Janssen-Cilag GmbH, Germany*

Statistical Analysis Plans – Cover page

Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm® initial/Fumaderm®) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment

POLARIS

Protocol CNTO1959PSO3008; Phase 3b

CNTO1959 guselkumab

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Content of this document

This document consists of four statistical analysis plans, each pertaining to the analyses performed:

- Week 24 analysis, document “Polaris_SAP_FINAL_signed_20170717.pdf”;
- Week 32 analysis, document “Polaris_SAP_W32_V1.0_15Aug2018_signed.pdf”;
- Week 64 analysis, document “Polaris_SAP_W64_V1.0_29Aug2018 signed.pdf”;
- Week 100 analysis, document ”Polaris_SAP_W100_V1.0_09May2019_signed.pdf”.

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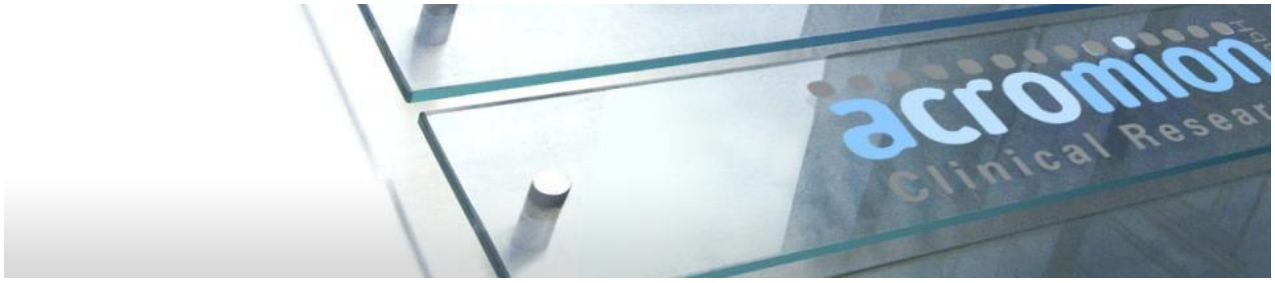

Statistical Analysis Plan

Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm® initial/ Fumaderm®) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment

POLARIS

- Week 24 Analysis -

Study Code	CNTO1959PSO3008
EudraCT Number	2016-002135-15
Development phase	Phase 3b
Study Design	randomized, open-label, efficacy assessor-blinded, single country, multicenter, active-comparator-controlled
Sponsor	Janssen-Cilag GmbH, Neuss Johnson & Johnson Platz 1, 41470 Neuss, Germany
Contract Research Organization	acromion GmbH Europaallee 27 – 29 50226 Frechen, Germany
Version No., Date	Final 1.0, 10-July-2017

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1.0 Signatures

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2.0 List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CRF	Case Report Form(s)
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e.g.	example given
FAE	Fumaric Acid Esters
HBV/ HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICH	International Council on Harmonization
i.e.	that is
IGA	Investigator´s Global Assessment
IL	Interleukin
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NTEAE	Not Treatment Emergent Adverse Event
NTESAE	Not Treatment Emergent Serious Adverse Event
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PRO	Patient-Reported Outcome(s)
PSSD	Psoriasis Symptom and Sign Diary
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form (36-item) health survey
SOC	System Organ Class
SOP	Standard Operating Procedure
ss	scalp-specific
TB	tuberculosis
TEAE	Treatment Emergent Adverse Event
TES	Time and Events Schedule
TESAE	Treatment Emergent Serious Adverse Event

3.0 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 and the relevant acromion SOPs and/or guidelines. This plan describes the statistical analyses planned to be performed for the Week 24 analysis of Janssen-Cilag GmbH Clinical Study Protocol CNTO1959PSO3008 and should be read in conjunction with the CSP and the electronic Case Report Form (eCRF). Statistical analyses of study data recorded after Week 24 will be specified in a separate SAP which will be based on protocol amendment 1 to the CSP.

The Week 24 analysis will include the confirmatory analysis of the primary endpoint and the major secondary endpoints and exploratory analyses for all other predefined efficacy and safety analyses until Week 24. Evaluations on health technology assessment (HTA) will also be specified in this SAP. No separate HTA SAP will be provided. The Week 24 analysis will be performed after all subjects have completed their visit at 24 weeks after randomization or discontinued earlier. Data base lock for the Week 24 analysis will be after the Week 24 visit data are ready for statistical analysis (i.e., clean data).

This SAP is the core document for all statistical programming planned to be performed for the Week 24 analysis and is based on the following study documents to protocol no. CNTO1959PSO3008:

Document	Version, Date
Protocol / Amendments	Version 1.0, 03-AUG-2016
eCRF	Version 1.0, 12-DEC-2016
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016

4.0 Responsibilities

The responsibilities for the biometrical tasks at acromion GmbH are assigned as follows:

Name	Function	Task
[redacted]	Statistician	Statistical Programming and Analysis
	Statistician	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Medical Data Analyst	Medical Data Review and Coding

5.0 Software Utilized

The statistical analysis and generation of tables, patient data listings and figures will be performed using the SAS® software package version 9.4 under the Microsoft Windows® 7 operating system at the computer facilities of acromion GmbH. Additional analyses regarding health technology assessment (HTA) may be performed by or under the responsibility of Janssen-Cilag GmbH.

6.0 Coding Systems Utilized

The MedDRA-dictionary version 19.1 is used for coding of prior and concomitant diseases and for coding of adverse events. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Medical History of Interest	Medical History Term	MH/MHTERM
Previous Phototherapy	Type of Phototherapy	MH/MHTERM
Concomitant Medication	Indication	CM/CMIND
Concomitant Therapy	Indication	CM/CMIND
Concomitant Therapy	Therapy	CM/CMTRT
(S)AE	Term	AE/AETERM

Prior and concomitant medications are coded according to the WHO terminology using the 2016/1 version of the WHO-Drug Dictionary. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Previous Topical Therapy	Medication/Therapy	MH/MHTERM
Concomitant Medication	Compound	CM/CMTRT

Details are specified in the Data Management Plan.

7.0 Study Objectives and Hypotheses

7.1 Objectives

Primary Objectives

The primary objectives of the study are

- to compare the efficacy of guselkumab to fumaric acid esters (FAE) in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.
- to assess the safety and tolerability of guselkumab in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.

Secondary Objective

The secondary objective is to compare improvement of health-related quality of life (QOL) and other patient-reported outcomes (PRO) when systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.

7.2 Hypotheses

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

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

8.0 Study Endpoints

Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 90% improvement of their psoriasis according to the Psoriasis Area and Severity Index (PASI 90 response) at Week 24.

Secondary Endpoints

The major secondary endpoints are:

- The proportion of subjects achieving at least a 75% improvement of their psoriasis according to the PASI at Week 24 (PASI 75 response)
- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

Other secondary endpoints are:

- The proportion of subjects achieving a 100% improvement of their psoriasis according to the PASI at Week 24 (PASI 100 response)
- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 24
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 24
- The proportion of subjects achieving an absolute PASI score ≤1 at Week 24
- The proportion of subjects achieving an IGA score of cleared (0) at Week 24
- The change from baseline of body surface area (BSA) psoriatic involvement at Week 24
- The change from baseline in DLQI score at Week 24
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 24 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
- The change from baseline in the physical and mental component summary scores of SF-36 at Week 24
- Safety and tolerability data will be summarized using descriptive statistics.

9.0 Study Design

9.1 Overview

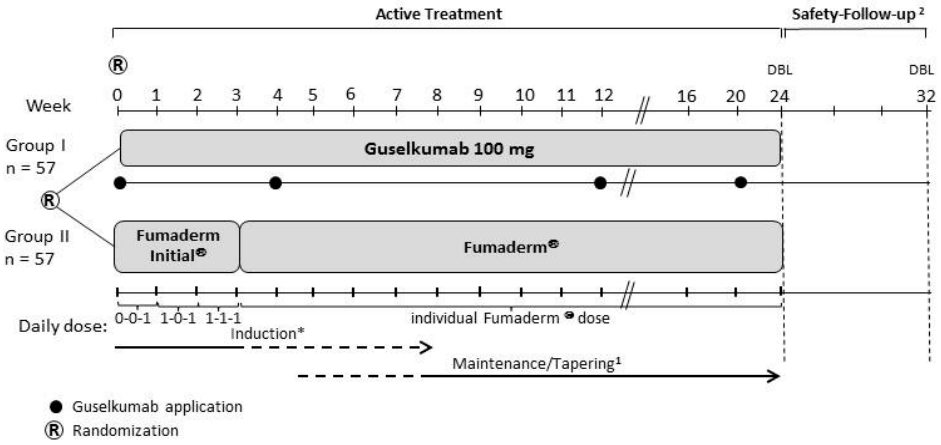
This is a randomized, open-label, efficacy assessor-blinded, single country, multicenter, active-comparator-controlled phase 3b study of guselkumab in adult subjects with moderate to severe plaque-type psoriasis who have not yet received any systemic therapy. The study will be performed at about 30 to 45 sites in Germany.

A total of 114 subjects will be randomized in a 1:1 ratio to either the study drug (guselkumab) or to the active comparator (FAE). Subjects of the guselkumab group will receive 100 mg guselkumab SC at Weeks 0, 4, 12, and 20. Subjects of the FAE group will receive commercially available Fumaderm® tablets specifically labeled for the study. An individual dosing for each subject representing the optimal benefit-risk ratio is aspired. As shown in Figure 1, the study will be conducted with a 24-week treatment phase and a subsequent post-treatment safety follow-up phase until Week 32. Together with a 3-week screening phase, the maximum duration of a subject´s participation in this study will be 35 weeks.

Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd PSSD 7 day version, and 3rd SF-36), and subsequently by a blinded efficacy assessor (BSA%, IGA, ss-IGA, and PASI). Safety evaluations will include the monitoring of adverse events (including injection site and allergic reactions), physical examinations, measurement of body weight, vital sign measurement, clinical laboratory testing (HBV, HCV, HIV, hematology, chemistry), concomitant medication review, tuberculosis test and evaluation, urinalysis and pregnancy testing. A confirmatory interim analysis will not be conducted. However, in addition to the main analysis after Week 24, a follow-up safety analysis will be performed.

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 14 months (start in December 2016, stop in February 2018). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

Figure 1: Schematic Overview of the Study



[1] The maximum daily dosage of 3 × 2 tablets Fumaderm® must not be exceeded. Fumaderm therapy according to local prescribing information (SmPC). For details see SmPC and Section 7.

[2] For subjects who were treated with guselkumab, it is recommended not to start a new therapy before week 32. If the investigator feels strongly that an additional therapy is needed, then this should be discussed with the medical monitor before initiation of the therapy.
For subjects treated with FAE, the investigator may either continue the actual FAE treatment with commercially available drug or switch to another commercially available treatment.

9.2 Sample Size Determination

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24.
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$). Due to the testing of ordered hypotheses, no adjustment of the significance level with respect to the threefold test procedure is required.

The assumptions for the sample size and power calculations using the threefold test procedure were based on guselkumab phase 2 data and unpublished data from the German PsoBest Registry and are as follows: PASI 90 responder rates for guselkumab and FAE in Week 24 are assumed to be 60% and 25%, respectively. PASI 75 responder rates are assumed to be 80% and 45%, respectively. DLQI responder rates are assumed to be 60% and 30%, respectively.

Based on these assumptions, with a total of 114 subjects planned to be randomized in a 1:1 ratio to guselkumab (n = 57) and to FAE (n = 57), superiority of guselkumab vs. FAE can be demonstrated at a 5% significance level (two-sided) with power of at least 90% for each test of the threefold test procedure as displayed in the table below.

Table 1: Power to detect a treatment effect on expected proportions of subjects achieving the primary and the major secondary endpoints

Order of testing	Endpoint in Week 24	Guselkumab (% responder)	FAE (% responder)	Power
1	PASI 90	60	25	97%
2	PASI 75	80	45	98%
3	DLQI 0/1	60	30	90%
type 1 error rate alpha 5% (two-sided) sequential testing with a-priori ordered hypotheses (only proceed with testing, if p <0.05) sample size n = 114 with 1:1 ratio guselkumab (n = 57) and FAE (n = 57) two group chi-square test; nQuery Advisor® Release 7.0				

9.3 Randomization and Blinding

Procedures for Randomization

Central randomization is implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) 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-based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC system.

Blinding

As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP.

10.0 Study Schedule

An overview of the study procedures is displayed in the following time and events schedule of the CSP.

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final Study visit)	ETV[h]	Notes
Week	max. -3	0	2	4	8	12	16	20	24	32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Screening/Administrative												
Informed consent	X											Must be signed before first study-related activity
Medical history and demographics	X											
Inclusion/ exclusion criteria	X	X										Minimum criteria for the availability of documentation supporting the eligibility criteria are described in protocol, Section 4; check clinical status again before first dose of study medication
Study Drug Administration												
Randomization		X										All baseline study procedures and evaluations are to be completed before randomization
Study drug administration		X[c] ----------X										All study procedures and evaluations are to be completed before study drug administration

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before administration of study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

c: Subjects randomized to guselkumab will get guselkumab 100 mg on site at Weeks 0, 4, 12 and 20. Subjects randomized to FAEs will start with Fumaderm® initial regimen (0-0-1) at the day of the baseline visit; thereafter, FAE doses will be increased to find the optimal Fumaderm® dose for each subject as described in Section 6

h: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before or at Week 24, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final Study visit)	ETV[h]	Notes
Week	max. -3	0	2	4	8	12	16	20	24	32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Safety Assessments												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis evaluation	X	X	X----------X								X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Chest radiograph	X											Taken within 3 months before the first administration of study drug and read by a qualified radiologist
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	Women of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits (prior to administration of study drug).
Height		X										
Weight		X							X	X	X	
Concomitant therapy	X----------X										X	
Adverse events	X----------X										X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before or at Week 24, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final Study visit)	ETV[h]	Notes
Week	max. -3	0	2	4	8	12	16	20	24	32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Efficacy Assessments												
DLQI	X	X		X	X		X		X		X	**Order of assessment: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit; completion of the baseline PROs has to be done before randomization
PSSD (7d)	X	X	X	X	X	X	X	X	X		X	
SF-36		X			X		X		X		X	
IGA[d]	X	X	X	X	X	X	X	X	X		X	
PASI[d]	X	X	X	X	X	X	X	X	X		X	
ss-IGA[d,e]		X			X		X		X		X	
BSA%[d]	X	X			X		X		X		X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

d: Dermatological evaluation of the subjects will be done by a blinded assessor starting with the Baseline visit; assessments will be done before any study related procedure will take place

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

h: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before or at Week 24, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final Study visit)	ETV[h]	Notes
Week	max. -3	0	2	4	8	12	16	20	24	32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Clinical Laboratory Assessment												
Tuberculosis test[f]	X											
Hepatitis B and C Serologies	X											
HIV antibody test	X											
Hematology[g]	X	X	X	X	X	X	X	X	X	X	X	Laboratory tests are listed in Section 9.3
Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	Laboratory tests are listed in Section 9.3
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤(+); one re-test (central urine analysis) is allowed.

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

f: The QuantiFERON-TB Gold Plus test will generally be performed by the central laboratory; however, if available, test results from local laboratory can be accepted

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before or at Week 24, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

11.0 Analysis Sets

In this study, subjects will be included in the efficacy analyses according to their assigned treatment. In contrast to the efficacy analysis set, safety analyses will be performed according to the actual treatment received during the study.

11.1 Definition of Analysis Sets

The following analysis data sets will be defined:

- **Efficacy Analysis Set**

  The efficacy analysis set is defined as the set of all subjects who were randomized to one of the two treatment groups (guselkumab or FAE) at Week 0 regardless of the treatment they actually received ("intent-to-treat" principle).

- **Per-Protocol Analysis Set**

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

- **Safety Analysis Set**

  The safety analysis set is defined as the set of all subjects who were randomized to one of the two treatment groups (guselkumab or FAE) at Week 0 and who received at least one dose of study drug according to the actual treatment received during the study irrespective of the treatment assigned at randomization.

Unless otherwise specified, data on study subjects (including subject disposition, reasons for discontinuation of study treatment, protocol deviations, analysis sets) will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

Demographic and other baseline characteristics as well as treatment compliance will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set') and on all treated subjects ('safety analysis set').

All efficacy analyses to compare guselkumab vs. FAE will be performed for all subjects randomized at Week 0 ('efficacy analysis set'). Additionally, all efficacy analysis will be performed for all treated subjects ('safety analysis set'). The primary and the major secondary endpoints will also be analyzed using the per-protocol analysis set.

All safety analyses to compare guselkumab vs. FAE will be performed for all treated subjects ('safety analysis set'). The safety analysis will be performed after all subjects have completed their visit 24 weeks after randomization or discontinued earlier.

If the efficacy analysis set and the safety analysis set will not be different, analyses of efficacy and safety will be performed on data from all subjects randomized at Week 0 ('efficacy analysis set').

11.2 Protocol Deviations

The determination of evaluability of subjects, especially in cases of protocol deviations, withdrawals or drop-outs and the assignment of subjects to the planned analysis sets will be performed according to the requirements of the study protocol. Minor and major and potentially major protocol deviations that can be expected based on the prescriptions in the protocol were defined by Janssen-Cilag GmbH during the trial set up period. A detailed description of major and potentially major protocol deviation criteria is included in a separate document.

Data on subjects who had a major protocol deviation will be documented continuously by Janssen-Cilag GmbH in a Clinical Trial Management System during the trial period. Final data on major protocol deviations regarding the Week 24 analysis will be transferred to the data management department of acromion GmbH as Excel spreadsheets and will be further processed for statistical analysis.

11.3 Screening Failures

The data of subjects who were not randomized will not be included in the statistical analyses. However, a separate listing will be presented providing the site / subject no. and the reason for not being randomized.

12.0 Definition and Calculation of Efficacy Endpoints

The following sections provide a detailed description of the definition and the planned calculation of the efficacy endpoints as defined in the CSP. The same applies also for additional endpoints not defined in the CSP.

12.1 Involved 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).

12.2 Investigator's Global Assessment (IGA)

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

The efficacy endpoint related to the IGA score is defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

12.3 Scalp Specific Investigator's Global Assessment (ss-IGA)

The scalp-specific (ss-)IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

The analyses for ss-IGA will be based on subjects randomized at Week 0 with baseline ss-IGA score ≥2.

ss-IGA absence of disease responder

Subjects with an ss-IGA score ≥2 at baseline who achieve ss-IGA score of absence of disease (0) will be considered ss-IGA absence of disease responders.

12.4 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.

In addition, the time to PASI 75/90/100 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response the time to PASI 75/90/100 response will be censored at the date of Week 24 or the date of discontinuation in case of early treatment discontinuation.

12.5 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 (e.g., 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.

In addition, the time to DLQI 0/1 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response the time to DLQI 0/1 response will be censored at the date of Week 24 or the date of discontinuation in case of early treatment discontinuation.

12.6 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.

12.7 Short Form Health Survey (SF-36)

The Short Form Health Survey (SF-36) is a 36-item questionnaire used for subjects' self-assessment of health-related quality of life, consisting of the following 8 dimensions: 1) limitations in physical functioning due to health problems, 2) limitations in usual role activities due to physical health problems, 3) bodily pain, 4) general mental health (psychological distress and well-being), 5) limitations in usual role activities due to personal or emotional problems, 6) limitations in social functioning due to physical or mental health problems, 7) vitality (energy and fatigue), and 8) general health perception.

A physical component summary (PCS) score and a mental component summary (MCS) score can be derived. The concepts measured by the SF-36 are not specific to age, disease or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

Each of these 8 scales (domains) is scored from 0 to 100 with higher scores indicating better health. Based on the scale scores, the summary scores, PCS and MCS, will be derived. These summary scores are also scaled with higher scores indicating better health.

The QualityMetric Health Outcomes™ Scoring Software 5.0 offered by QualityMetric Incorporated will be used to score the SF-36. The Software is designed to provide users with standard scoring methods in an easy-to-use way. By using this Software, users will have the confidence that the data they obtain on their SF form are scored in accordance with standards set by the developers of the SF tools. The Software also provides evaluation of data quality and applies methods for missing data recovery. The PCS score can be calculated when seven scale scores are available and the Physical Functioning scale is not missing. The MCS score can be calculated when at least seven scale scores are available and the Mental Health scale is not missing.

A more detailed description of the scoring procedure is provided in the User's Guide of QualityMetric Health Outcomes™ Scoring Software 5.0 (see especially Appendix F).

13.0 Statistical Methodology

The statistical analyses in this study will focus on the comparison of the two randomized treatment groups (i.e., guselkumab vs. FAE). The analyses will be confirmatory for the primary endpoint and the major secondary endpoints, and exploratory for all other secondary endpoints.

The biometrical evaluation will be carried out by acromion GmbH under the authority of the sponsor. Statistical programming and analyses will be performed using the statistical software system SAS®.

The following sections provide a more detailed description of the planned statistical methodology.

13.1 Data Handling Rules

13.1.1 Baseline and Post-baseline Points in Time of Interest

Baseline Definition

In general, the values of the Week 0 visit (= day of randomization = first day of week 1) or the values of the screening visit (= day within 3 weeks before their randomization visit) will be used as baseline values, as applicable. If data for the same variable are available from both (i.e., screening and Week 0) visits then the result of the Week 0 visit will be used as baseline value, i.e., for each variable the baseline measurement is defined as the closest measurement taken prior to or at the Week 0 visit.

Definition of Post-baseline Points in Time of Interest

The primary point in time for efficacy assessment will be the Week 24 visit (= end of treatment visit 24 weeks after randomization). Secondary points in time for efficacy assessment will be the study visits scheduled at Week 4 and Week 16 during the treatment phase. Handling of missing values is described in SAP section 13.1.6.

The safety analysis will cover the time period until Week 24.

13.1.2 Definition of Within- and Between-Group Treatment Differences

Within-group treatment differences will be computed as differences of the post-baseline visits as compared to the baseline visit, if applicable:

- post-baseline visit minus baseline visit

The following between-group treatment difference to assess the treatment effect will be computed, if applicable:

- guselkumab minus FAE

13.1.3 Visit Windows

Nominal visits (i.e., visits as recorded in the eCRF) will be used for all by-visit analyses in the study. The study visits scheduled post randomization should occur at the times delineated in the Time and Events Schedule. No visit windows will be defined and used for analysis.

13.1.4 Treatment Failure Criteria

Subjects who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures.

By time period the particular protocol-prohibited medications/therapies include:

Topical Therapy

Topical therapies that could affect psoriasis (e.g., corticosteroids, tar, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, pimecrolimus, tacrolimus, and traditional Taiwanese, Korean, or Chinese medicines) are not permitted until Week 24.

(The only allowable concomitant treatments for psoriasis throughout the study are shampoos (containing tar or salicylic acid only) and topical moisturizers. (Subjects should not use the topical agents on the day of a study visit; non-medicated shampoos may be used.))

Phototherapy

Phototherapy including, but not limited to PUVA, narrow-band UVB, balneophototherapy is not permitted until Week 24.

Systemic Therapy for Psoriasis

Systemic Therapy for Psoriasis is not permitted until the Week 24 visit.

These medications include those targeted for reducing TNF (including but not limited to infliximab, adalimumab or etanercept), drugs targeted for reducing IL-12, IL-17, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], secukinumab [AIN457], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), steroids, any conventional systemic therapy that could affect psoriasis (including but not limited to MTX, cyclosporine, acitretin), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis.

13.1.5 Treatment Failure Rules

No treatment failure rules will be applied.

13.1.6 Handling of Missing Values

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

Missing data for the efficacy endpoints at key visits Week 4, 16, and 24 will be handled as follows for all inferential statistical analyses (confirmatory or exploratory).

Missing data imputation for the efficacy endpoints at Week 4, 16, and 24:

- Nonresponder imputation will be applied for binary endpoints
    - i.e., subjects with missing data at Week 4/16/24 will be considered non-responders at Week 4/16/ 24.
- Last observation carried forward (LOCF) will be applied for continuous endpoints
    - i.e., in subjects with missing data at Week 4/16/24 the last available observation after baseline will be calculated and used for analysis for continuous response variables at Week 4/16/24. 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.

Sensitivity analyses with respect to the handling of missing values at Week 24 are described in SAP section 13.9.

13.1.7 Data Transformations

No data transformations (e.g. square root, logarithmic) to confirm basic statistical assumptions will be performed. All variables will be used in the analysis as reported.

13.2 Descriptive Statistics

13.2.1 Dichotomous and Categorical Variables

Categorical data will be presented in frequency tables using counts and percentages. Percentages will be based on the total number of subjects in the respective analysis set (i.e., missing values will be included in percentage calculation). Besides presentation of absolute values cross tabulation vs. baseline by study visit will be provided, if appropriate.

13.2.2 Continuous and Quasi-Continuous Variables

Standard descriptive summary statistics will be calculated for continuous and quasi-continuous variables: arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values. Besides presentation of absolute values tabulation for differences to baseline by study visit will be provided, if appropriate.

13.2.3 Graphical Presentations

Graphical presentation of pertinent data will be given by means of box plots, bar charts, and survival graphs, as appropriate. Additional forms of graphical presentations may be specified. Descriptions of graphical presentations are included in the appendix of this document.

13.3 Confirmatory Statistics

The statistical analyses will be confirmatory for the primary endpoint and the major secondary endpoints.

13.3.1 Statistical Hypotheses

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24.
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

13.3.2 Estimation, Confidence Intervals and Hypotheses Testing

In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$).

A two-sided ($\alpha = 0.05$) chi-square test will be used for the confirmatory comparisons. In addition, two-sided 95% confidence intervals will be calculated for the response rates at Week 24 per treatment arm and for the difference between the two arms.

13.3.3 Significance Level

All statistical testing will be performed two-sided. The confirmatory significance level is fixed to a type 1 error rate alpha of 5% (two-sided).

Due to the testing of ordered hypotheses, no adjustment of the significance level with respect to the threefold test procedure is required.

13.4 Exploratory Statistics

Exploratory statistical analyses will be performed for the primary endpoint, the major secondary endpoints and the other secondary endpoints at Week 24, and at Week 4 and Week 16. All statistical tests and confidence intervals will be calculated two-sided and are to be interpreted in the exploratory sense only.

13.4.1 Binary Endpoints

For binary endpoints counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for treatment effect using the chi-square test will be provided.

Time-to-event analyses will be performed for binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE using Kaplan-Meier product limit method and Cox proportional hazards model. Summary tables will provide counts and percentage of subjects per treatment 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 factor treatment group). The survival curves will also be displayed graphically. Time-to-event analyses of binary endpoints will be performed on the observed cases only (i.e., missing data will not be replaced for time-to-event analyses).

A logistic regression model will be used for subgroup analyses of selected binary endpoints (i.e., PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE) at Week 24 with factors for treatment group, the respective subgroup and the interaction term between treatment and subgroup. Only the p-value of the interaction term will be provided from these analyses.

13.4.2 Continuous Endpoints

The change from baseline of continuous endpoints will be analyzed by an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate. The Least-Squares means (LS means), the LS mean difference and the standardized mean difference (computed according to Hedges' g) with the 95% CI and two-sided p-value will be provided from the ANCOVA model. For subgroup analyses of continuous endpoints the ANCOVA model will be extended by the respective subgroup and the interaction term between treatment and subgroup.

13.5 Adjustment for Covariates

The baseline value will be used as covariate in the analysis of variance model (ANCOVA) for the change from baseline of continuous response parameters.

13.6 Interim Analyses

No confirmatory interim analysis is planned to be performed.

13.7 Multi-center Data

Exploration of possible heterogeneity of treatment effects across centers for the primary efficacy endpoint (i.e., the proportion of subjects achieving a PASI 90 response at Week 24) using nonresponder imputation will be performed by descriptive frequency statistics including graphical display of the results of the individual centers, as appropriate. No pooling of centers will be performed.

13.8 Subgroup Analyses

The following subgroup analyses at Week 24 are planned to be performed to evaluate consistency over demographics and baseline disease characteristics of the primary endpoint, all secondary efficacy endpoints and as well of the following safety endpoints: onset of any TEAE, serious TEAE, treatment discontinuation due to TEAE.

- Gender
  - male
  - female
- Age at baseline in years
  - < 45
  - ≥ 45 - < 65
  - ≥ 65
- PASI
  - < 20
  - ≥ 20

The subgroup analyses will also include time-to-event analyses for the binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

Subgroup analyses for the primary endpoint and all secondary efficacy endpoints will be performed using the following different imputation rules of missing values at Week 24 (see SAP sections 13.1.6 and 13.9):

- Binary endpoint:
  - Nonresponder imputation
  - LOCF (only PASI 75/90 response, and DLQI 0/1 response)
  - Multiple imputation
- Continuous endpoint:
  - Multiple Imputation

Subgroup analyses will NOT be performed for the per-protocol analysis set.

13.9 Sensitivity Analyses

The following sensitivity analyses at Week 24 with respect to the handling of missing values are planned to be performed:

- Multiple imputation will be used for all binary and continuous endpoints.
    - For the multiple imputation, the repeated nature of the analysis is restricted to the imputation step (procedure "MI" in SAS). Basic premise is the creation of several datasets in which missing data is imputed in a random fashion and then analyses are performed to check for changes for the conclusion. The analysis will be done with SAS Proc MIANALYZE.
- LOCF imputation will be used for all binary endpoints (see SAP section 13.1.6).
- An 'observed cases analysis' for all binary and continuous endpoints without substitution of missing data will be used (see SAP section 13.1.6).

Sensitivity analyses at Week 24 with respect to the handling of missing values will be performed for all binary and all continuous efficacy endpoints.

Sensitivity analyses at Week 24 with respect to the handling of missing values will NOT be performed for the per-protocol analysis set.

14.0 Statistical Analyses

A table of contents of planned data displays is provided in section 18.1 of this document. The following sections are intended to provide more details of the planned analyses. In addition, mock tables will be created and will be used as template for statistical programming.

Data will be appropriately summarized and analyzed using tabulation and graphs with respect to demographic/baseline characteristics and efficacy/safety observations and measurements. Standard descriptive summary statistics (i.e., n, arithmetic mean, standard deviation, median, minimum/maximum value, quartiles) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. In general, summary tables will be displayed by treatment group as the main classification variable and for the total of the sample in the respective analysis set. 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, center, subject number and study visit, if applicable.

14.1 Study Subjects

Unless otherwise specified, data on study subjects will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

14.1.1 Disposition of Subjects

The overview of subject disposition will provide the respective frequency counts and percentages regarding the following subjects:

- Treatment phase until Week 24
    - Subjects who were enrolled (i.e., signed informed consent)
    - Subjects who were randomized
    - Subjects who were treated
    - Subjects with premature discontinuation of study treatment
    - Subjects who completed the treatment phase

The table will also include the total number of study sites and the dates of the enrolment of the first subject and the last visit of the last subject. Moreover, the overview of subject disposition will be broken down by center. A flow diagram (according to the CONSORT statement) giving an overview of subject disposition will also be provided.

In addition, the number and percentage of randomized subjects continuing and attending by study visit will be displayed in a separate table. Subjects will be counted as continuing at the time of visit whether they attend the visit or not. Only those subjects that prematurely discontinued before the visit will not be counted as attending.

14.1.2 Discontinuation of Study Treatment

The number and percentage of randomized subjects who discontinued study treatment prematurely within the 24 Weeks treatment period of the study will be tabulated for each reason of premature discontinuation (including tabulation of specifications for category 'other'). Moreover, the number of subjects enrolled but not randomized (i.e., screening failures) and the reasons for not being randomized will be given.

14.1.3 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 trial. Subjects with major protocol deviations will be summarized by category for all randomized subjects.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

The summary table will provide the number of subjects per major protocol deviation and will also provide the number of major protocol deviations.

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.

14.1.4 Analysis Sets

The number and percentage of randomized subjects included in each analysis set, together with a breakdown of the reasons for exclusion for non-evaluable subjects, will be provided.

14.2 Demographic and Other Baseline Characteristics

Generally, assessments made at the screening visit and the baseline visit will be summarized by treatment group and overall. These assessments will include demographic characteristics and other parameters (such as medical history, previous psoriasis therapy by type (phototherapy and topical therapy)) substance use alcohol/tobacco, previous and concomitant diseases, prior and concomitant medication, physical examination). By-treatment summaries will serve to identify any imbalances between the treatment groups at baseline. Summary tables will be provided by means of descriptive statistics and frequency tables, where appropriate. Demographic and other baseline characteristics will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set') and on all treated subjects ('safety analysis set'). No analyses for baseline balance using statistical hypothesis tests or confidence intervals will be done.

14.2.1 Demographics

Age (categorized), gender, and race will be presented in a frequency table. Age group categories will be chosen as < 45; ≥ 45 - < 65; ≥ 65years. Descriptive summary statistics will be calculated for age, body height, body weight and body mass index (BMI).

Tables for demographic data will also be stratified by gender. Age and gender distribution will be presented in a bar chart.

Note: Age is documented as 'age at date of informed consent signature' at the screening visit. Body height and body weight data will be taken from the vital signs eCRF form at the Week 0 visit. BMI will be calculated as body weight in kg / body height in m^2.

14.2.2 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 terminology as described in SAP section 14.6. Summary tabulation will also consider whether the disease is ongoing or not at screening visit.

14.2.3 Diagnosis of Psoriasis

The time from date of initial diagnosis of psoriasis to date of screening visit will be calculated and will be displayed by descriptive statistics. If the day is unknown the day will be set to day = 1. If the month is unknown the month will be set to month = July.

In addition, the disease characteristics will be summarized by providing the following relevant results: descriptive summary statistics of the PASI and the DLQI index at baseline, frequency distribution of the IGA categories and the PASI < 20 and PASI ≥ 20 subgroups at baseline.

14.2.4 Previous Psoriasis Therapy

Categorical data on previous psoriasis therapy (including data on previous phototherapy and previous topical therapy) will be displayed in frequency tables providing the number and percentage of subjects per category. Summary tabulation of data on previous phototherapy will consider the type of phototherapy. The number and percentage of subjects with use of other previous topical psoriasis therapy will be displayed in WHO-DD terminology as described in SAP section 14.7.

14.2.5 Substance Use

Categorical data on substance use (alcohol or tobacco) will be displayed in a frequency table providing the number and percentage of subjects per category. Summary tabulation will also consider whether the substance usage is current or former.

14.2.6 Physical Examination

Abnormal findings in physical examination (additional to psoriasis findings) at screening and baseline visit 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.

14.2.7 Tuberculosis Evaluation

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

14.2.8 Chest Radiograph Result

Categorical data on chest radiograph result at screening visit will be displayed in a frequency table providing the number and percentage of subjects per category. Details on findings in verbatim terms will be displayed in individual data listings.

14.2.9 Concomitant Medication and Therapy

Analyses of concomitant medication and therapy will only consider the data recorded within the 24 Weeks treatment period of the study. In case of early treatment discontinuation before Week 24 concomitant medication and therapy with a start date at or after the discontinuation date will not be considered.

Concomitant Medication

The number and percentage of subjects with use of concomitant medication will be displayed in WHO-DD terminology as described in SAP section 14.7. Concomitant medication will be identified from the *Concomitant Medication* form of the eCRF.

The number and percentage of subjects with indication for concomitant medication will be displayed in MedDRA terminology as described in SAP section 14.6.

Concomitant Therapy

The number and percentage of subjects with use of concomitant therapy will be displayed in MedDRA terminology as described in SAP section 14.6. Concomitant therapy will be identified from the *Concomitant Therapy* form of the eCRF.

The number and percentage of subjects with indication for concomitant therapy will be displayed in MedDRA terminology as described in SAP section 14.6.

14.2.10 Shampoo and Moisturizer

The number and percentage of subjects with use of shampoo or moisturizer will be displayed in a frequency table.

14.3 Treatment Compliance

Treatment compliance will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set') and on all treated subjects ('safety analysis set').

14.3.1 Visit Windows

The number of days between the scheduled study visits and the baseline visit will be calculated using the reported visit dates per scheduled study visit and will be displayed by summary descriptive statistics.

14.3.2 Study Medication

Categorical data on guselkumab administration recorded at Week 0, 4, 12, 20 will be summarized by frequency tabulation providing the number and percentage of subjects per category. Frequency tabulation and descriptive statistics will be presented for the overall number of guselkumab administrations.

Compliance to guselkumab administration will be calculated as follows based on the eCRF data:

- Compliance guselkumab in % = (number of actual administrations x 100 / number of planned adminstrations)

Categorical data on Fumaderm® initial/ Fumaderm® administration during initial uptitration and/or maintenance period (including data on reasons for end of uptitration and reasons for dose selection) recorded at each week until Week 24 will be summarized by frequency tabulation providing the number and percentage of subjects per category. The number of planned tablets to be taken in the morning, at noon, and in the evening will also be summed up and analyzed descriptively.

The number of dispensed and returned tablets of Fumaderm® initial/ Fumaderm® (including the difference of dispensed - returned tablets = actual tablets) will be displayed by descriptive summary statistics.

Compliance to Fumaderm® initial and Fumaderm® administration will be calculated as follows based on the eCRF data:

- Compliance FAE in % = (number of actual tablets x 100 / total number of tablets supposed to be taken)

Treatment compliance will also be assessed by protocol deviations related to study drug administration (i.e., incorrect study drug received and missed administrations).

For subjects who completed the Week 24 visit the dose of Fumaderm® in mg at Week 24 will be summarized by descriptive statistics and frequency tabulation. In addition, the maximum dose of Fumaderm® initial and Fumaderm® in mg will be calculated for all subjects and will be summarized by descriptive statistics and frequency tabulation.

14.4 Analysis of Efficacy

All efficacy analyses to compare guselkumab vs. FAE will be performed for all subjects randomized at Week 0 ('efficacy analysis set'). Additionally, all efficacy analysis will be performed for all treated subjects ('safety analysis set'). The primary and the major secondary endpoints will also be analyzed using the per-protocol analysis set. However, subgroup and sensitivity analyses at Week 24 will NOT be performed for the per-protocol analysis set.

All statistical tests will be performed two-sided. In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$).

Handling of missing values, exploratory statistics, subgroup analyses, and sensitivity analyses will be performed as described in detail in the following sections of this SAP:

SAP Section No.	Topic
13.1.6	Handling of missing values
13.4.1	Exploratory statistics - binary endpoints
13.4.2	Exploratory statistics - continuous endpoints
13.8	Subgroup analyses
13.9	Sensitivity analyses

Data at the scheduled points Week 4 and Week 16 during the active treatment period will be analyzed analogously to the Week 24 data. However, no subgroup or sensitivity analyses will be performed for these points in time.

14.4.1 Primary Endpoint

The proportion of subjects achieving at least a 90% improvement of their psoriasis according to the Psoriasis Area and Severity Index (PASI 90 response) at Week 24 will be displayed in a frequency table providing the number and percentage of subjects. Graphical presentation will be presented by means of a bar chart.

To address the primary objective, a two-sided (α = 0.05) chi-square test will be used for the primary confirmatory comparison. In addition, two-sided 95% confidence intervals will be calculated for the PASI 90 response rate at Week 24 per treatment arm and for the difference between the two arms.

Exploratory statistical analyses (also including analyses of time to PASI 90 response) will be performed as described in SAP section 13.4.1.

14.4.2 Major Secondary Endpoints

14.4.2.1 Endpoint related to PASI

The proportion of subjects achieving at least a 75% improvement of their psoriasis according to the PASI at Week 24 (PASI 75 response) 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 24 per treatment arm and for the difference between the two arms.

Exploratory statistical analyses (also including analyses of time to PASI 75 response) will be performed as described in SAP section 13.4.1.

14.4.2.2 Endpoint related to DLQI

The proportion of subjects achieving a DLQI score of 0 or 1 at Week 24 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 24 per treatment arm and for the difference between the two arms.

Exploratory statistical analyses (also including analyses of time to DLQI 0/1 response) will be performed as described in SAP section 13.4.1.

14.4.3 Other Secondary Endpoints

14.4.3.1 Endpoints related to PASI

Other secondary endpoints related to PASI are:

- The proportion of subjects achieving a 100% improvement of their psoriasis according to the PASI at Week 24 (PASI 100 response)
- The proportion of subjects achieving an absolute PASI score ≤1 at Week 24

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 24 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses (also including analyses of time to PASI 100 response) will be performed as described in SAP section 13.4.1.

14.4.3.2 Endpoints related to PSSD

Other secondary endpoints related to PSSD are:

- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 24
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 24

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 24 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

In addition, the other individual scale scores will be analyzed analogously.

14.4.3.3 Endpoints related to IGA

Other secondary endpoints related to IGA are:

- The proportion of subjects achieving an IGA score of cleared (0) at Week 24

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 24 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

14.4.3.4 Endpoints related to BSA

Other secondary endpoints related to BSA are:

- The change from baseline of body surface area (BSA) psoriatic involvement at Week 24

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 24 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.5 Endpoints related to DLQI

Other secondary endpoints related to DLQI are:

- The change from baseline in DLQI score at Week 24

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 24 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.6 Endpoints related to ss-IGA

Other secondary endpoints related to ss-IGA are:

- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 24 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for response rate at Week 24 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

14.4.3.7 Endpoints related to SF-36

Other secondary endpoints related to SF-36 are:

- The change from baseline in the physical and mental component summary scores of SF-36 at Week 24

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 24 value and the change from the baseline value will displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.4 Other Efficacy Assessments

In addition to the efficacy analyses described above all efficacy data related to PASI, DLQI, PSSD, IGA, ss-IGA, and SF-36 at all scheduled study visits during the active treatment period until Week 24 will be summarized descriptively without any imputation of missing data ('observed cases analysis'; see SAP section 13.1.6).

14.5 Analysis of Safety

Safety data, including but not limited to, adverse events (AEs), serious adverse events (SAEs), infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized using descriptive statistics. All safety analyses to compare guselkumab vs. FAE will be performed for all treated subjects ('safety analysis set').

14.5.1 Extent of Exposure

Extent of exposure will be defined as the total number of days from baseline to Week 24 (for all patients still under treatment) or to study discontinuation.

Descriptive summary statistics and frequency tables (using appropriate categories) will be provided for the extent of exposure.

14.5.2 Adverse Events

Adverse events data will be processed in the statistical analysis after coding according to the MedDRA dictionary version 19.1. All reported AEs with onset date during the active treatment period until Week 24 (i.e., treatment emergent AEs) will be included in the analysis. In case of early treatment discontinuation before Week 24 all reported AEs with onset date during the safety follow-up period until Week 24 (i.e., treatment emergent AEs) will be included in the analysis. AEs reported after Week 24 will NOT be considered in the analysis.

14.5.2.1 Definitions

The following definitions will be applied in the present study

Crude Incidence Rate

Where percentages of subjects are reported in summary tables, incidences provide information on the proportion of subjects experiencing adverse events in relation to the total number of subjects exposed, i.e., if not otherwise specified, the crude incidence rate will be used.

The crude incidence rate is defined as the number of subjects experiencing a certain event, divided by the number of subjects exposed to study treatment, regardless of duration of use:

$$\text{Crude incidence rate} = 100 * \frac{\text{number of patients with adverse events}}{\text{number of patients exposed}}$$

Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are those AEs that occurred during the active treatment period until Week 24 after the start of initial study drug administration and those AEs that were present at baseline but worsened in severity after the start of initial study drug administration. AEs reported after Week 24 will NOT be considered in the analysis.

In case of early treatment discontinuation before Week 24 all reported AEs with onset date during the safety follow-up period until Week 24 will be included in the analyses. Thus, identification of TEAEs (distinguished by subjects who completed or discontinued the treatment period until Week 24) will be performed as follows:

- TEAE for Completer: Date of Week 0 < Start Date of AE < Date of Week 24
- TEAE for Non-Completer: Date of Week 0 < Start Date of AE < Date of Week 0 + 168 Days

AEs which are not classified as TEAEs will be considered as not treatment emergent adverse events (NTEAEs).

14.5.2.2 Analyses

Overview of adverse events

For summary presentation of the overall adverse event experience overview tables will be provided for AEs and SAEs including the following information:

Adverse events:

- n (%) of subjects with AEs *)
- n (%) of subjects with NTEAEs *)
- n (%) of subjects with TEAEs *)
- n (%) of subjects with TEAEs by highest causality to study medication
- n (%) of subjects with TEAEs by worst severity
- n (%) of subjects with TEAEs leading to dose modification *)
- n (%) of subjects with TEAEs leading to permanent stop of study medication *)

Serious Adverse events:

- n (%) of subjects with SAEs *)
- n (%) of subjects with NTESAEs *)
- n (%) of subjects with TESAEs *)
- n (%) of subjects with TESAEs leading to death *)
- n (%) of subjects with TESAEs by highest causality to study medication
- n (%) of subjects with TESAEs by worst severity
- n (%) of subjects with TESAEs leading to permanent stop of study medication *)

*) the number of events (i.e., number of coded preferred terms) will also be given.

TEAEs/TESAEs leading to dose modification will be defined as all events with 'Action taken with study treatment' is not equal to 'DOSE NOT CHANGED'.

In addition, the number of TEAEs will be displayed for the following investigator's ratings:

- severity
- seriousness
- causality
- action taken
- outcome

Detailed display of adverse events

For a more detailed display, adverse events will be presented in summary tables, listing these events in code form according to the preferred term. These tables will show the number of subjects per group presenting an adverse event and the incidence of its occurrence. Adverse events will be grouped by primary SOC (System Organ Class) and will be stratified additionally by highest causality to study treatment (not related, doubtful, possible, probable, or very likely) and by worst severity (mild, moderate, or severe). The incidence of adverse events will be presented by decreasing order of frequency at preferred term level within the primary SOC.

The following tables will be provided for the detailed display of adverse events:

Adverse events:

- TEAEs by primary SOC and preferred term *)
- TEAEs by primary SOC and preferred term stratified by highest causality
- TEAEs by primary SOC and preferred term stratified by worst severity
  - thereof
    - Drug related TEAEs
    - Not drug related TEAEs
- TEAEs leading to permanent stop of study medication by primary SOC and preferred term *)

Serious Adverse events:

- TESAEs by primary SOC and preferred term *)
- TESAEs by primary SOC and preferred term stratified by highest causality
- TESAEs by primary SOC and preferred term stratified by worst severity
- TESAEs leading to permanent stop of study medication by primary SOC and preferred term *)
- TESAEs leading to death by primary SOC and preferred term *)

Not treatment emergent adverse events:

- NTEAEs by primary SOC and preferred term *)

*) These tables will show additionally the number of events (i.e., number of coded preferred terms).

Summary tabulation of TEAEs and TESAEs by primary SOC and preferred term will also be provided for the following types of adverse events:

- injection site reactions (according to the tick box in the e-CRF)
- infections (according to the tick box in the e-CRF)
  - thereof, infections treated with oral or parenteral antibiotics
- adverse events of psoriasis (adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, inverse psoriasis, palmo-plantar psoriasis and worsening or exacerbation of psoriasis; final allocation will be performed after blinded data review).

Note that the summary tables will provide the number of subjects per event (i.e., coded as preferred term) and will also provide the number of events for certain tables.

For calculation of the number of subjects per event each preferred term will be counted only once per subject and will be linked to the primary SOC. A subject may contribute with more than one different adverse event (at preferred term level); however, a subject with more than one occurrence of the same adverse event (at preferred term level) is displayed and counted only once for this event in the tables.

Tables that are stratified by the severity of adverse events will summarize the worst severity per subject and preferred term.

Tables that are stratified by the relationship of adverse events will summarize the highest relationship per subject and preferred term.

For presentation of drug related/ not drug related adverse events the following categories will be used:

- drug related = very likely, probable, possible
- not drug related = doubtful, not related

For summarization of severity of drug related TEAEs, events with a causality assessment of 'doubtful/not related' will be excluded and the worst severity will be tabulated as described above. Summarization of severity of not drug related TEAEs will be performed likewise.

The following safety endpoints will be defined and used for the statistical analyses for HTA purposes:

- The proportion of subjects with any TEAE within the 24 Weeks treatment period
- The proportion of subjects with serious TEAE within the 24 Weeks treatment period
- The proportion of subjects with treatment discontinuation due to TEAE within the 24 Weeks treatment period
- The proportion of subjects with any TEAE by preferred term and SOC within the 24 Weeks treatment period

Counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for treatment effect using the chi-square test will be provided. In addition, time-to-event-analyses and logistic regression analyses as described in SAP section 13.4.1 will be conducted for the onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

Subgroup analyses will be performed for the subgroups defined in SAP section 13.8 for the proportion of subjects with any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

The cut-off ≥ 5% (i.e., percentage of subjects ≥ X% in at least one treatment group) will be used for analyses of TEAEs by preferred term for any TEAE.

Listings

All adverse events (AEs) and serious adverse events (SAEs) will be listed in the individual subject data listings by treatment group, study center and subject number including all information documented on the respective form of the eCRF. Separate listings of subjects with the following AEs will be provided: SAEs, SAEs leading to death, AEs of severe intensity, AEs leading to permanent discontinuation of study medication.

Verbatim description of the adverse event reported by the investigator, MedDRA preferred terms and primary SOCs (system organ class) for all adverse events will be contained in the data listings. Non treatment emergent adverse events will be flagged in the respective listings.

14.5.3 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory item at each scheduled time. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Results of tuberculosis testing, serology, urine pregnancy testing and local urinalysis (glucose, protein) will be displayed in frequency tables providing the number and percentage of subjects per category (i.e., negative or positive) at each scheduled time.

The results of all laboratory tests will be provided in individual subject data listings including the reference ranges. Abnormal values will be identified by flagging all values below and above the reference range.

A listing of subjects with any laboratory results outside the reference ranges will be provided.

For the lymphocyte count the following subjects will be listed and summarized in a frequency table:

- lowest lymphocyte count $< 500/\mu l$
- $500/\mu l \leq$ lowest lymphocyte count $<700/\mu l$
- $700/\mu l \leq$ lowest lymphocyte count < lower limit of normal range

Graphical presentation of quantitative laboratory data will be given by means of box plots.

14.5.4 Vital Signs

Descriptive statistics of pulse and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time. Subjects reporting vital signs findings beyond clinically important limits will be identified using the following criteria.

Criteria for Identifying Potentially Clinically Significant Vital Signs Findings

Variable (units)	Criterion Value[a]	Change from Baseline
Systolic Blood Pressure (mmHg)	>200 <80	Increase of >40 Decrease of >40
Diastolic Blood Pressure (mmHg)	>120 <40	Increase of >30 Decrease of >30
Heart Rate (bpm)	>110 <40	

a In order to be identified as an abnormality of potential clinical importance, a value would need to meet the criterion value **o**r also represent a change of at least the magnitude noted in the change column.

Vital signs values of potentially clinically significant importance will be analyzed by providing the number and percentages of subjects with values of potential clinical importance per scheduled study visit, overall during the study and with first occurrence after baseline.

14.5.5 Physical Examination

Physical examination findings will be tabulated by the body systems given in the eCRF at each scheduled time. Moreover, abnormal findings with first occurrence after baseline reported during the treatment phase and follow-up phase will be presented. Details on abnormal findings in verbatim terms will be displayed in individual subject data listings.

14.5.6 Body Weight

For body weight absolute values and changes from baseline values will be presented by descriptive statistics at each scheduled time.

14.5.7 Early Detection of Active Tuberculosis

Categorical data on early detection of active tuberculosis will be presented in a frequency table providing the number and percentage of subjects per category at each scheduled time.

14.6 Analysis of MedDRA Codes

Previous / concomitant diseases (including indications for use of concomitant and other medications) and adverse events will be coded with version 19.1 of the MedDRA-dictionary.

In general, tabulation will be displayed by preferred term and primary SOC.

14.7 Analysis of WHO Drug Dictionary Codes

The use of concomitant and other medications will be coded using the WHO Drug Dictionary (version 2016/1). Medications will be tabulated by preferred name (i.e., the decode of the code which results when SEQ1 and SEQ2 are set to 01 and 001, respectively (usually resulting in a decode close to the generic drug name)) and they will be grouped by level 2 of the Anatomical Therapeutic Chemical (ATC) code. Codes being linked to more than one ATC code at this level will be assigned to one primary ATC code by medical data analysts.

15.0 Changes to Planned Analyses

This statistical analysis plan includes the following relevant changes to the planned analyses which are described in the clinical study protocol.

- Evaluations on health technology assessment (HTA) will also be specified in this SAP. No separate SAP for evaluations on health technology assessment will be provided (see SAP section 3.0 and CSP section 11)
- A per-protocol analysis will be performed for the primary and the major secondary endpoints (see SAP section 11.0).
- No treatment failure imputation rules will be applied (see to SAP section 13.1.5 and CSP section 11.4)
- The following safety endpoints will be defined and used for the statistical analyses for HTA purposes:
    - The proportion of subjects with any TEAE within the 24 Weeks treatment period
    - The proportion of subjects with serious TEAE within the 24 Weeks treatment period
    - The proportion of subjects with treatment discontinuation due to TEAE within the 24 Weeks treatment period
    - The proportion of subjects with any TEAE, serious TEAE, treatment discontinuation due to TEAE by preferred term and SOC within the 24 Weeks treatment period
- Time-to-event analyses for binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of TEAE, serious TEAE, and treatment discontinuation due to TEAE will be performed using Kaplan-Meier product limit method and Cox proportional hazards model.

Any major changes to this plan after sign-off of the latest final version will be specified in the clinical study report.

16.0 Tabulation

16.1 General

The statistical output will be prepared in American English. No separate statistical report will be written.

16.2 Format of Data Displays

The layout of all tables, listings and figures will be drafted by acromion GmbH when providing the first draft tables, listings and figures on final data. No sponsor or other requirements for layout specifications have to be followed.

The SAS outputs will be post-processed within Microsoft Word®. SAS tables and listings will be integrated into Microsoft Word® using the SAS Monospace 8 points font.

Separate appendices will be provided for tables, listings, and figures. For each appendix a corresponding table of contents will be generated. All pages within one appendix will be numbered consecutively. Tables, listings and figures generally should be self-explaining. Abbreviations will be described in the footnote if necessary.

16.2.1 Tables

SAS summary tables will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

16.2.2 Listings

SAS subject data listings will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

Data listings will be created for groups of variables which logically belong together (e.g. demographic variables) and will be sorted by treatment group, center, subject and visit (if applicable).

16.2.3 Figures

Figures will be created using the following graphical SAS options, if not otherwise specified:

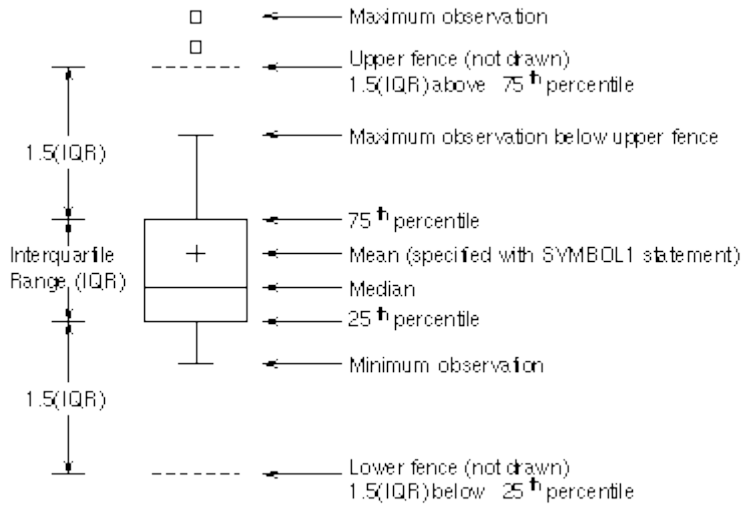
```
GOPTIONS
   RESET   = ALL
   NOBORDER
   KEYMAP = WINANSI
   DEVMAP = WINANSI
   DEV      = EMF
   TARGET = WINPRTC
   GUNIT   = CM
   CTEXT   = BLACK
   FTEXT   = 'Arial/bold'
   HTEXT   = 0.5 CM
   LFACTOR= 1
   HSIZE   = 6 IN
   VSIZE   = 5 IN;
```

Variables may be presented in the following graphical formats, if applicable:

Box plot

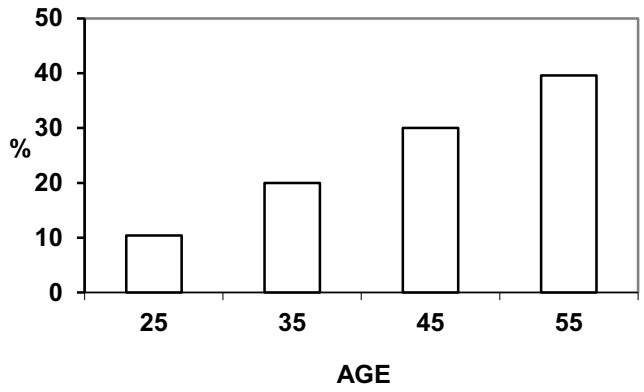
Box plots summarize the data by a box reaching from the 1st to the 3rd quartile. The median is displayed inside this box by a horizontal line. Above the box a vertical line indicates the region from the 3rd quartile to the max. value below the upper fence ; below the box a vertical line indicates the region from the 1st quartile to the min. value above the lower fence. The upper fence lies 1.5 interquartile-ranges above the 3rd quartile, the lower fence lies 1.5 interquartile ranges below the 1st quartile. Values outside the fences are displayed by a distinct marker.

A graphical presentation is given below:



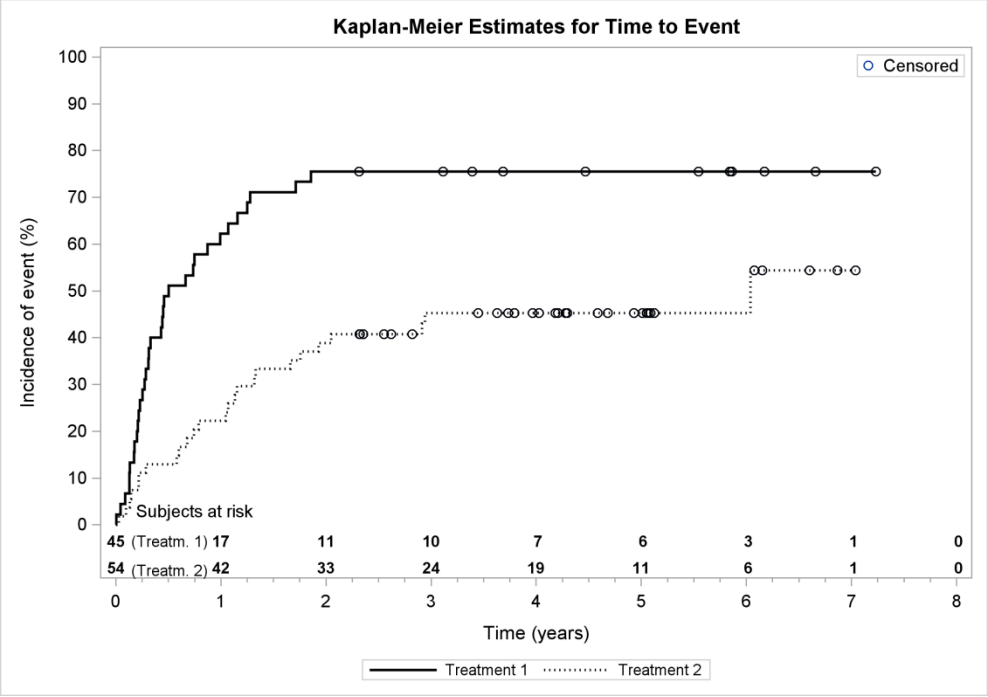
Bar chart

A bar chart displays a categorical variable. A sample display is provided below.



Survival Graph

A survival graph displays the survival distribution functions according to Kaplan-Meier. A sample display is provided below.



16.3 Data Format

Unless otherwise specified, percentage values will be printed with one digit to the right of the decimal point.

In general, minima and maxima will be quoted to the number of decimal places as recorded in the eCRF; means, standard deviations and medians will be quoted to one further decimal place.

All p-values will be given by four digits to the right of the decimal point. Verbatim terms documented in the eCRFs will be presented as entered in the clinical data base.

17.0 References

Study Documents:

Document	Version, Date
Protocol / Amendments	Version 1.0, 03-AUG-2016
eCRF	Version 1.0, 12-DEC-2016
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016

SOPs and Guidelines acromion:

Document	Title, Date
acromion SOP BM04	Statistical Analysis Plans, Oct-2016
acromion SOP BM05	Determination of Availability of Data for Analysis, Oct-2016
acromion SOP BM06	Generation and Release of Blinded Randomization Code, Oct-2016
acromion SOP BM07	Programming of Derived Data Sets, Oct-2016
acromion SOP BM08	Programming of SAS Data Displays, Oct-2016
acromion SOP BM11	Documentation and Project Close-Out, Oct-2016
acromion Guideline BM01	SAS Programming Guideline, Oct-2016
acromion Guideline BM02	Biometrics Naming Conventions for SAS Datasets and SAS Programs, Oct-2016

Other Documents:

Document	Title, Date
ICH Guideline E 9	Statistical Principles for Clinical Trials, final approval 1998

18.0 Appendices

18.1 Table of Contents for Data Displays

The tables, subject data listings and figures will be provided using the following numbering system, which will be updated after start of programming the data displays. However, this section does not include the HTA analyses for the topline results described in SAP section 14.6. The numbering system for the HTA analyses will be provided with the HTA mock tables.

All summary tables will start with the one-character identifier for the displayed analysis set followed by the one-digit identifier for the displayed analysis chapter as listed below.

Identifier for displayed analysis set:

- **A**: Efficacy analysis set
- **B**: Safety analysis set
- **C**: Per-protocol analysis set

Identifier for displayed analysis chapter:

- **1**: Study subjects
- **2**: Demographics and other baseline characteristics
- **3**: Treatment compliance
- **4**: Analysis of efficacy
- **5**: Analysis of safety

Data displays will be provided for the following analysis sets:

Chapter No.	Chapter Title	Analysis set
1	Study subjects	• A: efficacy analysis set
2	Demographic and other baseline characteristics	• A: efficacy analysis set • B: safety analysis set
3	Treatment compliance	• A: efficacy analysis set • B: safety analysis set
4	Analysis of efficacy	• A: efficacy analysis set • B: safety analysis set • C: per-protocol analysis set
5	Analysis of safety	• B: safety analysis set

All individual subject data listings will start with the one-digit identifier for the displayed chapter analogously as for the summary tables. Data displays and subject data listings will be provided in separate appendices and pages will be numbered for each appendix separately starting with page no. 1.

18.1.1 Tables

Study Subjects, Prefix A

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics, Prefix A, B

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance, Prefix A, B

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy, Prefix A, B, C

No.	Analysis Chapter
	- Primary Endpoint -
4.1	PASI 90% Response
	- Major Secondary Endpoints -
4.2.1	Endpoint Related to PASI
4.2.2	Endpoint Related to DLQI
	- Other Secondary Endpoints -
4.3.1	Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety, Prefix B

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight
5.7	Early Detection of Active Tuberculosis

18.1.2 Listings

Study Subjects

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy

No.	Analysis Chapter
	- Primary Endpoint -
4.1	PASI 90% Response
	- Major Secondary Endpoints -
4.2.1	Endpoint Related to PASI
4.2.2	Endpoint Related to DLQI
	- Other Secondary Endpoints -
4.3.1	Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight
5.7	Early Detection of Active Tuberculosis

18.1.3 Figures

Analysis of Efficacy, Prefix A, B, C

No.	Analysis Chapter	Type of Figure
	- Primary Endpoint -	
1	PASI 90% Response	Bar Chart, Survival Graph
	- Major Secondary Endpoints -	
2.1	Endpoint Related to PASI	Bar Chart, Survival Graph
2.2	Endpoint Related to DLQI	Bar Chart, Survival Graph
	- Other Secondary Endpoints -	
3.1	Endpoints related to PASI	Bar Chart, Survival Graph
3.2	Endpoints related to PSSD	Box Plot
3.3	Endpoints related to IGA	Bar Chart
3.4	Endpoints related to BSA	Box Plot
3.5	Endpoints related to DLQI	Bar Chart
3.6	Endpoints related to ss-IGA	Bar Chart
3.7	Endpoints related to SF-36	Box Plot
	- Other Efficacy Assessments -	
4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)	Bar Chart, Box Plot

Analysis of Safety, Prefix B

No.	Analysis Chapter	Type of Figure
5	Clinical Laboratory Tests	Box Plot
6	Vital Signs	Box Plot
7	Body Weight	Box Plot

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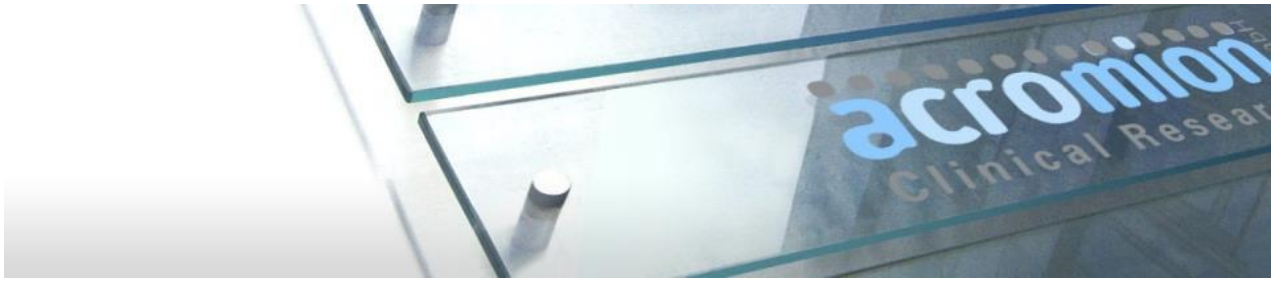

Statistical Analysis Plan

Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm® initial/ Fumaderm®) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment

POLARIS

- Study Part IIa: Week 32 Analysis -

Study Code	CNTO1959PSO3008
EudraCT Number	2016-002135-15
Development phase	Phase 3b
Study Design	randomized, open-label, efficacy assessor-blinded, single country, multicenter, active-comparator-controlled
Sponsor	Janssen-Cilag GmbH, Neuss Johnson & Johnson Platz 1, 41470 Neuss, Germany
Contract Research Organization	acromion GmbH Europaallee 27 – 29 50226 Frechen, Germany
Version No., Date	Final Version 1.0, 15-Aug-2018

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2.0 List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CRF	Case Report Form(s)
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e.g.	example given
FAE	Fumaric Acid Esters
HBV/ HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICH	International Council on Harmonization
i.e.	that is
IGA	Investigator´s Global Assessment
IL	Interleukin
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NTEAE	Non Treatment Emergent Adverse Event
NTESAE	Non Treatment Emergent Serious Adverse Event
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PRO	Patient-Reported Outcome(s)
PSSD	Psoriasis Symptom and Sign Diary
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form (36-item) health survey
SOC	System Organ Class
SOP	Standard Operating Procedure
ss	scalp-specific
TB	tuberculosis
TEAE	Treatment Emergent Adverse Event
TES	Time and Events Schedule
TESAE	Treatment Emergent Serious Adverse Event

3.0 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 and the relevant acromion SOPs and/or guidelines. This plan describes the statistical analyses planned to be performed for the Week 32 analysis Study Part IIa of Janssen-Cilag GmbH Clinical Study Protocol CNTO1959PSO3008 and should be read in conjunction with the statistical analysis plan for the Week 24 analysis, the protocol amendment INT-1 to the CSP and the electronic Case Report Form (eCRF).

An overview about all planned analyses is given in Section 13.6. The Week 32 analysis summarizes the study data unit Week 32 (Study Part IIa; Week 24 through Week 32) and will be conducted as part of the Week 64 analysis once all data of Study Part II are available. The Week 32 analysis will include the safety analysis and all efficacy measures after Week 24 and will cover the time until the Week 32 visit. All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32. Statistical analyses of study data until Week 64 (Study Part IIb; active treatment from Week 32 through Week 56 and safety follow-up until Week 64) will be provided in a separate SAP.

Confirmatory analyses for the primary endpoint and the major secondary endpoints were already performed at the Week 24 analysis as described in the statistical analysis plan for Week 24 (Final 1.0, 10-July-2017). Evaluations on health technology assessment (HTA) will also be specified in this SAP. No separate HTA SAP will be provided. The Week 32 analysis will be performed after all subjects have completed their visit at 64 weeks after randomization or discontinued earlier. Data base lock for the Week 32 analysis will be after the Week 64 visit data are ready for statistical analysis (i.e., clean data).

This SAP is the core document for all statistical programming planned to be performed for the Week 32 analysis and is based on the following study documents to protocol no. CNTO1959PSO3008:

Document	Version, Date
Protocol / Amendments	Protocol Amendment INT-1, Version 2.0, 25-APR-2017
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan - Week 24 Analysis	Version 1.0, 10-JUL-2017

4.0 Responsibilities

The responsibilities for the biometrical tasks at acromion GmbH are assigned as follows:

Name	Function	Task
[redacted]	Statistician	Statistical Programming and Analysis
	Statistician	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Medical Data Analyst	Medical Data Review and Coding

5.0 Software Utilized

The statistical analysis and generation of tables, patient data listings and figures will be performed using the SAS® software package version 9.4 under the Microsoft Windows® 7 operating system at the computer facilities of acromion GmbH. Additional analyses regarding health technology assessment (HTA) may be performed by or under the responsibility of Janssen-Cilag GmbH.

6.0 Coding Systems Utilized

The MedDRA-dictionary version 19.1 is used for coding of prior and concomitant diseases and for coding of adverse events. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Medical History of Interest	Medical History Term	MH/MHTERM
Previous Phototherapy	Type of Phototherapy	MH/MHTERM
Concomitant Medication	Indication	CM/CMIND
Concomitant Therapy	Indication	CM/CMIND
Concomitant Therapy	Therapy	CM/CMTRT
(S)AE	Term	AE/AETERM

Prior and concomitant medications are coded according to the WHO terminology using the 2016/1 version of the WHO-Drug Dictionary. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Previous Topical Therapy	Medication/Therapy	MH/MHTERM
Concomitant Medication	Compound	CM/CMTRT

Details are specified in the Data Management Plan.

7.0 Study Objectives and Hypotheses

7.1 Objectives

Primary Objectives

The primary objectives of the study are

- to compare the efficacy of guselkumab to fumaric acid esters (FAE) in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.
- to assess the safety and tolerability of guselkumab in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.

Secondary Objective

The secondary objectives of the study are

- in Study Parts I and II: to compare improvement of health-related quality of life (QOL) and other patient-reported outcomes (PRO) when systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.
- in Study Part II: to compare sustainability of response to treatment when systemic treatment naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.

7.2 Hypotheses

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

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

8.0 Study Endpoints

This section provides a description of all study endpoints as pre-specified in the CSP (Protocol Amendment INT-1) for the Week 24 and the Week 64 analyses. The Week 64 analysis includes the Week 32 analysis which is described in the present SAP.

Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 90% improvement of their psoriasis according to the Psoriasis Area and Severity Index (PASI 90 response) at Week 24.

Secondary Endpoints

The major secondary endpoints are:

- The proportion of subjects achieving at least a 75% improvement of their psoriasis according to the PASI at Week 24 (PASI 75 response)
- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

Other secondary endpoints are:

- The proportion of subjects achieving a 100% improvement of their psoriasis according to the PASI at Week 24 (PASI 100 response)
- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 24
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 24
- The proportion of subjects achieving an absolute PASI score ≤1 at Week 24
- The proportion of subjects achieving an IGA score of cleared (0) at Week 24
- The change from baseline of body surface area (BSA) psoriatic involvement at Week 24
- The change from baseline in DLQI score at Week 24
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 24 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
- The change from baseline in the physical and mental component summary scores of SF-36 at Week 24
- Maintenance of response. Proportion of subjects with a
  - PASI 75 response at Week 32 who maintain response at Week 56
  - PASI 90 response at Week 32 who maintain response at Week 56
  - a DLQI score 0 or 1 at Week 32 who maintain response at Week 56
- Proportion of subjects of the FAE group who were PASI 75 non-responders at Week 32 and switched to guselkumab with a
  - PASI 75 response (compared to Week 0) at Week 56
  - PASI 90 response (compared to Week 0) at Week 56
  - PASI 100 response (compared to Week 0) at Week 56
  - DLQI score 0 or 1 at Week 56
- Proportion of subjects with a
  - PASI 75 response at Week 32
  - PASI 90 response at Week 32
  - PASI 100 response at Week 32
  - DLQI score 0 or 1 at Week 32
- Safety and tolerability data will be summarized using descriptive statistics.

9.0 Study Design

This section provides a description of the study design as defined in the CSP (Protocol Amendment INT-1) for the Week 24 and the Week 64 analyses. The Week 64 analysis includes the Week 32 analysis which is described in the present SAP.

The description is written in future tense according to the wording in the CSP, even though some of the planned actions, analyses and procedures have been carried out meanwhile.

Note: References to 'Section' always refer to the respective section in the CSP (Protocol Amendment INT-1).

9.1 Overview

This is a randomized, open-label, efficacy assessor-blinded, single country, multicenter, active comparator-controlled phase 3b study of guselkumab in adult subjects with moderate to severe plaque-type psoriasis who have not yet received any systemic therapy. The study will be performed at about 30 to 45 sites in Germany.

This study will have a 3-week screening phase, a 56-week treatment phase and a safety follow-up phase until Week 64 (as shown in Figure 1). The maximum duration of a subject's participation in this study will be 67 weeks including the 3-week screening phase. With protocol Amendment 1, the study will be split into two parts (Study Part I and II):

Study Part I (Core Study)—Week 0 through Week 24:
Screening and treatment until Week 24

After screening, a total of 114 subjects will be randomized in a 1:1 ratio to either the study drug (guselkumab) or to the active comparator (FAE). Subjects of the guselkumab group will receive 100 mg guselkumab SC at Weeks 0, 4, 12, and 20. Subjects of the FAE group will receive commercially available Fumaderm® tablets specifically labeled for the study. An individual dosing for each subject representing the optimal benefit-risk ratio is aspired.

A subject will be considered to have completed Study Part I if he or she has completed assessments at Week 24 of the open-label phase. Subjects eligible for Study Part II at Week 24 (ICF Part II signed, study treatment ongoing, no protocol-prohibited treatment started) will enter study extension and continue study treatment. For subjects who discontinue study treatment or withdraw from study participation in Study Part I or who do not enter Study Part II, a safety follow-up visit (Study Part I) is completed at Week 32 or 12 weeks after the last treatment (whatever comes first). For subjects enrolled in Study Part I only, maximum duration of study participation in this study will be 35 weeks.

Study Part II (Extension)—Week 24 through Week 56:
Treatment

Subjects may enter the study extension at Week 24 only when the ICF for Study Part II was signed before or at Week 24, study treatment was not terminated prior to Week 24 and no protocol-prohibited medication/therapy was started. Study Part II is subdivided in two treatment periods:

- Part IIa—Week 24 through Week 32: All subjects who enter Study Part II will continue their assigned treatment (guselkumab or FAE) from Week 24 through Week 32. Study Part IIa is considered completed when the subject has completed assessments at Week 32.

  Part IIb—Week 32 through Week 56: Following Week 32, subjects with a PASI 75 response will continue assigned treatment (guselkumab or FAE). For PASI 75 non-responders at Week 32 the following options will be available:

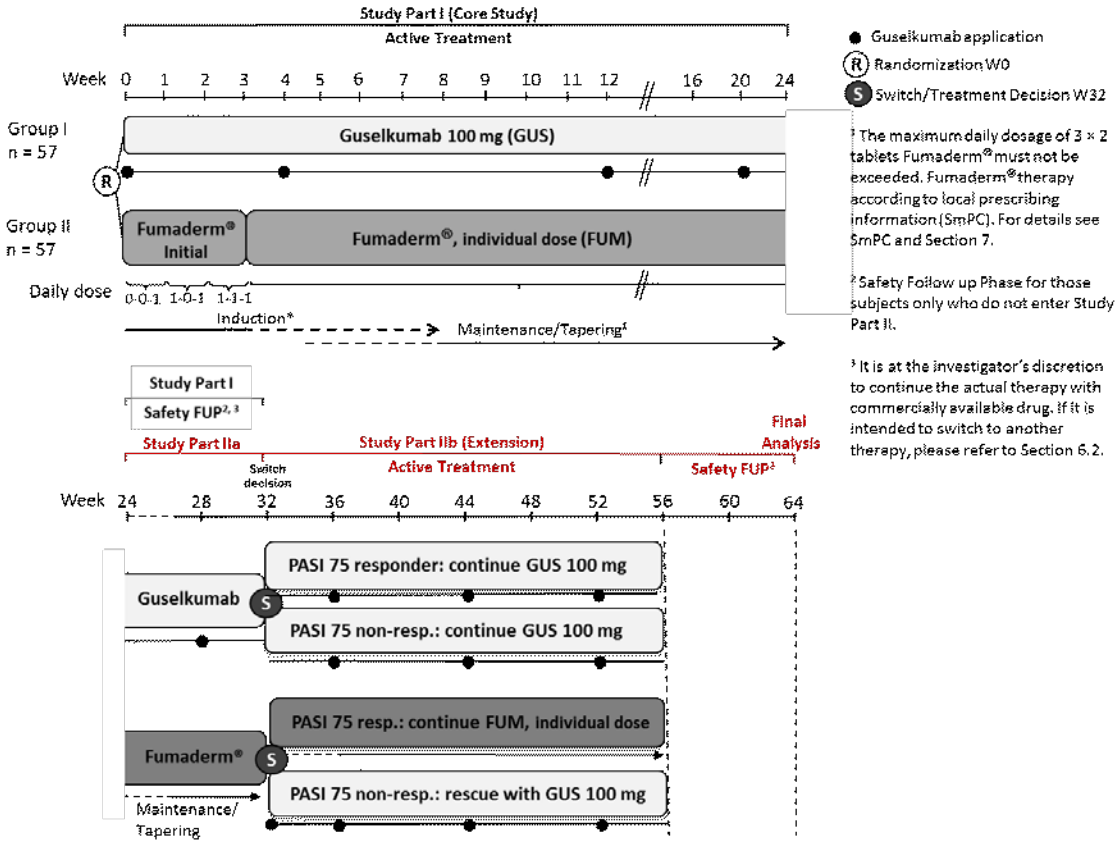
- Guselkumab group: Subjects may continue guselkumab treatment. It is at the investigator's discretion to continue therapy, if it is considered medically appropriate.
- FAE group: Subjects will switch to guselkumab unless barred by safety reasons (based on lab values ≥Week 28). Subjects who terminate FAE treatment prior to Week 32 cannot continue study treatment but will enter safety follow-up per protocol.

A subject will be considered to have completed Study Part II if he or she has completed assessments at Week 56 of the open-label phase. For Subjects who discontinue study treatment or withdraw from study participation in Study Part II, final study assessments are obtained and a safety follow-up visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first). For subjects completing Study Part II maximum duration of study participation in this study will be 67 weeks including a 3-week screening phase.

Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd PSSD 7-day version, and 3rd SF-36), and subsequently by a blinded efficacy assessor (BSA%, IGA, ss-IGA, and PASI). Safety evaluations will include the monitoring of adverse events (including injection site and allergic reactions), physical examinations, measurement of body weight, vital sign measurement, clinical laboratory testing (HBV, HCV, HIV, hematology, chemistry), concomitant medication review, tuberculosis test and evaluation, urinalysis and pregnancy testing. The confirmatory analysis will be conducted after the primary endpoint at Week 24 is reached including subjects who have completed the Week 24 visit and subjects who have terminated the study prematurely (Section 11.3). The second statistical analysis will be performed after Week 64 (see Section 11).

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be transferred to the sponsor (or designee) after completion of the final subject visit at that site, in the time specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 21 months (start in December 2016, stop in October2018). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

Figure 1: Schematic Overview of the Study



9.2 Sample Size Determination

As described in the CSP, the primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24.
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$). Due to the testing of ordered hypotheses, no adjustment of the significance level with respect to the threefold test procedure is required.

The assumptions for the sample size and power calculations using the threefold test procedure were based on guselkumab phase 2 data and unpublished data from the German PsoBest Registry and are as follows: PASI 90 responder rates for guselkumab and FAE in Week 24 are assumed to be 60% and 25%, respectively. PASI 75 responder rates are assumed to be 80% and 45%, respectively. DLQI responder rates are assumed to be 60% and 30%, respectively.

Based on these assumptions, with a total of 114 subjects planned to be randomized in a 1:1 ratio to guselkumab (n = 57) and to FAE (n = 57), superiority of guselkumab vs. FAE can be demonstrated at a 5% significance level (two-sided) with power of at least 90% for each test of the threefold test procedure as displayed in the table below.

Table 1: Power to detect a treatment effect on expected proportions of subjects achieving the primary and the major secondary endpoints

Order of testing	Endpoint in Week 24	Guselkumab (% responder)	FAE (% responder)	Power
1	PASI 90	60	25	97%
2	PASI 75	80	45	98%
3	DLQI 0/1	60	30	90%
type 1 error rate alpha 5% (two-sided) sequential testing with a-priori ordered hypotheses (only proceed with testing, if p <0.05) sample size n = 114 with 1:1 ratio guselkumab (n = 57) and FAE (n = 57) two group chi-square test; nQuery Advisor® Release 7.0				

9.3 Randomization and Blinding

Procedures for Randomization

Central randomization is implemented in this study as described in Section 5 of the CSP. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) 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-based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC (Electronic Data Capture) system.

Blinding

As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP.

10.0 Study Schedule

An overview of the study procedures is displayed in the following time and events schedule of the CSP. References to 'Section' always refer to the respective section in the CSP.

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Screening/Administrative												
Informed consent I (Study Part I)	X											Must be signed before first study-related activity
Informed consent II (Study Part II)	----------X											ICF addendum for Study Part II to be signed at Week 24 at the latest
Medical history and demographics	X											
Inclusion/ exclusion criteria	X	X										Minimum criteria for the availability of documentation supporting the eligibility criteria are described in protocol, Section 4; check clinical status again before first dose of study medication
Study Drug Administration												
Randomization		X										All baseline study procedures and evaluations are to be completed before randomization
Study drug administration		X[c]----------…										All study procedures and evaluations are to be completed before study drug administration

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before administration of study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

c: Subjects randomized to guselkumab will get guselkumab 100 mg on site at Weeks 0, 4, 12 and then every 8 weeks. Subjects randomized to FAEs will start with Fumaderm® initial regimen (0-0-1) at the day of the baseline visit; thereafter, FAE doses will be increased to find the optimal Fumaderm® dose for each subject as described in Section 6.

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit: for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4												
Safety Assessments												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis evaluation	X	X	X----------…							X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Chest radiograph	X											Taken within 3 months before the first administration of study drug and read by a qualified radiologist
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	Women of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits (prior to administration of study drug).
Height		X										
Weight		X							X	X	X	
Concomitant therapy	X----------…									X	X	
Adverse events	X----------…									X	X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Efficacy Assessments												
DLQI	X	X		X	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit; completion of the baseline PROs has to be done before randomization
PSSD (7d)	X	X	X	X	X	X	X	X	X		X	
SF-36		X			X		X		X		X	
IGA[d]	X	X	X	X	X	X	X	X	X		X	
PASI[d]	X	X	X	X	X	X	X	X	X		X	
ss-IGA[d,e]		X			X		X		X		X	
BSA%[d]	X	X			X		X		X		X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

d: Dermatological evaluation of the subjects will be done by a blinded assessor starting with the Baseline visit; assessments will be done before any study related procedure will take place

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Clinical Laboratory Assessment												
Tuberculosis test[f]	X											
Hepatitis B and C Serologies	X											
HIV antibody test	X											
Hematology[g]	X	X	X	X	X	X	X	X	X	X	X	Laboratory tests are listed in Section 9.3
Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤ +; one re-test (central urine analysis) is allowed.

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

f: The QuantiFERON-TB Gold Plus test will generally be performed by the central laboratory; however, if available, test results from local laboratory can be accepted

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Study Drug Administration											
Study drug administration	…---------X[i]----------X										Subjects may enter the study extension at Week 24 when ICF for Study Part II was signed, study treatment was not terminated and no protocol-prohibited medication/therapy was started.
Safety Assessments											
Physical examination	X	X		X		X		X	X	X	
Vital signs	X	X		X		X		X	X	X	
Tuberculosis evaluation	……----------X								X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	
Weight									X	X	

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II (≤Week 64): For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

i: Week 24 to Week 32 (Study Part IIa): subjects continue assigned treatments through Week 32. Subjects treated with 100 mg SC guselkumab continue q8w (ie, at Week 28). Subjects treated with FAE continue Fumaderm® tablets (individual dosing according to local SmPC) until Week 32.

Week 32 to Week 56 (Study Part IIb): Treatment decision based on PASI assessment at Week 32 and safety assessment (≥Week 28):

- PASI 75 responders at Week 32: subject continues assigned therapy. Subjects in the guselkumab group continue 100 mg guselkumab SC at Weeks 36, 44, 52. Subjects in the FAE group continue Fumaderm® treatment (individual dosing according to local SmPC) until Week 56.
- PASI 75 non-responders at Week 32: subjects in the FAE group may switch to guselkumab treatment unless barred by safety reasons (see treatment criteria Section 4.4). In case of safety concerns (based on lab values of Week ≥28), assessment can be repeated before Week 32. Subjects will receive guselkumab SC at Weeks 32, 36, 44 and Week 52. Non-responders in the guselkumab group may continue guselkumab (continuation of therapy is at the investigator's discretion).

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Safety Assessments (continued)											
Concomitant therapy	…----------X								X	X	
Adverse events	…----------X								X	X	
Efficacy Assessments											
DLQI	X	X	X*	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit. ***ONLY applicable for subjects who switched to guselkumab at Week 32**
PSSD (7d)	X	X	X*	X		X		X		X	
SF-36		X						X		X	
IGA[d]	X	X	X*	X		X		X		X	
PASI[d]	X	X	X*	X		X		X		X	
ss-IGA[d,e]		X	X*	X		X		X		X	
BSA%[d]		X						X		X	
Study Procedures[b]											

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

d: Dermatological evaluation of the subjects will be done by a blinded assessor as in Study Part I; assessments will be done before any study related procedure will take place

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Clinical Laboratory Assessment											
Hematology[g]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X	Laboratory tests are listed in Section 9.3 **[Δ] NOT applicable for subjects continuing guselkumab treatment since beginning of the study (Week 0)**
Chemistry[g]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X	
Urinalysis	X	X[β]	X	X[β]	X	X[β]	X	X[β]	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤+; one re-test (central urine analysis) is allowed. **[β] ONLY applicable for subjects treated with FAE**

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

11.0 Analysis Sets

In this study, subjects will be included in the efficacy analyses according to their assigned treatment. In contrast to the efficacy analysis set, safety analyses will be performed according to the actual treatment received during the study.

11.1 Definition of Analysis Sets

The following analysis data sets will be defined analogously to the definitions of the Week 24 analysis:

- **Efficacy Analysis Set**

  The efficacy analysis set is defined as the set of all subjects who were randomized to one of the two treatment groups (guselkumab or FAE) at Week 0 regardless of the treatment they actually received ("intent-to-treat" principle).

- **Per-Protocol Analysis Set**

  The per-protocol analysis set will consist of all subjects in the efficacy analysis set terminating the study without any major deviation of the protocol and its procedures. Subjects with major protocol deviations until Week 32 will be excluded from the per-protocol analysis.

- **Safety Analysis Set**

  The safety analysis set is defined as the set of all subjects who were randomized to one of the two treatment groups (guselkumab or FAE) at Week 0 and who received at least one dose of study drug according to the actual treatment received during the study irrespective of the treatment assigned at randomization.

Unless otherwise specified, data on study subjects (including subject disposition, reasons for discontinuation of study treatment, protocol deviations, analysis sets) will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

If not otherwise specified, demographic and other baseline characteristics as well as treatment compliance will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

All efficacy analyses to compare guselkumab vs. FAE will be performed for all subjects randomized at Week 0 ('efficacy analysis set'). The PASI 90, PASI 75 and DLQI 0/1 response rates will also be analyzed using the per-protocol analysis set.

All safety analyses to compare guselkumab vs. FAE will be performed for all treated subjects ('safety analysis set').

Since the safety analysis set differed only by one patient from the efficacy analysis set, it was decided that the efficacy analyses were not to be performed for all treated patients ('safety analysis set').

11.2 Protocol Deviations

The determination of evaluability of subjects, especially in cases of protocol deviations, withdrawals or drop-outs and the assignment of subjects to the planned analysis sets will be performed according to the requirements of the study protocol. Minor and major and potentially major protocol deviations that can be expected based on the prescriptions in the protocol were defined by Janssen-Cilag GmbH during the trial set up period and adapted during the study conduct. A detailed description of major and potentially major protocol deviation criteria is included in a separate document.

Data on subjects who had a major protocol deviation will be documented continuously by Janssen-Cilag GmbH in a Clinical Trial Management System during the trial period. Final data on major protocol deviations regarding the Week 32 analysis will be transferred to the data management department of acromion GmbH as Excel spreadsheets and will be further processed for statistical analysis.

11.3 Screening Failures

The data of subjects who were not randomized will not be included in the statistical analyses. However, a separate listing will be presented providing the site/subject no. and the reason for not being randomized.

12.0 Definition and Calculation of Efficacy Endpoints

The following sections provide a detailed description of the definition and the planned calculation of the efficacy endpoints as defined in the CSP. The same applies also for additional endpoints not defined in the CSP.

12.1 Involved 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).

12.2 Investigator's Global Assessment (IGA)

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

The efficacy endpoint related to the IGA score is defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

12.3 Scalp Specific Investigator's Global Assessment (ss-IGA)

The scalp-specific (ss-)IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

The analyses for ss-IGA will be based on subjects randomized at Week 0 with baseline ss-IGA score ≥2.

ss-IGA absence of disease responder

Subjects with an ss-IGA score ≥2 at baseline who achieve ss-IGA score of absence of disease (0) will be considered ss-IGA absence of disease responders.

12.4 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.

In addition, the time to PASI 75/90/100 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response the time to PASI 75/90/100 response will be censored at the date of Week 32 or the date of discontinuation in case of early treatment discontinuation.

12.5 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 (e.g., 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.

In addition, the time to DLQI 0/1 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response, the time to DLQI 0/1 response will be censored at the date of Week 32 or the date of discontinuation in case of early treatment discontinuation.

12.6 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.

12.7 Short Form Health Survey (SF-36)

The Short Form Health Survey (SF-36) is a 36-item questionnaire used for subjects' self-assessment of health-related quality of life, consisting of the following 8 dimensions: 1) limitations in physical functioning due to health problems, 2) limitations in usual role activities due to physical health problems, 3) bodily pain, 4) general mental health (psychological distress and well-being), 5) limitations in usual role activities due to personal or emotional problems, 6) limitations in social functioning due to physical or mental health problems, 7) vitality (energy and fatigue), and 8) general health perception.

A physical component summary (PCS) score and a mental component summary (MCS) score can be derived. The concepts measured by the SF-36 are not specific to age, disease or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments. The estimated completion time will be 10 minutes.

Each of these 8 scales (domains) is scored from 0 to 100 with higher scores indicating better health. Based on the scale scores, the summary scores, PCS and MCS, will be derived. These summary scores are also scaled with higher scores indicating better health.

The QualityMetric Health Outcomes™ Scoring Software 5.0 offered by QualityMetric Incorporated will be used to score the SF-36. The Software is designed to provide users with standard scoring methods in an easy-to-use way. By using this Software, users will have the confidence that the data they obtain on their SF form are scored in accordance with standards set by the developers of the SF tools. The Software also provides evaluation of data quality and applies methods for missing data recovery. The PCS score can be calculated when seven scale scores are available and the Physical Functioning scale is not missing. The MCS score can be calculated when at least seven scale scores are available and the Mental Health scale is not missing.

A more detailed description of the scoring procedure is provided in the User's Guide of QualityMetric Health Outcomes™ Scoring Software 5.0 (see especially Appendix F).

13.0 Statistical Methodology

The present Week 32 analysis of Study Part IIa summarizes the study data until Week 32 (Study Part IIa; Week 24 through Week 32) and will be part of the Week 64 analysis of Study Part II. This analysis will include the safety analysis and all efficacy measures after Week 24 and will cover the time until the Week 32 visit. All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32.

The biometrical evaluation will be carried out by acromion GmbH under the authority of the sponsor. Statistical programming and analyses will be performed using the statistical software system SAS®.

The following sections provide a more detailed description of the planned statistical methodology.

13.1 Data Handling Rules

13.1.1 Baseline and Post-baseline Points in Time of Interest

Baseline Definition

In general, the values of the Week 0 visit (= day of randomization = first day of week 1) or the values of the screening visit (= day within 3 weeks before their randomization visit) will be used as baseline values, as applicable. If data for the same variable are available from both (i.e., screening and Week 0) visits then the result of the Week 0 visit will be used as baseline value, i.e., for each variable the baseline measurement is defined as the closest measurement taken prior to or at the Week 0 visit.

Definition of Post-baseline Points in Time of Interest

The primary point in time for efficacy assessment will be the Week 32 visit (= the treatment visit 32 weeks after randomization). Secondary points in time for efficacy assessment will be the study visits scheduled at Week 28 during the treatment phase. Handling of missing values is described in SAP section 13.1.6.

The safety analysis will cover the time period until Week 32.

13.1.2 Definition of Within- and Between-Group Treatment Differences

Within-group treatment differences will be computed as differences of the post-baseline visits as compared to the baseline visit, if applicable:

- post-baseline visit minus baseline visit

The following between-group treatment difference to assess the treatment effect will be computed, if applicable:

- guselkumab minus FAE

13.1.3 Visit Windows

Nominal visits (i.e., visits as recorded in the eCRF) will be used for all by-visit analyses in the study. The study visits scheduled post randomization should occur at the times delineated in the Time and Events Schedule. No visit windows will be defined and used for analysis.

13.1.4 Treatment Failure Criteria

Not applicable.

13.1.5 Treatment Failure Rules

No treatment failure rules will be applied.

13.1.6 Handling of Missing Values

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

Missing data for the efficacy endpoints at key visits Week 28 and 32 will be handled as follows for all exploratory inferential statistical analyses.

Missing data imputation for the efficacy endpoints at Week 28 and 32:

- Nonresponder imputation will be applied for binary endpoints
    - i.e., subjects with missing data at Week 28/32 will be considered non-responders at Week 28/32.
- Last observation carried forward (LOCF) will be applied for continuous endpoints
    - i.e., in subjects with missing data at Week 28/32 the last available observation after baseline will be calculated and used for analysis for continuous response variables at Week 28/32. 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.

Sensitivity analyses with respect to the handling of missing values at Week 32 are described in SAP section 13.9.

13.1.7 Data Transformations

No data transformations (e.g. square root, logarithmic) to confirm basic statistical assumptions will be performed. All variables will be used in the analysis as reported.

13.2 Descriptive Statistics

13.2.1 Dichotomous and Categorical Variables

Categorical data will be presented in frequency tables using counts and percentages. Percentages will be based on the total number of subjects in the respective analysis set (i.e., missing values will be included in percentage calculation). Besides presentation of absolute values cross tabulation vs. baseline by study visit will be provided, if appropriate.

13.2.2 Continuous and Quasi-Continuous Variables

Standard descriptive summary statistics will be calculated for continuous and quasi-continuous variables: arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values. Besides presentation of absolute values tabulation for differences to baseline by study visit will be provided, if appropriate.

13.2.3 Graphical Presentations

Graphical presentation of pertinent data will be given by means of box plots, bar charts, and survival graphs, as appropriate. Additional forms of graphical presentations may be specified. Descriptions of graphical presentations are included in the appendix of this document.

13.3 Confirmatory Statistics

Not applicable for the present Week 32 analysis of Study Part IIa. The confirmatory analysis is described in the SAP for the Week 24 analysis (Final 1.0, 10-July-2017).

13.4 Exploratory Statistics

Exploratory statistical analyses will be performed for the other secondary endpoints at Week 32, and at Week 28. All statistical tests and confidence intervals will be calculated two-sided and will be interpreted in the exploratory sense only.

13.4.1 Binary Endpoints

For binary endpoints counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for treatment effect using the chi-square test will be provided.

Time-to-event analyses will be performed for binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE using Kaplan-Meier product limit method and Cox proportional hazards model. Summary tables will provide counts and percentage of subjects per treatment 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 factor treatment group). The survival curves will also be displayed graphically. Time-to-event analyses of binary endpoints will be performed on the observed cases only (i.e., missing data will not be replaced for time-to-event analyses).

A logistic regression model will be used for subgroup analyses of selected binary endpoints (i.e., PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE) at Week 32 with factors for treatment group, the respective subgroup and the interaction term between treatment and subgroup. Only the p-value of the interaction term will be provided from these analyses.

13.4.2 Continuous Endpoints

The change from baseline of continuous endpoints will be analyzed by an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate. The Least-Squares means (LS means), the LS mean difference and the standardized mean difference (computed according to Hedges' g) with the 95% CI and two-sided p-value will be provided from the ANCOVA model. For subgroup analyses of continuous endpoints, the ANCOVA model will be extended by the respective subgroup and the interaction term between treatment and subgroup.

13.5 Adjustment for Covariates

The baseline value will be used as covariate in the analysis of variance model (ANCOVA) for the change from baseline of continuous response parameters.

13.6 Planned Analyses

The following analyses are planned to be performed.

1. Main Analysis (Confirmatory Week 24 Analysis)

The confirmatory main analysis was performed at the end of Study Part I, i.e., after all subjects had completed their visit at 24 weeks after randomization or discontinued earlier. This analysis, described in a separate SAP ('SAP Week 24', final version 1.0, 10-July-2017), included the confirmatory analysis of the primary endpoint and the major secondary endpoints as well as all other exploratory predefined efficacy and safety analyses until Week 24. The results of the analysis are described in the Clinical Study Report Week 24, dated 14.05. 2018.

2. Interim Analysis (Exploratory Week 64 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) interim analysis will be performed at the end of Study Part II, i.e. after all subjects had completed their visits at 64 weeks after randomization or discontinued earlier. The Week 64 analysis will be split into 2 parts, the Week 32 analysis and the Week 64 analysis.

- The Week 32 analysis, described in this SAP ('SAP Week 32'), summarizes the study data until Week 32 (Study Part IIa; continuation of assigned treatment from Week 24 through Week 32). All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32.
- The Week 64 analysis, described in a separate SAP ('SAP Week 64'), summarizes the study data until Week 64 (Study Part IIb). The analysis will include all efficacy measures until Week 56 and safety measures until the Week 64 safety visit.

3. Final Analysis (Exploratory Week 100 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) final analysis will be performed at the end of Study Part III, i.e. after all subjects had completed their visits at 100 weeks after randomization or completed earlier (i.e., subjects meet the definition of loss of response) or discontinued earlier.

13.7 Multi-center Data

Exploration of possible heterogeneity of treatment effects across centers for the proportion of subjects achieving a PASI 90 response at Week 32 using nonresponder imputation will be performed by descriptive frequency statistics including graphical display of the results of the individual centers, as appropriate. No pooling of centers will be performed.

13.8 Subgroup Analyses

The following subgroup analyses are planned to be performed to evaluate consistency over demographics and baseline disease characteristics of all efficacy endpoints and as well of the following safety endpoints: onset of any TEAE, serious TEAE, treatment discontinuation due to TEAE.

- Gender
  - male
  - female
- Age at baseline in years
  - < 45
  - ≥ 45 - < 65
  - ≥ 65
- PASI
  - < 20
  - ≥ 20

The subgroup analyses will also include time-to-event analyses for the binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

Subgroup analyses for all efficacy endpoints will be performed using the following different imputation rules of missing values at Week 32 (see SAP sections 13.1.6 and 13.9):

- Binary endpoint:
  - Nonresponder imputation
  - LOCF (only PASI 75/90 response, and DLQI 0/1 response)
  - Multiple imputation
- Continuous endpoint:
  - Multiple Imputation

Subgroup analyses will NOT be performed for the per-protocol analysis set.

13.9 Sensitivity Analyses

The following sensitivity analyses at Week 32 with respect to the handling of missing values are planned to be performed:

- Multiple imputation will be used for all binary and continuous endpoints.
    - For the multiple imputation, the repeated nature of the analysis is restricted to the imputation step (procedure "MI" in SAS). Basic premise is the creation of several datasets in which missing data is imputed in a random fashion and then analyses are performed to check for changes for the conclusion. The analysis will be done with SAS Proc MIANALYZE.
- LOCF imputation will be used for all binary endpoints (see SAP section 13.1.6).
- An 'observed cases analysis' for all binary and continuous endpoints without substitution of missing data will be used (see SAP section 13.1.6).

Sensitivity analyses at Week 32 with respect to the handling of missing values will be performed for all binary and all continuous efficacy endpoints.

Sensitivity analyses at Week 32 with respect to the handling of missing values will NOT be performed for the per-protocol analysis set.

14.0 Statistical Analyses

A table of contents of planned data displays is provided in section 18.1 of this document. The following sections are intended to provide more details of the planned analyses. In addition, mock tables were created and were used as template for statistical programming at the Week 24 analysis. This mock tables will be used analogously for the present Week 32 analysis of Study Part IIa.

Data will be appropriately summarized and analyzed using tabulation and graphs with respect to demographic/baseline characteristics and efficacy/safety observations and measurements. Standard descriptive summary statistics (i.e., n, arithmetic mean, standard deviation, median, minimum/maximum value, quartiles) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. In general, summary tables will be displayed by treatment group as the main classification variable and for the total of the sample in the respective analysis set. 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, center, subject number and study visit, if applicable.

14.1 Study Subjects

Unless otherwise specified, data on study subjects will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

14.1.1 Disposition of Subjects

The overview of subject disposition will provide the respective frequency counts and percentages regarding the following subjects:

- Treatment phase from Week 0 until Week 32
    - Subjects who were enrolled (i.e., signed informed consent Part I)
    - Subjects who were randomized
    - Subjects who were treated
    - Subjects with premature discontinuation of study treatment until Week 24
    - Subjects who completed the treatment phase until Week 24
    - Subject who entered Study Part II (i.e., signed informed consent Part II)
    - Subjects with premature discontinuation of study treatment until Week 32
    - Subjects who completed the treatment phase until Week 32

The table will also include the total number of study sites and the dates of the enrolment of the first subject and the last visit of the last subject in Study Part IIa scheduled at Week 32. Moreover, the overview of subject disposition will be broken down by center. A flow diagram (according to the CONSORT statement) giving an overview of subject disposition will also be provided.

In addition, the number and percentage of randomized subjects continuing and attending by study visit will be displayed in a separate table. Subjects will be counted as continuing at the time of visit whether they attend the visit or not. Only those subjects that prematurely discontinued before the visit will not be counted as attending.

14.1.2 Discontinuation of Study Treatment

The number and percentage of randomized subjects who discontinued study treatment prematurely within the 32 Weeks treatment period of the study will be tabulated for each reason of premature discontinuation (including tabulation of specifications for category 'other'). Moreover, the number of subjects enrolled but not randomized (i.e., screening failures) and the reasons for not being randomized will be given.

14.1.3 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 trial. Subjects with major protocol deviations will be summarized by category for all randomized subjects.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

The summary table will provide the number of subjects per major protocol deviation and will also provide the number of major protocol deviations.

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.

14.1.4 Analysis Sets

The number and percentage of randomized subjects included in each analysis set, together with a breakdown of the reasons for exclusion for non-evaluable subjects, will be provided.

14.2 Demographic and Other Baseline Characteristics

In the Week 24 analysis, assessments made at the screening visit and the baseline visit were summarized by treatment group and overall. These assessments included demographic characteristics and other parameters (such as medical history, previous psoriasis therapy by type (phototherapy and topical therapy)) substance use alcohol/tobacco, previous and concomitant diseases, prior and concomitant medication, physical examination). By-treatment summaries should serve to identify any imbalances between the treatment groups at baseline. Summary tables were provided by means of descriptive statistics and frequency tables, where appropriate. Demographic and other baseline characteristics were analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set'). No analyses for baseline balance using statistical hypothesis tests or confidence intervals were done.

For the present Week 32 analysis only data on concomitant medication, concomitant therapy and shampoo and moisturizer will be analyzed including the time period from Week 0 until Week 32.

14.2.1 Demographics

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.2 Medical History

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.3 Diagnosis of Psoriasis

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.4 Previous Psoriasis Therapy

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.5 Substance Use

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.6 Physical Examination

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.7 Tuberculosis Evaluation

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.8 Chest Radiograph Result

Not applicable for the Week 32 analysis. The analysis was already performed at the Week 24 analysis.

14.2.9 Concomitant Medication and Therapy

Analyses of concomitant medication and therapy will consider the data recorded within the 32 Weeks treatment period of the study. In case of early treatment discontinuation before Week 32, concomitant medication and therapy with a start date at or after the discontinuation date will not be considered.

Concomitant Medication

The number and percentage of subjects with use of concomitant medication until Week 32 will be displayed in WHO-DD terminology as described in SAP section 14.7. Concomitant medication will be identified from the *Concomitant Medication* form of the eCRF.

The number and percentage of subjects with indication for concomitant medication will be displayed in MedDRA terminology as described in SAP section 14.6.

Concomitant Therapy

The number and percentage of subjects with use of concomitant therapy until Week 32 will be displayed in MedDRA terminology as described in SAP section 14.6. Concomitant therapy will be identified from the *Concomitant Therapy* form of the eCRF.

The number and percentage of subjects with indication for concomitant therapy until Week 32 will be displayed in MedDRA terminology as described in SAP section 14.6.

14.2.10 Shampoo and Moisturizer

The number and percentage of subjects with use of shampoo or moisturizer until Week 32 will be displayed in a frequency table.

14.3 Treatment Compliance

Treatment compliance will be analyzed based on data from all subjects randomized at Week 0 ('efficacy analysis set').

14.3.1 Visit Windows

The number of days between the scheduled study visits and the baseline visit will be calculated using the reported visit dates per scheduled study visit and will be displayed by summary descriptive statistics until Week 32.

14.3.2 Study Medication

Categorical data on guselkumab administration recorded until Week 32 will be summarized by frequency tabulation providing the number and percentage of subjects per category. Frequency tabulation and descriptive statistics will be presented for the overall number of guselkumab administrations until Week 32.

Compliance to guselkumab administration will be calculated as follows based on the eCRF data until Week 32:

- Compliance guselkumab in % = (number of actual administrations x 100 / number of planned adminstrations)

Categorical data on Fumaderm® initial/ Fumaderm® administration during initial uptitration and/or maintenance period (including data on reasons for end of uptitration and reasons for dose selection) recorded at each week until Week 32 and will be summarized by frequency tabulation providing the number and percentage of subjects per category. The number of planned tablets to be taken in the morning, at noon, and in the evening will also be summed up and analyzed descriptively.

The number of dispensed and returned tablets of Fumaderm® initial/ Fumaderm® until Week 32 is not documented in the eCRF. Therefore the compliance to Fumaderm® initial and Fumaderm® administration in % cannot be calculated.

Treatment compliance will also be assessed by protocol deviations related to study drug administration (i.e., incorrect study drug received and missed administrations).

For subjects who completed the Week 32 visit the dose of Fumaderm® in mg at Week 32 will be summarized by descriptive statistics and frequency tabulation. In addition, the maximum dose of Fumaderm® initial and Fumaderm® in mg will be calculated for all subjects and will be summarized by descriptive statistics and frequency tabulation.

14.4 Analysis of Efficacy

All efficacy analyses to compare guselkumab vs. FAE will be performed for all subjects randomized at Week 0 ('efficacy analysis set'). The PASI 90, PASI 75, and DLQI 0/1 response rates will also be analyzed using the per-protocol analysis set. However, subgroup and sensitivity analyses at Week 32 will NOT be performed for the per-protocol analysis set.

All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32. All statistical tests will be performed two-sided in an exploratory sense.

Handling of missing values, exploratory statistics, subgroup analyses, and sensitivity analyses will be performed as described in detail in the following sections of this SAP:

SAP Section No.	Topic
13.1.6	Handling of missing values
13.4.1	Exploratory statistics - binary endpoints
13.4.2	Exploratory statistics - continuous endpoints
13.8	Subgroup analyses
13.9	Sensitivity analyses

Data at the scheduled point Week 28 during the active treatment period will be analyzed analogously to the Week 32 data. However, no subgroup or sensitivity analyses will be performed for this point in time.

14.4.1 Primary Endpoint

Not applicable for the Week 32 analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2 Major Secondary Endpoints

14.4.2.1 Endpoint related to PASI

Not applicable for the Week 32 analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2.2 Endpoint related to DLQI

Not applicable for the Week 32 analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.3 Other Secondary Endpoints

The following sections provide a description of the planned statistical analyses of the other secondary endpoints as reported in the CSP (Protocol Amendment INT-1) and as well of additional endpoints not explicitly stated in the CSP (see SAP section 15.0).

14.4.3.1 Endpoints related to PASI

Other secondary endpoints related to PASI are:

- The proportion of subjects achieving a 75%/90%/100% improvement of their psoriasis according to the PASI at Week 32 (PASI 75/90/100 response)
- The proportion of subjects achieving an absolute PASI score ≤1, ≤2, ≤3, ≤5 at Week 32

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 32 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses (also including analyses of time to PASI 75/90/100 response) will be performed as described in SAP section 13.4.1.

14.4.3.2 Endpoints related to PSSD

Other secondary endpoints related to PSSD are:

- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 32
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 32

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 32 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

In addition, the other individual scale scores will be analyzed analogously.

14.4.3.3 Endpoints related to IGA

Other secondary endpoints related to IGA are:

- The proportion of subjects achieving an IGA score of cleared (0) at Week 32

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 32 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 32 will be analyzed analogously.

14.4.3.4 Endpoints related to BSA

Other secondary endpoints related to BSA are:

- The change from baseline of body surface area (BSA) psoriatic involvement at Week 32

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 32 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.5 Endpoints related to DLQI

Other secondary endpoints related to DLQI are:

- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 32
- The change from baseline in DLQI score at Week 32

The proportion of subjects achieving a DLQI score of 0 or 1 at Week 32 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 32 per treatment arm and for the difference between the two arms.

Exploratory statistical analyses (also including analyses of time to DLQI 0/1 response) will be performed as described in SAP section 13.4.1.

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 32 value and the change from the baseline value will be displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.6 Endpoints related to ss-IGA

Other secondary endpoints related to ss-IGA are:

- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 32 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline

The proportion of responding 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.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for response rate at Week 32 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 32 will be analyzed analogously.

14.4.3.7 Endpoints related to SF-36

Other secondary endpoints related to SF-36 are:

- The change from baseline in the physical and mental component summary scores of SF-36 at Week 32

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 32 value and the change from the baseline value will displayed.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.4 Other Efficacy Assessments

In addition to the efficacy analyses described above all efficacy data related to PASI, DLQI, PSSD, IGA, ss-IGA, and SF-36 at all scheduled study visits during the active treatment period until Week 32 will be summarized descriptively without any imputation of missing data (‘observed cases analysis’; see SAP section 13.1.6).

14.5 Analysis of Safety

Safety data, including but not limited to, adverse events (AEs), serious adverse events (SAEs), infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized using descriptive statistics. All safety analyses to compare guselkumab vs. FAE will be performed for all treated subjects ('safety analysis set').

14.5.1 Extent of Exposure

Extent of exposure will be defined as the total number of days from baseline to Week 32 (for all patients still under treatment) or to study discontinuation.

Descriptive summary statistics and frequency tables (using appropriate categories) will be provided for the extent of exposure.

14.5.2 Adverse Events

Adverse events data will be processed in the statistical analysis after coding according to the MedDRA dictionary version 19.1. All reported AEs with onset date during the active treatment period until Week 32 (i.e., treatment emergent AEs) will be included in the analysis. In case of early treatment discontinuation before Week 32, all reported AEs with onset date during the safety follow-up period until Week 32 (i.e., treatment emergent AEs) will be included in the analysis. AEs reported after Week 32 will NOT be considered in the analysis.

14.5.2.1 Definitions

The following definitions will be applied in the present study

Crude Incidence Rate

Where percentages of subjects are reported in summary tables, incidences provide information on the proportion of subjects experiencing adverse events in relation to the total number of subjects exposed, i.e., if not otherwise specified, the crude incidence rate will be used.

The crude incidence rate is defined as the number of subjects experiencing a certain event, divided by the number of subjects exposed to study treatment, regardless of duration of use:

$$\text{Crude incidence rate} = 100 * \frac{\text{number of patients with adverse events}}{\text{number of patients exposed}}$$

Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are those AEs that occurred during the active treatment period until Week 32 after the start of initial study drug administration and those AEs that were present at baseline but worsened in severity after the start of initial study drug administration. AEs reported after Week 32 will NOT be considered in the present analysis.

In case of early treatment discontinuation before Week 32, all reported AEs with onset date during the safety follow-up period until Week 32 will be included in the analyses. Thus, identification of TEAEs (distinguished by subjects who completed or discontinued the treatment period until Week 32) will be performed as follows:

- TEAE for Completer of Study Part IIa: Date of Week 0 ≤ Start Date of AE ≤ Date of Week 32
- TEAE for Non-Completer of Study Part IIa: Date of Week 0 ≤ Start Date of AE ≤ Date of Final Study Visit

AEs which are not classified as TEAEs will be considered as not treatment emergent adverse events (NTEAEs).

14.5.2.2 Analyses

Overview of adverse events

For summary presentation of the overall adverse event experience overview tables will be provided for AEs and SAEs including the following information:

Adverse events:

- n (%) of subjects with AEs *)
- n (%) of subjects with NTEAEs *)
- n (%) of subjects with TEAEs *)
- n (%) of subjects with TEAEs by highest causality to study medication
- n (%) of subjects with TEAEs by worst severity
- n (%) of subjects with TEAEs leading to dose modification *)
- n (%) of subjects with TEAEs leading to permanent stop of study medication *)

Serious Adverse events:

- n (%) of subjects with SAEs *)
- n (%) of subjects with NTESAEs *)
- n (%) of subjects with TESAEs *)
- n (%) of subjects with TESAEs leading to death *)
- n (%) of subjects with TESAEs by highest causality to study medication
- n (%) of subjects with TESAEs by worst severity
- n (%) of subjects with TESAEs leading to permanent stop of study medication *)

*) the number of events (i.e., number of coded preferred terms) will also be given.

TEAEs/TESAEs leading to dose modification will be defined as all events with 'Action taken with study treatment' is not equal to 'DOSE NOT CHANGED'.

In addition, the number of TEAEs will be displayed for the following investigator's ratings:

- severity
- seriousness
- causality
- action taken
- outcome

Detailed display of adverse events

For a more detailed display, adverse events will be presented in summary tables, listing these events in code form according to the preferred term. These tables will show the number of subjects per group presenting an adverse event and the incidence of its occurrence. Adverse events will be grouped by primary SOC (System Organ Class) and will be stratified additionally by highest causality to study treatment (not related, doubtful, possible, probable, or very likely) and by worst severity (mild, moderate, or severe). The incidence of adverse events will be presented by decreasing order of frequency at preferred term level within the primary SOC.

The following tables will be provided for the detailed display of adverse events:

Adverse events:

- TEAEs by primary SOC and preferred term *)
- TEAEs by primary SOC and preferred term stratified by highest causality
- TEAEs by primary SOC and preferred term stratified by worst severity
  - thereof
    - Drug related TEAEs
    - Not drug related TEAEs
- TEAEs leading to permanent stop of study medication by primary SOC and preferred term *)

Serious Adverse events:

- TESAEs by primary SOC and preferred term *)
- TESAEs by primary SOC and preferred term stratified by highest causality
- TESAEs by primary SOC and preferred term stratified by worst severity
- TESAEs leading to permanent stop of study medication by primary SOC and preferred term *)
- TESAEs leading to death by primary SOC and preferred term *)

Not treatment emergent adverse events:

- NTEAEs by primary SOC and preferred term *)

*) These tables will show additionally the number of events (i.e., number of coded preferred terms).

Summary tabulation of TEAEs and TESAEs by primary SOC and preferred term will also be provided for the following types of adverse events:

- injection site reactions (according to the tick box in the e-CRF)
- infections (according to the tick box in the e-CRF)
  - thereof, infections treated with oral or parenteral antibiotics
- adverse events of psoriasis (adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, inverse psoriasis, palmo-plantar psoriasis and worsening or exacerbation of psoriasis; final allocation will be performed after blinded data review).

Note that the summary tables will provide the number of subjects per event (i.e., coded as preferred term) and will also provide the number of events for certain tables.

For calculation of the number of subjects per event each preferred term will be counted only once per subject and will be linked to the primary SOC. A subject may contribute with more than one different adverse event (at preferred term level); however, a subject with more than one occurrence of the same adverse event (at preferred term level) is displayed and counted only once for this event in the tables.

Tables that are stratified by the severity of adverse events will summarize the worst severity per subject and preferred term.

Tables that are stratified by the relationship of adverse events will summarize the highest relationship per subject and preferred term.

For presentation of drug related/ not drug related adverse events the following categories will be used:

- drug related = very likely, probable, possible
- not drug related = doubtful, not related

For summarization of severity of drug related TEAEs, events with a causality assessment of 'doubtful/not related' will be excluded and the worst severity will be tabulated as described above. Summarization of severity of not drug related TEAEs will be performed likewise.

The following safety endpoints will be defined:

- The proportion of subjects with any TEAE within the 32 Weeks treatment period
- The proportion of subjects with serious TEAE within the 32 Weeks treatment period
- The proportion of subjects with treatment discontinuation due to TEAE within the 32 Weeks treatment period
- The proportion of subjects with any TEAE by preferred term and SOC within the 32 Weeks treatment period

Counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for treatment effect using the chi-square test will be provided. In addition, time-to-event-analyses and logistic regression analyses as described in SAP section 13.4.1 will be conducted for the onset of any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

Subgroup analyses will be performed for the subgroups defined in SAP section 13.8 for the proportion of subjects with any TEAE, serious TEAE, and treatment discontinuation due to TEAE.

The cut-off ≥ 5% (i.e., percentage of subjects ≥ X% in at least one treatment group) will be used for analyses of TEAEs by preferred term for any TEAE.

In addition, the rate of infections TEAEs (according to the tick box in the e-CRF) per subject per week for the treatment period Week 0-32 will be estimated using Poisson regression. Tabulated summaries will also display 95% CIs for the respective rates. The treatment duration will be calculated as time span (weeks) between baseline (week 0) and week 32 (for all subjects still under treatment) or to study discontinuation.

Listings

All adverse events (AEs) and serious adverse events (SAEs) will be listed in the individual subject data listings by treatment group, study center and subject number including all information documented on the respective form of the eCRF. Separate listings of subjects with the following AEs will be provided: SAEs, SAEs leading to death, AEs of severe intensity, AEs leading to permanent discontinuation of study medication.

Verbatim description of the adverse event reported by the investigator, MedDRA preferred terms and primary SOCs (system organ class) for all adverse events will be contained in the data listings. Non treatment emergent adverse events will be flagged in the respective listings.

14.5.3 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory item at each scheduled time. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Results of tuberculosis testing, serology, urine pregnancy testing and local urinalysis (glucose, protein) will be displayed in frequency tables providing the number and percentage of subjects per category (i.e., negative or positive) at each scheduled time.

The results of all laboratory tests will be provided in individual subject data listings including the reference ranges. Abnormal values will be identified by flagging all values below and above the reference range.

A listing of subjects with any laboratory results outside the reference ranges will be provided.

For the lymphocyte count the following subjects will be listed and summarized in a frequency table:

- lowest lymphocyte count < 500/µl
- 500/µl ≤ lowest lymphocyte count <700/µl
- 700/µl ≤ lowest lymphocyte count < lower limit of normal range

Graphical presentation of quantitative laboratory data will be given by means of box plots.

14.5.4 Vital Signs

Descriptive statistics of pulse and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time. Subjects reporting vital signs findings beyond clinically important limits will be identified using the following criteria.

Criteria for Identifying Potentially Clinically Significant Vital Signs Findings

Variable (units)	Criterion Value[a]	Change from Baseline
Systolic Blood Pressure (mmHg)	>200 <80	Increase of >40 Decrease of >40
Diastolic Blood Pressure (mmHg)	>120 <40	Increase of >30 Decrease of >30
Heart Rate (bpm)	>110 <40	

In order to be identified as an abnormality of potential clinical importance, a value would need to meet the criterion value **o**r also represent a change of at least the magnitude noted in the change column.

Vital signs values of potentially clinically significant importance will be analyzed by providing the number and percentages of subjects with values of potential clinical importance per scheduled study visit, overall during the study and with first occurrence after baseline.

14.5.5 Physical Examination

Physical examination findings will be tabulated by the body systems given in the eCRF at each scheduled time. Moreover, abnormal findings with first occurrence after baseline reported during the treatment phase and follow-up phase will be presented. Details on abnormal findings in verbatim terms will be displayed in individual subject data listings.

14.5.6 Body Weight

Not applicable for the Week 32 analysis. Body weight ist not documented at Week 32. The analysis until Week 24 was already performed at the Week 24 analysis.

14.5.7 Early Detection of Active Tuberculosis

Not applicable for the Week 32 analysis. Data on early detection of active tuberculosis is not documented at Week 32. The analysis until Week 24 was already performed at the Week 24 analysis.

14.6 Analysis of MedDRA Codes

Previous / concomitant diseases (including indications for use of concomitant and other medications) and adverse events will be coded with version 19.1 of the MedDRA-dictionary.

In general, tabulation will be displayed by preferred term and primary SOC.

14.7 Analysis of WHO Drug Dictionary Codes

The use of concomitant and other medications will be coded using the WHO Drug Dictionary (version 2016/1). Medications will be tabulated by preferred name (i.e., the decode of the code which results when SEQ1 and SEQ2 are set to 01 and 001, respectively (usually resulting in a decode close to the generic drug name)) and they will be grouped by level 2 of the Anatomical Therapeutic Chemical (ATC) code. Codes being linked to more than one ATC code at this level will be assigned to one primary ATC code by medical data analysts.

15.0 Changes to Planned Analyses

This statistical analysis plan includes the following relevant changes to the planned analyses which are described in the clinical study protocol.

- Evaluations on health technology assessment (HTA) will also be specified in this SAP. No separate SAP for evaluations on health technology assessment will be provided (see SAP section 3.0 and CSP section 11)
- A per-protocol analysis will be performed for the PASI 90, PASI 75, and DLQI 0/1 response rates (see SAP section 11.0).
- No treatment failure imputation rules will be applied (see to SAP section 13.1.5 and CSP section 11.4)
- The following safety endpoints will be defined and used for the statistical analyses for HTA purposes:
    - The proportion of subjects with any TEAE within the 32 Weeks treatment period
    - The proportion of subjects with serious TEAE within the 32 Weeks treatment period
    - The proportion of subjects with treatment discontinuation due to TEAE within the 32 Weeks treatment period
    - The proportion of subjects with any TEAE, serious TEAE, treatment discontinuation due to TEAE by preferred term and SOC within the 32 Weeks treatment period
- Time-to-event analyses for binary endpoints PASI 75/90/100 response, DLQI 0/1 response, onset of TEAE, serious TEAE, and treatment discontinuation due to TEAE will be performed using Kaplan-Meier product limit method and Cox proportional hazards model.

The following additional efficacy endpoints will be defined and used for the statistical analyses:

- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 32
- The change from baseline in the individual scale scores for itch, pain and scaling of PSSD components at Week 32
- The proportion of subjects achieving an absolute PASI score ≤1, ≤2, ≤3, ≤5 at Week 32
- Time to event analysis for PASI score ≤1, ≤2, ≤3, ≤5
- The proportion of subjects achieving an IGA score of cleared (0) at Week 32
- The proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 32
- The change from baseline of body surface area (BSA) psoriatic involvement at Week 32
- The change from baseline in DLQI score at Week 32
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 32 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 32 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline

- The change from baseline in the physical and mental component summary scores of SF-36 at Week 32

Any major changes to this plan after sign-off of the latest final version will be specified in the clinical study report.

16.0 Tabulation

16.1 General

The statistical output will be prepared in American English. No separate statistical report will be written.

16.2 Format of Data Displays

The layout of all tables, listings and figures will be drafted by acromion GmbH when providing the first draft tables, listings and figures on final data. No sponsor or other requirements for layout specifications have to be followed.

The SAS outputs will be post-processed within Microsoft Word®. SAS tables and listings will be integrated into Microsoft Word® using the SAS Monospace 8 points font.

Separate appendices will be provided for tables, listings, and figures. For each appendix a corresponding table of contents will be generated. All pages within one appendix will be numbered consecutively. Tables, listings and figures generally should be self-explaining. Abbreviations will be described in the footnote if necessary.

16.2.1 Tables

SAS summary tables will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

16.2.2 Listings

SAS subject data listings will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

Data listings will be created for groups of variables which logically belong together (e.g. demographic variables) and will be sorted by treatment group, center, subject and visit (if applicable).

16.2.3 Figures

Figures will be created using the following graphical SAS options, if not otherwise specified:

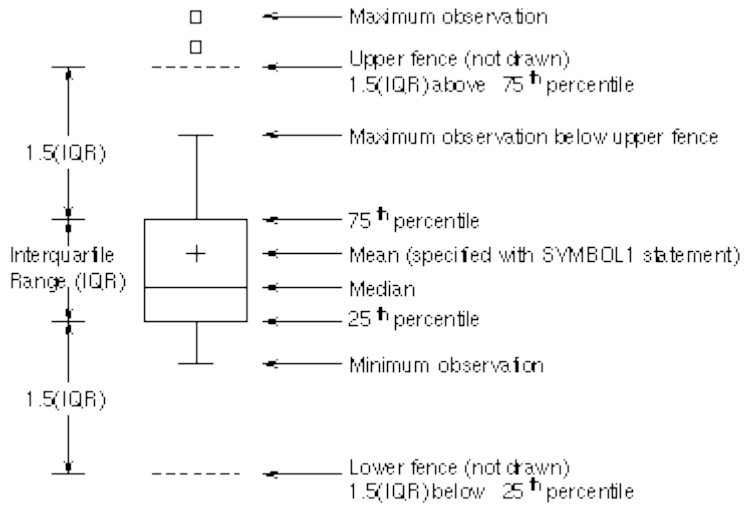
```
GOPTIONS
   RESET   = ALL
   NOBORDER
   KEYMAP = WINANSI
   DEVMAP = WINANSI
   DEV      = EMF
   TARGET = WINPRTC
   GUNIT   = CM
   CTEXT   = BLACK
   FTEXT   = 'Arial/bold'
   HTEXT   = 0.5 CM
   LFACTOR= 1
   HSIZE   = 6 IN
   VSIZE   = 5 IN;
```

Variables may be presented in the following graphical formats, if applicable:

Box plot

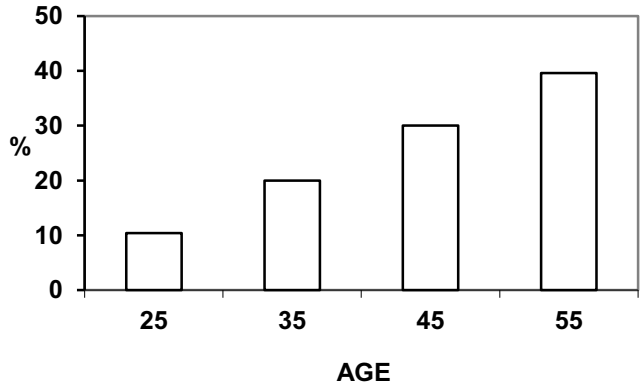
Box plots summarize the data by a box reaching from the 1st to the 3rd quartile. The median is displayed inside this box by a horizontal line. Above the box a vertical line indicates the region from the 3rd quartile to the max. value below the upper fence ; below the box a vertical line indicates the region from the 1st quartile to the min. value above the lower fence. The upper fence lies 1.5 interquartile-ranges above the 3rd quartile, the lower fence lies 1.5 interquartile ranges below the 1st quartile. Values outside the fences are displayed by a distinct marker.

A graphical presentation is given below:



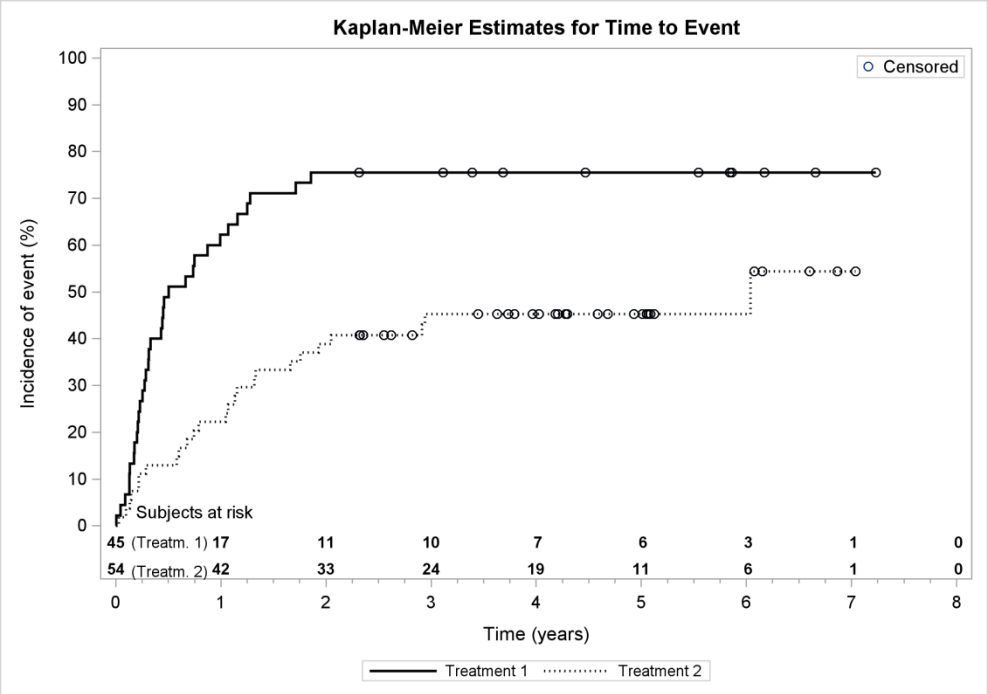
Bar chart

A bar chart displays a categorical variable. A sample display is provided below.



Survival Graph

A survival graph displays the survival distribution functions according to Kaplan-Meier. A sample display is provided below.



16.3 Data Format

Unless otherwise specified, percentage values will be printed with one digit to the right of the decimal point.

In general, minima and maxima will be quoted to the number of decimal places as recorded in the eCRF; means, standard deviations and medians will be quoted to one further decimal place.

All p-values will be given by four digits to the right of the decimal point. Verbatim terms documented in the eCRFs will be presented as entered in the clinical data base.

17.0 References

Study Documents:

Document	Version, Date
Protocol Amendment INT-1s	Version 2.0, 25-APR-2017
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan - Week 24 Analysis	Version 1.0, 10-JUL-2017

SOPs and Guidelines acromion:

Document	Title, Date
acromion SOP BM04	Statistical Analysis Plans, Oct-2016
acromion SOP BM05	Determination of Availability of Data for Analysis, Oct-2016
acromion SOP BM06	Generation and Release of Blinded Randomization Code, Oct-2016
acromion SOP BM07	Programming of Derived Data Sets, Oct-2016
acromion SOP BM08	Programming of SAS Data Displays, Oct-2016
acromion SOP BM11	Documentation and Project Close-Out, Oct-2016
acromion Guideline BM01	SAS Programming Guideline, Oct-2016
acromion Guideline BM02	Biometrics Naming Conventions for SAS Datasets and SAS Programs, Oct-2016

Other Documents:

Document	Title, Date
ICH Guideline E 9	Statistical Principles for Clinical Trials, final approval 1998

18.0 Appendices

18.1 Table of Contents for Data Displays

The tables, subject data listings and figures will be provided using the following numbering system, which will be updated after start of programming the data displays. However, this section does not include the HTA analyses for the topline results described in SAP section 14.6. The numbering system for the HTA analyses will be provided with the HTA mock tables.

All summary tables will start with the one-character identifier for the displayed analysis set followed by the one-digit identifier for the displayed analysis chapter as listed below.

Identifier for displayed analysis set:

- **A**: Efficacy analysis set
- **B**: Safety analysis set
- **C**: Per-protocol analysis set

Identifier for displayed analysis chapter:

- **1**: Study subjects
- **2**: Demographics and other baseline characteristics
- **3**: Treatment compliance
- **4**: Analysis of efficacy
- **5**: Analysis of safety

Data displays will be provided for the following analysis sets:

Chapter No.	Chapter Title	Analysis set
1	Study subjects	• A: efficacy analysis set
2	Demographic and other baseline characteristics	• A: efficacy analysis set
3	Treatment compliance	• A: efficacy analysis set
4	Analysis of efficacy	• A: efficacy analysis set • C: per-protocol analysis set
5	Analysis of safety	• B: safety analysis set

All individual subject data listings will start with the one-digit identifier for the displayed chapter analogously as for the summary tables. Data displays and subject data listings will be provided in separate appendices and pages will be numbered for each appendix separately starting with page no. 1.

18.1.1 Tables

Study Subjects, Prefix A

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics, Prefix A

No.	Analysis Chapter
2.1	Demographics – Not applicable
2.2	Medical history – Not applicable
2.3	Diagnosis of Psoriasis – Not applicable
2.4	Previous Psoriasis Therapy – Not applicable
2.5	Substance Use – Not applicable
2.6	Physical Examination – Not applicable
2.7	Tuberculosis Evaluation – Not applicable
2.8	Chest Radiograph Result – Not applicable
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance, Prefix A

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy, Prefix A, C

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90% Response
4.2.1	PASI 75% Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety, Prefix B

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight – Not applicable
5.7	Early Detection of Active Tuberculosis – Not applicable

18.1.2 Listings

Study Subjects

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics

No.	Analysis Chapter
2.1	Demographics – Not applicable
2.2	Medical history – Not applicable
2.3	Diagnosis of Psoriasis – Not applicable
2.4	Previous Psoriasis Therapy – Not applicable
2.5	Substance Use – Not applicable
2.6	Physical Examination – Not applicable
2.7	Tuberculosis Evaluation – Not applicable
2.8	Chest Radiograph Result – Not applicable
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90% Response
4.2.1	PASI 75% Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight – Not applicable
5.7	Early Detection of Active Tuberculosis – Not applicable

18.1.3 Figures

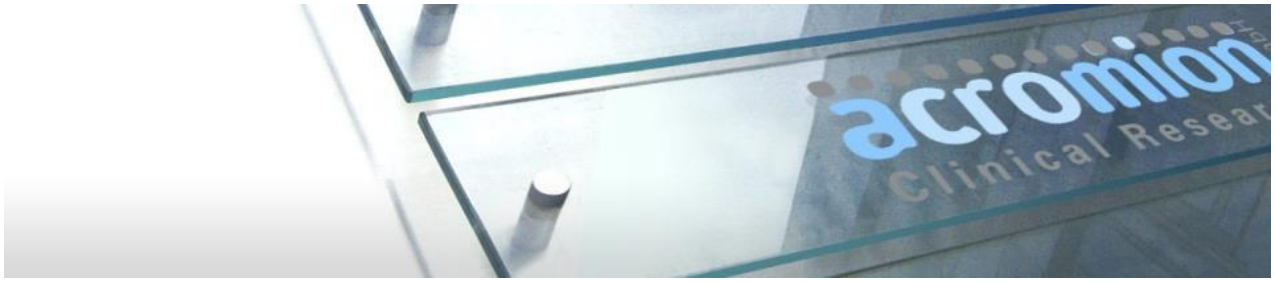
Analysis of Efficacy, Prefix A, B, C

No.	Analysis Chapter	Type of Figure
	- Other Secondary Endpoints -	
1	PASI 90% Response	Bar Chart, Survival Graph
2.1	PASI 75% Response	Bar Chart, Survival Graph
2.2	DLQI 0/1 Response	Bar Chart, Survival Graph
3.1	Other Endpoints related to PASI	Bar Chart, Survival Graph
3.2	Endpoints related to PSSD	Box Plot
3.3	Endpoints related to IGA	Bar Chart
3.4	Endpoints related to BSA	Box Plot
3.5	Other Endpoints related to DLQI	Bar Chart
3.6	Endpoints related to ss-IGA	Bar Chart
3.7	Endpoints related to SF-36	Box Plot
	- Other Efficacy Assessments -	
4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)	Bar Chart, Box Plot

Analysis of Safety, Prefix B

No.	Analysis Chapter	Type of Figure
5	Clinical Laboratory Tests	Box Plot
6	Vital Signs	Box Plot
7	Body Weight – Not applicable	Box Plot

NCT09251533



Statistical Analysis Plan

Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm® initial/ Fumaderm®) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment

POLARIS

- Study Part IIb: Week 64 Analysis -

Study Code	CNTO1959PSO3008
EudraCT Number	2016-002135-15
Development phase	Phase 3b
Study Design	randomized, open-label, efficacy assessor-blinded, single country, multicenter, active-comparator-controlled
Sponsor	Janssen-Cilag GmbH, Neuss Johnson & Johnson Platz 1, 41470 Neuss, Germany
Contract Research Organization	acromion GmbH Europaallee 27 – 29 50226 Frechen, Germany
Version No., Date	Final Version 1.0, 29-Aug-2018

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TRAUGOTT GRUPPE, MD Director Therapeutic Area, Janssen-Cilag GmbH, Neuss	_ _ / _ _ _ / _ _ Date	Traugott Ludwig Gruppe Digitally signed by Traugott Ludwig Gruppe DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=1490014408, cn=Traugott Ludwig Gruppe Reason: I am approving this document. Date: 2018.08.31 12:56:57 +02'00' Adobe Reader version: 11.0.10
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FRIEDEMANN TAUT, MD Country Medical Manager On behalf of Janssen-Cilag GmbH, Neuss	_ _ / _ _ _ / _ _ Date	Friedemann Taut Digitally signed by Friedemann Taut DN: c=US, o=JNJ, ou=Subscribers, cn=Friedemann Taut, 0.9.2342.19200300.100.1.1=7022212204 Reason: I am approving this document. Date: 2018.08.30 17:52:21 +02'00' Adobe Reader version: 11.0.10

2.0 List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CRF	Case Report Form(s)
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e.g.	example given
FAE	Fumaric Acid Esters
HBV/ HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICH	International Council on Harmonization
i.e.	that is
IGA	Investigator´s Global Assessment
IL	Interleukin
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NTEAE	Non Treatment Emergent Adverse Event
NTESAE	Non Treatment Emergent Serious Adverse Event
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PRO	Patient-Reported Outcome(s)
PSSD	Psoriasis Symptom and Sign Diary
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form (36-item) health survey
SOC	System Organ Class
SOP	Standard Operating Procedure
ss	scalp-specific
TB	tuberculosis
TEAE	Treatment Emergent Adverse Event
TES	Time and Events Schedule
TESAE	Treatment Emergent Serious Adverse Event

3.0 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 and the relevant acromion SOPs and/or guidelines. This plan describes the statistical analyses planned to be performed for the Week 64 analysis of Study Part IIb of Janssen-Cilag GmbH Clinical Study Protocol CNTO1959PSO3008 and should be read in conjunction with the statistical analysis plan for the Week 24 analysis, the protocol amendment INT-1 to the CSP and the electronic Case Report Form (eCRF).

An overview about all planned analyses is given in Section 13.6. The Week 64 analysis of Study Part IIb summarizes the study data in Study Part IIb from Week 32 until Week 64 (Study Part IIb: active treatment period from Week 32 through Week 56 and safety follow-up period from Week 56 through Week 64) and will be the second part of the Week 64 analysis of Study Part II (first part of the Week 64 analysis ist the Week 32 analysis of Study Part IIa). The Week 64 analysis of Study Part IIb will include the safety analysis and all efficacy measures beyond Week 32 and will cover the time until the Week 64 visit. All statistical analyses will be descriptive and exploratory and will be conducted only for the predefined efficacy and safety analyses until Week 64. Statistical analyses of study data until Week 32 (Study Part IIa; Week 24 through Week 32) have been laid out in a separate SAP.

Confirmatory analyses for the primary endpoint and the major secondary endpoints were already perfomed at the Week 24 analysis as described in the statistical analysis plan for Week 24 (Final 1.0, 10-July-2017). Evaluations on health technology assessment (HTA) were also specified in this SAP. No separate HTA SAP was provided. The Week 64 analysis of Study Part IIb will be performed after all subjects have completed their visit at 64 weeks after randomization or discontinued earlier. Data base lock for the Week 64 analysis will be after the Week 64 visit data are ready for statistical analysis (i.e., clean data).

This SAP is the core document for all statistical programming planned to be performed for the Week 64 analysis of Study Part IIb and is based on the following study documents to protocol no. CNTO1959PSO3008:

Document	Version, Date
Protocol / Amendments	Protocol Amendment INT-1, Version 2.0, 25-APR-2017
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan - Week 24 Analysis	Version 1.0, 10-JUL-2017

4.0 Responsibilities

The responsibilities for the biometrical tasks at acromion GmbH are assigned as follows:

Name	Function	Task
[redacted]	Statistician	Statistical Programming and Analysis
	Statistician	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Medical Data Analyst	Medical Data Review and Coding

5.0 Software Utilized

The statistical analysis and generation of tables, patient data listings and figures will be performed using the SAS® software package version 9.4 under the Microsoft Windows® 7 operating system at the computer facilities of acromion GmbH. Additional analyses regarding health technology assessment (HTA) may be performed by or under the responsibility of Janssen-Cilag GmbH.

6.0 Coding Systems Utilized

The MedDRA-dictionary version 19.1 is used for coding of prior and concomitant diseases and for coding of adverse events. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Medical History of Interest	Medical History Term	MH/MHTERM
Previous Phototherapy	Type of Phototherapy	MH/MHTERM
Concomitant Medication	Indication	CM/CMIND
Concomitant Therapy	Indication	CM/CMIND
Concomitant Therapy	Therapy	CM/CMTRT
(S)AE	Term	AE/AETERM

Prior and concomitant medications are coded according to the WHO terminology using the 2016/1 version of the WHO-Drug Dictionary. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Previous Topical Therapy	Medication/Therapy	MH/MHTERM
Concomitant Medication	Compound	CM/CMTRT

Details are specified in the Data Management Plan.

7.0 Study Objectives and Hypotheses

7.1 Objectives

Primary Objectives

The primary objectives of the study are

- to compare the efficacy of guselkumab to fumaric acid esters (FAE) in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.
- to assess the safety and tolerability of guselkumab in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.

Secondary Objective

The secondary objectives of the study are

- in Study Parts I and II: to compare improvement of health-related quality of life (QOL) and other patient-reported outcomes (PRO) when systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.
- in Study Part II: to compare sustainability of response to treatment when systemic treatment naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.

7.2 Hypotheses

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

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

8.0 Study Endpoints

This section provides a description of all study endpoints as pre-specified in the CSP (Protocol Amendment INT-1) for the Week 24 and Week 64 analyses. The Week 64 analysis includes the Week 32 and the Week 64 analysis, the latter is described in the present SAP.

Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 90% improvement of their psoriasis according to the Psoriasis Area and Severity Index (PASI 90 response) at Week 24.

Secondary Endpoints

The major secondary endpoints are:

- The proportion of subjects achieving at least a 75% improvement of their psoriasis according to the PASI at Week 24 (PASI 75 response)
- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

Other secondary endpoints are:

- The proportion of subjects achieving a 100% improvement of their psoriasis according to the PASI at Week 24 (PASI 100 response)
- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 24
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 24
- The proportion of subjects achieving an absolute PASI score ≤1 at Week 24
- The proportion of subjects achieving an IGA score of cleared (0) at Week 24
- The change from baseline of body surface area (BSA) psoriatic involvement at Week 24
- The change from baseline in DLQI score at Week 24
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 24 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
- The change from baseline in the physical and mental component summary scores of SF-36 at Week 24
- Maintenance of response. Proportion of subjects with a
  - PASI 75 response at Week 32 who maintain response at Week 56
  - PASI 90 response at Week 32 who maintain response at Week 56
  - a DLQI score 0 or 1 at Week 32 who maintain response at Week 56
- Proportion of subjects of the FAE group who were PASI 75 non-responders at Week 32 and switched to guselkumab with a
  - PASI 75 response (compared to Week 0) at Week 56
  - PASI 90 response (compared to Week 0) at Week 56
  - PASI 100 response (compared to Week 0) at Week 56
  - DLQI score 0 or 1 at Week 56
- Proportion of subjects with a
  - PASI 75 response at Week 32
  - PASI 90 response at Week 32
  - PASI 100 response at Week 32
  - DLQI score 0 or 1 at Week 32
- Safety and tolerability data will be summarized using descriptive statistics

9.0 Study Design

This section provides a description of the study design as defined in the CSP (Protocol Amendment INT-1) for the Week 24 and the Week 64 analyses. The Week 64 analysis includes Week 32 analysis and the Week 64 analysis, the latter is described in the present SAP.

The description is written in future tense according to the wording in the CSP, even though some of the planned actions, analyses and procedures have been carried out meanwhile.

Note: References to 'Section' always refer to the respective section in the CSP (Protocol Amendment INT-1).

9.1 Overview

This is a randomized, open-label, efficacy assessor-blinded, single country, multicenter, active comparator-controlled phase 3b study of guselkumab in adult subjects with moderate to severe plaque-type psoriasis who have not yet received any systemic therapy. The study will be performed at about 30 to 45 sites in Germany.

This study will have a 3-week screening phase, a 56-week treatment phase and a safety follow-up phase until Week 64 (as shown in Figure 1). The maximum duration of a subject's participation in this study will be 67 weeks including the 3-week screening phase. With protocol Amendment 1, the study will be split into two parts (Study Part I and II):

Study Part I (Core Study)—Week 0 through Week 24:
Screening and treatment until Week 24

After screening, a total of 114 subjects will be randomized in a 1:1 ratio to either the study drug (guselkumab) or to the active comparator (FAE). Subjects of the guselkumab group will receive 100 mg guselkumab SC at Weeks 0, 4, 12, and 20. Subjects of the FAE group will receive commercially available Fumaderm® tablets specifically labeled for the study. An individual dosing for each subject representing the optimal benefit-risk ratio is aspired.

A subject will be considered to have completed Study Part I if he or she has completed assessments at Week 24 of the open-label phase. Subjects eligible for Study Part II at Week 24 (ICF Part II signed, study treatment ongoing, no protocol-prohibited treatment started) will enter study extension and continue study treatment. For subjects who discontinue study treatment or withdraw from study participation in Study Part I or who do not enter Study Part II, a safety follow-up visit (Study Part I) is completed at Week 32 or 12 weeks after the last treatment (whatever comes first). For subjects enrolled in Study Part I only, maximum duration of study participation in this study will be 35 weeks.

Study Part II (Extension)—Week 24 through Week 56:
Treatment

Subjects may enter the study extension at Week 24 only when the ICF for Study Part II was signed before or at Week 24, study treatment was not terminated prior to Week 24 and no protocol-prohibited medication/therapy was started. Study Part II is subdivided in two treatment periods:

- Part IIa—Week 24 through Week 32: All subjects who enter Study Part II will continue their assigned treatment (guselkumab or FAE) from Week 24 through Week 32. Study Part IIa is considered completed when the subject has completed assessments at Week 32.

  Part IIb—Week 32 through Week 56: Following Week 32, subjects with a PASI 75 response will continue assigned treatment (guselkumab or FAE). For PASI 75 non-responders at Week 32 the following options will be available:

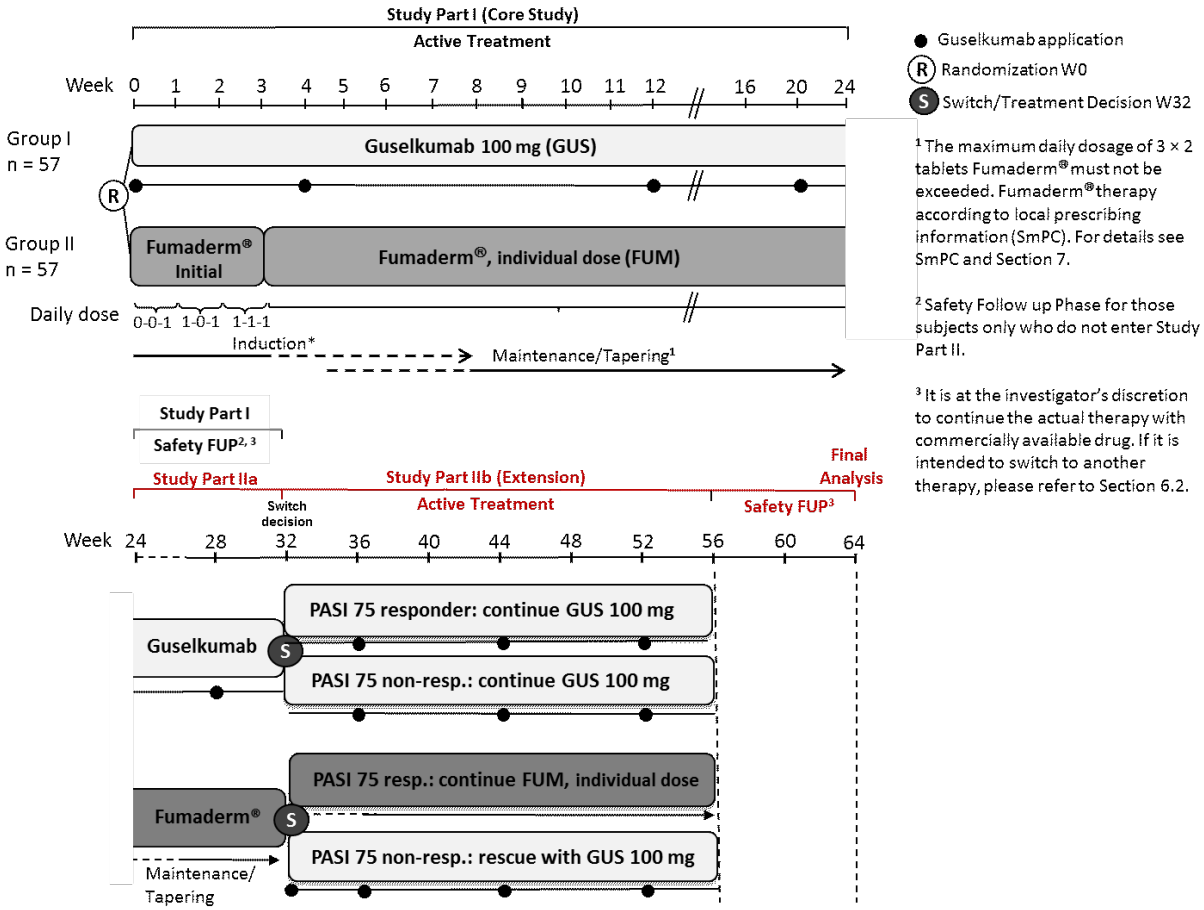
- Guselkumab group: Subjects may continue guselkumab treatment. It is at the investigator's discretion to continue therapy, if it is considered medically appropriate.
- FAE group: Subjects will switch to guselkumab unless barred by safety reasons (based on lab values at Week 28 or up to Week 32). Subjects who terminate FAE treatment prior to Week 32 cannot continue study treatment but will enter safety follow-up per protocol.

A subject will be considered to have completed Study Part II if he or she has completed assessments at Week 56 of the open-label phase. For Subjects who discontinue study treatment or withdraw from study participation in Study Part II, final study assessments are obtained and a safety follow-up visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first). For subjects completing Study Part II the maximum duration of study participation in this study will be 67 weeks including a 3-week screening phase.

Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd PSSD 7-day version, and 3rd SF-36), and subsequently by a blinded efficacy assessor (BSA%, IGA, ss-IGA, and PASI). Safety evaluations will include the monitoring of adverse events (including injection site and allergic reactions), physical examinations, measurement of body weight, vital sign measurement, clinical laboratory testing (HBV, HCV, HIV, hematology, chemistry), concomitant medication review, tuberculosis test and evaluation, urinalysis and pregnancy testing. The confirmatory analysis will be conducted after the primary endpoint at Week 24 is reached including subjects who have completed the Week 24 visit and subjects who have terminated the study prematurely (Section 11.3). The second statistical analysis will be performed after Week 64 (see Section 11).

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be transferred to the sponsor (or designee) after completion of the final subject visit at that site, in the time specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 21 months (start in December 2016, stop in October 2018). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

Figure 1: Schematic Overview of the Study



[1] The maximum daily dosage of 3 × 2 tablets Fumaderm® must not be exceeded. Fumaderm® therapy according to local prescribing information (SmPC). For details see SmPC and Section 7.

[2] Safety Follow up Phase for those subjects only who do not enter Study Part II.

[3] It is at the investigator's discretion to continue the actual therapy with commercially available drug. If it is intended to switch to another therapy, please refer to Section 6.2.

9.2 Sample Size Determination

As decribed in the CSP, the primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24.
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$). Due to the testing of ordered hypotheses, no adjustment of the significance level with respect to the threefold test procedure is required.

The assumptions for the sample size and power calculations using the threefold test procedure were based on guselkumab phase 2 data and unpublished data from the German PsoBest Registry and are as follows: PASI 90 responder rates for guselkumab and FAE in Week 24 are assumed to be 60% and 25%, respectively. PASI 75 responder rates are assumed to be 80% and 45%, respectively. DLQI responder rates are assumed to be 60% and 30%, respectively.

Based on these assumptions, with a total of 114 subjects planned to be randomized in a 1:1 ratio to guselkumab (n = 57) and to FAE (n = 57), superiority of guselkumab vs. FAE can be demonstrated at a 5% significance level (two-sided) with power of at least 90% for each test of the threefold test procedure as displayed in the table below.

Table 1: Power to detect a treatment effect on expected proportions of subjects achieving the primary and the major secondary endpoints

Order of testing	Endpoint in Week 24	Guselkumab (% responder)	FAE (% responder)	Power
1	PASI 90	60	25	97%
2	PASI 75	80	45	98%
3	DLQI 0/1	60	30	90%
type 1 error rate alpha 5% (two-sided) sequential testing with a-priori ordered hypotheses (only proceed with testing, if p <0.05) sample size n = 114 with 1:1 ratio guselkumab (n = 57) and FAE (n = 57) two group chi-square test; nQuery Advisor® Release 7.0				

9.3 Randomization and Blinding

Procedures for Randomization

Central randomization is implemented in this study as described in Section 5 of the CSP. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) 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-based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC (Electronic Data Capture) system.

Blinding

As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP.

10.0 Study Schedule

An overview of the study procedures is displayed in the following time and events schedule of the CSP. References to 'Section' always refer to the respective section in the CSP.

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Screening/Administrative												
Informed consent I (Study Part I)	X											Must be signed before first study-related activity
Informed consent II (Study Part II)	----------X											ICF addendum for Study Part II to be signed at Week 24 at the latest
Medical history and demographics	X											
Inclusion/ exclusion criteria	X	X										Minimum criteria for the availability of documentation supporting the eligibility criteria are described in protocol, Section 4; check clinical status again before first dose of study medication
Study Drug Administration												
Randomization		X										All baseline study procedures and evaluations are to be completed before randomization
Study drug administration		X[c]----------…										All study procedures and evaluations are to be completed before study drug administration

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before administration of study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

c: Subjects randomized to guselkumab will get guselkumab 100 mg on site at Weeks 0, 4, 12 and then every 8 weeks. Subjects randomized to FAEs will start with Fumaderm® initial regimen (0-0-1) at the day of the baseline visit; thereafter, FAE doses will be increased to find the optimal Fumaderm® dose for each subject as described in Section 6.

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit: for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4												
Safety Assessments												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis evaluation	X	X	X----------…							X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Chest radiograph	X											Taken within 3 months before the first administration of study drug and read by a qualified radiologist
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	Women of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits (prior to administration of study drug).
Height		X										
Weight		X							X	X	X	
Concomitant therapy	X----------…									X	X	
Adverse events	X----------…									X	X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Efficacy Assessments												
DLQI	X	X		X	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit; completion of the baseline PROs has to be done before randomization
PSSD (7d)	X	X	X	X	X	X	X	X	X		X	
SF-36		X			X		X		X		X	
IGA[d]	X	X	X	X	X	X	X	X	X		X	
PASI[d]	X	X	X	X	X	X	X	X	X		X	
ss-IGA[d,e]		X			X		X		X		X	
BSA%[d]	X	X			X		X		X		X	

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

d: Dermatological evaluation of the subjects will be done by a blinded assessor starting with the Baseline visit; assessments will be done before any study related procedure will take place

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]												
Clinical Laboratory Assessment												
Tuberculosis test[f]	X											
Hepatitis B and C Serologies	X											
HIV antibody test	X											
Hematology[g]	X	X	X	X	X	X	X	X	X	X	X	Laboratory tests are listed in Section 9.3
Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤ +; one re-test (central urine analysis) is allowed.

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

f: The QuantiFERON-TB Gold Plus test will generally be performed by the central laboratory; however, if available, test results from local laboratory can be accepted

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Study Drug Administration											
Study drug administration	…---------X[i]----------X										Subjects may enter the study extension at Week 24 when ICF for Study Part II was signed, study treatment was not terminated and no protocol-prohibited medication/therapy was started.
Safety Assessments											
Physical examination	X	X		X		X		X	X	X	
Vital signs	X	X		X		X		X	X	X	
Tuberculosis evaluation	……----------X								X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	
Weight									X	X	

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II (≤Week 64): For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

i: Week 24 to Week 32 (Study Part IIa): subjects continue assigned treatments through Week 32. Subjects treated with 100 mg SC guselkumab continue q8w (ie, at Week 28). Subjects treated with FAE continue Fumaderm® tablets (individual dosing according to local SmPC) until Week 32.

Week 32 to Week 56 (Study Part IIb): Treatment decision based on PASI assessment at Week 32 and safety assessment (≥Week 28):

- PASI 75 responders at Week 32: subject continues assigned therapy. Subjects in the guselkumab group continue 100 mg guselkumab SC at Weeks 36, 44, 52. Subjects in the FAE group continue Fumaderm® treatment (individual dosing according to local SmPC) until Week 56.
- PASI 75 non-responders at Week 32: subjects in the FAE group may switch to guselkumab treatment unless barred by safety reasons (see treatment criteria Section 4.4). In case of safety concerns (based on lab values of Week ≥28), assessment can be repeated before Week 32. Subjects will receive guselkumab SC at Weeks 32, 36, 44 and Week 52. Non-responders in the guselkumab group may continue guselkumab (continuation of therapy is at the investigator's discretion).

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Safety Assessments (continued)											
Concomitant therapy	…----------X								X	X	
Adverse events	…----------X								X	X	
Efficacy Assessments											
DLQI	X	X	X*	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit. ***ONLY applicable for subjects who switched to guselkumab at Week 32**
PSSD (7d)	X	X	X*	X		X		X		X	
SF-36		X						X		X	
IGA[d]	X	X	X*	X		X		X		X	
PASI[d]	X	X	X*	X		X		X		X	
ss-IGA[d,e]		X	X*	X		X		X		X	
BSA%[d]		X						X		X	
Study Procedures[b]											

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

d: Dermatological evaluation of the subjects will be done by a blinded assessor as in Study Part I; assessments will be done before any study related procedure will take place

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Clinical Laboratory Assessment											
Hematology[g]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X	Laboratory tests are listed in Section 9.3 **[Δ] NOT applicable for subjects continuing guselkumab treatment since beginning of the study (Week 0)**
Chemistry[g]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X[Δ]	X	X	
Urinalysis	X	X[β]	X	X[β]	X	X[β]	X	X[β]	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤+; one re-test (central urine analysis) is allowed. **[β] ONLY applicable for subjects treated with FAE**

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.4.

h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

11.0 Analysis Sets

For all efficacy and safety analyses to compare guselkumab vs. FAE in Study Part IIb (active treatment period from Week 32 through Week 56 and safety follow-up period from Week 56 through Week 64), subjects will be analyzed according to the treatment they actually received. If not otherwise specified, the following 4 treatment groups which are defined in the CSP will be analyzed in Study Part IIb.

- GUS_{resp}-GUS: PASI 75 responder at Week 32 who continue guselkumab 100 mg
- $GUS_{non\text{-}resp}$-GUS: PASI 75 non-responder at Week 32 who continue guselkumab 100 mg
- FAE_{resp}-FAE: PASI 75 responder at Week 32 who continue FAE, individual dose
- $FAE_{non\text{-}resp}$-GUS: PASI 75 non-responder at Week 32 who switch to guselkumab 100 mg ('Switcher')

Statistical analyses on combined treatment groups in Study Part IIb (e.g., $GUS_{resp/non\text{-}resp}$-GUS: PASI 75 responder or non-responder at Week 32 who continue guselkumab 100 mg) or additional statistical analyses using the randomized treatment groups in Study Part I are explicitly mentioned and described in the respective chapters of Section 14.

11.1 Definition of Analysis Sets

Subjects in Study Part IIb will be analyzed according to the treatment they actually received. The following analysis data sets will be defined:

- **Study Part IIb Analysis Set**

  The Study Part IIb analysis set is defined as the set of all subjects who entered Study Part IIb and were treated with one of the two treatments (guselkumab or FAE) at least once during the treatment period from Week 32 to Week 56.

- **Study Part IIb Per-Protocol Analysis Set**

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

Data on study subjects, demographic and baseline characteristics, treatment compliance, as well as all efficacy and safety analyses will be analyzed for the Study Part IIb analysis set. In addition, the PASI 90, PASI 75 and DLQI 0/1 response rates will also be analyzed using the Study Part IIb per-protocol analysis set.

Exploratory inferential statistical analyses to compare guselkumab vs. FAE in Study Part IIb will only be performed in the PASI 75 responder treatment arms at Week 32. The FAE PASI 75 non-responder and the GUS combined responder or non-responder arms will be analyzed with descriptive statistics only.

In addition, statistical analyses using the randomized treatment groups in Study Part I will also be performed using the safety analysis set as defined in the SAP - Week 24 Analysis. Such analyses are explicitly mentioned and described in the respective chapters of Section 14.

11.2 Protocol Deviations

The determination of evaluability of subjects, especially in cases of protocol deviations, withdrawals or drop-outs and the assignment of subjects to the planned analysis sets will be performed according to the requirements of the study protocol. Minor and major and potentially major protocol deviations that can be expected based on the prescriptions in the protocol were defined by Janssen-Cilag GmbH during the trial set up period and adapted during the study conduct. A detailed description of major and potentially major protocol deviation criteria is included in a separate document.

Data on subjects who had a major protocol deviation will be documented continuously by Janssen-Cilag GmbH in a Clinical Trial Management System during the trial period. Final data on major protocol deviations regarding the Week 64 analysis of Study Part IIb will be transferred to the data management department of acromion GmbH as Excel spreadsheets and will be further processed for statistical analysis.

11.3 Screening Failures

Not applicable for the present analysis.

12.0 Definition and Calculation of Efficacy Endpoints

The following sections provide a detailed description of the definition and the planned calculation of the efficacy endpoints as defined in the CSP. The same applies also for additional endpoints not defined in the CSP.

12.1 Involved 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).

12.2 Investigator's Global Assessment (IGA)

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

The efficacy endpoint related to the IGA score is defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

12.3 Scalp Specific Investigator's Global Assessment (ss-IGA)

The scalp-specific (ss-)IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

The analyses for ss-IGA will be based on subjects randomized at Week 0 with baseline ss-IGA score ≥2.

ss-IGA absence of disease responder

Subjects with an ss-IGA score ≥2 at baseline who achieve ss-IGA score of absence of disease (0) will be considered ss-IGA absence of disease responders.

12.4 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.

In addition, the time to PASI 75/90/100 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response the time to PASI 75/90/100 response will be censored at the date of Week 64 or the date of discontinuation in case of early treatment discontinuation.

12.5 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 (e.g., 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.

In addition, the time to DLQI 0/1 response defined as time from baseline to first onset of response will be calculated. In the absence of documented response the time to DLQI 0/1 response will be censored at the date of Week 64 or the date of discontinuation in case of early treatment discontinuation.

12.6 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 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.

12.7 Short Form Health Survey (SF-36)

The Short Form Health Survey (SF-36) is a 36-item questionnaire used for subjects' self-assessment of health-related quality of life, consisting of the following 8 dimensions: 1) limitations in physical functioning due to health problems, 2) limitations in usual role activities due to physical health problems, 3) bodily pain, 4) general mental health (psychological distress and well-being), 5) limitations in usual role activities due to personal or emotional problems, 6) limitations in social functioning due to physical or mental health problems, 7) vitality (energy and fatigue), and 8) general health perception.

A physical component summary (PCS) score and a mental component summary (MCS) score can be derived. The concepts measured by the SF-36 are not specific to age, disease or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments. The estimated completion time will be 10 minutes.

Each of these 8 scales (domains) is scored from 0 to 100 with higher scores indicating better health. Based on the scale scores, the summary scores, PCS and MCS, will be derived. These summary scores are also scaled with higher scores indicating better health.

The QualityMetric Health Outcomes™ Scoring Software 5.0 offered by QualityMetric Incorporated will be used to score the SF-36. The Software is designed to provide users with standard scoring methods in an easy-to-use way. By using this Software, users will have the confidence that the data they obtain on their SF form are scored in accordance with standards set by the developers of the SF tools. The Software also provides evaluation of data quality and applies methods for missing data recovery. The PCS score can be calculated when seven scale scores are available and the Physical Functioning scale is not missing. The MCS score can be calculated when at least seven scale scores are available and the Mental Health scale is not missing.

A more detailed description of the scoring procedure is provided in the User's Guide of QualityMetric Health Outcomes™ Scoring Software 5.0 (see especially Appendix F).

13.0 Statistical Methodology

The present Week 64 analysis of Study Part IIb summarizes the study data in Study Part IIb from Week 32 until Week 64 (Study Part IIb: active treatment period from Week 32 through Week 56 and safety follow-up period from Week 56 through Week 64) and will be part of the Week 64 analysis of Study Part II. This analysis will include the safety analysis and all efficacy measures after Week 32 and will cover the time from Week 32 until the Week 64 visit. All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses from Week 32 until Week 64.

In addition, statistical analyses using the data of from Week 0 to Week 32 will also be perfomed. Such analyses are explicitly mentioned and described in the respective chapters of Section 14.

The biometrical evaluation will be carried out by acromion GmbH under the authority of the sponsor. Statistical programming and analyses will be performed using the statistical software system SAS®.

The following sections provide a more detailed description of the planned statistical methodology.

13.1 Data Handling Rules

13.1.1 Baseline and Post-baseline Points in Time of Interest

Baseline Definition

In general, the values of the Week 0 visit (= day of randomization = first day of week 1) or the values of the screening visit (= day within 3 weeks before their randomization visit) will be used as baseline values, as applicable. If data for the same variable are available from both (i.e., screening and Week 0) visits then the result of the Week 0 visit will be used as baseline value, i.e., for each variable the baseline measurement is defined as the closest measurement taken prior to or at the Week 0 visit.

For the treatment group $FAE_{non\text{-}resp}$-GUS (PASI 75 non-responder at Week 32 who switch to guselkumab 100 mg ('Switcher')) the values of the Week 32 visit will also be used as baseline values for some analyses. If data for the Week 32 visit are missing then the result of the Week 28 visit will be used as baseline value. Such analyses are explicitly mentioned and described in the respective chapters of Section 14.

Definition of Post-baseline Points in Time of Interest

The primary point in time for efficacy assessment will be the Week 56 visit (= the treatment visit 56 weeks after randomization). Secondary points in time for efficacy assessment will be the study visits scheduled at Week 40 and Week 48 during the treatment phase. Handling of missing values is described in SAP section 13.1.6.

The safety analysis will cover the time period from Week 32 through 64.

In addition, statistical analyses using the data from Week 0 to Week 32 will also be perfomed. Such analyses are explicitly mentioned and described in the respective chapters of Section 14.

13.1.2 Definition of Within- and Between-Group Treatment Differences

Within-group treatment differences will be computed as differences of the post-baseline visits as compared to the baseline visit, if applicable:

- post-baseline visit minus baseline visit

The following between-group treatment difference to assess the treatment effect will be computed in the PASI 75 responder treatment groups, if applicable:

- guselkumab minus FAE

13.1.3 Visit Windows

Nominal visits (i.e., visits as recorded in the eCRF) will be used for all by-visit analyses in the study. The study visits scheduled post randomization should occur at the times delineated in the Time and Events Schedule. No visit windows will be defined and used for analysis.

13.1.4 Treatment Failure Criteria

Not applicable.

13.1.5 Treatment Failure Rules

No treatment failure rules will be applied.

13.1.6 Handling of Missing Values

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

Missing data for the efficacy endpoints at key visits Week 40, 48 and 56 will be handled as follows for all exploratory inferential statistical analyses (only for PASI 75 responders at Week 32).

Missing data imputation for the efficacy endpoints at Week 40, 48 and 56:

- Nonresponder imputation will be applied for binary endpoints
    - i.e., subjects with missing data at Week 40/48/56 will be considered non-responders at Week 40/48/56.
- Last observation carried forward (LOCF) will be applied for continuous endpoints
    - i.e., in subjects with missing data at Week 40/48/56 the last available observation after Week 32 will be calculated and used for analysis for continuous response variables at Week 40/48/56. 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.

Sensitivity analyses with respect to the handling of missing values at Week 56 are described in SAP section 13.9.

Deviations from this general plan for missing data imputation are explicitly mentioned and described in the respective chapters of Section 14.

13.1.7 Data Transformations

No data transformations (e.g. square root, logarithmic) to confirm basic statistical assumptions will be performed. All variables will be used in the analysis as reported.

13.2 Descriptive Statistics

13.2.1 Dichotomous and Categorical Variables

Categorical data will be presented in frequency tables using counts and percentages. Percentages will be based on the total number of subjects in the respective analysis set (i.e., missing values will be included in percentage calculation). Besides presentation of absolute values cross tabulation vs. baseline by study visit will be provided, if appropriate.

13.2.2 Continuous and Quasi-Continuous Variables

Standard descriptive summary statistics will be calculated for continuous and quasi-continuous variables: arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values. Besides presentation of absolute values tabulation for differences to baseline by study visit will be provided, if appropriate.

13.2.3 Graphical Presentations

Graphical presentation of pertinent data will be given by means of box plots, bar charts, and survival graphs, as appropriate. Additional forms of graphical presentations may be specified. Descriptions of graphical presentations are included in the appendix of this document.

13.3 Confirmatory Statistics

Not applicable for the present Week 64 analysis of Study Part IIb. The confirmatory analysis is described in the SAP for the Week 24 analysis (Final 1.0, 10-July-2017).

13.4 Exploratory Statistics

Exploratory statistical analyses will be performed for the endpoints listed under 'other secondary endpoints' relevant for Study Part IIb at Week 56, and at Week 40 and Week 48. All statistical tests and confidence intervals will be calculated two-sided and will be interpreted in the exploratory sense only.

Exploratory inferential statistical analyses to compare guselkumab vs. FAE in Study Part IIb will only be performed in the PASI 75 responder treatment arms at Week 32. The other arms will be analyzed with descriptive statistics only.

13.4.1 Binary Endpoints

For binary endpoints counts and percentage of subjects per treatment group along with odds ratio (OR), relative risk (RR) and risk difference (RD), 95% confidence intervals (95% CIs) and p-values for treatment effect using the chi-square test will be provided.

13.4.2 Continuous Endpoints

The change from baseline of continuous endpoints will be analyzed by an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate. The Least-Squares means (LS means), the LS mean difference and the standardized mean difference (computed according to Hedges' g) with the 95% CI and two-sided p-value will be provided from the ANCOVA model.

13.5 Adjustment for Covariates

The baseline value will be used as covariate in the analysis of variance model (ANCOVA) for the change from baseline of continuous response parameters.

13.6 Interim Analyses

The following analyses are planned to be performed.

1. Main Analysis (Confirmatory Week 24 Analysis)

The confirmatory main analysis was performed at the end of Study Part I, i.e., after all subjects had completed their visit at 24 weeks after randomization or discontinued earlier. This analysis, described in a separate SAP ('SAP Week 24', final version 1.0, 10-July-2017), included the confirmatory analysis of the primary endpoint and the major secondary endpoints as well as all other exploratory predefined efficacy and safety analyses until Week 24. The results of the analysis are described in the Clinical Study Report Week 24, dated 14.05. 2018.

2. Interim Analysis (Exploratory Week 64 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) interim analysis will be performed at the end of Study Part II, i.e. after all subjects had completed their visits at 64 weeks after randomization or discontinued earlier. The Week 64 analysis will be split into 2 parts, the Week 32 analysis and the Week 64 analysis.

- The Week 32 analysis, described in this SAP ('SAP Week 32'), summarizes the study data until Week 32 (Study Part IIa; continuation of assigned treatment from Week 24 through Week 32). All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32.
- The Week 64 analysis, described in a separate SAP ('SAP Week 64'), summarizes the study data until Week 64 (Study Part IIb). The analysis will include all efficacy measures until Week 56 and safety measures until the Week 64 safety visit.

3. Final Analysis (Exploratory Week 100 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) final analysis will be performed at the end of Study Part III, i.e. after all subjects had completed their visits at 100 weeks after randomization or completed earlier (i.e., subjects meet the definition of loss of response) or discontinued earlier.

13.7 Multi-center Data

Exploration of possible heterogeneity of treatment effects across centers for the proportion of subjects achieving a PASI 90 response at Week 56 using nonresponder imputation will be performed by descriptive frequency statistics including graphical display of the results of the individual centers, as appropriate. No pooling of centers will be performed.

13.8 Subgroup Analyses

The following subgroup analyses are planned to be performed for the treatment group GUS_{resp}-GUS (PASI 75 responder at Week 32 who continue guselkumab 100 mg) to evaluate consistency over demographics and baseline disease characteristics of the endpoints PASI 75/90/100 response, PASI ≤ 1, PASI ≤ 3, DLQI score 0 or 1, PSSD sign score, and PSSD symptom score:

- Gender
  - male
  - female
- Age at baseline in years
  - < 45
  - ≥ 45 - < 65
  - ≥ 65
- PASI
  - < 20
  - ≥ 20

Subgroup analyses for these efficacy endpoints will be performed using the following different imputation rules of missing values at Week 56 (see SAP sections 13.1.6 and 13.9):

- Binary endpoint:
  - Nonresponder imputation
  - LOCF (only PASI 75/90 response, and DLQI 0/1 response)
  - Multiple imputation
- Continuous endpoint:
  - Multiple Imputation

Subgroup analyses will NOT be performed for the Study Part IIb per-protocol analysis set.

13.9 Sensitivity Analyses

The following sensitivity analyses at Week 56 with respect to the handling of missing values are planned to be performed:

- Multiple imputation will be used for all binary and continuous endpoints.
    - For the multiple imputation, the repeated nature of the analysis is restricted to the imputation step (procedure "MI" in SAS). Basic premise is the creation of several datasets in which missing data is imputed in a random fashion and then analyses are performed to check for changes for the conclusion. The analysis will be done with SAS Proc MIANALYZE.
- LOCF imputation will be used for all binary endpoints (see SAP section 13.1.6).
- An 'observed cases analysis' for all binary and continuous endpoints without substitution of missing data will be used (see SAP section 13.1.6).

Sensitivity analyses at Week 56 with respect to the handling of missing values will be performed for all binary and all continuous efficacy endpoints.

Sensitivity analyses at Week 56 with respect to the handling of missing values will NOT be performed for the Study Part IIb per-protocol analysis set.

14.0 Statistical Analyses

A table of contents of planned data displays is provided in section 18.1 of this document. The following sections are intended to provide more details of the planned analyses. In addition, mock tables were created and were used as template for statistical programming at the Week 24 analysis. The mock tables will be used analogously at the present Week 64 analysis of Study Part IIb.

Data will be appropriately summarized and analyzed using tabulation and graphs with respect to demographic/baseline characteristics and efficacy/safety observations and measurements. Standard descriptive summary statistics (i.e., n, arithmetic mean, standard deviation, median, minimum/maximum value, quartiles) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. In general, summary tables will be displayed by the four treatment groups in Study Part IIb (see SAP section 11.0) as the main classification variable and for the total of the sample in the respective analysis set. Additional classification variables or statistical analyses on combined treatment groups in Study Part IIb or statistical analyses using the randomized treatment groups in Study Part I are explicitly mentioned in the following text. Individual subject data listings will be presented parameter wise and will be sorted by treatment group, center, subject number and study visit, if applicable.

14.1 Study Subjects

Unless otherwise specified, data on study subjects will be analyzed based on data from all subjects who entered Study Part IIb and were treated with one of the two treatments (guselkumab or FAE) at least once in the four treatment groups during the treatment period from Week 32 to Week 56 ('Study Part IIb analysis set').

14.1.1 Disposition of Subjects

The overview of subject disposition from Week 0 to Week 32 and from Week 32 to Week 56 will provide the respective frequency counts and percentages regarding the following subjects:

- Treatment phase from Week 0 until Week 32
  - Subjects who were enrolled (i.e., signed informed consent Part I)
  - Subjects who were randomized
  - Subjects who were treated
  - Subjects with premature discontinuation of study treatment until Week 24
  - Subjects who completed the treatment phase until Week 24
  - Subject who entered Study Part II (i.e., signed informed consent Part II)
  - Subjects with premature discontinuation of study treatment until Week 32
  - Subjects who completed the treatment phase until Week 32
- Treatment phase from Week 32 to Week 56
  - Subjects who were treated
  - Subjects with premature discontinuation of study treatment until Week 56
  - Subjects who completed the treatment phase until Week 56

The table will also include the total number of study sites and the dates of the entry of the first subject and the last visit of the last subject in Study Part IIb. A flow diagram (according to the CONSORT statement) giving an overview of subject disposition will also be provided.

In addition, the number and percentage of treated subjects continuing and attending by study visit will be displayed in a separate table. Subjects will be counted as continuing at the time of visit whether they attend the visit or not. Only those subjects that prematurely discontinued before the visit will not be counted as attending.

14.1.2 Discontinuation of Study Treatment

The number and percentage of treated subjects who discontinued study treatment prematurely within the treatment period from Week 32 to Week 56 will be tabulated for each reason of premature discontinuation (including tabulation of specifications for category 'other'). Moreover, the number of subjects not included in Study Part IIb and the reasons for not being included will be given.

14.1.3 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 trial. Subjects with major protocol deviations will be summarized by category for all randomized subjects.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

The summary table will provide the number of subjects per major protocol deviation and will also provide the number of major protocol deviations in Study Part IIb.

The treatment assignment criteria deviations (Study Part IIb) will also be given.

14.1.4 Analysis Sets

The number and percentage of treated subjects included in each analysis set, together with a breakdown of the reasons for exclusion for non-evaluable subjects, will be provided.

14.2 Demographic and Other Baseline Characteristics

Generally, assessments made at the screening visit and the baseline visit will be summarized by treatment group in Study Part IIb (i.e. 4 treatment arms) and overall. Note that this summary is different to the summary of the two randomized treatment groups in Study Part I. These assessments will include demographic characteristics and other parameters (such as medical history, diagnosis of psoriasis, concomitant diseases, and concomitant medication). By-treatment summaries will serve to identify any imbalances between the treatment groups at baseline. Summary tables will be provided by means of descriptive statistics and frequency tables, where appropriate. Demographic and other baseline characteristics will be analyzed based on data from all treated subjects in Study Part IIb ('Study Part IIb analysis set'). No analyses for baseline balance using statistical hypothesis tests or confidence intervals will be done.

14.2.1 Demographics

Age (categorized), gender, and race will be presented in a frequency table. Age group categories will be chosen as < 45; ≥ 45 - < 65; ≥ 65years. Descriptive summary statistics will be calculated for age, body height, body weight and body mass index (BMI).

Tables for demographic data will also be stratified by gender. Age and gender distribution will be presented in a bar chart.

Note: Age is documented as 'age at date of informed consent signature' at the screening visit. Body height and body weight data will be taken from the vital signs eCRF form at the Week 0 visit. BMI will be calculated as body weight in kg / body height in m².

14.2.2 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 terminology as described in SAP section 14.6. Summary tabulation will also consider whether the disease is ongoing or not at screening visit.

14.2.3 Diagnosis of Psoriasis

The time from date of initial diagnosis of psoriasis to date of screening visit will be calculated and will be displayed by descriptive statistics. If the day is unknown the day will be set to day = 1. If the month is unknown the month will be set to month = July.

In addition, the disease characteristics at baseline Week 32 will be summarized for the treatment group $FAE_{non\text{-}resp}$-GUS (PASI 75 non-responder at Week 32 who switch to guselkumab 100 mg ('Switcher')) by providing the following relevant results: descriptive summary statistics of the PASI and the DLQI index, frequency distribution of the IGA categories and the PASI < 20 and PASI ≥ 20 subgroups.

14.2.4 Previous Psoriasis Therapy

No statistical analysis will be performed.

14.2.5 Substance Use

No statistical analysis will be performed.

14.2.6 Physical Examination

No statistical analysis will be performed.

14.2.7 Tuberculosis Evaluation

No statistical analysis will be performed.

14.2.8 Chest Radiograph Result

No statistical analysis will be performed.

14.2.9 Concomitant Medication and Therapy

Analyses of concomitant medication and therapy will consider the data recorded within the treatment periods from Week 0 to Week 32 and from Week 32 to Week 56 and recorded during the safety follow-up period from Week 56 to Week 64.

Concomitant Medication

The number and percentage of subjects with use of concomitant medication from Week 32 to Week 56 will be displayed in WHO-DD terminology as described in SAP section 14.7. Concomitant medication will be identified from the *Concomitant Medication* form of the eCRF.

The number and percentage of subjects with indication for concomitant medication from Week 32 to Week 56 will be displayed in MedDRA terminology as described in SAP section 14.6.

Analyses of data recorded from week 0 to week 64 and of data recorded during the safety follow-up period from Week 56 to Week 64 will be performed analogously.

Concomitant Therapy

The number and percentage of subjects with use of concomitant therapy from Week 32 to Week 56 will be displayed in MedDRA terminology as described in SAP section 14.6. Concomitant therapy will be identified from the *Concomitant Therapy* form of the eCRF.

The number and percentage of subjects with indication for concomitant therapy from Week 32 to Week 56 will be displayed in MedDRA terminology as described in SAP section 14.6.

Analyses of data recorded from week 0 to week 64 and of data recorded during the safty follow-up period from Week 56 to Week 64 will be performed analogously.

14.2.10 Shampoo and Moisturizer

The number and percentage of subjects with use of shampoo or moisturizer from Week 32 to Week 56 will be displayed in a frequency table.

14.3 Treatment Compliance

Treatment compliance will be analyzed based on data from all treated subjects of the four treatment arms in Study Part IIb ('efficacy analysis set').

14.3.1 Visit Windows

The number of days between the scheduled study visits and the baseline visit will be calculated using the reported visit dates per scheduled study visit and will be displayed by summary descriptive statistics from Week 32 to Week 56 and from Week 56 to Week 64.

14.3.2 Study Medication

Categorical data on guselkumab administration recorded from Week 32 to Week 56 will be summarized by frequency tabulation providing the number and percentage of subjects per category. Frequency tabulation and descriptive statistics will be presented for the overall number of guselkumab administrations from Week 32 to Week 56.

Compliance to guselkumab administration will be calculated as follows based on the eCRF data from Week 32 to Week 56:

- Compliance guselkumab in % = (number of actual administrations x 100 / number of planned administrations)

Categorical data on Fumaderm® initial/ Fumaderm® administration recorded at each week from Week 32 to Week 56 and will be summarized by frequency tabulation providing the number and percentage of subjects per recorded category in the eCRF. The number of planned tablets to be taken in the morning, at noon, and in the evening will also be summed up and analyzed descriptively.

The number of dispensed and returned tablets of Fumaderm® initial/ Fumaderm® (including the difference of dispensed - returned tablets = actual tablets) will be displayed by descriptive summary statistics from Week 32 to Week 56.

Compliance to Fumaderm® initial and Fumaderm® administration will be calculated as follows based on the eCRF data from Week 32 to Week 56:

- Compliance FAE in % = (number of actual tablets x 100 / total number of tablets supposed to be taken)

Treatment compliance will also be assessed by protocol deviations related to study drug administration (i.e., incorrect study drug received and missed administrations).

For subjects who completed the Week 56 visit the dose of Fumaderm® in mg at Week 56 will be summarized by descriptive statistics and frequency tabulation. In addition, the maximum dose of Fumaderm® initial and Fumaderm® in mg will be calculated for all subjects and will be summarized by descriptive statistics and frequency tabulation.

For patients starting with guselkumab and staying on guselkumab and for patients starting with Fumaderm® and staying on Fumaderm®, compliance will also be calculated for the Week 0 to Week 56 period. For patients switching from Fumaderm® to guselkumab, compliance will be analyzed separately from Week 0 to Week 32 and from Week 32 to Week 56.

14.4 Analysis of Efficacy

All efficacy analyses to compare guselkumab vs. FAE will be performed for all treated subjects of the four treatment in Study Part IIb ('Study Part IIb analysis set'). The PASI 90, PASI 75, and DLQI 0/1 response rates will also be analyzed using the Study Part IIb per-protocol analysis set. However, subgroup and sensitivity analyses at Week 56 will NOT be performed for the Study Part IIb per-protocol analysis set.

All statistical analyses will be descriptive and exploratory only for the predefined efficacy analyses from Week 32 through Week 56. All statistical tests will be performed two-sided in an exploratory sense.

Exploratory inferential statistical analyses to compare guselkumab vs. FAE in Study Part IIb will only be performed in the PASI 75 responder treatment arms at Week 32. The PASI 75 non-responder arms will be analyzed with descriptive statistics only.

Handling of missing values, exploratory statistics, subgroup analyses, and sensitivity analyses will be performed as described in detail in the following sections of this SAP:

SAP Section No.	Topic
13.1.6	Handling of missing values
13.4.1	Exploratory statistics - binary endpoints
13.4.2	Exploratory statistics - continuous endpoints
13.8	Subgroup analyses
13.9	Sensitivity analyses

Data at the scheduled points Week 40 and Week 48 during the active treatment period will be analyzed analogously to the Week 56 data. However, no subgroup or sensitivity analyses will be performed for these points in time.

14.4.1 Primary Endpoint

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2 Major Secondary Endpoints

14.4.2.1 Endpoint related to PASI

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2.2 Endpoint related to DLQI

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.3 Other Secondary Endpoints

The following sections provide a description of the planned statistical analyses of the other secondary endpoints as reported in the CSP and as well as of additional endpoints not explicitly stated in the CSP (see SAP section 15.0).

14.4.3.1 Endpoints related to PASI

Other secondary endpoints related to PASI are:

- The proportion of subjects achieving a 75%/90%/100% improvement of their psoriasis according to the PASI at Week 56 (PASI 75/90/100 response) compared to baseline
- The proportion of subjects achieving an absolute PASI score ≤1, ≤2, ≤3, ≤5 at Week 56
- The proportion of subjects with a PASI 75/90 response at Week 32 who maintain response at Week 56

The proportion of responding 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.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 56 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

14.4.3.2 Endpoints related to PSSD

Other secondary endpoints related to PSSD are:

- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 56
- The change from baseline in the individual scale scores for itch, pain, and scaling of PSSD components at Week 56

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 56 value and the change from the baseline value will be displayed.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.3 Endpoints related to IGA

Other secondary endpoints related to IGA are:

- The proportion of subjects achieving an IGA score of cleared (0) at Week 56.

The proportion of responding 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.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 56 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 56 will be analyzed analogously.

14.4.3.4 Endpoints related to BSA

Other secondary endpoints related to BSA are:

- The change from baseline of body surface area (BSA) psoriatic involvement at Week 56

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 56 value and the change from the baseline value will be displayed.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.5 Endpoints related to DLQI

Other secondary endpoints related to DLQI are:

- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 56
- The change from baseline in DLQI score at Week 56
- The proportion of subjects with a DLQI score 0 or 1 at Week 32 who maintain response at Week 56

The proportion of responding 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.

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 56 value and the change from the baseline value will be displayed.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 56 per treatment arm and for the difference between the two arms.

Exploratory statistical analyses (also including analyses of time to DLQI 0/1 response) will be performed as described in SAP section 13.4.1.

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.3.6 Endpoints related to ss-IGA

Other secondary endpoints related to ss-IGA are:

- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 56 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline

The proportion of responding 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.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

The chi-square test will be used to compare the proportion of subjects responding to treatment. Two-sided 95% confidence intervals will be calculated for the response rate at Week 56 per treatment arm and for the difference between the two arms.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 56 will be analyzed analogously.

14.4.3.7 Endpoints related to SF-36

Other secondary endpoints related to SF-36 are:

- The change from baseline in the physical and mental component summary scores of SF-36 at Week 56

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 56 value and the change from the baseline value will displayed.

Exploratory statistical analyses for PASI 75 responder treatment arms at Week 32:

Exploratory statistical evaluation of the change from baseline will be based on an analysis of covariance model (ANCOVA) with the fixed effect factor for treatment group and the baseline value as covariate (see SAP section 13.4.2).

14.4.4 Other Efficacy Assessments

In addition to the efficacy analyses described above all efficacy data related to PASI, DLQI, PSSD, IGA, ss-IGA, and SF-36 at all scheduled study visits during the active treatment period from Week 0 until Week 56 will be summarized descriptively without any imputation of missing data ('observed cases analysis'; see SAP section 13.1.6). For binary endpoints summary results using nonresponder imputation will also be provided.

14.4.5 Additional Efficacy Analyses

Furthermore, the following additional efficacy analyses for the endpoints PASI 75/90/100 response, PASI ≤ 1, PASI ≤ 3, DLQI score 0 or 1, PSSD sign score, and PSSD symptom score will be performed:

- Analyses of Efficacy for $GUS_{resp/non-resp}$-GUS (Week 0 to Week 56) vs. FAE (Week 0 to Week 32)

Item	Specification
Treatment Groups	$GUS_{resp/non-resp}$-GUS vs. FAE
Treatment Periods	• $GUS_{resp/non-resp}$-GUS: Week 0 to Week 56 • FAE: Week 0 to Week 32
Analysis set	Safety Analysis Set Week 24 Analysis
Baseline	Week 0
Endpoints	PASI 75/90/100 Response, PASI≤1, ≤3, DLQI Score 0 or 1, PSSD Sum Scores
Observed Cases Analyses	Yes
Missing Data Imputation	at Week 4, 16, 24, 32, 40, 48, 56 • Binary Endpoint: NRI, MI, LOCF • Continuous Endpoint: MI, LOCF
Subgroups	No
Statistical Analysis	Descriptive
Tables	Yes
Figures	Yes

- Analyses of Efficacy for GUS_{resp} -GUS (Week 32 to Week 56) vs. FAE_{resp}-FAE (Week 32 to Week 56)

Item	Specification
Treatment Groups	GUS_{resp}-GUS vs. FAE_{resp}-FAE
Treatment Period	Week 32 to Week 56
Analysis set	Study Part IIb Analysis Set
Baseline	Week 0
Endpoints	PASI 75/90/100 Response, PASI≤1, ≤3, DLQI Score 0 or 1, PSSD Sum Scores
Observed Cases Analyses	Yes
Missing Data Imputation	at Week 36, 40, 44, 48, 56 • Binary Endpoint: NRI, LOCF • Continuous Endpoint: LOCF
Subgroups	No
Statistical Analysis	Descriptive, Exploratory Inferential
Tables	Yes
Figures	Yes

- Analyses of Efficacy for $FAE_{non\text{-}resp}$-GUS (Week 32 to Week 56) ('Switcher' Analysis)

Item	Specification
Treatment Group	$FAE_{non\text{-}resp}$-GUS ('Switcher')
Treatment Period	Week 32 to Week 56
Analysis set	Study Part IIb Analysis Set
Baseline	Week 0 AND Week 32
Endpoints	PASI 75/90/100 Response, PASI≤1, ≤3, DLQI Score 0 or 1, PSSD Sum Scores
Observed Cases Analyses	Yes
Missing Data Imputation	at Week 36, 40, 44, 48, 56 • Binary Endpoint: NRI, LOCF • Continuous Endpoint: LOCF
Subgroups	No
Statistical Analysis	Descriptive
Tables	Yes
Figures	Yes

- Analyses of Efficacy for GUS Starter vs. FAE Starter

Item	Specification
Treatment Group	GUS Starter vs. FAE Starter
Treatment Period	only Week 56
Analysis set	Safety Analysis Set Week 24 Analysis
Baseline	Week 0
Endpoints	PASI 75/90/100 Response, PASI≤1, ≤3, DLQI Score 0 or 1, PSSD Sum Scores
Observed Cases Analyses	Yes
Missing Data Imputation	at Week 56 • Binary Endpoint: NRI, MI, LOCF • Continuous Endpoint: MI, LOCF
Subgroups	No
Statistical Analysis	Descriptive
Tables	Yes
Figures	Yes

14.5 Analysis of Safety

Safety data, including but not limited to, adverse events (AEs), serious adverse events (SAEs), infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized using descriptive statistics. All safety analyses to compare guselkumab vs. FAE will be performed for all treated subjects ('Study Part IIb analysis set') in the four treatment arms.

14.5.1 Extent of Exposure

Extent of exposure will be defined as the total number of days from Week 32 to Week 56 (for all patients still under treatment) or to study discontinuation.

Descriptive summary statistics and frequency tables (using appropriate categories) will be provided for the extent of exposure.

In addition, extent of exposure from Week 0 to Week 56 for the PASI 75 responder treatment arms will be analyzed analogously.

14.5.2 Adverse Events

Adverse events data will be processed in the statistical analysis after coding according to the MedDRA dictionary version 19.1. All reported AEs with onset date during the active treatment period from Week 32 through Week 56 or the safety follow-up period from Week 56 through Week 64 (i.e., treatment emergent AEs) will be included in the analysis. In case of early treatment discontinuation before Week 56 all reported AEs with onset date during the safety follow-up period until Week 64 (i.e., treatment emergent AEs) will be included in the analysis. AEs reported after Week 64 will NOT be considered in the analysis.

14.5.2.1 Definitions

The following definitions will be applied in the present study

Crude Incidence Rate

Where percentages of subjects are reported in summary tables, incidences provide information on the proportion of subjects experiencing adverse events in relation to the total number of subjects exposed, i.e., if not otherwise specified, the crude incidence rate will be used.

The crude incidence rate is defined as the number of subjects experiencing a certain event, divided by the number of subjects exposed to study treatment, regardless of duration of use:

$$\text{Crude incidence rate} = 100 * \frac{\text{number of patients with adverse events}}{\text{number of patients exposed}}$$

Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are those AEs that occurred during the active treatment period from Week 32 to Week 56 or the safety follow-up period from Week 56 through Week 64 or those AEs that were present before Week 32 but worsened in severity after the Week 32. AEs reported after Week 64 will NOT be considered in the present analysis.

In case of early treatment discontinuation before Week 56 all reported AEs with onset date during the safety follow-up period until Week 64 will be included in the analyses. Thus, identification of TEAEs (distinguished by subjects who completed or discontinued the treatment period until Week 56) will be performed as follows:

- TEAE for Completer: Date of Week 32 ≤ Start Date of AE ≤ Date of Week 64
- TEAE for Non-Completer: Date of Week 32 ≤ Start Date of AE ≤ Date of Final Study Visit

AEs which are not classified as TEAEs will be considered as not treatment emergent adverse events (NTEAEs).

14.5.2.2 Analyses

Overview of adverse events

For summary presentation of the overall adverse event experience overview tables will be provided for AEs and SAEs including the following information:

Adverse events:

- n (%) of subjects with AEs *)
- n (%) of subjects with NTEAEs *)
- n (%) of subjects with TEAEs *)
- n (%) of subjects with TEAEs by highest causality to study medication
- n (%) of subjects with TEAEs by worst severity
- n (%) of subjects with TEAEs leading to dose modification *)
- n (%) of subjects with TEAEs leading to permanent stop of study medication *)

Serious Adverse events:

- n (%) of subjects with SAEs *)
- n (%) of subjects with NTESAEs *)
- n (%) of subjects with TESAEs *)
- n (%) of subjects with TESAEs leading to death *)
- n (%) of subjects with TESAEs by highest causality to study medication
- n (%) of subjects with TESAEs by worst severity
- n (%) of subjects with TESAEs leading to permanent stop of study medication *)

*) the number of events (i.e., number of coded preferred terms) will also be given.

TEAEs/TESAEs leading to dose modification will be defined as all events with 'Action taken with study treatment' is not equal to 'DOSE NOT CHANGED'.

In addition, the number of TEAEs will be displayed for the following investigator's ratings:

- severity
- seriousness
- causality
- action taken
- outcome

Detailed display of adverse events

For a more detailed display, adverse events will be presented in summary tables, listing these events in code form according to the preferred term. These tables will show the number of subjects per group presenting an adverse event and the incidence of its occurrence. Adverse events will be grouped by primary SOC (System Organ Class) and will be stratified additionally by highest causality to study treatment (not related, doubtful, possible, probable, or very likely) and by worst severity (mild, moderate, or severe). The incidence of adverse events will be presented by decreasing order of frequency at preferred term level within the primary SOC.

The following tables will be provided for the detailed display of adverse events:

Adverse events:

- TEAEs by primary SOC and preferred term *)
- TEAEs by primary SOC and preferred term stratified by highest causality
- TEAEs by primary SOC and preferred term stratified by worst severity
  - thereof
    - Drug related TEAEs
    - Not drug related TEAEs
- TEAEs leading to permanent stop of study medication by primary SOC and preferred term *)

Serious Adverse events:

- TESAEs by primary SOC and preferred term *)
- TESAEs by primary SOC and preferred term stratified by highest causality
- TESAEs by primary SOC and preferred term stratified by worst severity
- TESAEs leading to permanent stop of study medication by primary SOC and preferred term *)
- TESAEs leading to death by primary SOC and preferred term *)

Not treatment emergent adverse events:

- NTEAEs by primary SOC and preferred term *)

*) These tables will show additionally the number of events (i.e., number of coded preferred terms).

Summary tabulation of TEAEs and TESAEs by primary SOC and preferred term will also be provided for the following types of adverse events:

- injection site reactions (according to the tick box in the e-CRF)
- infections (according to the tick box in the e-CRF)
  - thereof, infections treated with oral or parenteral antibiotics
- adverse events of psoriasis (adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, inverse psoriasis, palmo-plantar psoriasis and worsening or exacerbation of psoriasis; final allocation will be performed after blinded data review).

Note that the summary tables will provide the number of subjects per event (i.e., coded as preferred term) and will also provide the number of events for certain tables.

For calculation of the number of subjects per event each preferred term will be counted only once per subject and will be linked to the primary SOC. A subject may contribute with more than one different adverse event (at preferred term level); however, a subject with more than one occurrence of the same adverse event (at preferred term level) is displayed and counted only once for this event in the tables.

Tables that are stratified by the severity of adverse events will summarize the worst severity per subject and preferred term.

Tables that are stratified by the relationship of adverse events will summarize the highest relationship per subject and preferred term.

For presentation of drug related/ not drug related adverse events the following categories will be used:

- drug related = very likely, probable, possible
- not drug related = doubtful, not related

For summarization of severity of drug related TEAEs, events with a causality assessment of 'doubtful/not related' will be excluded and the worst severity will be tabulated as described above. Summarization of severity of not drug related TEAEs will be performed likewise.

Analyses of adverse events per treatment week

The rate of TEAEs/TESAEs of special interest per subject per week for the treatment periods Week 0-32, and Week 32-64 will be estimated using Poisson regression. Tabulated summaries will also display 95% CIs for the respective rates.

The following TEAEs/TESAEs of special interest are planned to be analysed:

- infections (according to the tick box in the e-CRF)
- SOC ' INFECTIONS AND INFESTATIONS'
- SOC 'GASTROINTESTINAL DISORDERS'
- MACEs (major adverse cardiac events)
- Neoplasm
- Flushing

The final allocation of TEAEs/TESAEs of special interest will be performed after review of data from a locked data base. The planned analyses for the TEAEs/TESAEs of special interest are detailed below:

- Analyses of TEAEs/TESAEs of special interest from Week 0 to Week 32

Item	Specification
Treatment Group	GUS Starter vs. FAE Starter
Treatment Period	Week 0 to Week 32
Analysis set	Safety Analysis Set Week 24 Analysis

- Analyses of TEAEs/TESAEs of special interest from Week 32 to Week 64
  - a) subjects treated with GUS from W32 vs. subjects treated with FAE from W32

Item	Specification
Treatment Group	GUS_{resp}-GUS + $GUS_{non\text{-}resp}$-GUS + $FAE_{non\text{-}resp}$-GUS **vs.** FAE_{resp} - FAE
Treatment Period	Week 32 to Week 64
Analysis set	Study Part IIb Analysis Set

- b) all subjects treated with GUS-GUS vs. subjects on FAE-FAE vs. FAE-GUS

Item	Specification
Treatment Group	GUS_{resp}-GUS + $GUS_{non-resp}$-GUS **vs.** $FAE_{non-resp}$-GUS **vs.** FAE_{resp} - FAE
Treatment Period	Week 32 to Week 64
Analysis set	Study Part IIb Analysis Set

- c) single comparison of all 4 treatment groups

Item	Specification
Treatment Group	GUS_{resp}-GUS **vs.** $GUS_{non-resp}$-GUS **vs.** $FAE_{non-resp}$-GUS **vs.** FAE_{resp} - FAE
Treatment Period	Week 32 to Week 64
Analysis set	Study Part IIb Analysis Set

Analyses of adverse events from Week 0 to Week 64

Summary tables for TEAEs/TESAEs by primary SOC and preferred term in all subjects treated with GUS-GUS vs. subjects on FAE-FAE will also be provided for all reported AEs with onset date during the active treatment period from Week 0 through Week 56 or the respective safety follow-up period in case of early treatment discontinuation. The safety analysis set of the Week 24 analysis will be used for these analyses.

Listings

All adverse events (AEs) and serious adverse events (SAEs) will be listed in the individual subject data listings by treatment group in Study Part IIb, study center and subject number including all information documented on the respective form of the eCRF. Separate listings of subjects with the following AEs will be provided: SAEs, SAEs leading to death, AEs of severe intensity, AEs leading to permanent discontinuation of study medication.

Verbatim description of the adverse event reported by the investigator, MedDRA preferred terms and primary SOCs (system organ class) for all adverse events will be contained in the data listings. Non-treatment emergent adverse events will be flagged in the respective listings.

14.5.3 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test within the time period from Week 32 to Week 64. Reference ranges will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory item at each scheduled time. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges).

Results of tuberculosis testing, serology, urine pregnancy testing and local urinalysis (glucose, protein) will be displayed in frequency tables providing the number and percentage of subjects per category (i.e., negative or positive) at each scheduled time.

The results of all laboratory tests will be provided in individual subject data listings including the reference ranges. Abnormal values will be identified by flagging all values below and above the reference range.

A listing of subjects with any laboratory results outside the reference ranges will be provided.

For the lymphocyte count the following subjects will be listed and summarized in a frequency table:

- lowest lymphocyte count < 500/µl
- 500/µl ≤ lowest lymphocyte count <700/µl
- 700/µl ≤ lowest lymphocyte count < lower limit of normal range

Graphical presentation of quantitative laboratory data will be given by means of box plots.

14.5.4 Vital Signs

Descriptive statistics of pulse and blood pressure (systolic and diastolic) values within the time period from Week 32 to Week 64 and changes from baseline will be summarized at each scheduled time. Subjects reporting vital signs findings beyond clinically important limits will be identified using the following criteria.

Criteria for Identifying Potentially Clinically Significant Vital Signs Findings

Variable (units)	Criterion Value[a]	Change from Baseline
Systolic Blood Pressure (mmHg)	>200 <80	Increase of >40 Decrease of >40
Diastolic Blood Pressure (mmHg)	>120 <40	Increase of >30 Decrease of >30
Heart Rate (bpm)	>110 <40	

In order to be identified as an abnormality of potential clinical importance, a value would need to meet the criterion value **o**r also represent a change of at least the magnitude noted in the change column.

Vital signs values of potentially clinically significant importance will be analyzed by providing the number and percentages of subjects with values of potential clinical importance per scheduled study visit, overall during the study and with first occurrence after baseline.

14.5.5 Physical Examination

Physical examination findings within the time period from Week 32 to Week 64 will be tabulated by the body systems given in the eCRF at each scheduled time. Moreover, abnormal findings with first occurrence after baseline reported during the treatment phase and follow-up phase will be presented. Details on abnormal findings in verbatim terms will be displayed in individual subject data listings.

14.5.6 Body Weight

For body weight absolute values within the time period from Week 32 to Week 64 and changes from baseline values will be presented by descriptive statistics at each scheduled time.

14.5.7 Early Detection of Active Tuberculosis

Categorical data on early detection of active tuberculosis will be presented in a frequency table providing the number and percentage of subjects per category at each scheduled time within the time period from Week 32 to Week 64.

14.6 Analysis of MedDRA Codes

Previous / concomitant diseases (including indications for use of concomitant and other medications) and adverse events will be coded with version 19.1 of the MedDRA-dictionary.

In general, tabulation will be displayed by preferred term and primary SOC.

14.7 Analysis of WHO Drug Dictionary Codes

The use of concomitant and other medications will be coded using the WHO Drug Dictionary (version 2016/1). Medications will be tabulated by preferred name (i.e., the decode of the code which results when SEQ1 and SEQ2 are set to 01 and 001, respectively (usually resulting in a decode close to the generic drug name)) and they will be grouped by level 2 of the Anatomical Therapeutic Chemical (ATC) code. Codes being linked to more than one ATC code at this level will be assigned to one primary ATC code by medical data analysts.

15.0 Changes to Planned Analyses

This statistical analysis plan includes the following relevant changes to the planned analyses which are described in the clinical study protocol.

- A per-protocol analysis will be performed for the PASI 90, PASI 75, and DLQI 0/1 response rates (see SAP section 11.0).
- No treatment failure imputation rules will be applied (see to SAP section 13.1.5 and CSP section 11.4)

- The following additional efficacy endpoints will be defined and used for the statistical analyses:
    - The proportion of subjects achieving a 75%/90%/100% improvement of their psoriasis according to the PASI at Week 56 (PASI 75/90/100 response) compared to baseline
    - The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 56
    - The change from baseline in the individual scale scores for itch, pain and scaling of PSSD components at Week 56
    - The proportion of subjects achieving an absolute PASI score ≤1, 2, ≤3, ≤5 at Week 56
    - The proportion of subjects achieving an IGA score of cleared (0) at Week 56
    - The proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 56
    - The change from baseline of body surface area (BSA) psoriatic involvement at Week 56
    - The change from baseline in DLQI score at Week 56
    - The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 56 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
    - The proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 56 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
    - The change from baseline in the physical and mental component summary scores of SF-36 at Week 56

Any major changes to this plan after sign-off of the latest final version will be specified in the clinical study report.

16.0 Tabulation

16.1 General

The statistical output will be prepared in American English. No separate statistical report will be written.

16.2 Format of Data Displays

The layout of all tables, listings and figures will be drafted by acromion GmbH when providing the first draft tables, listings and figures on final data. No sponsor or other requirements for layout specifications have to be followed.

The SAS outputs will be post-processed within Microsoft Word®. SAS tables and listings will be integrated into Microsoft Word® using the SAS Monospace 8 points font.

Separate appendices will be provided for tables, listings, and figures. For each appendix a corresponding table of contents will be generated. All pages within one appendix will be numbered consecutively. Tables, listings and figures generally should be self-explaining. Abbreviations will be described in the footnote if necessary.

16.2.1 Tables

SAS summary tables will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

16.2.2 Listings

SAS subject data listings will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

Data listings will be created for groups of variables which logically belong together (e.g. demographic variables) and will be sorted by treatment group, center, subject and visit (if applicable).

16.2.3 Figures

Figures will be created using the following graphical SAS options, if not otherwise specified:

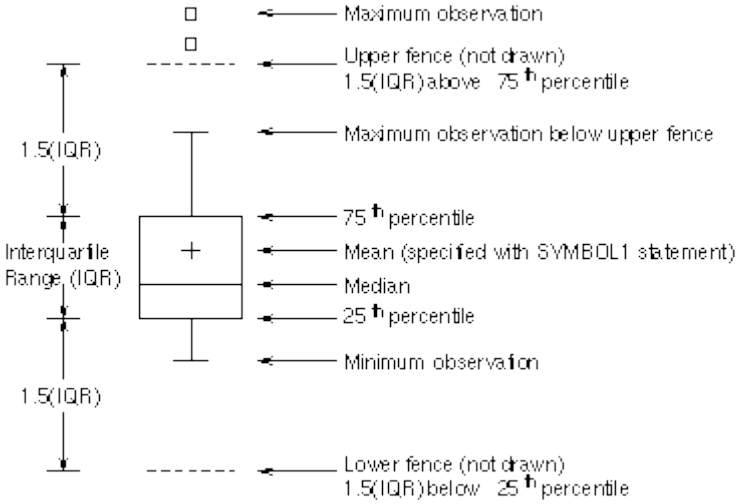
```
GOPTIONS
   RESET   = ALL
   NOBORDER
   KEYMAP = WINANSI
   DEVMAP = WINANSI
   DEV      = EMF
   TARGET = WINPRTC
   GUNIT   = CM
   CTEXT   = BLACK
   FTEXT   = 'Arial/bold'
   HTEXT   = 0.5 CM
   LFACTOR= 1
   HSIZE   = 6 IN
   VSIZE   = 5 IN;
```

Variables may be presented in the following graphical formats, if applicable:

Box plot

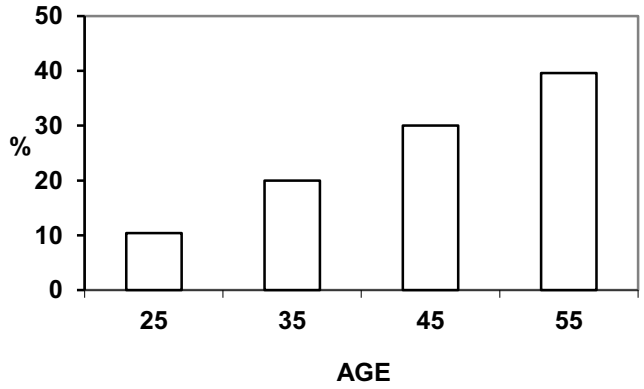
Box plots summarize the data by a box reaching from the 1st to the 3rd quartile. The median is displayed inside this box by a horizontal line. Above the box a vertical line indicates the region from the 3rd quartile to the max. value below the upper fence ; below the box a vertical line indicates the region from the 1st quartile to the min. value above the lower fence. The upper fence lies 1.5 interquartile-ranges above the 3rd quartile, the lower fence lies 1.5 interquartile ranges below the 1st quartile. Values outside the fences are displayed by a distinct marker.

A graphical presentation is given below:



Bar chart

A bar chart displays a categorical variable. A sample display is provided below.



16.3 Data Format

Unless otherwise specified, percentage values will be printed with one digit to the right of the decimal point.

In general, minima and maxima will be quoted to the number of decimal places as recorded in the eCRF; means, standard deviations and medians will be quoted to one further decimal place.

All p-values will be given by four digits to the right of the decimal point. Verbatim terms documented in the eCRFs will be presented as entered in the clinical data base.

17.0 References

Study Documents:

Document	Version, Date
Protocol / Amendments	Version 2.0, 25-APR-2017
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan - Week 24 Analysis	Version 1.0, 10-JUL-2017

SOPs and Guidelines acromion:

Document	Title, Date
acromion SOP BM04	Statistical Analysis Plans, Oct-2016
acromion SOP BM05	Determination of Availability of Data for Analysis, Oct-2016
acromion SOP BM06	Generation and Release of Blinded Randomization Code, Oct-2016
acromion SOP BM07	Programming of Derived Data Sets, Oct-2016
acromion SOP BM08	Programming of SAS Data Displays, Oct-2016
acromion SOP BM11	Documentation and Project Close-Out, Oct-2016
acromion Guideline BM01	SAS Programming Guideline, Oct-2016
acromion Guideline BM02	Biometrics Naming Conventions for SAS Datasets and SAS Programs, Oct-2016

Other Documents:

Document	Title, Date
ICH Guideline E 9	Statistical Principles for Clinical Trials, final approval 1998

18.0 Appendices

18.1 Table of Contents for Data Displays

The tables, subject data listings and figures will be provided using the following numbering system, which will be updated after start of programming the data displays.

All summary tables will start with the one-character identifier for the displayed analysis set followed by the one-digit identifier for the displayed analysis chapter as listed below.

Identifier for displayed analysis set:

- **A**: Study Part IIb analysis set
- **B**: Study Part IIb per-protocol analysis set
- **C**: Study Part I safety analysis set

Identifier for displayed analysis chapter:

- **1**: Study subjects
- **2**: Demographics and other baseline characteristics
- **3**: Treatment compliance
- **4**: Analysis of efficacy
- **5**: Analysis of safety

Data displays will be provided for the following analysis sets:

Chapter No.	Chapter Title	Analysis set
1	Study subjects	• A: Study Part IIb analysis set
2	Demographic and other baseline characteristics	• A: Study Part IIb analysis set
3	Treatment compliance	• A: Study Part IIb analysis set
4	Analysis of efficacy	• A: Study Part IIb analysis set • B: Study Part IIb per-protocol analysis set • C: Study Part I safety analysis Set
5	Analysis of safety	• A: Study Part IIb analysis set • C: Study Part I safety analysis Set

All individual subject data listings will start with the one-digit identifier for the displayed chapter analogously as for the summary tables. Data displays and subject data listings will be provided in separate appendices and pages will be numbered for each appendix separately starting with page no. 1.

18.1.1 Tables

Study Subjects, Prefix A

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics, Prefix A

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance, Prefix A

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy, Prefix A, B, C

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90% Response
4.2.1	PASI 75% Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)
4.5	Additional Efficacy Analyses (PASI, DLQI, PSSD)

Analysis of Safety, Prefix A, C

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight
5.7	Early Detection of Active Tuberculosis

18.1.2 Listings

Study Subjects

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study treatment
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer

Treatment Compliance

No.	Analysis Chapter
3.1	Visit windows
3.2	Study medication

Analysis of Efficacy

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90% Response
4.2.1	PASI 75% Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Clinical Laboratory Tests
5.4	Vital Signs
5.5	Physical Examination
5.6	Body Weight
5.7	Early Detection of Active Tuberculosis

18.1.3 Figures

Analysis of Efficacy, Prefix A, B, C

No.	Analysis Chapter	Type of Figure
	- Other Secondary Endpoints -	
1	PASI 90% Response	Bar Chart, Survival Graph
2.1	PASI 75% Response	Bar Chart, Survival Graph
2.2	DLQI 0/1 Response	Bar Chart, Survival Graph
3.1	Other Endpoints related to PASI	Bar Chart, Survival Graph
3.2	Endpoints related to PSSD	Box Plot
3.3	Endpoints related to IGA	Bar Chart
3.4	Endpoints related to BSA	Box Plot
3.5	Other Endpoints related to DLQI	Bar Chart
3.6	Endpoints related to ss-IGA	Bar Chart
3.7	Endpoints related to SF-36	Box Plot
	- Other Efficacy Assessments -	
4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)	Bar Chart, Box Plot
	- Additional Efficacy Analyses -	
5	Additional Efficacy Analyses (PASI, DLQI, PSSD)	Bar Chart, Box Plot

Analysis of Safety, Prefix A

No.	Analysis Chapter	Type of Figure
5	Clinical Laboratory Tests	Box Plot
6	Vital Signs	Box Plot
7	Body Weight	Box Plot

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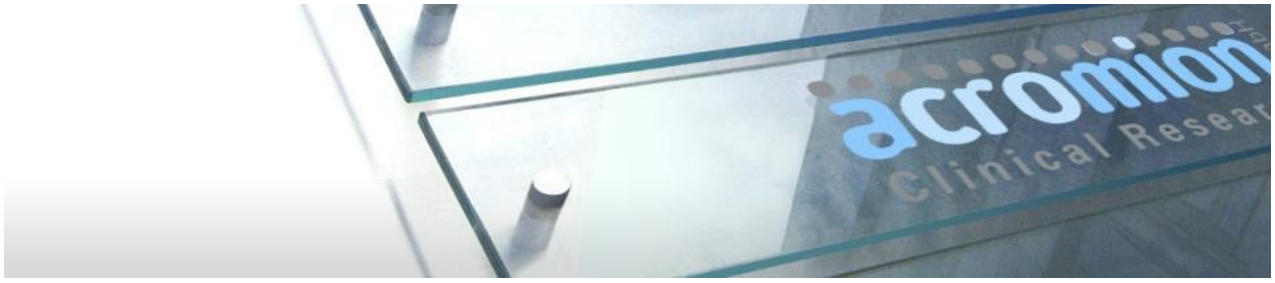

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Statistical Analysis Plan

Multicenter, randomized, open-label, efficacy assessor-blinded, active comparator-controlled phase 3b study to compare the efficacy of guselkumab to fumaric acid esters (Fumaderm® initial/ Fumaderm®) for adult patients with moderate to severe plaque psoriasis who are candidates for and naive to systemic treatment

POLARIS

- Study Part III: Week 100 Analysis -

Study Code	CNTO1959PSO3008
EudraCT Number	2016-002135-15
Development phase	Phase 3b
Study Design	randomized, open-label, efficacy assessor-blinded, single country, multicenter, active-comparator-controlled
Sponsor	Janssen-Cilag GmbH, Neuss Johnson & Johnson Platz 1, 41470 Neuss, Germany
Contract Research Organization	acromion GmbH Europaallee 27 – 29 50226 Frechen, Germany
Version No., Date	Final Version 1.0, 09-May-2019

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1.0 Signatures

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2.0 List of Abbreviations

ADR	Adverse Drug Reaction
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CRF	Case Report Form(s)
CSP	Clinical Study Protocol
DLQI	Dermatology Life Quality Index
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
e.g.	example given
FAE	Fumaric Acid Esters
FSV	Final Study Visit
HBV/ HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICH	International Council on Harmonization
i.e.	that is
IGA	Investigator´s Global Assessment
IL	Interleukin
LOCF	Last Observation Carried Forward
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PRO	Patient-Reported Outcome(s)
PSSD	Psoriasis Symptom and Sign Diary
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SC	subcutaneous
SF-36	Short Form (36-item) health survey
SOC	System Organ Class
SOP	Standard Operating Procedure
ss	scalp-specific
TB	tuberculosis
TES	Time and Events Schedule

3.0 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 and the relevant acromion SOPs and/or guidelines. This plan describes the statistical analyses planned to be performed for the Week 100 analysis (Study Part III) of Janssen-Cilag GmbH Clinical Study Protocol CNTO1959PSO3008 and should be read in conjunction with the statistical analysis plans for the Week 24 and week 64 analysis, the protocol amendments INT-1 and INT-2 to the CSP and the electronic Case Report Form (eCRF).

An overview about all planned analyses is given in Section 13.6. The Week 100 analysis summarizes the study data in Study Part III from Week 64 until Week 100 (Study Part III: follow-up extension period). All statistical analyses will be descriptive and exploratory. Statistical analyses of study data until Week 64 have been laid out in separate SAPs.

Confirmatory analyses for the primary endpoint and the major secondary endpoints were already performed at the Week 24 analysis as described in the statistical analysis plan for Week 24 (Final 1.0, 10-July-2017). Evaluations on health technology assessment (HTA) were also specified in this SAP. No separate HTA SAP was provided. Exploratory and descriptive analyses for the secondary endpoints at Week 32 and Week 56 were already performed at the Week 64 analysis and are described in the respective statistical analysis plans (Study Part IIa: Final 1.0, 15-Aug-2018; Study Part IIb: Final 1.0, 29-Aug-2018). The Week 100 analysis (Study Part III) will be performed after all subjects have completed the Week 100 visit, lost their response prior to Week 100, or have terminated the study prematurely. Data base lock for the Week 100 analysis will be after the Final Study Visit (FSV) /Week 100 visit data are ready for statistical analysis (ie, clean data).

This SAP is the core document for all statistical programming planned to be performed for the Week 100 analysis (Study Part III) and is based on the following study documents to protocol no. CNTO1959PSO3008:

Document	Version, Date
Protocol / Amendments	Version 1.0, 03-AUG-2016
	Protocol Amendment INT-1, Version 2.0, 25-APR-2017
	Protocol Amendment INT-2, Version 3.0, 25-JAN-2018
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan - Week 24 Analysis (Study Part I)	Version 1.0, 10-JUL-2017
Statistical Analysis Plan - Week 32 Analysis (Study Part IIa)	Version 1.0, 15-AUG-2018
Statistical Analysis Plan - Week 64 Analysis (Study Part IIb)	Version 1.0, 29-AUG-2018

Note: In the following text the term 'Week 100' always includes the Final Study Visit Part III (FSV) according to the documentation in the eCRF (i.e. Week 100 = Week 100 /FSV) even if the study was completed before W100 (i.e., subjects meet the definition of loss of response).

4.0 Responsibilities

The responsibilities for the biometrical tasks at acromion GmbH are assigned as follows:

Name	Function	Task
[redacted]	Statistician	Statistical Programming and Analysis
	Statistician	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Statistical Programmer	Statistical Programming and Analysis
	Medical Data Analyst	Medical Data Review and Coding

5.0 Software Utilized

The statistical analysis and generation of tables, patient data listings and figures will be performed using the SAS® software package version 9.4 under the Microsoft Windows® 7 operating system at the computer facilities of acromion GmbH. Additional analyses regarding health technology assessment (HTA) may be performed by or under the responsibility of Janssen-Cilag GmbH.

6.0 Coding Systems Utilized

The MedDRA-dictionary version 19.1 is used for coding of prior and concomitant diseases and for coding of adverse events. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Medical History of Interest	Medical History Term	MH/MHTERM
Previous Phototherapy	Type of Phototherapy	MH/MHTERM
Concomitant Medication	Indication	CM/CMIND
Concomitant Therapy	Indication	CM/CMIND
Concomitant Therapy	Therapy	CM/CMTRT
(S)AE	Term	AE/AETERM

Prior and concomitant medications are coded according to the WHO terminology using the 2016/1 version of the WHO-Drug Dictionary. The following items are coded.

eCRF Module	Item	SDTM Domain/ Variable Name
Previous Topical Therapy	Medication/Therapy	MH/MHTERM
Concomitant Medication	Compound	CM/CMTRT

Details are specified in the Data Management Plan.

7.0 Study Objectives and Hypotheses

7.1 Objectives

Primary Objectives

The primary objectives of the study are

- to compare the efficacy of guselkumab to fumaric acid esters (FAE) in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.
- to assess the safety and tolerability of guselkumab in systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis.

Secondary Objectives

The secondary objectives of the study are

- in Study Parts I and II: to compare improvement of health-related quality of life (QOL) and other patient-reported outcomes (PRO) when systemic treatment-naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.
- in Study Part II: to compare sustainability of response to treatment when systemic treatment naïve subjects with moderate to severe plaque-type psoriasis are treated with guselkumab compared to FAE.
- in Study Part III (guselkumab withdrawal): to investigate the maintenance of response in subjects withdrawn from study treatment, and to explore prediction parameters of disease modification.

7.2 Hypotheses

The primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

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

8.0 Study Endpoints

This section provides a description of all study endpoints as pre-specified in the CSP (Protocol Amendment INT-2) for the Week 24, the Week 64, and the Week 100 analyses.

Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 90% improvement of their psoriasis according to the Psoriasis Area and Severity Index (PASI 90 response) at Week 24.

Secondary Endpoints

The major secondary endpoints are:

- The proportion of subjects achieving at least a 75% improvement of their psoriasis according to the PASI (PASI 75 response) at Week 24
- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

Other secondary endpoints are:

- The proportion of subjects achieving a 100% improvement of their psoriasis according to the PASI (PASI 100 response) at Week 24
- The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 24
- The change from baseline in the individual scale scores for itch, pain and scaling of PSSD components at Week 24
- The proportion of subjects achieving an absolute PASI score ≤1 at Week 24
- The proportion of subjects achieving an IGA score of cleared (0) at Week 24
- The change from baseline of body surface area (BSA) psoriatic involvement at Week 24
- The change from baseline in DLQI score at Week 24
- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 24 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
- The change from baseline in the physical and mental component summary scores of SF-36 at Week 24
- Maintenance of response.
  - Proportion of subjects with a
    - PASI 75 response at Week 32 who maintain response at Week 56
    - PASI 90 response at Week 32 who maintain response at Week 56
    - DLQI score 0 or 1 at Week 32 who maintain response at Week 56
  - Proportion of subjects with a
    - PASI 75 response (compared to baseline) at Week 56
    - PASI 90 response (compared to baseline) at Week 56
    - PASI 100 response (compared to baseline) at Week 56
    - DLQI score 0 or 1 at Week 56
  - Proportion of subjects with a
    - PASI 75 response (compared to baseline) at Week 32
    - PASI 90 response (compared to baseline) at Week 32
    - PASI 100 response (compared to baseline) at Week 32
    - DLQI score 0 or 1 at Week 32
  - Maintenance of response after guselkumab withdrawal. Proportion of subjects of the guselkumab group (GUS-GUS and FAE-GUS) with a
    - PASI 90 response at Week 56 who maintain response at Week 100 (PASI ≤5)
    - Time to loss of response (PASI >5) from Week 56 after guselkumab withdrawal at Week 100
- Safety and tolerability data will be summarized using descriptive statistics

9.0 Study Design

This section provides a description of the study design as defined in the CSP (Protocol Amendment INT-2) for the Week 100 analysis.

The description is written in future tense according to the wording in the CSP, even though some of the planned actions, analyses and procedures have been carried out meanwhile.

Note: References to 'Section' always refer to the respective section in the CSP (Protocol Amendment INT-2).

9.1 Overview

This is a randomized, open-label, efficacy assessor-blinded, single country, multicenter, active comparator-controlled phase 3b study of guselkumab in adult subjects with moderate to severe plaque-type psoriasis who have not yet received any systemic therapy. The study will be performed at about 30 to 45 sites in Germany.

This study will have a 3-week screening phase, a 56-week treatment phase and a safety follow-up phase until Week 64, followed by a follow-up extension phase after withdrawal of guselkumab until loss of response or until Week 100 at the latest (as shown in Figure 1). The maximum duration of a subject's participation in this study will be 103 weeks. With protocol Amendments INT-1 and INT-2, the study will be split into three parts (Study Part I, II and III):

Study Part I (Core Study)—Week 0 through Week 24:

Subjects will be randomized in a 1:1 ratio to either the study drug (guselkumab) or to the active comparator (FAE). Efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd PSSD 7-day version, and 3rd SF-36), and subsequently, in Study Part I and II, by a blinded efficacy assessor (BSA%, IGA, ss-IGA, and PASI). Preferably the same efficacy assessor continues evaluation of the disease in Study Part III, but efficacy assessments are no longer blinded.

A subject will be considered to have completed Study Part I if he or she has completed assessments at Week 24 of the open-label phase. For subjects who discontinue study treatment or withdraw from study participation in Study Part I or who do not enter Study Part II, a safety follow-up visit (Study Part I) will be performed at Week 32 or 12 weeks after the last treatment (whatever comes first). For subjects enrolled in Study Part I only, maximum duration of study participation will be 35 weeks.

Study Part II (Extension, Continuation/Switch of Study Treatment)—Week 24 through Week 56

Subjects may enter the study extension at Week 24 only when the ICF for Study Part II was signed before or at Week 24, study treatment was not terminated prior to Week 24 and no protocol-prohibited medication/therapy was started. Study Part II is subdivided in two treatment periods:

- Part IIa – Week 24 through Week 32: All subjects who enter Study Part II will continue their assigned treatment (guselkumab or FAE) from Week 24 through Week 32. Study Part IIa is considered completed when the subject has completed assessments at Week 32.
- Part IIb – Week 32 through Week 56: Following Week 32, subjects with PASI 75 response will continue assigned treatment (guselkumab or FAE). For PASI 75 non-responders at Week 32 the following options will be available:
  - Guselkumab group: Subjects may continue guselkumab treatment, if the investigator considers therapy medically appropriate.

- FAE group: Subjects will switch to guselkumab unless barred by safety reasons (based on lab values ≥Week 28). Subjects who terminate FAE treatment prior to Week 32 cannot continue study treatment but will enter safety follow-up per protocol.

A subject will be considered to have completed Study Part II if he or she has completed assessments at Week 56 of the open-label phase. For subjects who discontinue study treatment or withdraw from study participation in Study Part II, final study assessments are obtained and a final safety follow-up visit (Study Part II) is completed at Week 64 or 12 weeks after last treatment.

For subjects completing Study Part II, and not entering Study Part III, maximum duration of study participation in this study will be 67 weeks including a 3-week screening phase.

Study Part III (Follow-up extension, guselkumab withdrawal, no study treatment)—Week 64 through Week 100

Subjects who received guselkumab in Study Part II (subjects who started guselkumab treatment at Week 0 or switched from FAE to guselkumab treatment in Week 32), had no psoriatic arthritis diagnosed at baseline and achieved a PASI 90 response at end of Study Part II (Week 56) may enter follow-up extension at Week 64. To be eligible for follow-up extension subjects must have signed ICF for Study Part III before or at Week 64, must not have started a new psoriasis treatment (including commercially available guselkumab therapy) or started any other protocol-prohibited medication/therapy. In Study Part III, subjects are withdrawn from guselkumab treatment and will be followed until loss of response (defined as an increase in absolute PASI >5), but until Week 100 at the latest, which is almost 1 year after the last guselkumab treatment at visit Week 52.

All other subjects may not enter Study Part III and complete the study at Week 64.

Efficacy assessments will be performed first by the subject him/herself, and subsequently by an efficacy assessor. Preferably, in Study Part III the same efficacy assessor as in Study Parts I and II continues evaluation of the disease, but efficacy assessments are no longer blinded.

A subject will be considered to have completed Study Part I or Study Part II if he or she has completed assessments at Week 24 and Week 56, respectively. A subject will be considered to have completed Study Part III if he or she has completed assessments at Week 100 or completed final assessments after loss of response. The maximum duration of a subject's participation will be 103 weeks including a 3-week screening phase.

Safety Follow-up Phase

- **Safety FUP (Part I) – Week 24 through Week 32**

  For subjects who complete study treatment at Week 24 a final safety follow-up visit is completed at Week 32.
- **Safety Follow-up (Part II) – Week 56 through Week 64**

  All ongoing subjects complete the safety follow-up until Week 64. For subjects who complete study treatment at Week 56 a final safety follow-up visit is completed at Week 64. For subjects entering Study Part III, the safety follow-up visit will be conducted and subjects will continue as described below.
- **Safety Follow-up after discontinuation/withdrawal – 12 weeks after last treatment**

  For subjects who discontinue study treatment or withdraw from study participation, final study assessments are obtained and a final safety follow-up visit is completed 12 weeks after the last treatment.

The efficacy of treatment will be assessed before any tests, procedures or other evaluations, first by the subject him/herself (1st DLQI, 2nd PSSD 7-day version, and 3rd SF-36), and subsequently, in Study Part I and II, by a blinded efficacy assessor (BSA%, IGA, ss-IGA, and PASI). Preferably, the same efficacy assessor continues evaluation of these outcome parameters in Study Part III, but efficacy assessments are no longer blinded.

Safety evaluations will include the monitoring of adverse events (including injection site and allergic reactions), physical examinations, measurement of body weight, vital sign measurement, clinical laboratory testing (HBV, HCV, HIV, hematology, chemistry), concomitant medication review, tuberculosis test and evaluation, urinalysis and pregnancy testing.

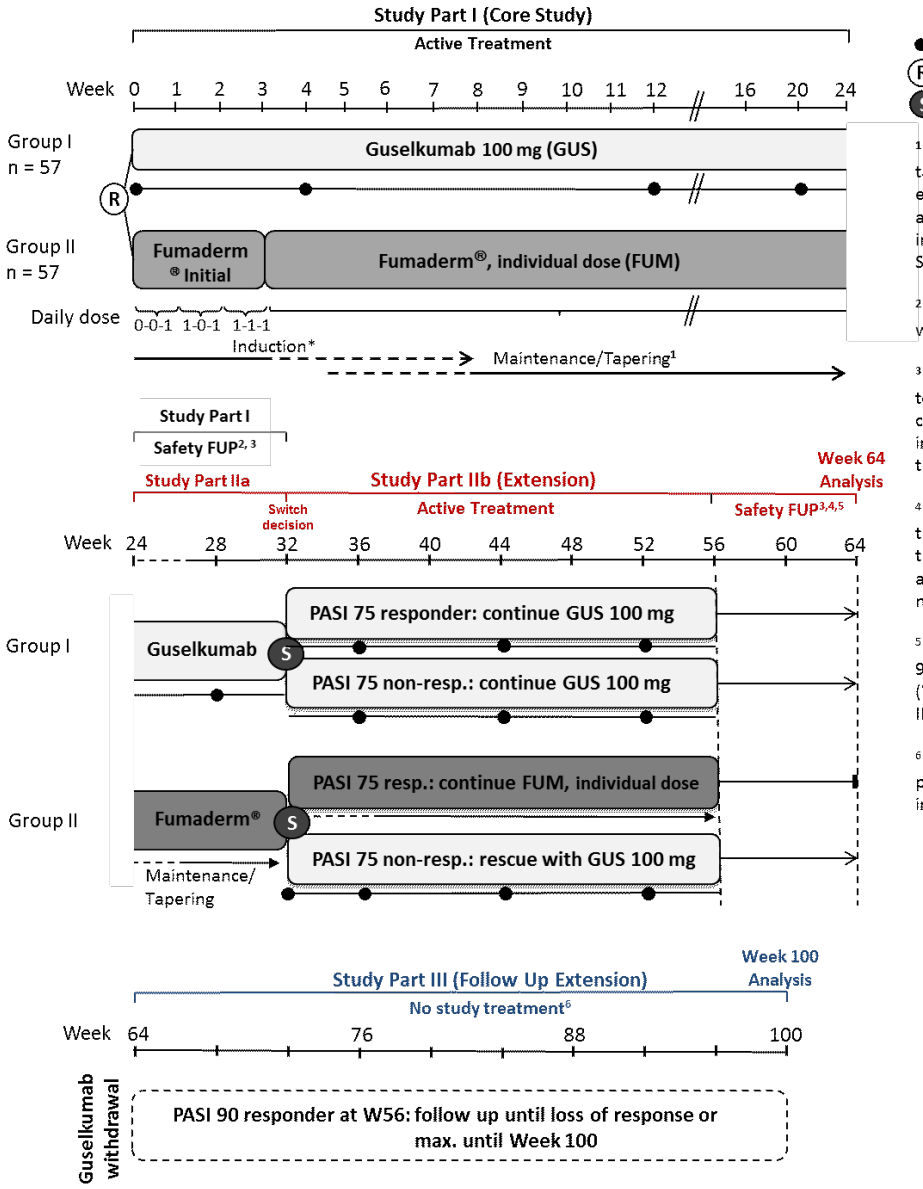
The confirmatory analysis will be conducted after the primary endpoint at Week 24 is reached including subjects who have completed the Week 24 visit and subjects who have terminated the study prematurely (Section 11.3). The second and third statistical analyses will be performed after Week 64 and after Week 100 (see Section 11).

A subject will be considered to have completed Study Part I or Study Part II if he or she has completed assessments at Week 24 and Week 56, respectively. A subject will be considered to have completed Study Part III if he or she has completed assessments at Week 100 or completed final assessments after loss of response. The maximum duration of a subject's participation will be 103 weeks including a 3-week screening phase.

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be transferred to the sponsor (or designee) after completion of the final subject visit at that site, in the time specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately 30 months (start in December 2016, stop in July 2019).

The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).

Figure 1: Schematic Overview of the Study



● Guselkumab application
Ⓡ Randomization W0
Ⓢ Switch/Treatment Decision W32

[1] The maximum daily dosage of 3 × 2 tablets Fumaderm® must not be exceeded. Fumaderm® therapy according to local prescribing information (SmPC). For details see SmPC and Section 7.

[2] Safety FUP for those subjects only who do not enter Study Part II.

[3] It is at the investigator's discretion to continue the actual therapy with commercially available drug. If it is intended to switch to another therapy, please refer to Section 6.2.

[4] Subjects who start a new psoriasis treatment or continue guselkumab treatment with commercially available drug during Safety FUP are not eligible for Study Part III.

[5] Only Gus-treated subjects with PASI 90 response at end of study Part II (Week 56) are eligible for Study Part III; please refer to Section 4.4.2.

[6] During Study Part III, use of topical psoriasis treatment is allowed at the investigator's discretion.

9.2 Sample Size Determination

As described in the CSP, the primary hypothesis of this study is that guselkumab treatment is superior to FAE (Fumaderm® initial/ Fumaderm®) treatment as assessed by the proportion of subjects achieving a PASI 90 response at Week 24.

The major secondary hypotheses are:

- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a PASI 75 response at Week 24.
- Guselkumab treatment is superior to FAE as assessed by the proportion of subjects achieving a DLQI score of 0 or 1 at Week 24.

In order to control the overall experiment wise type 1 error rate, the primary endpoint and the two major secondary endpoints will be tested in a fixed sequence as a-priori ordered hypotheses. That is, the first major secondary endpoint will be tested only if the primary endpoint is positive (i.e., $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive (i.e., $p < 0.05$). Due to the testing of ordered hypotheses, no adjustment of the significance level with respect to the threefold test procedure is required.

The assumptions for the sample size and power calculations using the threefold test procedure were based on guselkumab phase 2 data and unpublished data from the German PsoBest Registry and are as follows: PASI 90 responder rates for guselkumab and FAE in Week 24 are assumed to be 60% and 25%, respectively. PASI 75 responder rates are assumed to be 80% and 45%, respectively. DLQI responder rates are assumed to be 60% and 30%, respectively.

Based on these assumptions, with a total of 114 subjects planned to be randomized in a 1:1 ratio to guselkumab (n = 57) and to FAE (n = 57), superiority of guselkumab vs. FAE can be demonstrated at a 5% significance level (two-sided) with power of at least 90% for each test of the threefold test procedure as displayed in the table below.

Table 1: Power to detect a treatment effect on expected proportions of subjects achieving the primary and the major secondary endpoints

Order of testing	Endpoint in Week 24	Guselkumab (% responder)	FAE (% responder)	Power
1	PASI 90	60	25	97%
2	PASI 75	80	45	98%
3	DLQI 0/1	60	30	90%
type 1 error rate alpha 5% (two-sided) sequential testing with a-priori ordered hypotheses (only proceed with testing, if $p < 0.05$) sample size n = 114 with 1:1 ratio guselkumab (n = 57) and FAE (n = 57) two group chi-square test; nQuery Advisor® Release 7.0				

9.3 Randomization and Blinding

Procedures for Randomization

Central randomization is implemented in this study as described in Section 5 of the CSP. Subjects will be randomly assigned to 1 of 2 treatment groups (1:1 ratio) 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-based eCRF will assign a unique treatment code, which will dictate the treatment assignment at baseline visit of the subject. The investigator will not be provided with randomization codes. The randomization codes will be stored invisible for the investigator in a separate, blind part of the EDC (Electronic Data Capture) system.

Blinding

As this is an open study, blinding procedures for the treatment are not applicable. However, a blinded efficacy evaluator will assess effectiveness of treatment as described in Section 9.2.3 of the CSP.

10.0 Study Schedule

An overview of the study procedures is displayed in the following time and events schedule of the CSP. References to 'Section' always refer to the respective section in the CSP.

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures[b]												
Screening/Administrative												
Informed consent I (Study Part I)	X											Must be signed before first study-related activity
Informed consent II (Study Part II)	----------X											ICF addendum for Study Part II to be signed at Week 24 at the latest
Medical history and demographics	X											
Inclusion/ exclusion criteria	X	X										Minimum criteria for the availability of documentation supporting the eligibility criteria are described in protocol, Section 4; check clinical status again before first dose of study medication
Study Drug Administration												
Randomization		X										All baseline study procedures and evaluations are to be completed before randomization
Study drug administration		X[c]----------…										All study procedures and evaluations are to be completed before study drug administration

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before administration of study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

c: Subjects randomized to guselkumab will get guselkumab 100 mg on site at Weeks 0, 4, 12 and then every 8 weeks. Subjects randomized to FAEs will start with Fumaderm® initial regimen (0-0-1) at the day of the baseline visit; thereafter, FAE doses will be increased to find the optimal Fumaderm® dose for each subject as described in Section 6.

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures[b]												
h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).												
h2: Early Termination Visit: for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**												
Safety Assessments												
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Tuberculosis evaluation	X	X	X----------						….	X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Chest radiograph	X											Taken within 3 months before the first administration of study drug and read by a qualified radiologist
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	Women of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits (prior to administration of study drug).
Height		X										
Weight		X							X	X	X	
Concomitant therapy	X----------								….	X	X	
Adverse events	X----------								….	X	X	
a: To occur within 3 weeks prior to Week 0												
b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2												

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures[b]												
h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).												
h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**												
Efficacy Assessments												
DLQI	X	X		X	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit; completion of the baseline PROs has to be done before randomization
PSSD (7d)	X	X	X	X	X	X	X	X	X		X	
SF-36		X			X		X		X		X	
IGA[d]	X	X	X	X	X	X	X	X	X		X	
PASI[d]	X	X	X	X	X	X	X	X	X		X	
ss-IGA[d,e]		X			X		X		X		X	
BSA%[d]	X	X			X		X		X		X	
a: To occur within 3 weeks prior to Week 0												
b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2												
d: Dermatological evaluation of the subjects will be done by a blinded assessor starting with the Baseline visit; assessments will be done before any study related procedure will take place												
e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)												
h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).												
h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**												

Phase	Screen-ing[a]	Active Treatment								Safety FUP (Final study visit Part I)[h1]	ETV[h2]	Notes
Week	max. –3	0	2	4	8	12	16	20	24	≤32		All visits should occur within ±7 days of the scheduled visit, Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures[b]												
Clinical Laboratory Assessment												
Tuberculosis test[f]	X											
Hepatitis B and C Serologies	X											
HIV antibody test	X											
Hematology[g]	X	X	X	X	X	X	X	X	X	X	X	Laboratory tests are listed in Section 9.3
Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤ +; one re-test (central urine analysis) is allowed.

a: To occur within 3 weeks prior to Week 0

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

f: The QuantiFERON-TB Gold Plus test will generally be performed by the central laboratory; however, if available, test results from local laboratory can be accepted

g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual

h1: Safety Follow-up/Final Study Visit Part I (≤Week 32): only for subjects who do not enter Study Part II. Visit is completed at Week 32 or 12 weeks after last treatment (whatever comes first).

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
Study Drug Administration											
Study drug administration	…---------X[i]----------X										Subjects may enter the study extension at Week 24 when ICF for Study Part II was signed, study treatment was not terminated and no protocol-prohibited medication/therapy was started.
Safety Assessments											
Physical examination	X	X		X		X		X	X	X	
Vital signs	X	X		X		X		X	X	X	
Tuberculosis evaluation	……----------X								X	X	To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (Section 9.3)
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	
Weight									X	X	

b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2

h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**.

h3: Safety Follow-up/Final Study Visit Study Part II (≤Week 64): For subjects who complete Study Part II or discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).

i: Week 24 to Week 32 (Study Part IIa): subjects continue assigned treatments through Week 32. Subjects treated with 100 mg SC guselkumab continue q8w (ie, at Week 28). Subjects treated with FAE continue Fumaderm® tablets (individual dosing according to local SmPC) until Week 32.

Week 32 to Week 56 (Study Part IIb): Treatment decision based on PASI assessment at Week 32 and safety assessment (≥Week 28):

- PASI 75 responders at Week 32: subject continues assigned therapy. Subjects in the guselkumab group continue 100 mg guselkumab SC at Weeks 36, 44, 52. Subjects in the FAE group continue Fumaderm® treatment (individual dosing according to local SmPC) until Week 56.

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
- PASI 75 non-responders at Week 32: subjects in the FAE group may switch to guselkumab treatment unless barred by safety reasons (see treatment criteria Section 4.4). In case of safety concerns (based on lab values of Week ≥28), assessment can be repeated before Week 32. Subjects will receive guselkumab SC at Weeks 32, 36, 44 and Week 52. Non-responders in the guselkumab group may continue guselkumab (continuation of therapy is at the investigator's discretion).											
Safety Assessments (continued)											
Concomitant therapy	…----------X								X	X	
Adverse events	…----------X								X	X	
Efficacy Assessments											
DLQI	X	X	X*	X		X		X		X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any tests, procedures or other evaluations (PASI, IGA, ss-IGA, BSA) for that visit. ***ONLY applicable for subjects who switched to guselkumab at Week 32**
PSSD (7d)	X	X	X*	X		X		X		X	
SF-36		X						X		X	
IGA[d]	X	X	X*	X		X		X		X	
PASI[d]	X	X	X*	X		X		X		X	
ss-IGA[d,e]		X	X*	X		X		X		X	
BSA%[d]		X						X		X	
Study Procedures[b]											
b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2											
d: Dermatological evaluation of the subjects will be done by a blinded assessor as in Study Part I; assessments will be done before any study related procedure will take place											
e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)											
h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**.											

Phase	Active Treatment								Safety FUP (Final Study visit Part II)[h3]	ETV[h2]	Notes
Week	28	32	36	40	44	48	52	56	≤64		All visits should occur within ±7 days of the scheduled visit, Section 7
Study Procedures[b]											
h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who complete Study Part II or discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).											
Clinical Laboratory Assessment											
Hematology[g]	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X	Laboratory tests are listed in Section 9.3 **$^{\Delta}$ NOT applicable for subjects continuing guselkumab treatment since beginning of the study (Week 0)**
Chemistry[g]	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X$^{\Delta}$	X	X	
Urinalysis	X	X$^{\beta}$	X	X$^{\beta}$	X	X$^{\beta}$	X	X$^{\beta}$	X	X	Urinalysis by dipstick: glucose and protein; if there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally; here, protein and glucose levels must not exceed trace levels, eg, ≤+; one re-test (central urine analysis) is allowed. **$^{\beta}$ ONLY applicable for subjects treated with FAE**
b: All study procedures and evaluations are to be completed before the subject administers study drug. For assessments on subjects who discontinue administration of study treatments, see Section 10.2 g: All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled; fasting is not necessary; details will be provided in the Laboratory Manual h2: Early Termination Visit; for subjects who discontinue study treatment or withdraw from study participation before end of treatment, every effort should be made to conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**. h3: Safety Follow-up/Final Study Visit Study Part II ≤Week 64: For subjects who complete Study Part II or discontinue study treatment or withdraw from study participation in Study Part II. Safety FUP Part II visit is completed at Week 64 or 12 weeks after last treatment (whatever comes first).											

	Study Part II			Study Part III				
Phase	Active treatment		Safety FUP / FSV Part II	Guselkumab withdrawal			FSV[j] Part III	Notes
Week	52	56	≤64	64	76	88	≤100	After visit Week 64, all visits should occur within ±14 days of the scheduled visit, see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures								
Administrative								
Informed consent III	…----------X							ICF addendum for Study Part III signed at W64 at the latest (before efficacy assessments)
Eligibility criteria for Study Part III	…----------X							Criteria include: subject treated with Gus in Study Part II (ie, last application at W52), no PsA diagnosis at baseline, PASI 90 response at W56, no start of new psoriasis treatment including commercially available guselkumab or any other prohibited treatment/therapy before W64; details see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Drug Administration								

	Study Part II			Study Part III				
Phase	Active treatment		Safety FUP / FSV Part II	Guselkumab withdrawal			FSV[j] Part III	Notes
Week	52	56	≤64	64	76	88	≤100	After visit Week 64, all visits should occur within ±14 days of the scheduled visit, see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures								
Guselkumab	X	Not allowed for subjects participating in Study Part III						Last study drug application at W52. Subjects may start a commercially available topical psoriasis treatment at Week 64 or later at the investigator's discretion; topical corticosteroids class IV (alone or in combination) and phototherapy are prohibited
Safety Assessments								
Concomitant therapy	X, see Table 2			X---------psoriasis therapy----------X				In case any prohibited therapy is applied (for psoriasis or any other indication) the subject is withdrawn from study participation. Prohibited therapy is recorded at the end of study participation (FSV Part III). If already known, planned next psoriasis therapy is recorded at the end of study,
Physical examination	X, see Table 2				X	X	X	
Vital signs	X, see Table 2				X	X	X	
Weight	X, see Table 2							
Adverse Events/ ADRs	(S)AEs, see Table 2				(S)ADRs and death -- X			During Study Part III, Adverse Drug Reactions (ADRs) and deaths are recorded until FSV. Details see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Clinical Laboratory Assessments	X, see Table 2							No lab assessments during Study Part III

FSV=final study visit

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

j: FSV Study Part III ≤ Week 100; FSV is done at loss of response (defined as an increase in absolute PASI >5), upon withdrawal from study participation or at Week 100 at the latest.

	Study Part II			Study Part III				
Phase	Active treatment		Safety FUP / FSV Part II	Guselkumab withdrawal			FSV[j] Part III	Notes
Week	52	56	≤64	64	76	88	≤100	After visit Week 64, all visits should occur within ±14 days of the scheduled visit, see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**
Study Procedures								
Efficacy Assessments								
DLQI				X	X	X	X	**Order of assessments: 1st DLQI, 2nd PSSD, 3rd SF-36;** should be performed before any other evaluations (PASI, IGA, ss-IGA, BSA) for that visit
PSSD (7d)				X	X	X	X	
SF-36				X	X	X	X	
IGA				X	X	X	X	As only subjects treated with guselkumab may enter follow-up extension phase, efficacy assessments are not blinded during Study Part III. However, it is recommended to have the efficacy assessments done by the same assessor as in Study Parts I and II.
PASI[j]				X	X	X	X	
ss-IGA[e]				X	X	X	X	
BSA%				X	X	X	X	

e: To be performed only for those subjects with a corresponding diagnosis at baseline (Week 0)

j: FSV Study Part III ≤Week 100: FSV is done at loss of response (defined as an increase in absolute PASI >5), upon withdrawal from study participation or at Week 100 at the latest. FSV should also be performed for subjects who withdraw from study participation.

11.0 Analysis Sets

If not otherwise specified, the following study groups will be analyzed in Study Part III.

- $GUS_{withdrawal}$: PASI 90 responder GUS 'overall' withdrawal group (FAE-$GUS_{withdrawal}$ + GUS-$GUS_{withdrawal}$)
- FAE-$GUS_{withdrawal}$: PASI 90 responder FAE-GUS 'switcher' withdrawal group
- GUS-$GUS_{withdrawal}$: PASI 90 responder GUS-GUS 'non-switcher' withdrawal group

11.1 Definition of Analysis Sets

The following analysis data sets will be defined:

- **Study Part III Analysis Set**

  The Study Part III analysis set is defined as the set of all subjects receiving guselkumab treatment in Study Part IIb and who were eligible to enter Study Part III and who were withdrawn from study treatment.

- **Study Part III Per-Protocol Analysis Set**

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

Data on study subjects, demographic and baseline characteristics, as well as all efficacy and safety analyses will be analyzed for the Study Part III analysis set. A per-protocol analysis using the Study Part III per-protocol analysis set will not be performed because of the low number of subjects with major protocol deviations.

11.2 Protocol Deviations

The determination of evaluability of subjects, especially in cases of protocol deviations, withdrawals or drop-outs and the assignment of subjects to the planned analysis sets will be performed according to the requirements of the study protocol. Minor and major and potentially major protocol deviations that can be expected based on the prescriptions in the protocol were defined by Janssen-Cilag GmbH during the trial set up period and adapted during the study conduct. A detailed description of major and potentially major protocol deviation criteria is included in a separate document.

Data on subjects who had a major protocol deviation will be documented continuously by Janssen-Cilag GmbH in a Clinical Trial Management System during the trial period. Final data on major protocol deviations regarding the Week 100 analysis of Study Part III will be transferred to the data management department of acromion GmbH as Excel spreadsheets and will be further processed for statistical analysis.

11.3 Screening Failures

Not applicable for the present analysis.

12.0 Definition and Calculation of Efficacy Endpoints

The following sections provide a detailed description of the definition and the planned calculation of the efficacy endpoints as defined in the CSP. The same applies also for additional endpoints not defined in the CSP.

12.1 Involved 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).

12.2 Investigator's Global Assessment (IGA)

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

The efficacy endpoint related to the IGA score is defined below:

IGA cleared responder

Subjects who achieve an IGA score of cleared (0) will be considered IGA cleared responders.

12.3 Scalp Specific Investigator's Global Assessment (ss-IGA)

The scalp-specific (ss-)IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

The analyses for ss-IGA will be based on subjects randomized at Week 0 with baseline ss-IGA score ≥2.

ss-IGA absence of disease responder

Subjects with an ss-IGA score ≥2 at baseline who achieve ss-IGA score of absence of disease (0) will be considered ss-IGA absence of disease responders.

12.4 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.

Maintenance of response after guselkumab withdrawal

- Proportion of subjects with a PASI 90 response at Week 56 who maintain response at Week 100 (defined as an absolute PASI ≤5)
- Time to loss of response (defined as an absolute PASI >5) from Week 56 after guselkumab withdrawal at Week 100

The time to loss of response from Week 56 after guselkumab withdrawal at Week 100 will be calculated as time from Week 56 to first onset of loss of response. In the absence of documented loss of response the time will be censored at the date of Week 100 or the date of discontinuation in case of early discontinuation.

12.5 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 (e.g., not all 10 answers in the DLQI questionnaire were available) the following rules will be applied:

- 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.
- If two or more questions are left unanswered the questionnaire will not be scored.
- 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.

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12.6 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 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)

- Symptom score includes itch (Q1), pain (Q11), stinging (Q10), burning (Q9) and skin tightness (Q4).
- 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)

- Sign score includes skin dryness (Q2), cracking (Q3), scaling (Q5), shedding or flaking (Q6), redness (Q7) and bleeding (Q8).
- 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.

12.7 Short Form Health Survey (SF-36)

The Short Form Health Survey (SF-36) is a 36-item questionnaire used for subjects' self-assessment of health-related quality of life, consisting of the following 8 dimensions: 1) limitations in physical functioning due to health problems, 2) limitations in usual role activities due to physical health problems, 3) bodily pain, 4) general mental health (psychological distress and well-being), 5) limitations in usual role activities due to personal or emotional problems, 6) limitations in social functioning due to physical or mental health problems, 7) vitality (energy and fatigue), and 8) general health perception.

A physical component summary (PCS) score and a mental component summary (MCS) score can be derived. The concepts measured by the SF-36 are not specific to age, disease or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments. The estimated completion time will be 10 minutes.

Each of these 8 scales (domains) is scored from 0 to 100 with higher scores indicating better health. Based on the scale scores, the summary scores, PCS and MCS, will be derived. These summary scores are also scaled with higher scores indicating better health.

The QualityMetric Health Outcomes™ Scoring Software 5.0 offered by QualityMetric Incorporated will be used to score the SF-36. The Software is designed to provide users with standard scoring methods in an easy-to-use way. By using this Software, users will have the confidence that the data they obtain on their SF form are scored in accordance with standards set by the developers of the SF tools. The Software also provides evaluation of data quality and applies methods for missing data recovery. The PCS score can be calculated when seven scale scores are available and the Physical Functioning scale is not missing. The MCS score can be calculated when at least seven scale scores are available and the Mental Health scale is not missing.

A more detailed description of the scoring procedure is provided in the User's Guide of QualityMetric Health Outcomes™ Scoring Software 5.0 (see especially Appendix F).

13.0 Statistical Methodology

The present Week 100 analysis summarizes the study data in Study Part III from Week 64 until Week 100. All statistical analyses will be descriptive and exploratory only.

The biometrical evaluation will be carried out by acromion GmbH under the authority of the sponsor. Statistical programming and analyses will be performed using the statistical software system SAS®.

The following sections provide a more detailed description of the planned statistical methodology.

13.1 Data Handling Rules

13.1.1 Baseline and Post-baseline Points in Time of Interest

Baseline Definition

- All Endpoints: The values of the Week 56 visit will be used as baseline values, as applicable.

Definition of Post-baseline Points in Time of Interest

The primary point in time for efficacy assessment will be the Week 100 visit (= the study visit 100 weeks after randomization) or the Final Study Visit Part III after loss of response. Secondary points in time for efficacy assessment will be the study visits scheduled at Week 64, at Week 76, and at Week 88 during the follow-up extension phase. Handling of missing values is described in SAP section 13.1.6.

The safety analysis will cover the time period from Week 64 through Week 100.

13.1.2 Definition of Within- and Between-Group Differences

Within-group differences for continuous endpoints will be computed as differences of the post-baseline visits as compared to the baseline visit (Week 56), if applicable:

- post-baseline visit minus baseline visit

The following between-group differences will be calculated, if applicable:

- $FAE\text{-}GUS_{withdrawal}$ - $GUS\text{-}GUS_{withdrawal}$

13.1.3 Visit Windows

Nominal visits (i.e., visits as recorded in the eCRF) will be used for all by-visit analyses in the study. The study visits scheduled post randomization should occur at the times delineated in the Time and Events Schedule. No visit windows will be defined and used for analysis.

13.1.4 Treatment Failure Criteria

Not applicable.

13.1.5 Treatment Failure Rules

No treatment failure rules will be applied.

13.1.6 Handling of Missing Values

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

Missing data for the efficacy endpoints at key visits Week 64, 76, 88 and 100 will be handled as follows for all exploratory inferential statistical analyses.

Missing data imputation for the efficacy endpoints at Week 64, 76, 88 and 100:

1. Nonresponder imputation (NRI) will be applied for binary endpoints
    - i.e., subjects with missing data at Week 64/76/88/100 will be considered non-responders at Week 64/76/88/100.

2. Last observation carried forward (LOCF) will be applied for continuous endpoints
    - i.e., in subjects with missing data at Week 64/76/88/100 the last available observation after Week 64 will be calculated and used for analysis for continuous response variables at Week 64/76/88/100. 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.

Sensitivity analyses with respect to the handling of missing values at Week 100 are described in SAP section 13.9.

13.1.7 Data Transformations

No data transformations (e.g. square root, logarithmic) to confirm basic statistical assumptions will be performed. All variables will be used in the analysis as reported.

13.2 Descriptive Statistics

13.2.1 Dichotomous and Categorical Variables

Categorical data will be presented in frequency tables using counts and percentages. Percentages will be based on the total number of subjects in the respective analysis set (i.e., missing values will be included in percentage calculation). Besides presentation of absolute values cross tabulation vs. baseline by study visit will be provided, if appropriate.

13.2.2 Continuous and Quasi-Continuous Variables

Standard descriptive summary statistics will be calculated for continuous and quasi-continuous variables: arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values. Besides presentation of absolute values tabulation for differences to baseline by study visit will be provided, if appropriate.

13.2.3 Graphical Presentations

Graphical presentation of pertinent data will be given by means of box plots, bar charts, and survival graphs, as appropriate. Additional forms of graphical presentations may be specified. Descriptions of graphical presentations are included in the appendix of this document.

13.3 Confirmatory Statistics

Not applicable for the present Week 100 analysis (Study Part III). The confirmatory analysis is described in the SAP for the Week 24 analysis (Final 1.0, 10-July-2017).

13.4 Exploratory Statistics

Exploratory statistical analyses will be performed for the endpoints listed under 'other secondary endpoints' relevant for Study Part III at Week 100, and at Week 64, at Week 76, and at Week 88. All confidence intervals and p-values will be calculated two-sided and will be interpreted in the exploratory sense only.

13.4.1 Binary Endpoints

For binary endpoints counts and percentage of subjects with 95% confidence intervals (95% CIs) using normal approximation will be provided.

A two-sided chi-square test will be used to compare the FAE-GUS$_{withdrawal}$ vs GUS-GUS$_{withdrawal}$ with respect to the following endpoint:

- The proportion of subjects with a PASI 90 response at Week 56 who maintain response (PASI ≤5) at Week 100

The time to loss of response from Week 56 after guselkumab withdrawal at Week 100 will be calculated as time from Week 56 to first onset of loss of response (defined as an absolute PASI >5). In the absence of documented loss of response the time will be censored at the date of Week 100 or the date of discontinuation in case of early discontinuation.

The time-to-event analysis will be performed using Kaplan-Meier product limit method. A summary table will provide the number of subjects analyzed, the 25%, 50% (median), and 75% quantiles time-to-event with 95% confidence intervals (CI). The survival curve will also be displayed graphically. The time-to-event analysis will be performed on the observed cases only (i.e., missing data will not be replaced for the time-to-event analysis).

13.4.2 Continuous Endpoints

For the change from baseline of continuous endpoints 95% confidence intervals (95% CIs) using normal approximation will be provided.

13.5 Adjustment for Covariates

Not applicable.

13.6 Main, Interim, and Final Analyses

The following analyses are planned to be performed.

1. Main Analysis (Confirmatory Week 24 Analysis)

The confirmatory main analysis was performed at the end of Study Part I, i.e., after all subjects had completed their visit at 24 weeks after randomization or discontinued earlier. This analysis, described in a separate SAP ('SAP Week 24', final version 1.0, 10-July-2017), included the confirmatory analysis of the primary endpoint and the major secondary endpoints as well as all other exploratory predefined efficacy and safety analyses until Week 24. The results of the analysis are described in the Clinical Study Report Week 24, dated 14.05.2018.

2. Interim Analysis (Exploratory Week 64 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) interim analysis will be performed at the end of Study Part II, i.e. after all subjects had completed their visits at 64 weeks after randomization or discontinued earlier. The Week 64 analysis will be split into 2 parts, the Week 32 analysis and the Week 64 analysis.

- The Week 32 analysis, described in a separate SAP ('SAP Week 32'), summarizes the study data until Week 32 (Study Part IIa; continuation of assigned treatment from Week 24 through Week 32). All statistical analyses will be descriptive and exploratory only for the predefined efficacy and safety analyses until Week 32.
- The Week 64 analysis, described in a separate SAP ('SAP Week 64'), summarizes the study data until Week 64 (Study Part IIb). The analysis will include all efficacy measures until Week 56 and safety measures until the Week 64 safety visit.

The results of the analysis are described in the Clinical Study Report Week 32, dated 15.03.2019 and in the Clinical Study Report Week 64, dated 07.05.2019

3. Final Analysis (Exploratory Week 100 Analysis)

No confirmatory analysis is planned to be performed. The (exploratory) final analysis will be performed at the end of Study Part III, i.e. after all subjects had completed their visits at 100 weeks after randomization or completed earlier (i.e., subjects meet the definition of loss of response) or discontinued earlier.

13.7 Multi-center Data

Analyses with respect to the results of the individual centers will not be performed.

13.8 Subgroup Analyses

The following subgroup analyses are planned to be performed to evaluate consistency over demographics and baseline disease characteristics:

Analyses set:

- $GUS_{withdrawal}$ group of the Study Part III analysis set

Endpoints:

- PASI 90 response at Week 56 who maintain response at Week 100 (PASI ≤5)
- Time to loss of response (PASI >5) from Week 56 after guselkumab withdrawal at Week 100

Subgroups:

- Gender
  - male
  - female
- Age at baseline Week 0 in years
  - ≤35
  - > 35
- PASI at baseline Week 0
  - < 20
  - ≥ 20
- Duration of disease in years
  - ≤ 5
  - ≤ 10
  - > 10 - ≤18
  - > 18
- BMI at baseline Week 0
  - 18.5 - < 25
  - ≥ 25 - < 30
  - ≥ 30
- PASI 100
  - at Week 24
  - at Week 56

Subgroup analyses for the efficacy endpoints will be performed using the imputation rules of missing values at Week 100 as specified in SAP section 13.1.6.

13.9 Sensitivity Analyses

An 'observed cases analysis' for all binary and continuous endpoints without substitution of missing data will be used (see SAP section 13.1.6).

14.0 Statistical Analyses

A table of contents of planned data displays is provided in section 18.1 of this document. The following sections are intended to provide more details of the planned analyses. In addition, mock tables were created and were used as template for statistical programming at the Week 24 analysis. The mock tables will be used analogously at the present Week 100 analysis of Study Part III.

Data will be appropriately summarized and analyzed using tabulation and graphs with respect to demographic/baseline characteristics and efficacy/safety observations and measurements. Standard descriptive summary statistics (i.e., n, arithmetic mean, standard deviation, median, minimum/maximum value, quartiles) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. In general, summary tables will be displayed for the total sample in the respective analysis set. Additional classification variables or statistical analyses on subgroups are explicitly mentioned in the following text. Individual subject data listings will be presented parameter wise and will be sorted by treatment group (in Study Parts I and II), center, subject number and study visit, if applicable.

14.1 Study Subjects

Unless otherwise specified, data on study subjects will be analyzed based on data from all subjects who entered Study Part III ('Study Part III analysis set').

14.1.1 Disposition of Subjects

The overview of subject disposition from Week 0 to Week 32, from Week 32 to Week 56, and from Week 64 to Week 100 will provide the respective frequency counts and percentages regarding the following subjects:

- Treatment phase from Week 0 until Week 32
  - Subjects who were enrolled (i.e., signed informed consent Part I)
  - Subjects who were randomized
  - Subjects who were treated
  - Subjects with premature discontinuation of study treatment until Week 24
  - Subjects who completed the treatment phase until Week 24
  - Subject who entered Study Part II (i.e., signed informed consent Part II)
  - Subjects with premature discontinuation of study treatment until Week 32
  - Subjects who completed the treatment phase until Week 32
- Treatment phase from Week 32 to Week 56
  - Subjects who were treated
  - Subjects with premature discontinuation of study treatment until Week 56
  - Subjects who completed the treatment phase until Week 56
- Follow-up extension phase from Week 64 to Week 100
  - Subjects who were enrolled (i.e., signed informed consent Part III)
  - Subjects with premature discontinuation until Week 100
  - Subjects who completed the follow-up extension phase until Week 100 or due to loss of response
    - Subjects who completed the follow-up extension phase until Week 100
    - Subjects who completed the follow-up extension phase due to loss of response

The table will also include the total number of study sites and the dates of the entry of the first subject and the last visit of the last subject. A flow diagram (according to the CONSORT statement) giving an overview of subject disposition will also be provided in the clinical study report.

In addition, the number and percentage of treated/observed subjects continuing and attending by study visit will be displayed in a separate table. Subjects will be counted as continuing at the time of visit whether they attend the visit or not. Only those subjects that prematurely discontinued before the visit will not be counted as attending.

14.1.2 Discontinuation of Study

The number and percentage of subjects who discontinued the Study Part III prematurely within the time period from Week 64 to Week 100 will be tabulated for each reason of premature discontinuation (including tabulation of specifications for category 'other'). Moreover, the number of subjects not included in Study Part III will be given. Categorical data on the planned next psoriasis therapy and the planned start will be summarized in a frequency table providing the number and percentages of subjects within each category.

14.1.3 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 trial. Subjects with major protocol deviations will be summarized by category for all subjects in Study Part III.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

The summary table will provide the number of subjects per major protocol deviation and will also provide the number of major protocol deviations in Study Part III.

14.1.4 Analysis Sets

The number and percentage of subjects included in each analysis set, together with a breakdown of the reasons for exclusion for non-evaluable subjects, will be provided.

14.2 Demographic and Other Baseline Characteristics

Generally, assessments made at the screening visit and the baseline visit will be summarized. These assessments will include demographic characteristics and other parameters (such as medical history, diagnosis of psoriasis, concomitant diseases, and concomitant medication). Summary tables will be provided by means of descriptive statistics and frequency tables, where appropriate. Demographic and other baseline characteristics will be analyzed based on data from all enrolled subjects in Study Part III ('Study Part III analysis set').

14.2.1 Demographics

Age (categorized), gender, and race will be presented in a frequency table. Age group categories will be chosen as < 45; ≥ 45 - < 65; ≥ 65years. Descriptive summary statistics will be calculated for age, body height, body weight and body mass index (BMI).

Tables for demographic data will also be stratified by gender. Age and gender distribution will be presented in a bar chart.

Note: Age is documented as 'age at date of informed consent signature' at the screening visit. Body height and body weight data will be taken from the vital signs eCRF form at the Week 0 visit. BMI will be calculated as body weight in kg / body height in m^2.

14.2.2 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 terminology as described in SAP section 14.6. Summary tabulation will also consider whether the disease is ongoing or not at screening visit.

14.2.3 Diagnosis of Psoriasis

The time from date of initial diagnosis of psoriasis to date of screening visit will be calculated and will be displayed by descriptive statistics. If the day is unknown the day will be set to day = 1. If the month is unknown the month will be set to month = July.

14.2.4 Previous Psoriasis Therapy

No statistical analysis will be performed.

14.2.5 Substance Use

No statistical analysis will be performed.

14.2.6 Physical Examination

No statistical analysis will be performed.

14.2.7 Tuberculosis Evaluation

No statistical analysis will be performed.

14.2.8 Chest Radiograph Result

No statistical analysis will be performed.

14.2.9 Concomitant Medication and Therapy

Only topical psoriasis medication/therapy and prohibited medication (if applicable) should be documented. Other medication/therapy should not be documented in Study Part III. Analyses of concomitant medication and therapy will consider the data recorded within the time period from Week 64 to Week 100. Analyses may also be performed for subjects with and without loss of PASI response.

Concomitant Medication

The number and percentage of subjects with use of concomitant medication from Week 64 to Week 100 will be displayed in WHO-DD terminology as described in SAP section 14.7. Concomitant medication will be identified from the *Concomitant Medication* form of the eCRF.

The number and percentage of subjects with indication for concomitant medication from Week 64 to Week 100 will be displayed in MedDRA terminology as described in SAP section 14.6.

Concomitant Therapy

The number and percentage of subjects with use of concomitant therapy from Week 64 to Week 100 will be displayed in MedDRA terminology as described in SAP section 14.6. Concomitant therapy will be identified from the *Concomitant Therapy* form of the eCRF.

The number and percentage of subjects with indication for concomitant therapy from Week 64 to Week 100 will be displayed in MedDRA terminology as described in SAP section 14.6.

14.2.10 Shampoo and Moisturizer

The number and percentage of subjects with use of shampoo or moisturizer from Week 64 to Week 100 will be displayed in a frequency table.

14.2.11 Planned Next Psoriasis Therapy

The number and percentage of subjects with planned next psoriasis therapy will be tabulated by type and planned start of therapy

14.3 Treatment Compliance

Calculation of treatment compliance is not applicable because no study treatment was provided in Study Part III. Analyses of visit windows will be based on data from all enrolled subjects in Study Part III ('Study Part III analysis set').

14.3.1 Visit Windows

The number of days between the scheduled study visits and the baseline visit will be calculated using the reported visit dates per scheduled study visit and will be displayed by summary descriptive statistics from Week 64 to Week 100.

14.3.2 Study Medication

Not applicable because no study treatment was provided.

14.4 Analysis of Efficacy

All efficacy analyses will be performed for all enrolled subjects in Study Part III ('Study Part III analysis set').

All statistical analyses will be descriptive and exploratory only for the predefined efficacy analyses from Week 56 through Week 100.

Handling of missing values, exploratory statistics, subgroup analyses, and sensitivity analyses will be performed as described in detail in the following sections of this SAP:

SAP Section No.	Topic
13.1.6	Handling of missing values
13.4.1	Exploratory statistics - binary endpoints
13.4.2	Exploratory statistics - continuous endpoints
13.8	Subgroup analyses
13.9	Sensitivity analyses

Data at the scheduled points Week 64, Week 76 and Week 88 during the follow-up extension period will be analyzed analogously to the Week 100 data. However, no subgroup or sensitivity analyses will be performed for these points in time.

14.4.1 Primary Endpoint

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2 Major Secondary Endpoints

14.4.2.1 Endpoint related to PASI

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.2.2 Endpoint related to DLQI

Not applicable for the present analysis. The confirmatory statistical analysis was already performed at the Week 24 analysis.

14.4.3 Other Secondary Endpoints

The following sections provide a description of the planned statistical analyses of the other secondary endpoints as reported in the CSP and as well as of additional endpoints for Study Part III not explicitly stated in the CSP (see SAP section 15.0).

14.4.3.1 Endpoints related to PASI

Other secondary endpoints related to PASI are:

- The proportion of subjects achieving an absolute PASI score ≤1, ≤2, ≤3 at Week 100
- The proportion of subjects with a PASI 90 response at Week 56 who maintain response (PASI ≤5) at Week 100
- The proportion of subjects with a PASI 90 response at Week 56 who maintain PASI 90 response at Week 100
- Time to loss of response (PASI >5) from Week 56 after guselkumab withdrawal

The proportion of responding 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. The time to loss of response will be analyzed using Kaplan-Meier product limit method.

Exploratory statistical analyses will be performed as described in SAP section 13.4.1.

14.4.3.2 Endpoints related to PSSD

Other secondary endpoints related to PSSD are:

- The change from baseline (Week 56) in the signs and symptoms aggregate scores of the PSSD at Week 100

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 100 value and the change from the baseline value will be displayed.

Exploratory statistical analyses will be performed as described in SAP section 13.4.2.

14.4.3.3 Endpoints related to IGA

Other secondary endpoints related to IGA are:

- The proportion of subjects achieving an IGA score of cleared (0) at Week 100.

The proportion of responding 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.

Additional exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 100 will be analyzed analogously.

14.4.3.4 Endpoints related to BSA

Other secondary endpoints related to BSA are:

- The change from baseline (Week 56) of body surface area (BSA) psoriatic involvement at Week 100

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 100 value and the change from the baseline value will be displayed.

Exploratory statistical analyses will be performed as described in SAP section 13.4.2.

14.4.3.5 Endpoints related to DLQI

Other secondary endpoints related to DLQI are:

- The proportion of subjects achieving a DLQI score of 0 or 1 at Week 100
- The change from baseline in DLQI score at Week 100
- The proportion of subjects with a DLQI score 0 or 1 at Week 56 who maintain response at Week 100

The proportion of responding 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.

The change from Week 56 will be summarized by descriptive statistics using appropriate tabulation and box plots. The Week 56 value, the Week 100 value and the change from the Week 56 value will be displayed.

Additional exploratory statistical analyses will be performed as described in SAP sections 13.4.1 and 13.4.2.

14.4.3.6 Endpoints related to ss-IGA

Other secondary endpoints related to ss-IGA are:

- The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 100 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline

The proportion of responding 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.

Exploratory statistical analyses will be performed as described in SAP section 13.4.1.

In addition, the proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 100 will be analyzed analogously.

14.4.3.7 Endpoints related to SF-36

Other secondary endpoints related to SF-36 are:

- The change from baseline (Week 56) in the physical and mental component summary scores of SF-36 at Week 100

The change from baseline will be summarized by descriptive statistics using appropriate tabulation and box plots. The baseline value, the Week 100 value and the change from the baseline value will displayed.

Exploratory statistical analyses will be performed as described in SAP section 13.4.2.

14.4.4 Other Efficacy Assessments

In addition to the efficacy analyses described above all efficacy data related to PASI, DLQI, PSSD, IGA, ss-IGA, and SF-36 at Week 56 and all scheduled study visits during the follow-up extension period from Week 64 until Week 100 will be summarized descriptively without any imputation of missing data ('observed cases analysis'; see SAP section 13.1.6). For binary endpoints summary results using nonresponder imputation will also be provided.

14.5 Analysis of Safety

All safety analyses will be performed for all enrolled subjects in Study Part III ('Study Part III analysis set').

14.5.1 Extent of Exposure

Not applicable because no study treatment was administered.

14.5.2 Adverse Drug Reactions/Death

During Study Part III, only Adverse Drug Reactions (ADRs) and deaths (regardless of causality) should be recorded until the final study visit. ADRs will be processed in the statistical analysis after coding according to the MedDRA dictionary version 19.1. Deaths were not reported during Study Part III.

All reported ADRs (i.e. those ADRs with an onset date during the follow-up extension period from Week 64 through Week 100 and those ADRs that were present before Week 64 but were ongoing at Week 64) will be included in the analysis. In addition, analyses will be perfomed for those ADRs that were present before Week 64 but were ongoing at Week 65.

14.5.2.1 Definitions

The following definitions will be applied for the analysis of Study Part III.

Crude Incidence Rate

Where percentages of subjects are reported in summary tables, incidences provide information on the proportion of subjects experiencing ADRs in relation to the total number of subjects enrolled in Study Part III, i.e., if not otherwise specified, the crude incidence rate will be used.

The crude incidence rate is defined as the number of subjects experiencing a certain ADR, divided by the number of subjects enrolled in Study Part III, regardless of duration of observation:

$$\text{Crude incidence rate} = 100 * \frac{\text{number of patients with ADRs}}{\text{number of patients enrolled}}$$

Adverse Drug Reactions

ADRs are those AEs with causality 'very likely', 'probable', or 'possible' that occurred during the follow-up extension period from Week 64 to Week 100 or those ADRs that were present before Week 64 but were ongoing at Week 64.

14.5.2.2 Analyses

Overview of Deaths from Week 64 to Week 100

A frequency table with n (%) of subjects who died will be provided.

Overview of ADRs from Week 64 to Week 100

For summary presentation of the overall ADRs experience overview, tables will be provided for ADRs and serious ADRs (SADRs) including the following information:

ADRs:

- n (%) of subjects with ADRs *)

SADRs:

- n (%) of subjects with SADRs *)
- n (%) of subjects with SADRs leading to death *)

*) the number of events (i.e., number of coded preferred terms) will also be given.

In addition, the number of ADRs will be displayed for the following investigator's ratings:

- severity
- seriousness
- causality
- action taken
- outcome

Detailed display of ADRs from Week 64 to Week 100

For a more detailed display, (S)ADRs will be presented in summary tables, listing these events in code form according to the preferred term. These tables will show the number of subjects presenting an (S)ADR and the incidence of its occurrence. (S)ADRs will be grouped by primary SOC (System Organ Class) and will be stratified additionally by highest causality to study treatment (possible, probable, or very likely) and by worst severity (mild, moderate, or severe). The incidence of (S)ADRs will be presented by decreasing order of frequency at preferred term level within the primary SOC.

The following tables will be provided for the detailed display of (S)ADRs:

ADRs:

- ADRs by primary SOC and preferred term *)

SADRs:

- SADRs by primary SOC and preferred term *)
- SADRs leading to death by primary SOC and preferred term *)

*) These tables will show additionally the number of events (i.e., number of coded preferred terms).

Note that the summary tables will provide the number of subjects per event (i.e., coded as preferred term) and will also provide the number of events for certain tables.

For calculation of the number of subjects per event each preferred term will be counted only once per subject and will be linked to the primary SOC. A subject may contribute with more than one different (S)ADR (at preferred term level); however, a subject with more than one occurrence of the same (S)ADR (at preferred term level) is displayed and counted only once for this event in the tables.

Tables that are stratified by the severity of (S)ADRs will summarize the worst severity per subject and preferred term.

Tables that are stratified by the relationship of (S)ADRs will summarize the highest relationship per subject and preferred term.

Analyses of ADRs present before Week 64 but ongoing at Week 64.

Summary tables for (S)ADRs that were present before Week 64 but were ongoing at Week 64 will be provided by primary SOC and preferred term.

Listings

All ADRs and death will be listed in the individual subject data listings by study center and subject number including all information documented on the respective form of the eCRF. Separate listings of subjects with the following ADRs will be provided: SADRs, SADRs leading to death, ADRs of severe intensity.

Verbatim description of the (S)ADR reported by the investigator, MedDRA preferred terms and primary SOCs (system organ class) for all (S)ADRs will be contained in the data listings.

14.5.3 Clinical Laboratory Tests

No lab assessments were performed during Study Part III.

14.5.4 Vital Signs

Descriptive statistics of pulse and blood pressure (systolic and diastolic) values within the time period from Week 64 to Week 100 and changes from baseline (Week 56) will be summarized at each scheduled time.

14.5.5 Physical Examination

Physical examination findings within the time period from Week 64 to Week 100 will be tabulated by the body systems given in the eCRF at each scheduled time. Moreover, abnormal findings with first occurrence after baseline reported during the treatment phase and follow-up phase will be presented. Details on abnormal findings in verbatim terms will be displayed in individual subject data listings.

14.5.6 Body Weight

No body weight measurements were performed during Study Part III.

14.5.7 Early Detection of Active Tuberculosis

Categorical data on early detection of active tuberculosis will be presented in a frequency table providing the number and percentage of subjects per category at each scheduled time within the time period from Week 64 to Week 100.

14.6 Analysis of MedDRA Codes

Previous / concomitant diseases (including indications for use of concomitant and other medications) and (S)ADRs will be coded with version 19.1 of the MedDRA-dictionary.

In general, tabulation will be displayed by preferred term and primary SOC.

14.7 Analysis of WHO Drug Dictionary Codes

The use of concomitant and other medications will be coded using the WHO Drug Dictionary (version 2016/1). Medications will be tabulated by preferred name (i.e., the decode of the code which results when SEQ1 and SEQ2 are set to 01 and 001, respectively (usually resulting in a decode close to the generic drug name)) and they will be grouped by level 2 of the Anatomical Therapeutic Chemical (ATC) code. Codes being linked to more than one ATC code at this level will be assigned to one primary ATC code by medical data analysts.

15.0 Changes to Planned Analyses

This statistical analysis plan includes the following relevant changes to the planned analyses of Study Part III which are described in the clinical study protocol.

- No treatment failure imputation rules will be applied (see to SAP section 13.1.5 and CSP section 11.4)
- The following additional efficacy endpoints will be defined and used for the statistical analyses of Study Part III:
    - The change from baseline in the signs and symptoms aggregate scores of the PSSD at Week 100
    - The proportion of subjects achieving an absolute PASI score ≤1, ≤2, ≤3 at Week 100
    - The proportion of subjects with a PASI 90 response at Week 56 who maintain PASI 90 response at Week 100
    - The proportion of subjects achieving an IGA score of cleared (0) at Week 100
    - The proportion of subjects achieving an IGA score of cleared (0) or minimal (1) at Week 100
    - The change from baseline of body surface area (BSA) psoriatic involvement at Week 100
    - The change from baseline in DLQI score at Week 100
    - The proportion of subjects achieving an ss-IGA score of absence of disease (0) at Week 100 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
    - The proportion of subjects achieving an ss-IGA score of absence of disease (0) or very mild disease (1) at Week 100 in randomized subjects with scalp psoriasis and an ss-IGA score ≥2 at baseline
    - The change from baseline in the physical and mental component summary scores of SF-36 at Week 100

Any major changes to this plan after sign-off of the latest final version will be specified in the clinical study report.

16.0 Tabulation

16.1 General

The statistical output will be prepared in American English. No separate statistical report will be written.

16.2 Format of Data Displays

The layout of all tables, listings and figures will be drafted by acromion GmbH when providing the first draft tables, listings and figures on final data. No sponsor or other requirements for layout specifications have to be followed.

The SAS outputs will be post-processed within Microsoft Word®. SAS tables and listings will be integrated into Microsoft Word® using the SAS Monospace 8 points font.

Separate appendices will be provided for tables, listings, and figures. For each appendix a corresponding table of contents will be generated. All pages within one appendix will be numbered consecutively. Tables, listings and figures generally should be self-explaining. Abbreviations will be described in the footnote if necessary.

16.2.1 Tables

SAS summary tables will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

16.2.2 Listings

SAS subject data listings will be produced using a landscape page. The maximum number of lines per page will be pagesize = 40 and the number of characters in one line will be linesize = 140.

Data listings will be created for groups of variables which logically belong together (e.g. demographic variables) and will be by treatment group (in Study Parts I and II),, center, subject and visit (if applicable).

16.2.3 Figures

Figures will be created using the following graphical SAS options, if not otherwise specified:

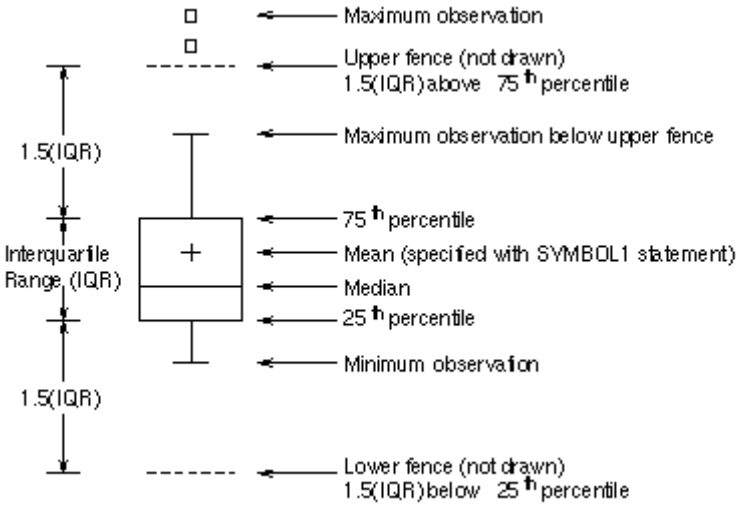
```
GOPTIONS
   RESET   = ALL
   NOBORDER
   KEYMAP = WINANSI
   DEVMAP = WINANSI
   DEV      = EMF
   TARGET = WINPRTC
   GUNIT   = CM
   CTEXT   = BLACK
   FTEXT   = 'Arial/bold'
   HTEXT   = 0.5 CM
   LFACTOR= 1
   HSIZE   = 6 IN
   VSIZE   = 5 IN;
```

Variables may be presented in the following graphical formats, if applicable:

Box plot

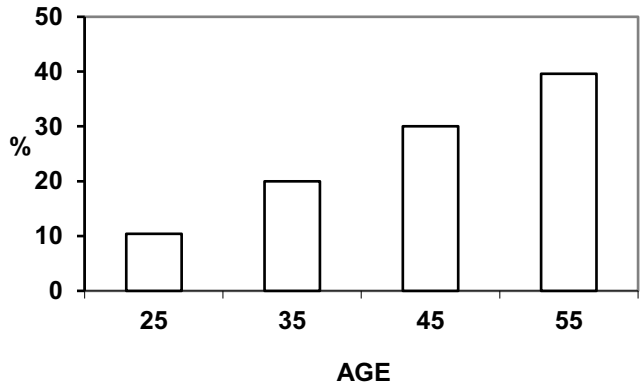
Box plots summarize the data by a box reaching from the 1st to the 3rd quartile. The median is displayed inside this box by a horizontal line. Above the box a vertical line indicates the region from the 3rd quartile to the max. value below the upper fence ; below the box a vertical line indicates the region from the 1st quartile to the min. value above the lower fence. The upper fence lies 1.5 interquartile-ranges above the 3rd quartile, the lower fence lies 1.5 interquartile ranges below the 1st quartile. Values outside the fences are displayed by a distinct marker.

A graphical presentation is given below:



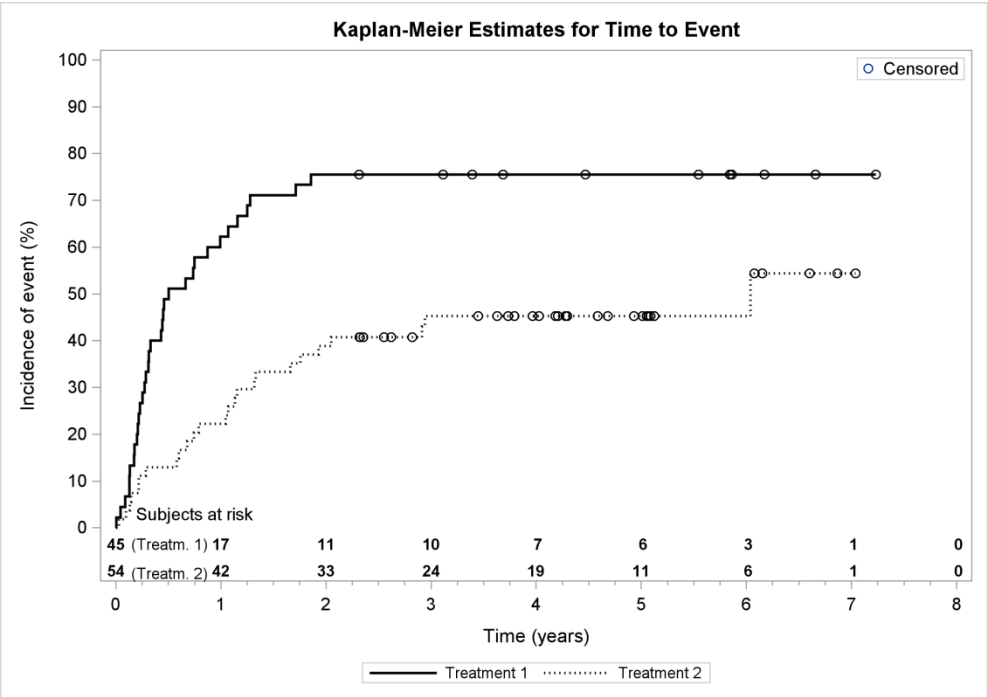
Bar chart

A bar chart displays a categorical variable. A sample display is provided below.



Survival Graph

A survival graph displays the survival distribution functions according to Kaplan-Meier. A sample display is provided below.



16.3 Data Format

Unless otherwise specified, percentage values will be printed with one digit to the right of the decimal point.

In general, minima and maxima will be quoted to the number of decimal places as recorded in the eCRF; means, standard deviations and medians will be quoted to one further decimal place.

All p-values will be given by four digits to the right of the decimal point. Verbatim terms documented in the eCRFs will be presented as entered in the clinical data base.

17.0 References

Study Documents:

Document	Version, Date
Protocol / Amendments	Version 1.0, 03-AUG-2016
	Protocol Amendment INT-1, Version 2.0, 25-APR-2017
	Protocol Amendment INT-2, Version 3.0, 25-JAN-2018
eCRF	Version 2.0, 08-JUN-2017
Data Management Plan	Version 1.0, 09-DEC-2016
Data Validation Plan	Version 1.0, 09-DEC-2016
Statistical Analysis Plan – Week 24 Analysis (Study Part I)	Version 1.0, 10-JUL-2017
Statistical Analysis Plan – Week 32 Analysis (Study Part IIa)	Version 1.0, 15-AUG-2018
Statistical Analysis Plan – Week 64 Analysis (Study Part IIb)	Version 1.0, 29-AUG-2018

SOPs and Guidelines acromion:

Document	Title, Date
acromion SOP BM04	Statistical Analysis Plans, Oct-2016
acromion SOP BM05	Determination of Availability of Data for Analysis, Oct-2016
acromion SOP BM06	Generation and Release of Blinded Randomization Code, Oct-2016
acromion SOP BM07	Programming of Derived Data Sets, Oct-2016
acromion SOP BM08	Programming of SAS Data Displays, Oct-2016
acromion SOP BM11	Documentation and Project Close-Out, Oct-2016
acromion Guideline BM01	SAS Programming Guideline, Oct-2016
acromion Guideline BM02	Biometrics Naming Conventions for SAS Datasets and SAS Programs, Oct-2016

Other Documents:

Document	Title, Date
ICH Guideline E 9	Statistical Principles for Clinical Trials, final approval 1998

18.0 Appendices

18.1 Table of Contents for Data Displays

The tables, subject data listings and figures will be provided using the following numbering system, which will be updated after start of programming the data displays.

All summary tables will start with the one-character identifier for the displayed analysis set followed by the one-digit identifier for the displayed analysis chapter as listed below.

Identifier for displayed analysis set:

- **A**: Study Part III analysis set

Identifier for displayed analysis chapter:

- **1**: Study subjects
- **2**: Demographics and other baseline characteristics
- **3**: Treatment compliance
- **4**: Analysis of efficacy
- **5**: Analysis of safety

Data displays will be provided for the following analysis sets:

Chapter No.	Chapter Title	Analysis set
1	Study subjects	• A: Study Part III analysis set
2	Demographic and other baseline characteristics	• A: Study Part III analysis set
3	Treatment compliance	• A: Study Part III analysis set
4	Analysis of efficacy	• A: Study Part III analysis set
5	Analysis of safety	• A: Study Part III analysis set

All individual subject data listings will start with the one-digit identifier for the displayed chapter analogously as for the summary tables. Data displays and subject data listings will be provided in separate appendices and pages will be numbered for each appendix separately starting with page no. 1.

18.1.1 Tables

Study Subjects, Prefix A

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics, Prefix A

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer
2.11	Planned next Psoriasis Therapy

Treatment Compliance, Prefix A

No.	Analysis Chapter
3.1	Visit windows

Analysis of Efficacy, Prefix A

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90 Response
4.2.1	PASI 75 Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)
4.5	Additional Efficacy Analyses (PASI, DLQI, PSSD)

Analysis of Safety, Prefix A

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Physical Examination
5.4	Body Weight
5.5	Early Detection of Active Tuberculosis

18.1.2 Listings

Study Subjects

No.	Analysis Chapter
1.1	Disposition of subjects
1.2	Discontinuation of study
1.3	Protocol deviations
1.4	Analysis sets

Demographic and Other Baseline Characteristics

No.	Analysis Chapter
2.1	Demographics
2.2	Medical history
2.3	Diagnosis of Psoriasis
2.4	Previous Psoriasis Therapy
2.5	Substance Use
2.6	Physical Examination
2.7	Tuberculosis Evaluation
2.8	Chest Radiograph Result
2.9	Concomitant Medication and Therapy
2.10	Shampoo and Moisturizer
2.11	Planned next Psoriasis Therapy

Treatment Compliance

No.	Analysis Chapter
3.1	Visit windows

Analysis of Efficacy

No.	Analysis Chapter
	- Other Secondary Endpoints -
4.1	PASI 90 Response
4.2.1	PASI 75 Response
4.2.2	DLQI 0/1 Response
4.3.1	Other Endpoints related to PASI
4.3.2	Endpoints related to PSSD
4.3.3	Endpoints related to IGA
4.3.4	Endpoints related to BSA
4.3.5	Other Endpoints related to DLQI
4.3.6	Endpoints related to ss-IGA
4.3.7	Endpoints related to SF-36
	- Other Efficacy Assessments -
4.4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)

Analysis of Safety

No.	Analysis Chapter
5.1	Extent of Exposure
5.2	Adverse Events
5.3	Vital Signs
5.4	Physical Examination
5.5	Early Detection of Active Tuberculosis

18.1.3 Figures

Analysis of Efficacy, Prefix A

No.	Analysis Chapter	Type of Figure
	- Other Secondary Endpoints -	
1	PASI 90 Response	Bar Chart, Survival Graph
2.1	PASI 75 Response	Bar Chart, Survival Graph
2.2	DLQI 0/1 Response	Bar Chart, Survival Graph
3.1	Other Endpoints related to PASI	Bar Chart, Survival Graph
3.2	Endpoints related to PSSD	Box Plot
3.3	Endpoints related to IGA	Bar Chart
3.4	Endpoints related to BSA	Box Plot
3.5	Other Endpoints related to DLQI	Bar Chart
3.6	Endpoints related to ss-IGA	Bar Chart
3.7	Endpoints related to SF-36	Box Plot
	- Other Efficacy Assessments -	
4	Other Efficacy Assessments (PASI, DLQI, PSSD, IGA, BSA, ss-IGA, SF-36)	Bar Chart, Box Plot

Analysis of Safety, Prefix A

No.	Analysis Chapter	Type of Figure
5	Vital Signs	Box Plot