of Study Part 2).

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 1 concomitant therapy. Prior therapies (incl. psoriasis therapies) will be summarized by ATC level 2 term and Preferred Name.

Update after the Dry Run Meeting: The frequency table of subjects’ prior psoriasis therapy history will be repeated by displaying preferred names by category used for hierarchization. This will be done by disease duration and by response status.

5. EFFICACY

If not otherwise specified, the ITT analysis set will be used for all tabulations of efficacy data from Study Part 1. Summary tabulation will be provided by disease duration (≤2 and >2 years) and overall.

The analyses of Study Part 1 will be exploratory. The exploratory analysis of Study Part 1 will occur after all subjects have completed their visit at week 28 (ie, 28 weeks after study inclusion) or discontinued earlier. This analysis will include all efficacy measures after week 0 and will cover the time until the week 28 visit.

For all continuous efficacy variables, descriptive statistics will include the N, mean, standard deviation, median, IQ range, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Graphical data displays will also be used to summarize the data.

5.1. Analysis Specifications

5.1.1. Level of Significance

Not applicable for Study Part 1 analysis.

5.1.2. Data Handling Rules

5.1.2.1. Treatment Failure Criteria

Subjects who discontinue study agent due to lack of efficacy, an AE, worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study period that could improve psoriasis are considered treatment failures. The protocol-prohibited medications/therapies are listed in section 8.1 of the CSP.

5.1.2.2. Treatment Failure Rules

No treatment failure rules will be applied in Study Part 1 analysis.

5.1.2.3. Missing Data Imputation

Non-responder imputation (for binary endpoints) or Last Observation Carried Forward (LOCF) imputation (for continuous endpoints) will be applied for subjects with missing data for the major and secondary endpoints in Study Part 1. Time-to-event analyses of binary endpoints will be performed on the observed cases only (ie, missing data will not be replaced for time-to-event analyses).

An 'observed cases analysis' for all binary and continuous endpoints in Study Part 1 without imputation of missing data will also be done.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

Not applicable for Study Part 1 analysis.

5.2.2. Estimand

Not applicable for Study Part 1 analysis.

5.2.3. Analysis Methods

Not applicable for Study Part 1 analysis.

5.3. Major Secondary Endpoints

Major secondary endpoints of this study in Study Part 1 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
- 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.

5.3.1. Definition

5.3.1.1. 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.

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 improvement in PASI

The time to improvement in PASI is defined as time from baseline (week 0) to first onset of response. In the absence of documented improvement, the time to improvement will be censored at the date of week 28 or the date of discontinuation in case of early treatment discontinuation.

Update after the Dry Run Meeting: The time to improvement in PASI will be computed as:

- Date of improvement - Date of Study Day 1, if the subject shows improvement,
- Date of week 28 or date of discontinuation - Date of Study Day 1, if the subject shows no improvement.

5.3.2. Analysis Methods

5.3.2.1. Psoriasis Area and Severity Index (PASI)

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 for subjects with short (≤ 2 years) and longer (>2 years) disease duration, 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 factor '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 (ie, no missing data imputation for time-to-event analyses).

A Chi-square test will be used to test the difference between subjects with short (≤2 years) and longer (>2 years) disease duration for binary endpoints. A 95% confidence interval for the difference will be calculated based on Wald statistic. For binary endpoints counts and percentages for subjects with short (≤ 2 years) and longer (>2 years) disease duration, along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for the factor effect 'disease duration' using the Chi-square test will be provided.

Subgroup analyses will be performed as specified in section 2.4.

Update after the Dry Run Meeting: The time to PASI response will be evaluated only for all subjects and by disease duration, but not for other subgroups. Instead, the number of PASI responders by visit will be shown by disease duration and the following subgroups:

- Response status (Super-Responder, Non-Super-Responder)
- PSO-pretreatment with biologics (ever used, never used)
- PSO-pretreatment with biologics (0, 1, 2 or more).

The survival curves will also be displayed by response status (Super-Responder, Non-Super-Responder) and by PSO-pretreatment with biologics (never used, ever used; 0, 1, 2 or more).

5.4. Other Secondary Endpoints

Other secondary endpoints of this study in Study Part 1 are:

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 20, 28
- Proportion of subjects with an absolute PASI score = 0 at all of the following visits: weeks 12, 16, 20 and 28
- The change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at week 28

- Proportion of subjects who achieve a DLQI score 0/1 and <5 at week 28
- The change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 12 and 28
- The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at week 28 among subjects with nail psoriasis at baseline (week 0)
- The change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at week 28

5.4.1. Definition

5.4.1.1. Psoriasis Area and Severity Index (PASI)

Refer to section 5.3.1.1.

5.4.1.2. 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 were 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.

Update after the Dry Run Meeting: The answer "Not relevant" will be scored 0, as intended by the score developers.

5.4.1.3. 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).

5.4.1.4. 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 NAPP-QOL global score is computed by averaging all items. In case more than 25% of the items are missing (5 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 (=5 or more item pairs with missing values), no global score will be calculated.
3. NAPPA-CLIN has been developed from the 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 feed)) 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.

Update after the Dry Run Meeting:

For NAPPA-QOL, the last sentence is changed to: In case more than 25% of the items are missing (6 or more items missing), the score is not computed for the respective patient.

For NAPPA-PBI, the last sentence is changed to: Only if more than 25% of items pairs are unanswered (=7 or more item pairs with missing values), no global score will be calculated.

5.4.1.5. 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 TES.

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.

5.4.2. Analysis Methods

5.4.2.1. Psoriasis Area and Severity Index (PASI)

- Proportion of subjects who achieve a PASI 75/90/100 response at weeks 20, 28
- Proportion of subjects with an absolute PASI score = 0 at all of the following visits: weeks 12, 16, 20 and 28

The proportion of subjects will be displayed in a frequency table providing the number and percentage of subjects. Graphical presentation will be presented by means of a bar chart.

A Chi-square test will be used to test the difference of proportions between subjects with short (≤2 years) and longer (>2 years) disease duration. A 95% confidence interval for the difference will be calculated based on Wald statistic.

5.4.2.2. Dermatology Life Quality Index (DLQI)

- The change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at week 28
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at week 28

The change from baseline in DLQI will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the week 28 value and the change from baseline value will be displayed.

The proportion of subjects achieving a DLQI score of 0 or 1 and <5 at week 28 will be displayed in a frequency table providing the number and percentage of subjects. Graphical presentation will be presented by means of a bar chart. In addition, cross-tabulations will be provided between the

proportion of subjects who achieve a DLQI score 0/1 and <5 at week 28 and the proportion of subjects who achieve a PASI 75/90/100 response at weeks 28.

An analysis of covariance (ANCOVA) model will be used to test the difference in change from baseline between subjects with short (≤2 years) and longer (>2 years) disease duration ; the change from baseline being the dependent variable, and 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. A Chi-square test will be used to test the difference of proportions between subjects with short (≤2 years) and longer (>2 years) disease duration. A 95% confidence interval for the difference will be calculated based on Wald statistic.

Update after the Dry Run Meeting: No cross-tabulations between PASI and DLQI will be done. Also, the box plots will not be presented.

5.4.2.3. Body Surface Area (BSA%)

- The change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 12 and 28

The change from baseline in BSA will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the week 12/28 value and the change from baseline value will be displayed.

An ANCOVA model will be used to test the difference in change from baseline between subjects with short (≤2 years) and longer (>2 years) disease duration; the change from baseline being the dependent variable, and disease duration, and baseline value of endpoint as independent variables. A 95% confidence interval for the difference in LSmeans and p-value will be calculated based on contrast test statistics.

Update after the Dry Run Meeting: The box plots will not be presented.

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

- The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) scores at week 28 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 and box plots. The baseline value, the week 28 value and the change from the baseline value will be displayed. According to the definition of the global score of NAPPA-PBI the week 28 value is already the change from baseline value.

An ANCOVA model will be used to test the difference in change from baseline between subjects with short (≤2 years) and longer (>2 years) disease duration; the change from baseline being the dependent variable, and disease duration, and baseline value of endpoint as independent variables. A 95% confidence interval for the difference in LSmeans and p-value will be calculated based on contrast test statistics. For the global score of NAPPA-PBI a corresponding ANOVA model without baseline value as covariate will be used.

Update after the Dry Run Meeting: The box plots will not be presented.

5.4.2.5. Psoriasis Symptom and Sign Diary (PSSD)

- The change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at week 28

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the week 28 value and the change from the baseline value will be displayed.

An ANCOVA model will be used to test the difference in change from baseline between subjects with short (≤2 years) and longer (>2 years) disease duration; the change from baseline being the dependent variable, and disease duration, and baseline value of endpoint as independent variables. A 95% confidence interval for the difference in LSmeans and p-value will be calculated based on contrast test statistics.

Update after the Dry Run Meeting: The box plots will not be presented.

5.5. Additional Endpoint(s)

5.5.1. Definition

Additional endpoints of this study in Study Part 1 are:

- Proportion of 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)

Update after the Dry Run Meeting: The definition for super-response only includes PASI values at weeks 20 and 28 and is independent from the number of injections given. So even with less than 4 injections, a subject may be a Super-Responder.

5.5.2. Analysis Methods

The proportion of Super-Responders will be displayed in a frequency table providing the number and percentage of subjects. Graphical presentation will be presented by means of a bar chart.

A Chi-square test will be used to test the difference of proportions between subjects with short (≤2 years) and longer (>2 years) disease duration. A 95% confidence interval for the difference will be calculated based on Wald statistic.

Subgroup analyses will be performed as specified in section 2.4.

Univariate and multivariate logistic regression analyses may also be used to investigate the relationship between potential prognostic or risk factors (ie, factors defined as subgroups in section 2.4) and the single binary outcome variable SRe.

Update after the Dry Run Meeting: The impact of confounders on super-response will be investigated in the following univariate logistic regression models:

- Disease duration (categorical: disease duration ≤2 years, >2 years)
- Age at baseline (continuous, and categorical: <45, 45-65, >65 years)
- Age at PSO onset (continuous)
- BMI at baseline (continuous and categorical: ≤25, >25 to 30, >30 kg/m²)
- PSO pretreatment with biologics (categorical; ever used, never used)
- PASI at baseline (continuous)
- BSA affected at baseline (continuous)
- Body weight at baseline (continuous)
- Gender (categoric: Male, Female)
- DLQI at baseline (continuous).

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 the active treatment period until Week 28 will be summarized descriptively (observed cases analysis for continuous endpoints; observed cases analysis and non-responder imputation for binary endpoints).

6. SAFETY

All safety analyses in Study Part 1 will be based on the ITT analysis set. Data from the safety follow-up will not be included in Study Part 1 analysis; last visit to be included for Study Part 1 analysis is week 28 or early termination visit in case of discontinuation in Study Part 1. Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, and changes in vital signs will be summarized by disease duration (≤2 and >2 years) and overall. Treatment-emergent AEs (TEAEs) will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred terms (PT).

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

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent until the day of week 28 visit (or early termination visit, if applicable.) in Study Part 1 is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each treatment adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Summary tabulation will also provide the number of events, if applicable.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent
- 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

- Had AEs leading to discontinuation of study agent

Deaths will be displayed by actual treatment received. 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 be provided.

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the ITT analysis set.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points.

Change from baseline (week 0) to postbaseline time points (week 12, week 20) will be summarized for chemistry and hematology tests. Box plots of change from baseline to postbaseline time points will be provided.

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 to post-baseline time points with respect to abnormality criteria (low, normal, high).

Update after the Dry Run Meeting: Lab values given as borderline value only (eg <8 or >200) will be evaluated by ignoring the sign. Also, the box plots will not be presented.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, pulse, blood pressure (systolic and diastolic), will be summarized at each assessment time point. Change from baseline will be summarized for the open-label treatment period until week 28. Descriptive statistics (mean, standard deviation, median, IQ range, 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 3, will be summarized for subjects who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 3: [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 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline

Abnormal findings in physical examination (additional to psoriasis findings) at screening, baseline visit (week 0), week 20 and week 28 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.

6.4. Electrocardiogram

Not applicable

6.5. Other Safety Parameters

Tuberculosis Evaluation

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

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Not applicable for Study Part 1 analysis.

7.2. Immune Response

Not applicable for Study Part 1 analysis.

7.3. Pharmacodynamics

Not applicable for Study Part 1 analysis.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable for Study Part 1 analysis.

8. BIOMARKERS

Not applicable for Study Part 1 analysis.

9. HEALTH ECONOMICS

Not applicable for Study Part 1 analysis.

REFERENCES

None

ATTACHMENTS

None

Janssen Cilag GmbH

Statistical Analysis Plan – Study Part 2

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)**

Status:	Final
Date:	15 Dec 2021
Prepared by:	Janssen-Cilag GmbH, Germany
Document No.:	EDMS-RIM-612870

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	15 Dec 2021	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 Clinical Study Protocol CNTO1959PSO3012 will be performed for each of the three Study Parts.

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

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

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

This plan describes the statistical analyses planned to be performed for the analysis of Study Part 2 (randomized, double blind treatment phase) and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF). Statistical analyses of study data recorded before week 28 and after week 68 are specified in separate SAPs, if not otherwise specified.

This SAP is the core document for all statistical programming planned to be performed for the analysis of Study Part 2 of study protocol no. CNTO1959PSO3012. The statistical analyses will focus on the comparison of the two randomized, double blind treatment groups (ie, group **2a**: guselkumab 100 mg q8w vs. group **2b**: guselkumab 100 mg q16w) in Study Part 2. If not otherwise specified, descriptive statistical analyses of study group **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 in Study Part 2) will be performed likewise.

Note: Subjects losing control of disease, defined as PASI score >5 at any visit during Study Part 2 or 3 (ie, until week 116), 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.

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 will feature the following structure and design:

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

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

guselkumab 100 mg q8w until week 60 (last administration at week 60 visit) with final study assessments at week 68 and final safety follow-up visit at week 72 (defined as study group **2c**).

Study Part 2: Week 28 through Week 68:

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

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

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

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

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

Study Part 3: Week 68 through Week 220:

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

Re-treatment

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

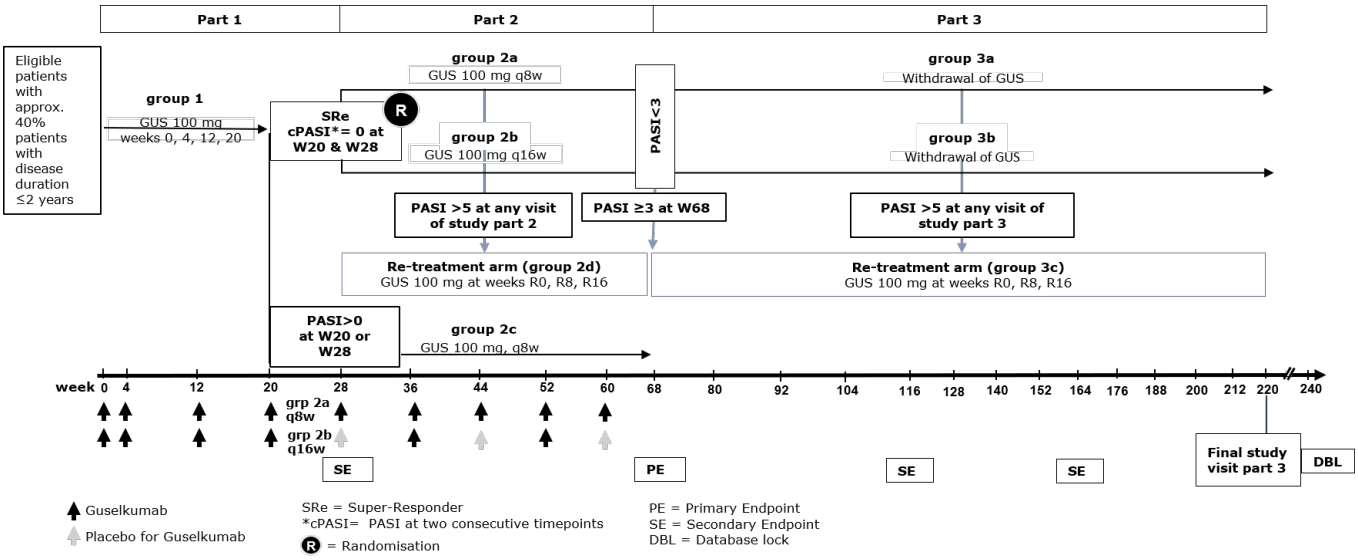
If re-treatment is started at a visit which would usually not require all PROs needed at the first re-treatment visit, those PROs will be obtained immediately after efficacy assessments (basis for re-treatment-decision) and prior to drug administration at that visit.

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

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

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

A schematic diagram of the study design is provided below.



Study groups:

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

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

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

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

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

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

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

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

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 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 2

In Study Part 2 the following analysis sets will be defined for the efficacy and safety analyses.

4.1. All Enrolled Analysis Set

Not applicable for Study Part 2 (only applicable for Study Part 1). However, for Study Part 2 the number of 'Subjects starting Study Part 2' will be reported and used for display of summary tables, if applicable.

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

4.2. Efficacy Analysis Set(s)

The confirmatory efficacy analysis of the primary endpoint variable and the exploratory analyses of the secondary endpoint variables will be performed both for the intent-to-treat analysis set (ITT) and the per-protocol analysis set (PP).

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

For all efficacy analyses to compare guselkumab 100 mg q16 (group **2b)** vs. guselkumab 100 mg q8w (group **2a)** in Study Part 2, all randomized subjects at week 28 will be included in the intent-to-treat analysis set (ITT). Subjects will be analyzed according to the treatment group to which they were randomized regardless of the treatment they actually received.

For all efficacy analyses of study group **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 in Study Part 2) all subjects treated with at least one dose of study agent during Study Part 2 will be included in the intent-to-treat analysis set (ITT).

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.

4.2.2. Per-protocol Analysis Set (PP)

The per-protocol analysis set (PP) will consist of all subjects in the intent-to-treat analysis set (ITT) completing or terminating the Study Part 2 without any major deviation of the protocol and its procedures until the week 68 visit. Subjects with major protocol deviations (except those not effecting the primary endpoint) 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 week 28, 52, and 68 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 both for the intent-to-treat analysis set (ITT) and the per-protocol analysis set (PP).

4.2.4. Safety Analysis Set

For all safety analyses, all subjects treated with at least one dose of study agent during Study Part 2 will be included. For all the safety analyses, subjects will be analyzed according to the treatment they actually received.

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 2

Description of planned statistical analyses in Study Part 2 will focus on the comparison of the two randomized treatment groups (ie, group **2a**: guselkumab 100 mg q8w vs. group **2b**: guselkumab 100 mg q16w) in Study Part 2. If not otherwise specified, descriptive statistical analyses of study group **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 in Study Part 2) will be performed likewise. Inferential statistics (ie, p-values, confidence intervals, etc.) will be provided only for the week 68 data of endpoints in Study Part 2.

Note: Statistical analysis of Study Part 2 will also include analyses of study data recorded before week 28. Data of Study Part 1 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 Part 1.

5.1. General Considerations

The following general analysis definitions refer only to Study Part 2.

The primary analysis of Study Part 2 will be confirmatory. The confirmatory significance level for non-inferiority testing is fixed to a one-sided $\alpha = 0.05$. Besides the confirmatory testing of the primary endpoint all other inferential statistical testing (including calculation of confidence intervals) are to be interpreted in the exploratory sense only.

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 responding to treatment. Continuous response parameters will be compared using a univariate analysis of variance model with fixed effects for treatment group and disease duration and baseline value as a covariate. In addition, a multivariate linear mixed model for repeated measures (MMRM) will be used to test the difference in change from baseline between treatment groups; the repeated measures of change from baseline being the dependent variables, treatment, disease duration, and baseline value of endpoint as independent variables. 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 treatment group (for SRe and non-SRe) as the main classification variable and for the total of the sample (SRe only; not for efficacy analyses) in the respective analysis set, if not otherwise specified; ie, results will be provided for group **2a,** group **2b,** total of group **2a** and group **2b (**not for efficacy analyses)**,** and group **2c.** Additional classification variables are explicitly mentioned in the following text. Individual subject data listings will be presented parameter wise and will be sorted by treatment group, study site, subject's identification number and study visit, if applicable. A more detailed description of the planned statistical analyses are 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 2 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 2 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 1) are the visit windows and the target days for each visit defined in the protocol.

Table 1 – 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 155	141
	1	W28	Week 28	183 to 211	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 491	477

*Relative to [Study Day 1]

If there are visits outside of the defined windows, final decisions on the allocation of the actual visit to an earlier or later planned visit or if 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 2 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 2 is defined as the last available postbaseline result within the analysis period from week 28 until week 68. Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period from week 28 until week 68.

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

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event 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
  - The 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
  - The 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 adverse event 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 2 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 2 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 in Study Part 2.
- Last Observation Carried Forward (LOCF) imputation for continuous efficacy endpoints will be applied for subjects with missing data in Study Part 2.
    - 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).
- In addition, the following alternative approaches will be applied (supplementary analyses):
    - Multiple imputation will be used for calculation of response rates regarding PASI < 3 (ie, the primary endpoint), PASI <= 1 and PASI = 0.
        - Multiple imputation methods generate multiple copies of the original dataset by replacing missing values using an appropriate stochastic model, analyze them as complete sets and finally combine the different parameter estimates across the datasets to produce a unique point estimate and standard error taking into account the uncertainty of the imputation process.

- Derived variables will not be imputed but will be derived from imputed values (eg, if the PASI score <3 at week 68 is missing, the PASI score at week 68 will be imputed to calculate whether the patient achieves an absolute PASI score <3 at week 68).
- Multiple imputation will only be done for the two randomized treatment groups. For the multiple imputation, the SAS procedures MI and MIANALYZE will be used. The exact multiple imputation procedure is data-dependent (method, missing data pattern, etc.) and will be determined prior to unblinding. The number of imputations will be set to 100. The Fully Conditional Specification (FCS) regression method will be used to impute values for continuous data with an arbitrary missing data pattern. The FCS method is more flexible in that it allows for classification variables as covariates in the imputed model. Covariates that are considered for inclusion in the multiple imputation model for better prediction of the missing values are: treatment group, disease duration, and non-missing values of the analysis variables at all scheduled times within the analysis period from week 28 until week 68.

- For continuous endpoints the missing data issues will be handled implicitly through using the mixed model repeated measures (MMRM) approach which does not employ formal imputation. The use of MMRM is based on the assumption of missing at random (MAR) and the assumption that dropouts would behave similarly to other patients in the same treatment group, and possibly with similar covariate values, had they not dropped out.

An 'observed cases analysis' for all binary and continuous endpoints in Study Part 2 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 Part 1 (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 2 by treatment groups (ie, groups **2a, 2b, 2c)** and overall total of group **2a** and group **2b**:

- Subjects randomized (only for SRe)
- Subjects who received study agent within Study Part 2
- Subjects who completed Study Part 2
- Subjects who discontinued study agent within Study Part 2
- Reasons for discontinuation of study agent within Study Part 2
- Subjects who terminated study prematurely within Study Part 2
- Reasons for termination of study within Study Part 2.

5.3. Primary Endpoint(s) Analysis

The confirmatory analysis of the primary endpoint variable will be performed both for the intent-to-treat analysis set and the per-protocol analysis set.

5.3.1. Definition of Endpoint(s)

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

5.3.2. Estimand

Primary Trial 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*

Estimand Scientific Question of Interest: Is guselkumab 100 mg q16w treatment 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 and a non-inferiority margin of 10%?

Study intervention:

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

Population: Subjects of at least 18 years of age with moderate to severe plaque-type psoriasis. Subjects with a PASI score = 0 at weeks 20 **and** 28 will be defined as SRe and randomly assigned at week 28 to the following two treatment groups: **2a**) guselkumab 100 mg q8w or **2b**) guselkumab 100 mg q16w. The confirmatory analysis of the primary endpoint variable will be performed for both the intent-to-treat analysis set and the per-protocol analysis set.

Variable: Responder binary variable, where a responder is defined as a subject in study groups **2a** and **2b** achieving an absolute PASI score <3 at week 68 who does not:

- discontinue study agent due to lack of efficacy, an AE, worsening of psoriasis, or
- started a protocol-prohibited medication/therapy during the study period that could improve psoriasis are considered non-responders.

Summary measure (Population-level summary): proportion (percentage) of subjects; after the rule for handling of protocol-prohibited medication/therapy is applied, non-responder imputation will be applied for subjects with missing data.

Intercurrent events and their corresponding strategies:

Intercurrent events	Strategy for addressing intercurrent events
• Discontinuation of study agent due to lack of efficacy, an AE, worsening of psoriasis	**Composite Strategy:** A participant with this intercurrent event is considered as a non-responder after this event, the occurrence of this intercurrent event being captured in the variable definition.
• Start of protocol-prohibited medication/therapy during the study period that could improve psoriasis.	**Composite Strategy:** Same as above

Sensitivity and Supplementary Analysis for Estimands

The following sensitivity analyses will be performed (after the rule for handling of protocol-prohibited medication/therapy and non-responder imputation are applied).

- Stratified Newcombe confidence limits for the common proportion difference with respect to the primary endpoint will also be provided by using the method of Yan and Su (Yan und Su 2010).
- The primary endpoint will also be analyzed without adjustment for disease duration ('unstratified analysis'). The two-group large-sample normal approximation Z-test will be used along with
  - the two-sided 90% Wald type confidence interval, and
  - the two-sided 90% Newcombe confidence interval.

The sensitivity analyses described above will also be performed using multiple imputation after the rule for handling of protocol-prohibited medication/therapy is applied. Details on handling of missing data are described in section 5.1.8.

No supplementary analyses to target alternative estimands will be performed.

5.3.3. Analysis Methods

The proportion of subjects with an absolute PASI score <3 at week 68 will be displayed in a frequency table providing the number and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type confidence intervals (90% CIs) stratified by 'disease duration'. For single proportions within each treatment group unstratified two-sided 90% CIs according to Clopper-Pearson will be calculated. Graphical presentation will be presented by means of a bar chart.

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

Stratified Newcombe confidence limits for the common proportion difference with respect to the primary endpoint will also be provided by using the method of Yan and Su (Yan und Su 2010) as specified in section 5.3.2.

In addition, the primary endpoint will also be analyzed without adjustment for disease duration ('unstratified analysis' of non-inferiority). The two-group large-sample normal approximation Z-test along with the two-sided 90% Wald type and Newcombe confidence interval will be computed as specified in section 5.3.2.

Subgroup analyses will be performed unstratified for the subgroups as specified in section 5.8.8.

5.4. Major Secondary Endpoint(s) Analysis

Statistical analyses will be descriptive and exploratory only, and will be performed both for the intent-to-treat analysis set and the per-protocol analysis set.

Major secondary endpoints of this study in Study Part 2 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 (group **2c** only)
- Proportion of subjects who achieve an absolute PASI score of 0, ≤1 and <3 at week 68.

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.

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 improvement in PASI (group 2**c** only**)**

The time to improvement in PASI is defined as time from baseline (week 0) to first onset of response. In the absence of documented improvement, the time to improvement will be censored at the date of week 68 or the date of discontinuation in case of early treatment discontinuation.

The time to improvement in PASI will be computed as:

- Date of improvement - Date of Study Day 1, if the subject shows improvement,
- Date of week 68 or date of discontinuation - Date of Study Day 1, if the subject shows no improvement.

5.4.2. Estimand(s)

NA

5.4.3. Analysis Methods

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, the median time-to-event with 90% confidence intervals (CI), and the hazard ratio (including 90% CI and the p-value calculated from Cox-regression with the factors 'treatment 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).

The proportion of subjects responding to treatment will be displayed in frequency tables providing the number and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 90% confidence intervals (90% CIs) stratified by 'disease duration'. For single proportions within each treatment group unstratified two-sided 90% 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 responding to treatment. The Mantel-Haenszel estimate, the two-sided Wald-type 90% 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).

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.

5.5. Other Secondary Endpoint(s)

Statistical analyses will be descriptive and exploratory only, and will be performed both for the intent-to-treat analysis set and the per-protocol analysis set. Details on handling of missing data are described in section 5.1.8.

Other secondary endpoints of this study in Study Part 2 are:

- Proportion of subjects who achieve a PASI 75/90/100 response at week 68
- The change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at week 68
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at week 68
- The change from baseline (week 0) in affected Body Surface Area (BSA) at weeks 52, and 68
- The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) score at week 68 among subjects with nail psoriasis at baseline (week 0).
- The change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at week 68
- The proportion of subjects who achieve a PSSD sign score = 0 at week 68 among subjects with a PSSD sign score ≥1 at week 28

5.5.1. Definition of Endpoint(s)

5.5.1.1. Psoriasis Area and Severity Index (PASI)

Refer to section 5.4.1.1.

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 were 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 feed)) 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 TES.

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 week 68

The proportion of subjects responding to treatment will be displayed in frequency tables providing the number and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 90% confidence intervals (90% CIs) stratified by 'disease duration'. For single proportions within each treatment group unstratified two-sided 90% 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 responding to treatment. The Mantel-Haenszel estimate, the two-sided Wald-type 90% 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).

5.5.3.2. Dermatology Life Quality Index (DLQI)

- The change from baseline (week 0) in Dermatology Life Quality Index (DLQI) score at week 68
- Proportion of subjects who achieve a DLQI score 0/1 and <5 at week 68

The change from baseline in DLQI will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the week 28 and week 68 values and the respective changes 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 treatment groups; the change from baseline being the dependent variable, treatment, disease duration, and baseline value of endpoint as independent variables. A 90% 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) with the 90% CI and two-sided p-value will be provided from the ANCOVA model.

In addition, a multivariate linear mixed model for repeated measures (MMRM) will be used to test the difference in change from baseline between treatment groups; the repeated measures of change from baseline at week s 28, 52, and 68 being the dependent variables, treatment, disease duration,

and baseline value of endpoint as independent variables. Inferential results will be provided likewise as for the univariate model.

The proportion of subjects responding to treatment will be displayed in a frequency table providing the number and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 90% confidence intervals (90% CIs) stratified by 'disease duration'. For single proportions within each treatment group unstratified two-sided 90% 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 responding to treatment. The Mantel-Haenszel estimate, the two-sided Wald-type 90% 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).

5.5.3.3. Body Surface Area (BSA%)

- The change from baseline (week 0) in affected Body Surface Area (BSA) at week 68

The change from baseline in BSA will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the weeks 12, 28, and 68 values and the respective changes 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 treatment groups; the change from baseline being the dependent variable, treatment, disease duration, and baseline value of endpoint as independent variables. A 90% 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) with the 90% CI and two-sided p-value will be provided from the ANCOVA model.

In addition, a multivariate linear mixed model for repeated measures (MMRM) will be used to test the difference in change from baseline between treatment groups; the repeated measures of change from baseline at week s 28, 52, and 68 being the dependent variables, treatment, disease duration, and baseline value of endpoint as independent variables. Inferential results will be provided likewise as for the univariate model.

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

- The change from baseline (week 0) in the Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA) scores at week 68 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 and box plots. The baseline value, the week 28 and 68 values and the respective changes from the baseline value will be displayed. According to the definition of the global score of NAPPA-PBI the week 28 and 68 value are already the change from 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)

- The change from baseline (week 0) in the signs and symptoms aggregate scores of the Psoriasis Symptoms and Signs Diary (PSSD) at week 68
- 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

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the week 28 and 68 values and the respective changes 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 treatment groups; the change from baseline being the dependent variable, treatment, disease duration, and baseline value of endpoint as independent variables. A 90% 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) with the 90% CI and two-sided p-value will be provided from the ANCOVA model.

In addition, a multivariate linear mixed model for repeated measures (MMRM) will be used to test the difference in change from baseline between treatment groups; the repeated measures of change from baseline at week s 28, 52, and 68 being the dependent variables, treatment, disease duration, and baseline value of endpoint as independent variables. Inferential results will be provided likewise as for the univariate model.

The proportion of subjects responding to treatment will be displayed in a frequency table providing the number and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), and two-sided Wald-type 90% confidence intervals (90% CIs) stratified by 'disease duration'. For single proportions within each treatment group unstratified two-sided 90% 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 responding to treatment. The Mantel-Haenszel estimate, the two-sided Wald-type 90% 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).

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 the active treatment periods in Study Parts 1 and 2 (Week 0 until Week 68) 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).

5.7. Safety Analyses

All safety analyses in Study Part 2 will be based on the safety analysis set based on actual treatment received. Data from the safety follow-up will not be included in Study Part 2 analysis; last visit to be included for Study Part 2 analysis is week 68 or early termination visit in case of discontinuation in Study Part 2. Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, and changes in vital signs will be summarized by treatment group and overall. Treatment-emergent AEs (TEAEs) will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred terms (PT).

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, IQ range, 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 receive study agent will be summarized. Descriptive statistics will be presented for number of study agent administrations.

5.7.2. Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the day of week 28 until the day of week 68 visit (or early termination visit, if applicable.) in Study Part 2 is considered to be treatment emergent. If the event occurs on the day of week 28, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent in Study Part 2 based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each treatment adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Summary tabulation will also provide the number of events, if applicable.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent
- 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
- Had AEs leading to discontinuation of study agent

Deaths will be displayed by actual treatment received. 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 be provided.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

All clinical laboratory tests will be displayed 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 0, 12, 20, 28, 36, 52, and 68) in Study Parts 1 and 2.

Change from baseline (week 0) to postbaseline time points (weeks 12, 20, 28, 36, 52, and 68) in Study Parts 1 and 2 will be summarized for chemistry and hematology tests.

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 to post-baseline time points (weeks 36, 52, and 68) in Study Part 2 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, blood pressure (systolic and diastolic), will be summarized at each assessment time point (weeks 0, 4, 12, 16, 20, 28, 36, 44, 52, 60, and 68). Change from baseline (week 0) will be summarized for the randomized treatment period from week 28 until week 68. Descriptive statistics (mean, standard deviation, median, IQ range, 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 3, will be summarized for subjects who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 3: [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 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline

Abnormal findings in physical examination (additional to psoriasis findings) at baseline visit (week 0), week 28, 60, and week 68 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 Study Part 2 analysis.

5.7.3.4. Other Safety Parameters

Tuberculosis Evaluation

Categorical data on tuberculosis evaluation at each scheduled visit from week 28 until week 68 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 from week 28 until week 68 will be displayed in a frequency table providing the number and percentage of subjects per category.

5.8. Other Analyses

5.8.1. Pharmacokinetics

The PK analysis is out of scope for this SAP.

5.8.2. Immunogenicity

Not applicable for Study Part 2 analysis.

5.8.3. Pharmacodynamics

Not applicable for Study Part 2 analysis.

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable for Study Part 2 analysis.

5.8.5. Biomarkers

Not applicable for Study Part 2 analysis.

5.8.6. Health Economics

Not applicable for Study Part 2 analysis.

5.8.7. Other Variables and/or Parameters

Not applicable for Study Part 2 analysis.

5.8.8. Definition of Subgroups

Subgroup analyses are planned to be performed for the primary endpoint and for the major secondary endpoints for the following subgroups in study groups **2a**, **2b**, and **2c**. All subgroup analysis will be performed unstratified, ie, without use of 'disease duration' as stratification factor in the exploratory inferential statistical analysis.

- Disease duration
  - ≤ 2 years
  - > 2 years
- Age at baseline in years
  - < 45
  - ≥ 45 to 65
  - > 65
- BMI
  - normal ≤ 25
  - overweight > 25 – 30
  - obese > 30
- Weight in kg
  - ≤ 90
  - > 90
- Disease duration in years
  - > 2 to 10
  - > 10
- PSO-pretreatment (for hierarchical categorization see section 6.5):
  - Topical therapy
  - Phototherapy
  - Non-biologic systemic therapy
  - Biologic therapy
- PSO-pretreatment with biologics:
  - 0 biologics
  - 1 biologic
  - 2 or more biologics

Subgroup analyses for the primary endpoint and for the major secondary endpoints will be performed on either ITT or PP analysis set (not for both sets) after the rule for handling of protocol-prohibited medication/therapy is applied using non-responder imputation for binary endpoints and observed cases analyses for time-to-event endpoints. The decision which analysis set should be used for the subgroup analyses will be taken at the Data Review Meeting for Study Part 2.

Note: At the Data Review Meeting and/or Dry Run Meeting for Study Part 2 it will be decided which subgroup analyses will actually be performed for Study Part 2.

5.9. Interim Analyses

Statistical analyses will be performed separately for each of the three Study Parts. No formal confirmatory interim analysis is planned for this study.

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

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
EP	Endpoint
FAE	Fumaric acid ester
FOIA	Freedom of Information Act
FCS	Fully Conditional Specification
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ie	that is
IQ	Interquartile range
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mmHg	Millimeter of mercury
MMRM	Multivariate linear mixed model for repeated measures
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
PROs	Patient reported outcomes
PSO	Psoriasis
PSSD	Psoriasis Symptoms and Signs Diary
PT	Preferred terms
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
TEAE	Treatment-emergent adverse event
TES	Time and Events Schedule
ULN	Upper limit normal
UVB	Ultra violet 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 were performed.

6.3. Appendix 3 Demographics and Baseline Characteristics

Subjects' demographic data (eg, age, weight, BMI, height, sex, child bearing 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 2 presents a list of the demographic variables that will be summarized.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg) BMI	
Height (cm)	
Categorical Variables	
Age ([< 45, >= 45 to 65, > 65 years)])	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female) Child bearing potential (of child bearing potential, permanently sterilized, postmenopausal) BMI (normal ≤ 25, overweight > 25 – 30, Obese > 30)	
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.

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.

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 2 analysis, which started before or at the date of week 68 (start of Study Part 3).

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 1 concomitant therapy. Prior therapies (incl. psoriasis therapies) will 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 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 will also be assessed by protocol deviations related to study drug administration (ie, incorrect and missed administrations).

6.8. Appendix 8 Adverse Events of Special Interest

Not applicable for Study Part 2 analysis.

6.9. Appendix 9 Medications of Special Interest

Not applicable for Study Part 2 analysis.

6.10. Appendix 10 Laboratory Toxicity Grading

Not applicable for Study Part 2 analysis.

7. REFERENCES

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

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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)**

Status:	Final
Date:	14 Feb 2023
Prepared by:	Janssen-Cilag GmbH, Germany
Document No.:	EDMS-EDMS-RIM-852786

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

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

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.

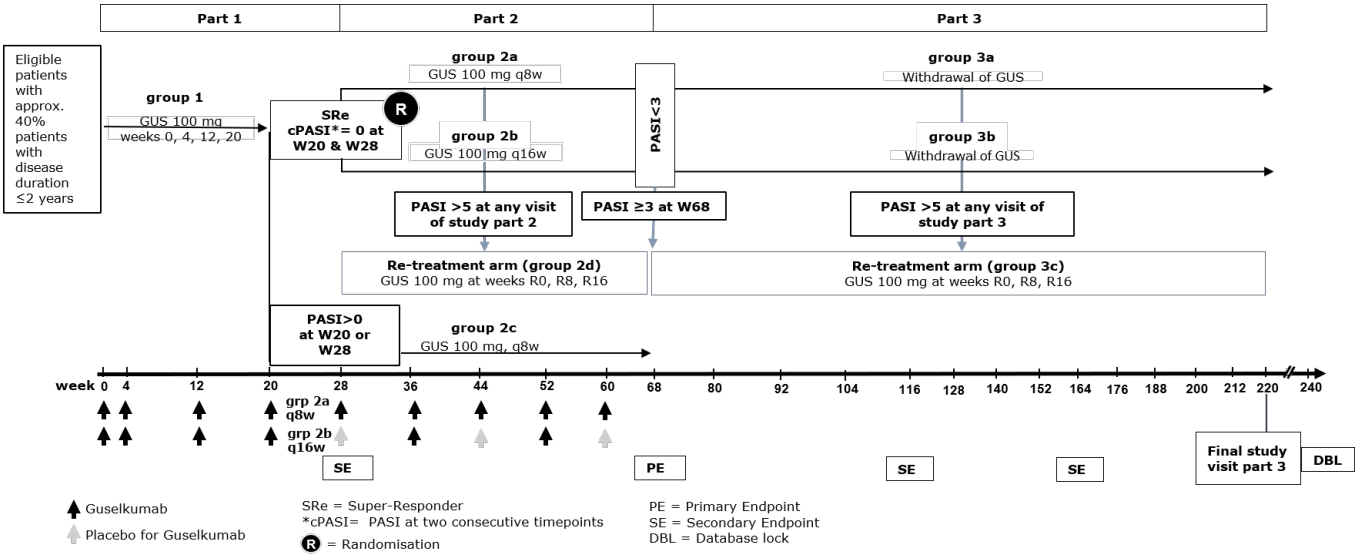
The final efficacy assessment for all subjects in the re-treatment arms takes place 24 weeks after loss of control, and study termination is 28 weeks after loss of control (final study visit/safety follow-up). At visit week 24 of the re-treatment, the investigator may continue actual treatment

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). If decided at the Dry Run Meeting, also the Per-protocol analysis set (PP) will be evaluated.

Update after the Dry Run Meeting: 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 Intent-to-treat analysis set (ITT) and, if requested, the Per-protocol analysis set (PP).

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.

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 155	141
	1	W28	Week 28	183 to 211	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 491	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	785 to 841	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	1121 to 1177	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).

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.

Update after the Dry Run Meeting: The windows for the week 28, week 68, week 116 and week 164 visits were expanded. All values obtained at visits outside of defined windows will not be taken into account for by-visit analyses. The new visit windows are as follows:

Table 2 – Visit Windows

Parameter	Analysis Period	Scheduled Visit	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
	1	W28	Week 28	183 to 238	197
	2	W68	Week 68	463 to 532	477
	3	W116 #	Week 116	758 to 968	813
	3	W164 #	Week 164	1094 to 1204	1149

* 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).

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.
  - Update after the Dry Run Meeting: 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 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 #
- 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
- Reasons for termination of study within Study Part 3 (subjects of groups 3a and 3b).

without those subjects who started re-treatment already at the week 68 visit

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' (NRI analysis only). 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 overall, providing exploratory p-values (unadjusted Chi^2 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.

Update after the Dry Run Meeting: Statistical testing will also be performed for the OC analysis.

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' (NRI analysis only). 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).

Update after the Dry Run Meeting: Statistical testing will also be performed for the OC analysis. 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) and overall, providing exploratory p-values (unadjusted log-rank test) for the difference between disease duration categories.

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' (NRI analysis only). 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.

Update after the Dry Run Meeting: Statistical testing will also be performed for the OC analysis. 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' (NRI analysis only). 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) and overall, providing exploratory p-values (unadjusted Chi² test) for the difference between disease duration categories.

Update after the Dry Run Meeting: Statistical testing will also be performed for the OC analysis. 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. 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, ≤2 years, >2 years) and overall, providing exploratory p-values (unadjusted log-rank test) for the difference between disease duration categories.

- 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.

Update after the Dry Run Meeting: Percentages will be based on the available number of subjects with non-missing data per visit.

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 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.

Update after the Dry Run Meeting: 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:

- Disease duration at baseline
  - ≤ 2 years
  - > 2 years
- Age at baseline
  - < 45 years
  - ≥ 45 to 65 years
  - > 65 years
- BMI at baseline
  - normal (≤ 25 kg/m²)
  - overweight (> 25 – 30 kg/m²)
  - obese (> 30 kg/m²)

- Body weight at baseline
  - ≤ 90 kg
  - > 90 kg
- PSO-pretreatment (for hierarchical categorization see section 6.5)
  - No prior therapy
  - Topical therapy
  - Phototherapy
  - Non-biologic systemic therapy
  - Biologic therapy
- 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:

- 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 will be taken at the Data Review Meeting for Study Part 3.

Note: At the Data Review Meeting and/or Dry Run Meeting for Study Part 3 it will be decided which subgroup analyses will actually be performed for Study Part 3.

Update after the Dry Run Meeting: No PP analysis will be performed. All subgroups defined in the final SAP (version 1.0) will be kept for analysis, and none will be added. In new tables, 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. New figures to display subgroups will be generated for the time to end of the treatment-free period.

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.

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'

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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