Janssen-Cilag GmbH*, Germany

Clinical Protocol

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

AMENDMENT INT-2

CNTO1959 (guselkumab)

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

Confidentiality Statement

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TABLE OF CONTENTS

Page

LIST OF ATTACHMENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	3. August 2016
Amendment INT-1	25. April 2017
Amendment INT-2	22. January 2018

AMENDMENT INT-2

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Rationale

Amendment INT-2 is implemented to investigate maintenance of response after guselkumab withdrawal in a 36-week study extension in subjects who responded well (PASI 90 response) to guselkumab.

Implementation

Amendment INT-2 will be implemented at study sites with subjects under guselkumab treatment.

Study Design Overview

With protocol Amendment INT-2, the study will be split into three parts (Study Part I, II and III):

- **Study Part I (Core Study, Active Comparative Treatment)— Week 0 through Week 24**
  No change in treatment plan.
- **Study Part II (Extension, Continuation/Switch of Study Treatment)—Week 24 through Week 56**
  No change in treatment plan but adaption of a secondary endpoint.
- **Safety Follow-up Phase—Week 56 through Week 64**
  No change. Wording adapted for clarity reasons.
  Note: Subjects who start a new systemic psoriasis treatment including commercially available guselkumab therapy or received another protocol-prohibited medication/therapy during safety follow-up phase are not eligible to enter Study Part III.
- **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 with guselkumab from Week 0 and subjects who switched from fumaric acid esters 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 (Study Part III) subjects must not have started a new psoriasis treatment including commercial guselkumab therapy, or started any other prohibited treatment/therapy. In Study Part III, subjects are withdrawn from study 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.

Statistical Analysis

Confirmatory analysis of the primary endpoint and secondary analysis for Study Part I and II data remain unchanged. However, one secondary endpoint for Study Part II has been adapted to capture the proportion of patients with PASI 75, 90 or 100 responses throughout the study period baseline to Week 56 for all

patients enrolled. Previously this parameter was to be analyzed for subjects of the FAE group who were PASI 75 non-responders at Week 32 and switched to guselkumab, only. The final exploratory statistical analysis of Study Part III will be performed after the last subject has lost response, discontinued study participation or has completed the visit at Week 100. New secondary endpoints for exploratory analysis of study results are defined as follows.

- Proportion of subjects with a PASI 75/90/100 response compared to baseline and DLQI score 0 or 1 at Week 56
- Maintenance of PASI 90 response after guselkumab withdrawal
- Time to loss of response after guselkumab withdrawal

All significant changes to the protocol are summarized in the following table. Deleted sections are crossed out. Amended sections are presented in bold script and underlined. Additionally, minor changes to the language of the protocol and minor editorial changes are implemented with this amendment to improve clarity. Changes of minor significance are not listed below.

Applicable Section(s)	Description of Change(s)
Synopsis and Section 2.1, 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.**
Rationale: Implementation of Study Part III objectives.	

Applicable Section(s)	Description of Change(s)
Synopsis and Section 3.1, overview of study design	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 ~~67~~ **103** weeks. With protocol Amendment**s** **INT-**1 and **INT-2**, the study will be split into ~~two~~ **three** parts (Study Part I**,** ~~and~~ II **and III**): … 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 II, but efficacy assessments are no longer blinded.** … Study Part II (Extension**, Continuation/Switch of Study Treatment**)—Week 24 through Week 56 … **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 terminate 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.** **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**

Applicable Section(s)	Description of Change(s)
Synopsis and Section 3.1, overview of study design *(continued)*	**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 last treatment.** … The overall duration of the study is expected to be approximately ~~21~~ **30** months (start in December 2016, stop in **July 2019**~~October 2018~~). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES).
Section 3.1 only	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.** … 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 ~~final~~**second and third** statistical analys**e**~~is~~ will be performed after Week 64 **and after Week 100** (see Section 11).
Synopsis and Section 3.1, overview of study design	**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 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 study site, in the time specified in the Clinical Trial Agreement. The overall duration of the study is expected to be approximately ~~21~~ **30** months (start in December 2016, stop in **July 2019**~~October 2018~~). The estimated frequency and timing of the study visits are summarized in the 'Time and Events Schedule' (TES). *Note: Figure 1 has been adapted to new study design!*
Rationale: Description of new study design, safety follow-up changed for clarity reasons and adjustment of study duration.	

Applicable Section(s)	Description of Change(s)
Synopsis and Section 6, Dosage and administration	Study Part IIb, **continuation/switch of study treatment**~~active treatment~~: Week 32 through Week 56 … Subjects who complete Study Part II enter the safety follow-up phase after completion of all Study Part II assessments at Week 56. For these subjects, the safety follow-up phase spans Week 56 to Week 64. **All subjects, regardless whether they continue with Study Part III or not, complete the safety follow-up visit at Week 64. For all subjects who do not enter Study Part III, study participation** ends with ~~a~~**the** safety FUP visit at Week 64. **Subjects who discontinue study treatment or withdraw from study participation, safety follow-up visit is completed 12 weeks after last treatment.** During the safety follow-up phase treatments for psoriasis may be administered at the investigator's discretion as follows: • Group I (Gus): If commercially available, investigator may continue actual treatment with guselkumab **or switch to another commercially available treatment**. Due to the half-life of guselkumab, it is recommended not to start a new therapy **other than commercially available guselkumab** during safety follow-up period. If the investigator feels strongly that an**other** ~~additional~~ therapy is needed, this should be discussed with the sponsor before initiation of the new therapy. **Note: Subjects who start a new psoriasis treatment, including commercially available guselkumab, during safety follow-up phase are not eligible to enter Study Part III.** • Group II (FAE): Investigator may either continue the actual FAE treatment with commercially available drug or switch to another commercially available treatment. **Study Part III, follow-up extension phase, guselkumab withdrawal, no study treatment: Week 64 through Week 100** **Subjects in the guselkumab group who are eligible to enter Study Part III are withdrawn from study treatment and followed until loss of response or until Week 100 at the latest. Eligible subjects in the guselkumab group may enter Study Part III after end of safety FUP. All subjects complete the safety FUP visit and eligible subjects continue with efficacy assessments at visit Week 64. Subjects may start a commercially available topical psoriasis treatment at Week 64 or later at the investigator's discretion, except topical corticosteroids class IV (alone or in combination) and phototherapy.**
Section 6, section headings	6.1.2. Study Part IIb: **Continuation/Switch of Study Treatment** (Week 32 through Week 56) **6.1.4. Study Part III, Follow-up Extension Phase: Guselkumab Withdrawal, No Study Treatment (Week 64 through Week 100)**
Rationale: Implementation of Study Part III; additional editorial changes.	
Synopsis, Statistical methods	They will be exploratory for all other secondary endpoints including Study Part II **and Part III** endpoints.
Rationale: Implementation of Part III statistical analysis.	

Applicable Section(s)	Description of Change(s)
Synopsis and Section 9.2.2, Statistical methods and Endpoints	- 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~~**baseline**) at Week 56 - PASI 90 response (compared to ~~Week 0~~**baseline**) at Week 56 - PASI 100 response (compared to ~~Week 0~~**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 until Week 100** - **Time to loss of response from Week 56 after guselkumab withdrawal until Week 100**
Synopsis and Section 11.3, Efficacy analyses	**For all efficacy analyses in the follow-up extension phase (Study Part III; Week 100 analysis), all subjects who entered Study Part III and received guselkumab from Week 0 and subjects who received FAE from Week 0 to Week 32 and switched to guselkumab will be analyzed.**
Synopsis, DBL	Data base lock**s** (DBL) will be after the Week **24**/64/**100** visit data are ready for statistical analysis (ie, clean data). All analyses including all primary and secondary analyses as well as additional analyses as described in detail in the SAP**s** will be performed after **the respective** DBL**s.**
Rationale: Adjustment of statistical analysis to changed study design; adaption of secondary endpoint for analysis of Study Part II to capture proportion of subjects with PASI 75/90/100 response in all patients from baseline to Week 56; minor editorial changes. Statistical analyses will be performed after completion of each study part.	
Time and events schedule	*Table 2, footnote 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). **Table 3: Time and Events Schedule: Follow-Up Extension Week 64 through Week 100 (Study Part III)** *(new table describing schedule of Study Part II: please refer to table)*
Rationale: Adjustment of time and events schedule to changed study design.	
Section 1.1, Background	As of **30 June 2017**~~31 August 2016~~, ~~15~~ **18** clinical studies of guselkumab have been completed or are ongoing. ~~Seven~~ **Ten** clinical studies have been completed and eight studies are ongoing.
Rationale: Adjustment to current development; three more studies have been completed since implementation of Amendment INT-1.	
Section 1.3., Overall Rationale of the Study	**Finally, a withdrawal element has been incorporated into the study design (Study Part III) to assess the maintenance of response in subjects who discontinue guselkumab. Maintenance of response after drug withdrawal is indicative of disease modification.**
Rationale: Overall rationale for Study Part III.	

Applicable Section(s)	Description of Change(s)
Section 3.2, Study design rationale *(continued)*	To help improve objectivity and decrease bias, given the open-label design, **during Study Part I and II** efficacy assessments will be performed by a blinded assessor, meaning the assessor of dermatological evaluation will not know the treatment group the subject to be evaluated belongs to. … Part II of this study **(Week 24 to 56)** is designed to exploratorily assess the sustainability of treatment efficacy (guselkumab and FAE). … **Part III of this study (Week 64 to 100) is designed to assess the maintenance of response after guselkumab withdrawal in subjects who responded well (PASI 90 response) to guselkumab. Maintenance of response after drug withdrawal is indicative of disease modification.**
Rationale: Specification and description of rationale of new study design.	
Section 4.3, Prohibitions and restrictions	2. Agree to follow the contraceptive requirements as noted in the inclusion criteria. **Women participating in Study Part III, who are of childbearing potential (e.g. not premenarchal, not postmenopausal and not permanently sterile) and use a highly effective method of contraception, have to agree to remain on a highly effective method of contraception throughout the study.** … 4. Avoid donating blood for at least 90 days after **last study treatment** ~~completion~~ (ie, ~~final~~ **safety** follow-up visit) of the study. **Subjects entering Study Part III should avoid donating blood until end of study (Final Study Visit),.**
Rationale: Implementation of Part III restrictions regarding contraceptive requirements and caution against blood donation.	
Section 4.5, Patient eligibility	**4.5. Eligibility Criteria for Study Part III: Week 64 until loss of response or Week 100** **Subjects treated with guselkumab in Study Part II (subjects who started guselkumab treatment at Week 0 or switched from FAE to guselkumab treatment in Week 32) may enter Study Part III at Week 64 when he/she:** • **Signed ICF of Study Part III before or at Week 64** • **Achieved a PASI 90 response at the end of Study Part II (Week 56)** • **Had no diagnosis of psoriatic arthritis (PsA) at baseline** • **Did not start a new psoriasis treatment before Week 64, including commercially available guselkumab** • **Did not start any other protocol-prohibited medication/therapy** • **Is a woman and used a highly effective method of contraception during Study Part I and II and agrees to remain on a highly effective method of contraception throughout the study.**
Rationale: Definition of eligibility criteria for Study Part III.	
Section 5, Treatment allocation and blinding	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. **During Study Part III, subjects who received guselkumab during Study Parts I or II only are eligible for Study Part III. During Study Part III subjects are no longer on study treatment, thus, efficacy assessments during Study Part III are no longer blinded.**
Rationale: Description of Study Part III procedures.	

Applicable Section(s)	Description of Change(s)
Section 7, Treatment compliance	**During Study Part III visits should occur within ±14 days of the scheduled visit.**
Rationale: Sentence added to implement Part III visits.	
Section 8, Prestudy and Concomitant therapy	… **For subjects entering Study Part III, psoriasis therapy/medication will be recorded until end of study. In case any protocol-prohibited therapy is applied (for psoriasis or any other indication), the subject is withdrawn from study participation. Prohibited therapy is recorded as well as any newly planned psoriasis therapy, if already known at the end of the study.** 8.1.1. Treatment Phase … Topical therapies that could affect psoriasis (eg, 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 56, **for subjects entering Study Part III until Week 64 (see Section 8.1.2. and 8.1.3)**. …. The use of phototherapy or systemic anti-psoriatic medications is not permitted until the Week 56 visit, **for subjects entering Study Part III until end of study (see Section 8.1.2 and 8.1.3).** … 8.1.2 Safety Follow-Up Phase See section 6.1.3 for instructions regarding treatment of psoriasis during the follow-up phase. **Furthermore, for subjects to be eligible for Study Part III all psoriasis treatments/therapies, including commercially available guselkumab and topical treatments that could affect psoriasis (see Section 8.1.1), are prohibited.** **8.1.3 Follow-up Extension Phase** **During Study Part III use of commercially available topical psoriasis treatment is allowed at the investigator's discretion. However, topical corticosteroids class IV (alone or in combination) and phototherapy are prohibited until end of study (Week 100). Systemic psoriasis therapies, including commercially available guselkumab, are prohibited during Study Part III. Patients starting any protocol-prohibited therapy will be withdrawn.**
Rationale: Implementation of Study Part III documentation.	

Applicable Section(s)	Description of Change(s)
Section 9.1.1, Study procedures, overview	The **Time and Events Schedules (**TES**),** ~~positioned after the SYNPOSIS~~**, (Table 1 [Part I], Table 2 [Part II] and Table 3 [Part III])** summarize~~s the~~ frequency and timing of efficacy, immunogenicity, and safety measurements ~~applicable to~~ **performed during** this study. **All subjects will be asked to sign the consent form(s) (ICF I, II and III) before any study-related procedures of the respective study part (I, II, III) are conducted.** **Note: At the time amendment INT-1 has been implemented all subjects were enrolled and had signed the ICF established at study initiation (identical to ICF I). All subjects on study treatment were asked to acknowledge and sign ICF II for Study Part II (study extension). ICF II had to be signed by Week 24 at the latest by all subjects continuing with Study Part II.** **All subjects that might be eligible to enter Study Part III will be asked to acknowledge and sign ICF III (follow-up extension) by Week 64 at the latest.** **Adverse events and concomitant medication recording will start after ICF I has been signed and will continue until the last study-related procedure of Study Part I and II, respectively, has been completed. During Study Part III, adverse drug reactions and deaths will be recorded until end of study. Concomitant therapies will be recorded beyond Week 64 if they are in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2. In addition, any psoriasis treatment will be recorded throughout Study Part III.**
Rationale: Implementation of Study Part III procedures.	
Section 9.1.2, Study procedures, screening phase	The subjects will be asked to sign the consent form at the screening visit before any study related procedures are conducted (ICF I). ~~Note: At the time this amendment is implemented all subjects will have been enrolled and will have signed the ICF established at study initiation (identical to ICF I). All subjects on study treatment will be asked to consent ICF II for Study Part II (study extension). ICF II has to be signed by Week 24 at the latest by all patients continuing to Study Part II. FAdverse events and concomitant medication recording will start after signing the informed consent and will continue until the last study-related procedure has been completed. Concomitant therapies will be recorded beyond Week 64 if they are in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2.~~
Rationale: Editorial change, paragraph has been shifted to Section 9.1.1.	
Sections 9.1.5 and 9.1.6, Study procedures, safety follow-up and follow-up extension	Subjects will be instructed that study drug will not be made available to them after they have completed/ discontinued the drug and that they should return to their physician to determine standard of care **if not entering Study Part III.** **9.1.6. Follow-up Extension Phase after Guselkumab Withdrawal** **No study treatment is applied during the follow-up extension phase. During Study Part III, subjects may start a commercially available topical psoriasis treatment at Week 64 or later at the investigator's discretion, except topical corticosteroids class IV (alone or in combination) and phototherapy. Subjects will be followed for safety information (ie, vital signs, physical examination, ADRs and death; no laboratory assessments) and unblinded efficacy assessments as specified in the TES until loss of response or until Week 100 at the latest. Subjects starting a systemic psoriasis treatment including commercially available guselkumab or other prohibited medication/therapy will be withdrawn. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety evaluations as listed in the TES (FSV Part III, see Section 10.2).**

Applicable Section(s)	Description of Change(s)
Rationale: Implementation of Study Part III procedures.	
Section 9.2, Efficacy, Evaluations	Efficacy evaluations chosen for this study are consistent with those used to evaluate other therapies for psoriasis. Efficacy evaluations will be first done by subjects (PROs) and then by the blinded efficacy assessor **(Study Parts I and II; during Part III the assessor is no longer blinded).**
Rationale: Specification of procedures.	
Section 9.2.3, Blinded efficacy assessment	An independent, blinded efficacy assessor, approved by the Sponsor, will be designated at each study site to perform all efficacy assessments (BSA%, IGA, ss-IGA, and PASI) starting with baseline visit **until end of treatment phase (ie, Week 56)**. **As only subjects treated with guselkumab may enter the follow-up extension phase, efficacy assessments are not blinded during Study Part III.** It is recommended to have the efficacy assessments at screening be done by the same blinded assessor as the following assessments, **including assessments during the follow-up extension phase**.
Rationale: Specification of procedures.	
Section 9.3, Safety evaluations	Safety will be monitored ~~through Week 64~~**until end of study**. … Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) ~~for the duration of the study~~ **until end of Study Part II (ie, Week 64). During Study Part III (after Week 64) only adverse drug reactions and deaths will be recorded.** Adverse events/**adverse drug reactions** will be followed by the investigator as specified in Section 12.
Rationale: Implementation of Study Part III procedures.	
Section 9.3, Safety evaluations	Urine pregnancy testing is required for all women of childbearing potential at all study visits **until end of Study Part II.** … Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis will be collected **at visits specified in the TES**.
Rationale: Specification of procedures.	
Section 10.1, Completion	**A subject will be considered to have completed Study Part III when he or she has completed last assessments after loss of response, withdrawal from study participation or at Week 100 at the latest.**
Rationale: Implementation of Study Part III.	

Applicable Section(s)	Description of Change(s)
Section 10.2, Discontinuation, withdrawal	However, regular safety follow-up ends for all subjects **not entering Study Part III** at Week 64. … A subject will be withdrawn from the study for any of the following reasons: • Lost to follow-up • Withdrawal of consent • Death • **Start of a protocol-prohibited medication/therapy during Study Part III** … **A subject's study participation from Study Part III must be discontinued if a protocol-prohibited medication/therapy (for his/her psoriasis or another indication) is started before completion of the final study visit after loss of response or at Week 100.** … **Similarly, for subjects who are not eligible for Study Part III, the Study Part II safety follow-up visit (Week 64) should be performed, as indicated in the TES. For subjects not completing Study Part III, every effort should be made to conduct a final study visit (FSV Part III) as indicated in the TES.**
Rationale: Implementation of Study Part III procedures.	
Section 11, Statistical analysis	The SAP will be divided in **three**~~two~~ separate documents describing analyses for the **three**~~two~~ study parts. … The analyses will be confirmatory for the primary endpoint and the major secondary endpoints, and exploratory for all other secondary endpoints including Study Part II **and Part III** analyses.
Section 11.3 Analysis data set	**For all efficacy analyses in the follow-up extension phase (Study Part III, Week 100 analysis), all subjects who entered Study Part III and received guselkumab from Week 0 and subjects who received FAE from Week 0 to Week 32 and switched to guselkumab will be analyzed.** … The ~~final~~ **second** statistical analysis will be performed after all subjects have completed the Week 64 visit or have terminated the study prematurely. … **The third statistical analysis will be performed after all subjects have completed the Week 100 visit or have terminated the study prematurely or lost their response. Third data base lock (DBL) will be after the Final Study Visit/Week 100 visit data are ready for statistical analysis (ie, clean data). All analyses will be performed after DBL and will be described in detail in the SAP for Week 100 analysis. Following the rationale for Study Part III, the Week 100 analysis will focus on PASI 90 responders at Week 56 taking into account baseline disease characteristics and study treatment to explore prediction parameters of disease modification.**
Rationale: Implementation of Study Part III procedures.	

Applicable Section(s)	Description of Change(s)
Other secondary endpoints	The other secondary endpoints will comprise the endpoints as defined in Section 9.2.2. For the other secondary analyses including Study Part II and **Part III** analyses, the chi-square test will be used to compare the proportion of subjects responding to treatment. … **Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event.**
Rationale: Implementation of Study Part III procedures.	
Section 11.3, Primary endpoint	Graphical presentation will be presented by means of a bar chart. Subjects who ~~meet treatment failure criteria (eg, subjects who~~ discontinue study treatment or who started a protocol-prohibited medication/therapy during the study~~,~~ **(**Section 11.4, Section 8.1) before Week 24 will be considered non-responders for the primary endpoint at Week 24.
Rationale: Treatment failure criteria as previously specified in the Protocol were not used in Week 24 analysis. Analysis has been detailed in the corresponding SAP.	
Section 11.3, Subgroup analysis	Subgroup analyses will be performed to evaluate consistency of the primary endpoint and selected major secondary endpoints over demographics ~~(including baseline weight)~~ and baseline disease characteristics.
Rationale: Week 24 analyses were performed as specified in the corresponding SAP.	
Section 11.3, Missing Data	Subjects who **discontinue study treatment** ~~meet treatment failure criteria before Week 24 will be considered as non-responders at Week 24. In addition, subjects~~ or who do not return for evaluation at Week 24 **or 56** will be considered non-responders at Week 24 **or 56, respectively**.
Rationale: Treatment failure criteria as previously specified in the Protocol were not used in Week 24 analysis. Analysis has been detailed in the corresponding SAP.	
Section 11.4, Criteria for endpoints	~~Treatment Failure: 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. The treatment failure rules will be documented in detail in the SAP.~~
Rationale: Treatment failure criteria as previously specified in the Protocol were not used in Week 24 analysis. Analysis has been detailed in the corresponding SAP.	
Section 11.4, Criteria for endpoints	**Loss of Response, Study Part III: Increase in absolute PASI >5**
Rationale: Implementation of Study Part III criteria.	
Section 11.5 Safety analysis	Safety data, including but not limited to, AEs, SAEs, **ADRs, SADRs,** infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.
Analysis Data Set	~~The final safety~~ Safety analys**e**~~i~~s covering the time until ~~the~~ Week 64 **and until Week 100** safety visit**s** will be performed separately with the ~~final~~ **Week 64 and Week 100** analys**e**~~i~~s.

Applicable Section(s)	Description of Change(s)
Adverse Events/Adverse Drug Reactions	Adverse Events**/Adverse Drug Reactions** The verbatim terms used in the eCRF by investigators to identify adverse events (AEs) **or adverse drug reactions (ADRs)** will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. **(S)ADRs documented during Study Part III will be treated correspondingly.** Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious adverse event (SAE) **or serious adverse drug reaction (SADR)**. The incidence of injection site reactions, SAEs, **SADRs** and premature discontinuations due to AEs**/ADRs** will be summarized separately.
Rationale: Implementation of Study Part III.	
Section 11.6, Interim and final analyses	11.6. Interim **and Final** Analyses … The ~~final~~ **second** exploratory analysis will occur after all subjects have completed their visit at 64 weeks after randomization or discontinued earlier. This analysis will include the ~~final~~ safety analysis and all efficacy measures after Week 24 and will cover the time until the Week 64 safety visit. **The third and final exploratory analysis will occur after all subjects have completed their visit at 100 weeks after randomization or discontinued earlier. This analysis will include the safety analysis and all efficacy measures after Week 64 and will cover the time until the Week 100 safety visit.**
Rationale: Implementation of Study Part III procedures.	
Section 12, Adverse events/adverse drug reactions	adverse event**/adverse drug reaction** *(various passages in the text as applicable)* **Adverse Drug Reaction** **An ADR is defined as all untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered. 'Response to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is possible, probable, or very likely. Thus, an ADR is characterized by the fact that a causal relationship between the medicinal product and the occurrence of the event is suspected. All adverse events judged by either the investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.**
Rationale: ADRs/SADRs will be reported during Study Part III: definition added and text adjusted accordingly where applicable.	

Applicable Section(s)	Description of Change(s)
Section 12.3.1 All Adverse Events/ **Adverse Drug Reactions** and 12.3.2, Serious adverse events/ **Serious Adverse Drug Reactions**	**During follow-up extension phase (Study Part III), all adverse events suspected to be related to the use of the drug (Adverse Drug Reactions, ADRs, Section 12.1.1) and deaths are recorded until final study visit of Study Part III.** … All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, and **all adverse drug reactions regardless of seriousness and severity** must be recorded using medical terminology in the source document and the eCRF. … **During participation in Study Part III, the cause of death of a subject is also considered a serious adverse event. Death of a subject related to use of a medicinal product and meeting ADR definitions is a serious adverse drug reaction and will be reported correspondingly.**
Rationale: ADRs/SADRs will be reported during Study Part III. ADRs and subject death will be followed during Study Part III.	
Section 12.3.3, Pregnancy	Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above **until end of Study Part II**.
Rationale: Specification of procedures.	
Section 14.5, Drug accountability	**Counting remaining FAE tablets during the study visits for compliance check is not considered as a return and re-dispense.**
Rationale: Specification of procedures.	
Section 16.2.3, Informed consent	To meet the scope of this amendment ~~two~~ **three** separate ICFs have been developed to cover Study Parts I**,** ~~and~~ II **and III**. The ICF(s) must be signed before performance of any study-related activity (ICF I at screening, ICF II at Week 24 at the latest**, ICF III at Week 64 at the latest)**. … Before enrollment in the study or in Part**s** II **or III** of the study, if applicable, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail.
Rationale: Implementation of Study Part III.	
Section 17.5, Case report form completion	Results of efficacy assessments performed by the blinded efficacy assessor **(in Study Part I and II)** will be entered in the eCRF by unblinded study personnel as described in Section 9.2.3.
Rationale: Implementation of Study Part III, specification of procedures.	

SYNOPSIS

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

Protocol Number: CNTO1959PSO3008

CNTO 1959 (guselkumab) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. Guselkumab has been studied in Phase 1, 2 and 3 studies for the treatment of moderate to severe psoriasis.

EudraCT NUMBER: 2016-002135-15

OBJECTIVES AND HYPOTHESIS

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.

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

OVERVIEW OF STUDY DESIGN

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.

The maximum duration of a subject's participation will be 103 weeks including a 3-week screening phase.

Safety Follow-up Phase

- **Safety Follow-up (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 as well 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 last treatment.

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 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 study 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).

SUBJECT POPULATION

The target population comprises adult men and women with a diagnosis of plaque-type psoriasis for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by Psoriasis Area and Severity Index (PASI) >10 or involved body surface area (BSA) >10%, and Dermatology Quality of Life Index (DLQI) >10. Subjects must be naïve but candidates for systemic therapy for psoriasis, and FAE must be considered as an appropriate treatment option. Subjects with non-plaque forms of psoriasis (eg, erythrodermic, guttate or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers,

or lithium) are excluded. A total number of 114 subjects will be randomly assigned in this study with 57 subjects planned per treatment group.

DOSAGE AND ADMINISTRATION

A 100 mg/mL solution of guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUSTM Passive Needle Guard (PFS-U). Commercially available Fumaderm® initial/ Fumaderm® tablets will be supplied.

Study Part I and Study Part IIa, active comparative treatment: Week 0 through Week 24 and Week 24 through Week 32

Subjects randomized to guselkumab will receive 100 mg guselkumab SC by trained study personnel at the study site, subjects randomized to FAE will receive commercially available Fumaderm® initial/ Fumaderm® tablets intended for self-administration at home, and specifically labeled for the study.

The dose regimens are as follows:

- Group I (Gus, n = 57): 100 mg guselkumab SC at Weeks 0, 4, 12 and 20 (Study Part I); every 8 weeks, ie, at Week 28 (Study Part IIa)

Group II (FAE, n = 57): Fumaderm® initial/Fumaderm® tablets; individual dosing according to local prescribing information (SmPC) for each subject representing the optimal benefit-risk ratio; the maximum daily dosage of 3 × 2 tablets Fumaderm® must not be exceeded.

Study Part IIb, continuation/switch of study treatment: Week 32 through Week 56

Subjects with a PASI 75 response will continue treatment as before.

- Group I (Gus): continue 100 mg guselkumab SC every 8 weeks (ie. at Weeks 36, 44, and Week 52)
- Group II (FAE): continue Fumaderm® initial/Fumaderm® tablets, individual dosing according to local prescribing information (SmPC) (2)

PASI 75 non-responders will be offered treatment as follows:

- Group I (Gus): continue 100 mg guselkumab SC every 8 weeks (ie, at Weeks 36, 44 and Week 52). It is at the investigator's discretion to continue therapy, if treatment is considered medically appropriate.
- Group II (FAE): switch to 100 mg guselkumab SC at Weeks 32, 36, 44 and Week 52

Safety follow-up phase, psoriasis treatment: Week 24 through Week 32 (Study Part I) or Week 56 through Week 64 (Study Part II)

Subjects who are not eligible for Study Part II will enter the safety follow-up phase after completion of all Study Part I assessments. For these subjects, the safety follow-up phase spans Week 24 to Week 32 and ends with a safety FUP visit at Week 32.

Subjects who complete Study Part II enter the safety follow-up phase after completion of all Study Part II assessments at Week 56. For these subjects, the safety follow-up phase spans Week 56 to Week 64. All subjects, regardless whether they continue with Study Part III or not, complete the safety follow-up visit at Week 64. For all subjects who do not enter Study Part III, study participation ends with the safety FUP visit at Week 64.

Subjects who discontinue study treatment or withdraw from study participation, safety follow-up visit is completed 12 weeks after last treatment.

During the safety follow-up phase treatments for psoriasis may be administered at the investigator's discretion as follows:

- Group I (Gus): If commercially available, investigator may continue actual treatment with guselkumab or switch to another commercially available treatment. Due to the half-life of guselkumab, it is recommended not to start a new therapy other than commercially available guselkumab during safety follow-up period. If the investigator feels strongly that another therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

Note: Subjects who start a new psoriasis treatment, including commercially available guselkumab, during safety follow-up phase are not eligible to enter Study Part III.

- Group II (FAE): Investigator may either continue the actual FAE treatment with commercially available drug or switch to another commercially available treatment.

Study Part III, follow-up extension phase, guselkumab withdrawal, no study treatment: Week 64 through Week 100

Subjects in the guselkumab group who are eligible to enter Study Part III are withdrawn from study treatment and followed until loss of response or until Week 100 at the latest. Eligible subjects in the guselkumab group may enter Study Part III after end of safety FUP. All subjects complete the safety FUP visit and eligible subjects continue with efficacy assessments at visit Week 64. Subjects may start a commercially available topical psoriasis treatment at Week 64 or later at the investigator's discretion, except topical corticosteroids class IV (alone or in combination) and phototherapy.

EFFICACY EVALUATIONS

The chosen efficacy evaluations are consistent with those used to evaluate other therapies for psoriasis.

Efficacy evaluations will be first done by subjects (PROs) and then by the blinded efficacy assessor:

- Dermatology Life Quality Index (DLQI) **[PRO#1]**
- Psoriasis Symptom and Sign Diary (PSSD 7-day version) **[PRO#2]**
- Medical Outcomes Study 36-Item Short Form (SF-36) **[PRO#3]**
- Involved Body Surface Area (BSA)
- Investigator's Global Assessment (IGA)
- Scalp Specific Investigator's Global Assessment (ss-IGA)
- Psoriasis Area and Severity Index (PASI)

SAFETY EVALUATIONS

Safety evaluations will include the monitoring of adverse events (AEs), including injection site and allergic reactions, physical examinations, measurement of body weight and vital signs, clinical laboratory testing (Hepatitis B and C, HIV, hematology, and chemistry), concomitant medication review, tuberculosis (TB) test and evaluation, urinalysis, and pregnancy testing.

STATISTICAL METHODS

The statistical analyses in this study will focus on the comparison of the two randomized treatment groups (ie, guselkumab vs. FAE). The analyses will be confirmatory for the primary endpoint and for the major secondary endpoints. They will be exploratory for all other secondary endpoints including Study Part II and Part III endpoints. Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data.

The chi-square test will be used to compare the proportion of subjects responding to treatment. Continuous response parameters will be compared using an analysis of variance model with baseline value as a covariate. 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).

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
- Time to loss of response from Week 56 after guselkumab withdrawal at Week 100
- Safety and tolerability data will be summarized using descriptive statistics.

Sample size

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 (ie, $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive. 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.

Efficacy analyses

For all efficacy analyses to compare guselkumab vs. FAE in Study Part I (Week 24 analysis), all randomized subjects will be included. For all the efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized regardless of the treatment they actually received ('intent-to-treat principle'). Additionally, all efficacy analyses will be performed with all randomized subjects that received at least one dose of study drug. For all efficacy analyses to compare guselkumab vs. FAE in Study Part II (Week 64 analysis), subjects will be analyzed according to the treatment they actually received. For all efficacy analyses in the follow-up extension phase (Study Part III; Week 100 analysis), all subjects who entered Study Part III and received guselkumab from Week 0 and subjects who received FAE from Week 0 to Week 32 and switched to guselkumab will be analyzed.

Safety analyses

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

For all safety analyses to compare guselkumab vs. FAE, all randomized subjects treated with at least one dose of study drug will be included. For all the safety analyses, subjects will be analyzed according to the treatment they actually received.

Data base locks (DBL) will be after the Week 24/64/100 visit data are ready for statistical analysis (ie, clean data). All analyses including all primary and secondary analyses as well as additional analyses as described in detail in the SAPs will be performed after the respective DBLs.

Table 1: Time and Events Schedule: From Screening through Week 24 (Study Part I)

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 conduct the final assessments (Early Termination Visit) and to conduct the post-treatment assessments (Safety Follow-up), see Section 9.1.5

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]												
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 9.1.5

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 9.1.5

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	
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

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 9.1.5

Table 2: Time and Events Schedule: From Week 24 through Week 64 (Study Part II)

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 9.1.5.

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.
- 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 9.1.5.

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).

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 9.1.5.

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).

Table 3: Time and Events Schedule: Follow-Up Extension Week 64 through Week 100 (Study Part III)

	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 7
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 4.5
Study Drug Administration								
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 12
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 7
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.

ABBREVIATIONS

AE	Adverse Event
BSA	Body Surface Area
CRF	Case Report Form(s)
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
FAE	Fumaric Acid Esters
FSV	Final Study Visit
FUP	Follow-up Phase
EDC	Electronic Data Capture
eg	example given
GCP	Good Clinical Practice
HBV/ HCV	Hepatitis B virus/ Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ie	that is
IEC	Independent Ethics Committee
IGA	Investigator´s Global Assessment
IGRA	Interferon-gamma-release-assay
IL	Interleukin
IRB	Institutional Review Board
mAB	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PASI	Psoriasis Area and Severity Index
PFS-U	Prefilled Syringe assembled with the UltraSafe PLUS™ Passive Needle Guard
PGA	Physician´s Global Assessment
PML	Progressive Multifocal Leukoencephalopathy
PQC	Product Quality Complaint
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
ss	scalp-specific
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TES	Time and Events Schedule
ULN	Upper Limit of the Norm

1. INTRODUCTION

CNTO 1959 (guselkumab) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to the p19 protein subunit of human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 specific intracellular signaling and subsequent activation and cytokine production. Guselkumab has been studied in Phase 1, 2 and 3 studies for the treatment of moderate to severe psoriasis.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Clinical Studies

The clinical development program for guselkumab includes studies in subjects with psoriasis, psoriatic arthritis, palmoplantar pustulosis, and rheumatoid arthritis as well as healthy subjects. As of 30 June 2017, 18 clinical studies of guselkumab have been completed or are ongoing. Ten clinical studies have been completed and eight studies are ongoing. One Phase 2 study and two Phase 1 studies of guselkumab for the treatment of moderate to severe psoriasis have been completed and demonstrated a favorable efficacy and safety profile for guselkumab. A Phase 1 pharmacokinetic (PK) study of guselkumab in healthy subjects has also been completed. The different studies are summarized below; more details about the individual studies are provided in the Investigator's Brochure.

Phase 2 Study (CNTO1959PSO2001, X-PLORE)

In the X-PLORE study, 293 subjects with moderate to severe plaque-type psoriasis were randomized to receive 1 of 5 guselkumab SC dose regimens (5 mg at Weeks 0, 4, and then every 12 weeks [q12w], 15 mg every 8 weeks [q8w], 50 mg at Weeks 0, 4, and then q12w, 100 mg q8w, or 200 mg at Weeks 0, 4, and then q12w), placebo, or adalimumab (HUMIRA®) 80 mg at Week 0, 40 mg at Week 1, and then 40 mg every 2 weeks (q2w).

The proportions of subjects who achieved a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) were significantly higher at Week 16 in all guselkumab treatment groups compared with the placebo group. In addition, higher proportions of subjects in the guselkumab 50 mg q12w, 100 mg q8w, and 200 mg q12w groups achieved a PGA score of 0 or 1 compared with the adalimumab group at Week 16. Improvements in psoriasis were demonstrated at Week 4 in the guselkumab groups and continued to improve through Week 16. A dose-response in efficacy was observed up to 100 mg q8w; the proportions of subjects who achieved a PGA of 0 or 1 were similar in the 100 mg q8w and 200 mg q12w dose groups. Results for improvements in Psoriasis Area and Severity Index (PASI) scores were generally similar to those observed for PGA.

Treatment with guselkumab was generally well-tolerated through Week 52. The proportions of subjects with 1 or more adverse events (AEs) were comparable across the combined guselkumab, placebo, and the adalimumab groups through Week 16, with no evidence of a dose-response in the occurrence of AEs across the guselkumab groups. The most common events in the combined guselkumab group were nasopharyngitis, headache, and upper respiratory tract infection (URTI). Through Week 16, the proportion of subjects with 1 or more serious adverse events (SAEs) was low across all treatment groups. Two serious infections (guselkumab 50 mg group), no malignancies, and no major cardiovascular events (MACE) were reported. Similar patterns of AEs were observed through Week 52. Events of interest through Week 52 included the 2 serious infections noted through Week 16, 1 malignancy in the 200 mg q12w group, and 3 MACE (1 in the 5 mg q12w group and 2 in the 100 mg q8w group).

Approximate dose-proportionality in serum guselkumab concentrations through Week 52 was observed after multiple SC administrations at dose levels ranging from 15 to 200 mg. Steady-state serum guselkumab concentrations were achieved by approximately Week 16 for both the q8w and q12w regimens. In each treatment group, mean or median trough serum guselkumab concentrations were maintained at steady state through Week 40 (q8w groups) or Week 52 (q12w groups). There was no evidence of accumulation in serum guselkumab concentrations over time with SC q8w or q12w administrations. Serum guselkumab concentrations appeared to be affected by body weight; higher-weight subjects (>90 kg) had lower mean steady-state trough serum guselkumab concentrations compared with lower-weight subjects (≤90 kg).

The overall incidence of antibodies to guselkumab across all guselkumab treatment groups through Week 52 was 6.3%, with generally low titers. None of the subjects who were positive for antibodies to guselkumab had antibodies that were able to neutralize the bioactivity of guselkumab in vitro. No consistent impact of antibodies to guselkumab on serum guselkumab concentrations was observed across the guselkumab treatment groups.

Phase 3 Study (CNTO1959PSO3001, VOYAGE 1)

CNTO1959PSO3001 is an ongoing Phase 3, randomized, double-blind, multicenter placebo- and active-comparator-controlled study in subjects with moderate to severe plaque psoriasis. The target population is adult men or women with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by Investigator's Global Assessment (IGA). They must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis. Subjects with non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab or adalimumab are also excluded.

The primary analysis has been completed, follow-up is ongoing. A total of 837 subjects were randomized into the study. The co-primary endpoints and all major secondary endpoints were achieved (all $p<0.001$). Beginning at Week 8 and continuing through Week 48, guselkumab-treated subjects maintained higher rates of all 4 PASI responses (PASI 100, PASI 90, PASI 75, and PASI 50) compared with adalimumab-treated subjects. The guselkumab group demonstrated a greater improvement compared with placebo at Week 16 in the following types of regional psoriasis: scalp psoriasis (ss-IGA), fingernail psoriasis (f-PGA, NAPSI), and hand and foot psoriasis (hf-PGA). The guselkumab group had also a significant and clinically meaningful improvement in health-related quality of life and psoriasis symptoms and signs as measured by DLQI and PSSD compared with the placebo and adalimumab groups.

Phase 3 Study (CNTO1959PSO3002, VOYAGE 2)

CNTO1959PSO3002 is an ongoing Phase 3, randomized, double-blind, multicenter, placebo- and active-comparator-controlled study of guselkumab in subjects with moderate to severe plaque psoriasis with randomized withdrawal and retreatment. The target population is adult men or women with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis defined by IGA. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis. Subjects with non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab or adalimumab are also excluded.

Primary analysis has been completed, follow-up is ongoing. A total of 992 subjects were randomized into the study. The guselkumab group demonstrated a greater improvement compared with placebo at Week 16 in the following types of regional psoriasis: scalp psoriasis (ss-IGA), fingernail psoriasis (f-PGA, NAPSI), and hand and foot psoriasis (hf-PGA). More subjects of the guselkumab group achieved ss-IGA scores of 0, and 0 or 1, and hf-PGA scores of 0 and 0 or 1 compared with adalimumab at Week 24, while no significant difference was observed in the proportion of subjects achieving an f-PGA score of 0/1 or the percent improvement in NAPSI between the guselkumab and adalimumab groups at Week 24. The guselkumab group demonstrated a significant and clinically meaningful improvement in health-related quality of life and psoriasis symptoms and signs as measured by DLQI and PSSD, compared with the placebo and adalimumab groups at Weeks 16 and 24, respectively.

Phase 3 Study (CNTO1959PSO3003, NAVIGATE)

This is a Phase 3, randomized, double-blind, multicenter study evaluating the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis and an inadequate (IGA $\geq$ 2) response to ustekinumab at Week 16. The target population is adult men or women with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug. Subjects must have moderate to severe plaque-type psoriasis, as defined by IGA $\geq$ 3, PASI $\geq$ 12, and involved BSA $\geq$ 10%. Subjects must be candidates for either systemic therapy or phototherapy for psoriasis, and may have previously received some systemic therapies or phototherapy for psoriasis. Subjects with non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium) are excluded. Subjects who have ever received guselkumab or ustekinumab are also excluded. A total of 871 subjects were enrolled into this study. The final analyses demonstrated that the guselkumab group achieved clinical responses approximately twice as often as the ustekinumab group. The proportion of randomized subjects in the guselkumab group with a PASI 90 response increased from Week 16 through Week 36 and was maintained through Week 40. The difference of achieved response over time between the subjects randomized to the guselkumab group and the ustekinumab group was apparent as early as the first visit after randomization (Week 20). Difference increased over time reaching a maximum at Week 40. Randomized subjects treated with guselkumab also had a significantly greater mean number of visits at which subjects reported a score of 0 for both the PSSD sign and symptom scores and DLQI score of 0 or 1 between Week 28 and Week 40 as compared with subjects randomized to ustekinumab.

Phase 1 Pharmacokinetic Results

In the Phase 1 studies in subjects with psoriasis (CNTO1959PSO1001 [Part 2] and CNTO1959PSO1002) and in healthy subjects (CNTO1959PSO1001, Part 1 and CNTO1959NAP1001), guselkumab was slowly absorbed into the systemic circulation, with a median T_{max} of approximately 3 to 6 days after a single SC administration. Systemic exposure (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous (IV) administration at doses ranging from 0.03 to 10 mg/kg or after a single SC administration at doses ranging from 10 to 300 mg. After a single IV administration, the mean V_z values were approximately 6.7 to 10.1 L (98 to 123 mL/kg) and mean clearance (CL) values were approximately 0.288 to 0.479 L/day (3.6 to 6.0 mL/day/kg). The mean $T_{1/2}$ values ranged from approximately 12.3 to 19.1 days after a single IV administration and approximately 14.7 to 17.2 days after a single SC administration. The mean absolute bioavailability of guselkumab after a single 100 mg SC administration was between 47.6% and 54.9%. Overall, the PK of guselkumab was comparable between Japanese (CNTO1959PSO1002) and non-Japanese (CNTO1959PSO1001) subjects with psoriasis.

Phase 1 and Phase 2 Safety, Tolerability and Efficacy Results

Improvements in PASI scores were observed in all dose groups in CNTO1959PSO1001 (Part 2), with the maximum clinical response between Weeks 8 and 16. Guselkumab SC was generally safe and well

tolerated, with no dose-dependent response in the incidence of AEs; all AEs were considered to be mild to moderate in intensity by the investigator. In CNTO1959PSO1002, improvements in PASI scores and PGA were observed in all guselkumab dose groups and administration of guselkumab SC was generally safe and well tolerated. No dose-dependent response in the incidence of AEs was observed, and all AEs were considered mild in severity by the investigator.

In Study CNTO1959PSO2001, treatment with guselkumab at doses ranging from 5 mg q12w to 200 mg q12w from Week 0 through Week 52 was generally well tolerated through the end of the study (Week 52) and improvements in PASI scores and PGA were observed in all guselkumab dose groups.

1.2. Comparator

Fumaderm® initial/Fumaderm® are mixtures of fumaric acid esters (FAE) that are approved for the treatment of moderate to severe plaque-type psoriasis in Germany. FAE consist of dimethylfumarate and monoethylfumarate salts, which can modulate the immune system; however, the exact mechanism of action is unclear (1). Detailed information about Fumaderm® initial/ Fumaderm® can be found in the current Summary of Product Characteristics (SmPC) (2).

1.3. Overall Rationale for the Study

Traditionally, biologic compounds like guselkumab with a precisely defined therapeutic target were used after failure of conventional systemic therapy such as MTX, FAE or cyclosporine. Years of experience with a variety of biologic compounds led to the assessment that the benefit-risk ratio of biologic compounds might also be favorable for psoriasis subjects without prior conventional systemic therapy ("1st line systemic subject population").

Guselkumab specifically targets IL-23, which contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases (3), (4). The clinical response to guselkumab observed in previous psoriasis studies demonstrates the specific importance of IL-23 in the pathogenesis of plaque psoriasis.

In the current phase 3 program, guselkumab is compared to adalimumab in subjects suffering from moderate to severe psoriasis in two independent trials (CNTO1959PSO3001 and CNTO1959PSO3002). Additionally, the efficacy and safety of guselkumab is assessed in subjects with moderate to severe psoriasis and an inadequate response to ustekinumab (CNTO1959PSO3003). However, the phase 3 program lacks a head-to-head trial vs. conventional systemic compounds. In Germany, FAE are the most commonly prescribed 1st line systemic therapy (1) for moderate to severe plaque-type psoriasis. FAE are considered to be more effective in treating plaque-psoriasis than methotrexate and to be better suited for long-term treatment of psoriasis than cyclosporine (5). Therefore, FAE were selected as appropriate comparator to evaluate guselkumab in treating subjects with moderate to severe psoriasis who are candidates for and naïve to systemic treatment (1st line systemic subject population).

The profile of side effects (eg, GI-symptoms and flush; lymphopenia) of FAE is very characteristic, will affect the majority of subjects and will lead to a *de facto* unblinding of treatment groups. Therefore, this clinical study will utilize an open-label design. To help improve objectivity and decrease bias, given the open-label design, efficacy assessments will be performed by a blinded assessor during Study Part I and II. Part II of this study is designed to exploratorily assess the sustainability of treatment efficacy (guselkumab and FAE), while non-responders will be offered to switch to or continue guselkumab.

Finally, a withdrawal element has been incorporated into the study design (Study Part III) to assess the maintenance of response in subjects who discontinue guselkumab. Maintenance of response after drug withdrawal is indicative of disease modification.

2. OBJECTIVES AND HYPOTHESES

2.1. 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.

2.2. 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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

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:
Screening and treatment until primary endpoint is reached

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, continuation/switch of study treatment)—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.

Study Part III (Follow-up extension after 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 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 last treatment.

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.

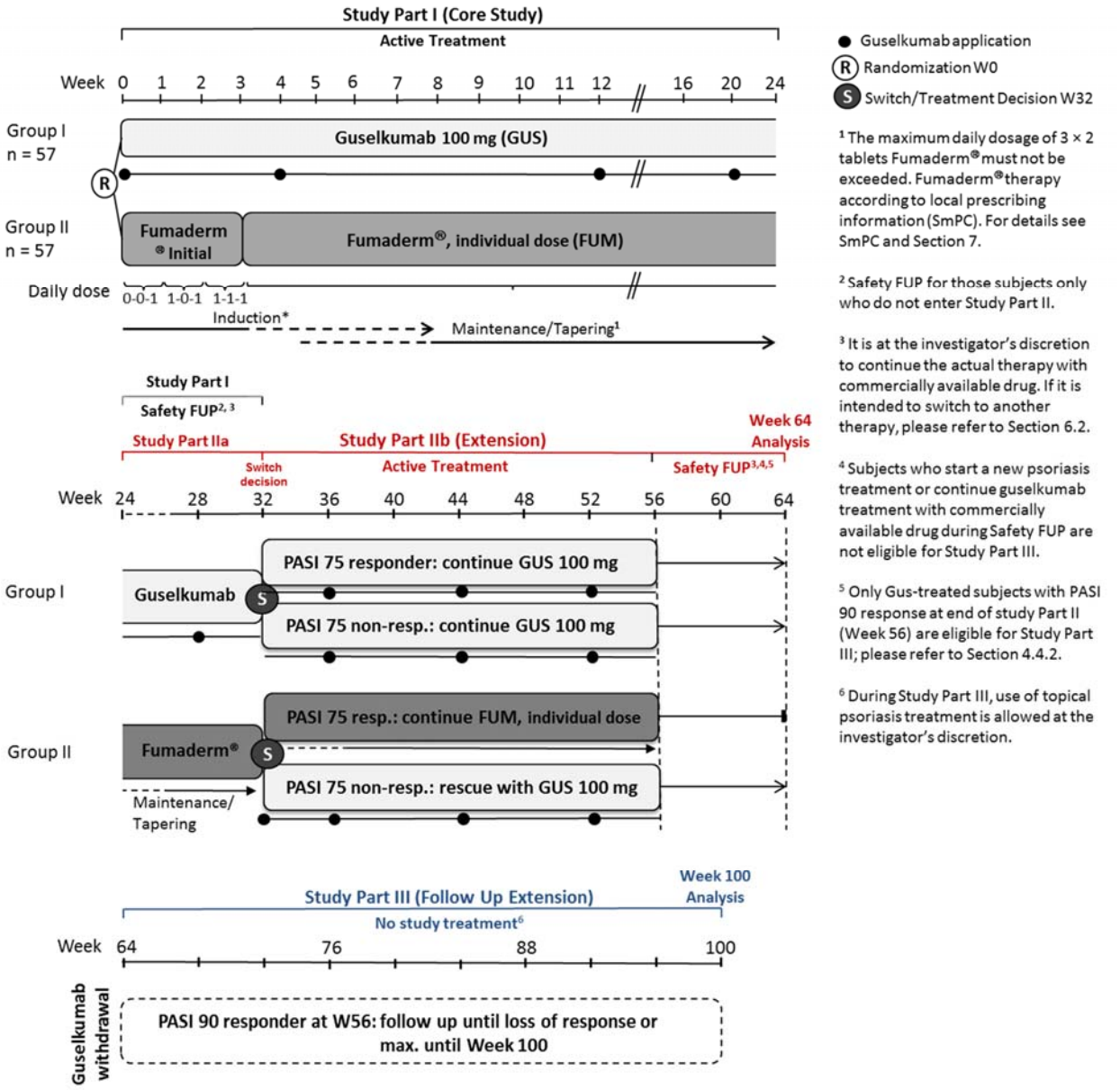
Safety evaluations will include the monitoring of adverse events (including injection site and allergic reactions), physical examinations, measurement of body weight, vital sign measurement, clinical laboratory testing (HBV, HCV, HIV, hematology, chemistry), concomitant medication review, tuberculosis 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



3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups

FAE are the most commonly prescribed 1st line systemic therapy (1) for moderate to severe plaque-type psoriasis in Germany. For this reason, FAE were selected as appropriate comparator to evaluate guselkumab in treating subjects with moderate to severe psoriasis who are candidates for and naïve to systemic treatment (1st line systemic subject population).

The profile of side effects (eg, GI-symptoms and flush; lymphopenia) of FAE is very characteristic, will affect the majority of subjects and will lead to a *de facto* unblinding of treatment groups. Therefore, this clinical study will utilize an open-label design. To help improve objectivity and decrease bias, given the open-label design, during Study Part I and II efficacy assessments will be performed by a blinded assessor,

meaning the assessor of dermatological evaluation will not know the treatment group the subject to be evaluated belongs to. Thus, investigators and investigational staff must not disclose the randomization table to the assessor. Additionally, it is prohibited to involve the assessor in study drug application and its preparation. The assessor must not have access to the electronic data capture (EDC) system or subject's medical records or study drug administration information.

Part I of this study (Week 0 to 24) is designed and powered to assess the efficacy of psoriasis therapy with guselkumab and FAE, respectively, after a 24-week treatment phase. This duration allows for an adequate treatment period. Part II of this study (Week 24 to 56) is designed to exploratorily assess the sustainability of treatment efficacy (guselkumab and FAE). So far, no randomized clinical trials evaluated the efficacy of FAE after Week 16. However, real-world data and anecdotal evidence suggest that the effectiveness of FAE treatment increases for up to 6 months. Part IIa of this study (Week 24 to 32) addresses the question if FAE efficacy might improve after Week 24. In Part IIb of this study (Week 32 to 56) the sustainability of response in subjects with a PASI 75 response will be addressed, while PASI 75 non-responders will be offered to switch to or continue guselkumab at Week 32. Part III of this study (Week 64 to 100) is designed to assess the maintenance of response after guselkumab withdrawal in subjects who responded well (PASI 90 response) to guselkumab. Maintenance of response after drug withdrawal is indicative of disease modification.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

4. SUBJECT POPULATION

The target population comprises adult men and women with a diagnosis of plaque-type psoriasis for at least 6 months before the first administration of the study drug. Subjects must have moderate to severe plaque-type psoriasis defined by Psoriasis Area and Severity Index (PASI) >10 or involved body surface area (BSA) >10%, and Dermatology Quality of Life Index (DLQI) >10. Subjects must be candidates for systemic psoriasis therapy, and FAE must be considered as an appropriate treatment option. Subjects with non-plaque forms of psoriasis (eg, erythrodermic, guttate or pustular) or with drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers or lithium) are excluded.

A total number of 114 subjects will be randomly assigned in this study with 57 subjects planned per treatment group.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. Male or female and ≥18 years of age
2. Have a diagnosis of plaque-type psoriasis for at least 6 months before the first administration of study drug
3. Have a PASI >10 or BSA >10 at screening and at baseline
4. Have a DLQI >10 at screening and at baseline

5. Be a candidate for systemic treatment for psoriasis
6. Topical psoriasis therapy is considered to be inadequate by the investigator due to
   - inadequate response to, intolerance to or contraindication against topical therapy in the subject's medical history (documented or reported by the subject)
   - and/or disease severity at screening and at baseline
7. Must be eligible for Fumaderm® treatment according to the SmPC
8. Fumaderm® is considered, in the opinion of the investigator, to be an appropriate treatment option
9. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies

   Before randomization, a woman must be either:

   a. Not of childbearing potential defined as:

   Premenarchal

   A premenarchal state is one in which menarche has not yet occurred.

   Postmenopausal

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   Permanently sterile

   Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

   b. Of childbearing potential and

   - practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

   Examples of highly effective contraceptives include:

   - user-independent methods:

   implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (*sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to study duration and the preferred and usual lifestyle of the subject.*)

   - user-dependent methods:

   combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

   Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- agrees to remain on a highly effective method throughout the study and for at least 90 days after the last dose of study drug. A woman using oral contraceptives should use an additional birth control method.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

10. A woman of childbearing potential must have a negative urine pregnancy test at screening and at Week 0
11. A woman must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the study and for a period of at least 12 weeks after receiving the last administration of study treatment
12. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, in addition to the highly effective method of contraception, a man
    - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository), during the study and for at least 12 weeks after receiving the last study treatment.
    - who is sexually active with a woman who is pregnant must use a condom, during the study and for at least 12 weeks after receiving the last administration of study treatment.
    - must agree not to donate sperm during the study and for at least 12 weeks after receiving the last administration of study treatment.
13. Considered eligible according to the following tuberculosis (TB) screening criteria:
    - Have no history of latent or active TB before screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB before the first administration of study drug, or have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study drug. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.
    - Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination
    - Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before first administration of study drug
    - Within 2 months before the first administration of study drug, have a negative QuantiFERON®-TB Gold Plus test result (6) (7), or have a newly identified positive QuantiFERON®-TB Gold Plus test result (Attachment 3) in which active TB has been ruled out and for which appropriate treatment for latent TB (Section 9.1.2) has been initiated before the first administration of study drug. Indeterminate results should be handled as outlined in Section 9.1.2.

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

14. Have a chest radiograph (posterior-anterior and lateral views), taken within 3 months before the first administration of study drug and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB
15. Agree not to receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study drug; for information on Bacille Calmette-Guérin (BCG) vaccination, see Inclusion Criterion 16
16. Agree not to receive a BCG vaccination during the study, or within 12 months after the last administration of study drug
17. Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:
    - Hematology panel within normal limits
    - Serum creatinine ≤1 × upper limit of normal (ULN)
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-GT, total bilirubin and alkaline phosphatase (AP) levels must be ≤2 × ULN
18. No dipstick detection of proteins or glucose in urine. 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.
19. Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet (UV) light sources during study
20. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol
21. Sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.

4.2. Exclusion Criteria

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

1. Has received prior systemic treatment of psoriasis including but not limited to
    - conventional systemic therapy (eg, methotrexate, cyclosporine, fumaric acid esters and acitretine)
    - apremilast and tofacitinib
    - drugs 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)
2. Has a history or current signs or symptoms of severe, progressive, or uncontrolled liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances
3. Has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study drug administration, or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before first study drug administration)
4. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly

5. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study drug)
6. Has a history of an infected joint prosthesis, or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced
7. Has or has had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening
8. Has or has had herpes zoster within the 2 months before screening
9. Has current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)
10. Has a non-plaque form of psoriasis (eg, erythrodermic, guttate, or pustular)
11. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic non-remitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers
12. Known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (more information can be found in the current version of the Investigator's Brochure)
13. Contraindications to the use of Fumaderm® initial/ Fumaderm® per local prescribing information
14. Has received phototherapy (including, but not limited to, PUVA, narrow-band UVB, balneophototherapy) within 4 weeks of the first administration of study drug
15. Has used topical medications/ treatments that could affect psoriasis (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study drug
16. Has received, or is expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study drug; for BCG vaccine, see Exclusion Criterion 17
17. Has had a BCG vaccination within 12 months of screening
18. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mABs, or antibody fragments
19. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening (regarding eligibility with a history of latent TB, see Inclusion Criterion 13)
20. Has a chest radiograph within 3 months before the first administration of study drug that shows an abnormality suggestive of a malignancy or current active infection, including TB
21. Has ever had a non-tuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, or aspergillosis)
22. Has persistently indeterminate (indeterminate on repeat sampling) IGRA, eg, QuantiFERON®-TB Gold Plus test results; indeterminate results should be handled as described in Section 9.1.2
23. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody)
24. Tests positive for hepatitis B virus (HBV) infection or seropositive for antibodies to hepatitis C virus (HCV) at screening (Attachment 4)
25. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 3 months before the planned first dose of study drug or is currently enrolled in an investigational study
26. Is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study drug

27. Plans to attempt to have a child while enrolled in this study or within 12 weeks after the last dose of study drug
28. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months
29. Is unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins
30. Lives in an institution on court or authority order
31. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
32. Had major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
33. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

Note: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. See Section "Prestudy and Concomitant Therapy" for details regarding prohibited and restricted therapy during the study.
2. Agree to follow the contraceptive requirements as noted in the inclusion criteria. Women participating in Study Part III, who are of childbearing potential (e.g. not premenarchal, not postmenopausal and not permanently sterile) and use a highly effective method of contraception, have to agree to remain on a highly effective method of contraception throughout the study.
3. Subjects must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of any study drug; see Prohibition 5 for information regarding BCG vaccination
4. Avoid donating blood for at least 90 days after last study treatment (ie, safety follow-up visit) of the study. Subjects entering Study Part III should avoid donating blood until end of study (Final Study Visit).
5. Subjects must not receive a BCG vaccination during the study and for 12 months after the last administration of study drug.
6. Subjects must avoid prolonged sun exposure and avoid use of tanning booths or other UV light sources during the study.

4.4. Treatment Assignment Criteria for Study Part II (Week 24 through Week 56)

Study Part IIa: Week 24 through Week 32

Subject may enter Study Part II at Week 24 when he/she did

1. sign informed consent form (ICF) for Study Part II indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study
2. not terminate study treatment prior to Week 24
3. not start a protocol-prohibited medication/therapy.

Until Week 32, subjects will continue assigned treatment (guselkumab or FAE) as randomized at Week 0.

Study Part IIb: Week 32 through Week 56

At Week 32 the following treatment assignments will be performed based on the Week 32 PASI assessment and safety considerations:

- Subjects with a PASI 75 response in both groups will continue assigned treatment.
- PASI 75 non-responders in the guselkumab group may continue guselkumab treatment, if the investigator considers therapy medically appropriate.
- PASI 75 non-responders in the FAE group may switch to guselkumab when it is considered a safe treatment option (see Section 4.4.1).

4.4.1. Study Part IIb: Treatment Switch Safety Criteria

Subject of the FAE group with PASI 75 non-response may switch to guselkumab when he/she

1. had laboratory results at Week 28 within the following ranges:

Hemoglobin	≥10 g/dL (SI: ≥100 g/L)
Leukocytes	≥3.5 × 10^3/µL (SI: ≥3.5 GI/L)
Neutrophils	≥1.5 × 10^3/µL (SI: ≥1.5 GI/L)
Lymphocytes	≥0.7 × 10^3/µL (SI: ≥0.7 GI/L)
Platelets	≥100 × 10^3/µL (SI: ≥100 GI/L)
Serum creatinine	≤1.5 mg/dL (SI: ≤129 µmol/L)
Aspartate aminotransferase (AST)	≤2 × upper limit of normal (ULN)*
Alanine aminotransferase (ALT)	≤2 × ULN*
Alkaline phosphatase (AP)	≤2 × ULN*
* laboratory-specific	

Note: If one or more parameters are out of range, one single retest is permitted before the Week 32 visit.

2. is eligible according to the following tuberculosis (TB) criteria:
    - Have no signs or symptoms of an active TB infection according to the early detection guidelines for TB (Section 9.3)
    - Subjects with a positive QuantiFERON®-TB Gold Plus test result must have completed appropriate treatment for latent TB within 5 years before the first administration of guselkumab, must continue appropriate treatment for latent, or must initiate appropriate treatment of latent TB before first administration of guselkumab. It is in the responsibility of the investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation.

4.5. Eligibility Criteria for Study Part III: Week 64 until loss of response or Week 100

Subjects treated with guselkumab in Study Part II (subjects who started guselkumab treatment at Week 0 or switched from FAE to guselkumab treatment in Week 32) may enter Study Part III at Week 64 when he/she:

- Signed ICF of Study Part III before or at Week 64
- Achieved a PASI 90 response at the end of Study Part II (Week 56)
- Had no diagnosis of psoriatic arthritis (PsA) at baseline
- Did not start a new psoriasis treatment before Week 64, including commercially available guselkumab
- Did not start any other protocol-prohibited medication/therapy
- Is a woman and used a highly effective method of contraception during Study Part I and II and agrees to remain on a highly effective method of contraception throughout the study.

5. TREATMENT ALLOCATION AND BLINDING

Procedures for Randomization

Central randomization will be 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. During Study Part III, subjects who received guselkumab during Study Parts I or II only are eligible for Study Part III. During Study Part III subjects are no longer on study treatment, thus, efficacy assessments during Study Part III are no longer blinded.

6. DOSAGE AND ADMINISTRATION

A 100 mg/mL solution of guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U). Commercially available Fumaderm® initial/ Fumaderm® tablets will be supplied.

Study-site personnel will instruct subjects on how to store study drug for at-home use (only Fumaderm® initial/ Fumaderm®) as indicated for this protocol.

6.1. Study Drug Dosage

6.1.1. Study Part I and Study Part IIa: Active Comparative Treatment

Active comparative treatment phases are Week 0 through Week 24 (Study Part I) and Week 24 through Week 32 (Study Part IIa).

Subjects randomized to guselkumab will receive 100 mg guselkumab SC by trained study personnel at the study site, subjects randomized to FAE will receive commercially available Fumaderm® initial/ Fumaderm® tablets intended for self-administration at home, and specifically labeled for the study. An individual FAE dosing for each subject representing the optimal benefit-risk ratio is aspired. The maximum daily dosage of 3 × 2 tablets Fumaderm® must not be exceeded.

Subjects will receive study drug through Week 56 with a rescue option for FAE group PASI 75 non-responders at Week 32. PASI evaluation will be used to decide if the current treatment can be considered satisfactory as defined by subject reaching a PASI 75 response.

The dose regimens are as follows:

Study Part I (Week 0 through Week 24):

- Group I (Gus, n = 57): 100 mg Guselkumab SC at weeks 0, 4, 12 and 20
- Group II (FAE, n = 57): Fumaderm® initial/Fumaderm® tablets; individual dosing according to local prescribing information (SmPC) (2)

Study Part IIa (Week 24 through Week 32):

Both groups continue their assigned treatment.

- Group I (Gus): 100 mg guselkumab SC every 8 weeks (ie, at Week 28)
- Group II (FAE): Fumaderm® initial/Fumaderm® tablets; individual dosing according to local prescribing information (SmPC) (2)

6.1.2. Study Part IIb: Continuation/Switch of Study Treatment (Week 32 through Week 56)

Study Part IIb is designed to assess sustainability of treatment efficacy and as rescue treatment phase for subjects of the FAE group with PASI 75 non-response. Part IIb spans Week 32 through Week 56. Treatment depends on PASI response.

a. PASI 75 responders at Week 32:

Both groups continue their assigned treatment.

- Group I (Gus): 100 mg guselkumab SC every 8 weeks (ie, at Weeks 36, 44 and Week 52)
- Group II (FAE): Fumaderm® initial/ Fumaderm® tablets; individual dosing according to local prescribing information (SmPC) (2)

b. PASI 75 non-responders at Week 32:

For non-responders of the guselkumab group, it is at the investigator's discretion to continue guselkumab treatment, if it is considered medically appropriate. Non-responder subjects of the FAE group may switch to guselkumab treatment unless barred by safety reasons (for details see Section 4.4).

- Group I (Gus): continue 100 mg guselkumab SC every 8 weeks (ie, at Weeks 36, 44 and Week 52)
- Group II (FAE): switch to 100 mg guselkumab SC at Weeks 32, 36, 44 and Week 52

If the subject does not continue assigned treatment or does not switch to guselkumab, subject terminates study treatment and enters safety follow-up.

6.1.3. Safety Follow-up Phase: Psoriasis Treatment

During the safety follow-up period Week 24 through Week 32 (Study Part I) or Week 56 through Week 64 (Study Part II) or 12 weeks after the last application of study drug (whatever comes first), concomitant treatments for psoriasis may be administered at the investigator's discretion as follows:

- Group I (Gus): If commercially available, investigator may continue actual treatment with guselkumab or switch to another commercially available treatment. Due to the half-life of guselkumab, it is recommended not to start a new therapy other than commercially available guselkumab during safety follow-up period. If the investigator feels strongly that another therapy is needed, this should be discussed with the sponsor before initiation of the new therapy.

  Note: Subjects who start a new psoriasis treatment, including commercially available guselkumab, during safety follow-up phase are not eligible to enter Study Part III.

- Group II (FAE): Investigator may either continue the actual FAE treatment with commercially available drug or switch to another commercially available treatment.

6.1.4. Study Part III, Follow-up Extension Phase: Guselkumab Withdrawal, No Study Treatment (Week 64 through Week 100)

Subjects who are eligible to enter Study Part III are withdrawn from guselkumab treatment and are followed until loss of response (defined as an increase in absolute PASI >5) or until Week 100 at the latest. Subjects may start a commercially available topical psoriasis treatment after end of safety follow up (at Week 64 or later) at the investigator's discretion, except topical corticosteroids class IV (alone or in combination) and phototherapy.

6.2. Study Drug Administration

6.2.1. Guselkumab

A 100 mg/mL solution of guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUSTM Passive Needle Guard (PFS-U).

6.2.2. Fumaric Acid Esters

Commercially available Fumaderm® initial/ Fumaderm® tablets will be repackaged and supplied as an active comparator to the study sites. Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Fumaderm® initial/ Fumaderm® tablets need to be swallowed unchewed during a meal or directly after a meal with plenty of liquid. Subjects will be instructed to drink at least 1½ to 2 liters per day. The optimal FAE dose representing the optimal benefit-risk ratio for each individual subject needs to be identified. All dose adjustments must be documented together with the reason for dose adjustment in the medical records.

Uptitration of FAE (Fumaderm® initial/ Fumaderm®)

The FAE dose is increased starting with Fumaderm® initial (containing 30 mg dimethylfumarate) for the first 3 weeks according to *Table 4* (40 tablets Fumaderm® initial total):

Table 4: Uptitration of Fumaderm® initial

Week	Fumaderm® initial dose (tablets with 30 mg dimethylfumarate)		
	in the morning	at noon	in the evening
0	0	0	1
1	1	0	1
2*	1	1	1

* Until 40 tablets are consumed

Directly after finishing the last tablet of Fumaderm® initial, subjects will continue with Fumaderm® tablets (containing 120 mg dimethylfumarate) starting with one tablet per day in the evening. Fumaderm® dose can be increased to a maximum of 3 × 2 tablets per day according to *Table 5*. In many cases, the maximum daily Fumaderm® dose is not necessary. First therapy effects usually can be detected after 4 to 6 weeks of treatment.

Table 5: Uptitration of Fumaderm®

Week	Fumaderm® dose (tablets with 120 mg dimethylfumarate)		
	in the morning	at noon	in the evening
2*- 3	0	0	1
4	1	0	1
5	1	1	1
6	1	1	2
7	2	1	2
8	2	2	2

* Start at last day of Week 2 directly after finishing Fumaderm® initial (40 tablets)

Uptitration of Fumaderm® may be stopped/interrupted/decelerated for one of the following reasons:

a) The maximum of 3 × 2 tablets Fumaderm® per day has been reached.

b) Reaching the therapeutic goal: When subjects achieved a reduction of the baseline PASI score of ≥90% (PASI 90 response). See section "Maintenance/Tapering of Fumaderm®" below for further dosing instructions.

c) Lack of tolerability: When subjects report side effects (eg, GI symptoms or flush), uptitration of FAE can be stopped/interrupted/decelerated at the discretion of the investigator. It may be necessary to taper FAE dose to increase tolerability again (see below). Additional safety/tolerability visits can be scheduled, if needed. After ceasing of the side effects/improvement of tolerability, it is at the discretion of the investigator to increase the FAE dose (again) according to *Table 4* and *Table 5*.

d) Laboratory findings: It is in the discretion of the investigator to stop/interrupt/decelerate uptitration of FAE due to laboratory findings. It may be feasible/necessary to taper FAE dose. Additional safety/tolerability visits can be scheduled. Some laboratory findings require tapering of FAE or termination of FAE treatment (see below).

Maintenance/tapering of Fumaderm®

a) After achieving the therapeutic goal (PASI 90 response), it is at the discretion of the investigator to taper FAE dose slowly to the individually required maintenance dose. It is recommended, to verify sustainability of PASI 90 response at the subsequent visit before tapering the FAE dose unless safety findings or lack of tolerability demand FAE tapering. Instead of tapering, FAE dose may be maintained or even further increased to achieve higher efficacy levels (up to a maximum of 3 × 2 tablets per day) as long as the benefit-risk ratio is considered to be positive. Reasons for maintaining/increasing/tapering the FAE dose after achieving a PASI 90 response need to be documented. If efficacy drops after FAE tapering, the Fumaderm® dose may be increased again according to *Table 4* and *Table 5*.

b) Tapering of the FAE dose due to side effects (eg, GI problems, flush, laboratory findings) is at the discretion of the investigator. It is suggested not to decrease the daily FAE dose by more than 1 tablet per week. However, the investigator may decide to taper FAE more rapidly. Reasons for tapering must be documented. After the side effects have ceased, FAE dose may be increased again according to *Table 4* and *Table 5*. Additional safety/tolerability visits can be scheduled. Some laboratory findings require tapering of FAE or an end of FAE treatment (see below).

Mandatory reasons to taper FAE dose or stop FAE treatment

a) Leukopenia: After a pronounced drop of the leukocyte count and definitely if leukocyte count is less than 3000/µl, the FAE treatment must be terminated immediately.

b) Lymphopenia: FAE treatment must be terminated immediately, if lymphocyte counts drop below 500/µl. FAE dose must be tapered by 50% of the latest dosage immediately (not stepwise), if the lymphocyte count drops below 700/µl. If the lymphocyte count does not recover to at least 700/µl 4 weeks later, FAE treatment must be terminated.

c) A prolonged severe or moderate lymphopenia is considered to be a risk factor for progressive multifocal leukoencephalopathy (PML). Subjects developing lymphopenia should be screened for signs of opportunistic infections, especially signs indicative for PML including neurologic, cognitive and/or psychiatric symptoms. If a PML is suspected, FAE treatment must be terminated immediately and further appropriate neurologic/radiologic investigations need to be initiated.

d) Other hematological findings: All other clinically relevant pathologic changes of the hematology panel should lead to immediate FAE treatment termination. One single retest is permitted.

e) Creatinine: FAE treatment must be terminated when creatinine increases above ULN. One single retest is permitted.

All pathological laboratory changes will be closely monitored until the parameters are within normal limits again.

7. TREATMENT COMPLIANCE

Subjects will receive instructions on compliance with study drug administration at the Week 0 visit. Subjects will be trained to self-administer study drug (only Fumaderm® initial/Fumaderm®) at their Week 0 visit, and all subsequent Fumaderm® initial/Fumaderm® administrations will be performed at home.

During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study drug. Compliance with the treatment schedule is strongly encouraged. Study-site personnel will keep a log of study drug dispensed and will compare the amount of study drug dispensed with the amount returned. Additional details may be provided in the Site Investigational Product Manual that is provided separately.

Visits through Week 56 should occur within ±7 days of the scheduled visit. The subject should resume his or her normal dose schedule relative to the baseline visit (Week 0). During Study Part III visits should occur within ±14 days of the scheduled visit.

8. PRESTUDY AND CONCOMITANT THERAPY

Concomitant therapies must be recorded throughout the study from screening to Week 64. Concomitant therapies should be recorded beyond Week 64 only in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2. For patients entering Study Part III, psoriasis therapy/medication will be recorded until end of study. In case any protocol-prohibited therapy is applied (for psoriasis or any other indication), the subject is withdrawn from study participation. Prohibited therapy is recorded as well as any newly planned psoriasis therapy, if already known at the end of the study.

All therapies different from the study drug (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) must be recorded in the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

8.1. Concomitant Medications for Treatment of Psoriasis

8.1.1. Treatment Phase

Topical Therapy

Topical therapies that could affect psoriasis (eg, 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 56, for subjects entering Study Part III until Week 64 (see Section 8.1.2. and 8.1.3). 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 or Systemic Therapy for Psoriasis

The use of phototherapy or systemic anti-psoriatic medications is not permitted until the Week 56 visit, for subjects entering Study Part III until end of study (see Section 8.1.2 and 8.1.3). 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.

8.1.2. Safety Follow-Up Phase

See section 6.1.3 for instructions regarding treatment of psoriasis during the follow-up phase. Furthermore, for subjects to be eligible for Study Part III all systemic treatments including commercially available guselkumab and topical therapies that could affect psoriasis (see Section 8.1.1) are prohibited.

8.1.3. Follow-up Extension Phase

During Study Part III use of topical psoriasis treatment is allowed at the investigator's discretion. However, topical corticosteroids class IV (alone or in combination) and phototherapy are prohibited until end of the study (Week 100). Systemic psoriasis therapies, including commercially available guselkumab and phototherapy, are prohibited during Study Part III. Patients starting any prohibited therapy, including medications for conditions other than psoriasis, will be withdrawn.

8.2. Concomitant Medications for Conditions Other than Psoriasis

Every effort should be made to keep subjects on stable concomitant medications. If the medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the eCRF.

If needed, the occasional use of nonsteroidal anti-inflammatory drugs (NSAID) is allowed. NSAID as well as acetaminophen (paracetamol) are not allowed as long-term medication, eg, as part of a treatment of a chronic inflammatory disease, but only for acute clinical situations. NSAID dosage and time of use should be kept as low and short as possible and should not exceed 2 weeks of daily NSAID administration. Disease-modifying agents such as MTX, sulfasalazine, or IM gold, which may have an effect on psoriasis, are prohibited during the study.

The use of corticosteroids for indications other than psoriasis should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer-term use of corticosteroids should be discussed with the sponsor and may require discontinuation of study drug. Inhaled, otic, ocular, nasal or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (TES) (Table 1 [Part I], Table 2 [Part II] and Table 3 [Part III]) summarize frequency and timing of efficacy, immunogenicity, and safety measurements performed during this study.

All subjects will be asked to sign the consent form(s) (ICF I, II and III) before any study-related procedures of the respective study part (I, II, III) are conducted.

Note: At the time amendment INT-1 has been implemented all subjects were enrolled and had signed the ICF established at study initiation (identical to ICF I). All subjects on study treatment were asked to acknowledge and sign ICF II for Study Part II (study extension). ICF II had to be signed by Week 24 at the latest by all patients continuing to Study Part II.

Adverse events and concomitant medication recording will start after ICF I has been signed and will continue until the last study-related procedure of Study Part I and II, respectively, has been completed. During Study Part III, adverse drug reactions and deaths will be recorded until end of study. Concomitant therapies will be recorded beyond Week 64 if they are in conjunction with serious adverse events that meet the criteria outlined in Section 12.3.2. Any topical psoriasis treatment will be recorded throughout Study Part III and all prohibited medication at subject's withdrawal.

All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions. Completion of baseline PROs has to be done before randomization. All other efficacy evaluations should be completed before study drug administrations.

The following PRO assessments (1st DLQI, 2nd PSSD, and 3rd SF-36) and efficacy outcomes (BSA%, IGA, ss-IGA, and PASI) will be captured on paper sheets at the appropriate visits, as outlined by the TES.

Study drug administration information will be captured at the appropriate visit through Week 56, as outlined by the TES.

Details about who will perform and/or complete the assessments/data and the order of completion are provided in Section 9.2.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

All blood samples must be collected before study drug administration (Table 6). Fasting is not necessary. For each subject, the total volume of blood drawn from each subject in this study is approximately 200 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 6: Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	Max. no. of Samples per Subject	Max. total Volume of Blood (mL)[a]
Safety (including screening and posttreatment assessments)			
- Hematology	2.7	17	46
- Glucose (Plasma)	2.7	17	46
- Chemistry[b]	5.5	17	94
- Serology (HBV, HCV, HIV); HBV DNA testing[c]	5.0	1	5
- TB testing	4.0	1	4
Approximate total[d]			195

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Includes FSH testing for selected female subjects to confirm postmenopausal state.
c. Performed only in subjects who test positive for core HBV antibody.
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
Max.=maximum

9.1.2. Screening Phase

All subjects will have a screening visit that will occur within 3 weeks before their randomization visit (Week 0). The screening phase is designed to assess inclusion/exclusion criteria and to establish baseline characteristics for a subject's psoriasis.

The subjects will be asked to sign the consent form at the screening visit before any study related procedures are conducted (ICF I).

With the exception of subjects with a history of appropriately treated latent TB within 5 years of the first administration of study drug (see Inclusion Criterion 13), subjects must undergo testing for TB (see Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be

asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

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.

Subjects with a negative interferon-gamma-release-assay (IGRA) test result (eg, QuantiFERON®-TB Gold Plus test) (6), (7) are eligible to continue with pre-randomization procedures. Subjects with a newly identified positive IGRA test result (eg, QuantiFERON®-TB Gold Plus test) must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects.

A subject whose first QuantiFERON®-TB Gold Plus test result is indeterminate should have the test repeated. If the second QuantiFERON®-TB Gold Plus test result is also indeterminate, the subject has to be excluded from the study.

Subjects will undergo screening for HBV (see Attachment 4) and antibodies to HCV and HIV.

9.1.3. Screening Failure/Re-screening

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

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

In general, if a subject is a screening failure but at some point in the future meets all of the subject eligibility criteria, the subject may be re-screened after a new informed consent has been obtained.

Subjects who are re-screened will be assigned a new subject number and will restart a new screening phase. Re-screening will be permitted once.

9.1.4. Open-Label Assessor-blinded Treatment Phase

Week 0/Randomization

At Week 0, subjects who meet all inclusion criteria and do not demonstrate any exclusion criteria will be randomized. Randomization visit procedures will be performed as specified in the TES.

Week 0 through Week 56: Study Part I and Study Part II

During the treatment phase (Week 0 through Week 56), the site staff will be encouraged to contact subjects belonging to the FAE treatment group approximately 1 to 3 days prior to each scheduled visit with a reminder to bring their used study medication to the study site.

All visit procedures will be performed as specified in the TES. All study procedures and evaluations are to be completed before administration of study drug. End of Treatment/Early Withdrawal

All subjects who prematurely stop taking the study drug should complete the early termination visit (ETV) as listed in the TES. After ETV, safety follow-up should be conducted for 12 weeks after the last administration of study drug (see Section 9.1.5).

For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety evaluations as listed in the TES (FSV Part I or Part II; see Section 10.2).

9.1.5. Safety Follow-up Phase

All subjects will enter a post-treatment safety follow-up phase. Subjects who prematurely stop taking the study drug should complete the ETV and safety follow-up should be conducted for 12 weeks after the last administration of study drug. The safety follow-up phase ends with a safety follow-up visit. The regular safety follow-up visit for subjects who completed Study Part I only and do not continue to Study Part II is scheduled for Week 32 at the latest. Subjects who continue in Study Part II through Week 56 will be followed for safety information through Week 64 at the latest.

Subjects will be instructed that study drug will not be made available to them after they have completed/ discontinued the drug and that they should return to their physician to determine standard of care if not entering Study Part III.

9.1.6. Follow-up Extension Phase after Guselkumab Withdrawal

No study treatment is applied during the follow-up extension phase. During Study Part III, subjects may start a commercially available topical psoriasis treatment at Week 64 or later at the investigator's discretion, except topical corticosteroids class IV (alone or in combination) and phototherapy. Subjects will be followed for safety information (ie, vital signs, physical examination, ADRs and death; no laboratory assessments) and unblinded efficacy assessments as specified in the TES until loss of response or until Week 100 at the latest. Subjects starting a systemic psoriasis treatment including commercially available guselkumab or other prohibited medication/therapy will be withdrawn. For subjects who withdraw from study participation, every eff

ort should be made to conduct final efficacy and safety evaluations as listed in the TES (FSV Part III, see Section 10.2).

9.2. Efficacy

9.2.1. Evaluations

Efficacy evaluations chosen for this study are consistent with those used to evaluate other therapies for psoriasis. Efficacy evaluations will be first done by subjects (PROs) and then by the blinded efficacy assessor Study Parts I and II; during Part III the assessor is no longer blinded. Completion of Baseline-PROs has to be done before randomization.

Efficacy evaluations include:

- Dermatology Life Quality Index (DLQI) **[PRO #1]**
- Psoriasis Symptom and Sign Diary (PSSD, 7-day version) **[PRO #2]**
- Medical Outcomes Study 36-Item Short Form (SF-36) **[PRO #3]**
- Involved Body Surface Area (BSA)
- Investigator's Global Assessment (IGA)
- Scalp Specific Investigator's Global Assessment (ss-IGA)
- Psoriasis Area and Severity Index (PASI)

9.2.2. 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
- 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 56Proportion 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
- Time to loss of response from Week 56 after guselkumab withdrawal until Week 100
- Safety and tolerability data will be summarized using descriptive statistics.

9.2.3. Blinded Efficacy Assessment

An independent, blinded efficacy assessor, approved by the Sponsor, will be designated at each study site to perform all efficacy assessments (BSA%, IGA, ss-IGA, and PASI) starting with baseline visit until end

of treatment phase (ie, Week 56). As only subjects treated with guselkumab may enter the follow-up extension phase, efficacy assessments are not blinded during Study Part III. It is recommended to have the efficacy assessments at screening be done by the same blinded assessor as the following assessments, including assessments during the follow-up extension phase.

The blinded efficacy assessor should preferably be a dermatologist or, if a dermatologist is not available, a health care provider with at least 1 year of experience in performing the efficacy assessments. Health care providers with less than 1 year of experience may serve as a blinded efficacy assessor based upon the discretion and approval of the Sponsor. It is recommended that the designated blinded efficacy assessor identifies an appropriate back-up for coverage in the event of absences of the designated blinded efficacy assessor.

It is strongly recommended that the same blinded efficacy assessor who performs the baseline efficacy assessments for a subject should also perform the efficacy assessments for that subject at every subsequent visit. The blinded efficacy assessor must have no contact with the subject during the study other than the efficacy assessments. Furthermore, the blinded efficacy assessor must not discuss the subject's treatment with the subject, subject's caregiver or any site personnel at any time. Reviewing the subject's medical records, study drug administration documentation, questionnaires or the electronic CRF are not permitted. Documentation of the blinded efficacy assessment will be performed on separate forms provided by the sponsor and will be part of the source data. Data will be entered in the eCRF by the unblinded site staff.

The sponsor will provide specific BSA%, IGA, ss-IGA, PASI trainings for each site's designated efficacy assessor prior to the screening of the first subject at each site. If the efficacy assessor was trained by the sponsor in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), this training will be considered adequate for the present study. However, repetition of training prior to study start is encouraged. Training documentation of each efficacy evaluator will be maintained at the site. All efficacy assessors at a site must be listed on the Delegation Log at the site.

9.2.3.1. 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 (7). Involved BSA is calculated by using the palm of the subject's hand as equivalent to 1% of the BSA (rule of palm). In general, a BSA under 5% suggests mild psoriasis, a BSA of 5% to 10% is considered moderate, and an involved BSA of over 10% indicates severe psoriasis.

9.2.3.2. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment (IGA) (8) documents the investigator's assessment of the subject's psoriasis at a given time (Attachment 1). 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).

9.2.3.3. Scalp Specific Investigator Global Assessment (ss-IGA)

The scalp-specific (ss-)IGA instrument is used to evaluate the disease severity of scalp psoriasis (Attachment 5). 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).

9.2.3.4. Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) (8), (9) is an instrument used for assessing and grading the severity of psoriatic lesions and their response to therapy (Attachment 2). 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 to 72. A higher score indicates more severe disease.

9.2.4. Patient-reported outcomes (PROs)

The patient-reported outcomes (PRO) assessments include DLQI, PSSD (7-day version), and SF-36. The current version valid at the time point of finalization of the protocol will be used. The questionnaires contain an instruction section and will be provided in German. They will be completed on paper sheets at the study site by subjects at the appropriate visits as outlined by the TES. The order of administration is 1st DLQI, 2nd PSSD, and 3rd SF-36. All visit-specific PRO assessments during a visit should be conducted before any tests, procedures or other consultations for that visit to prevent influencing subject perceptions. Completion of the baseline PROs has to be done before randomization. Data collected on the paper sheets will be handled as source data and will be entered in the eCRF by the unblinded site staff.

9.2.4.1. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) (10) 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 produces a numeric score that can range from 0 to 30. A higher score indicates a low quality of life due to more severe disease. The estimated time to complete the questionnaire will be 2 to 5 minutes.

9.2.4.2. Psoriasis Symptom and Sign Diary

The Psoriasis Symptom and Sign Diary (PSSD) is a 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 to 10 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 average completion time will be 5 to 10 minutes.

9.2.4.3. 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.

9.3. Safety Evaluations

Safety will be monitored until end of study. Any clinically relevant health state changes occurring during the study must be recorded in the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The safety and tolerability of study drugs (guselkumab or FAE) will be monitored by collecting information on AEs, including injection site and allergic reactions, clinical laboratory testing (Hepatitis B and C, HIV, hematology, and chemistry), physical examinations, measurement of body weight and vital signs, concomitant medication review, TB test and evaluation, urinalysis, and pregnancy testing, as specified in the TES.

The study will include the following evaluations of safety and tolerability according to the times provided in the TES:

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) until end of Study Part II (ie, Week 64). During Study Part III (after Week 64) only adverse drug reactions and deaths will be recorded. Adverse events/adverse drug reactions will be followed by the investigator as specified in Section 12.

Early Detection of Active Tuberculosis (TB)

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 the scheduled visits. The following series of questions is suggested for use during the evaluation:

- Have you had a new cough of >14 days' duration or a change in a chronic cough
- Have you had any of the following symptoms: persistent fever/unintentional weight loss/night sweats
- Have you had close contact with an individual with active TB? (If there is uncertainty as to whether a contact should be considered 'close', a physician specialized in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB. Investigators should be aware that TB reactivation in immuno-compromised subjects may present as disseminated disease or with extra-pulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON® TB Gold Plus test (7), and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted.

Study drug administration should be interrupted during the investigation. A positive IGRA test result (eg, QuantiFERON® TB Gold Plus test) should be considered detection of latent TB. If the IGRA test result (eg. QuantiFERON® TB Gold Plus test) is indeterminate the test should be repeated as outlined in Section 9.1.2. Subjects in the guselkumab group who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and be encouraged to return for all subsequent scheduled study visits (see Attachment 3 for details of TB testing).

Allergic Reactions

The sponsor will proactively monitor reported AEs and query the injection site, if necessary, to capture anaphylactic reaction/serum sickness events in eCRFs.

Injection Site Reactions

An injection site reaction is any unfavorable or unintended sign that occurs at the study drug injection site. After administration of study drug at Week 0, all subjects will be carefully observed at the study site for at least 30 minutes after the SC-injection of study drug for symptoms of an injection-site reaction. If an injection site reaction is observed, the subject should be treated at the investigator's discretion. Any adverse reaction (eg, pain, erythema, and/or induration) should be noted in the Adverse Event section of the eCRF.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology, and a random urine sample for urinalysis will be collected at visits specified in the TES. Tests will be performed by a central laboratory. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents.

All abnormal laboratory values will be evaluated for clinical significance by the investigator. If clinically significant abnormal laboratory values (in the opinion of the investigator) are detected, then the test(s) should be repeated until they return to normal or are otherwise explained by the Investigator.

Instructions for collection, handling, and shipping of blood samples are provided in a Laboratory Manual.

The following tests will be performed by the central laboratory (synlab Pharma Institute, Munich):

- Hematology Panel
  - hemoglobin
  - hematocrit
  - red blood cell (RBC) count
  - white blood cell (WBC) count
  - platelet count
  - lymphocytes [%, absolute]*
  - monocytes [%, absolute]*
  - eosinophils [%, absolute]*
  - basophils [%, absolute]*
  - neutrophils [%, absolute]*

  *Subjects will be considered eligible if absolute counts are within normal limits
- Serum Chemistry Panel
  - sodium
  - potassium
  - chloride
  - alkaline phosphatase (AP)
  - urea
  - creatinine
  - glucose
  - aspartate aminotransferase (AST)
  - calcium
  - albumin
  - total protein
  - alanine aminotransferase (ALT)
  - total bilirubin
  - gamma-GT
  - follicle stimulating hormone (FSH*)

  * Testing required for selected female subjects for confirmation of the postmenopausal state as defined for the Inclusion Criteria.
- Serology: HBV, including HBV serology and HBV DNA (see Attachment 4), and antibodies to HCV and HIV.
- IGRA: eg, QuantiFERON®-TB Gold Plus test will generally be performed by the central laboratory. However, if available, test results from local laboratory can be accepted.
- Urinalysis by dipstick (eg, Combur-Test 10): If there are signs of proteins and/or glucose on urine test strip, the urine sample must be analyzed centrally.
- Central urinalysis: color, proteins, glucose, nitrites, pH, specific gravity, urobilirubin, bilirubin, ketones, blood, bacteria, yeast, crystals, casts, squamous epithelial cells, WBC, RBC

Pregnancy Testing

Urine pregnancy testing is required for all women of childbearing potential at all study visits until end of Study Part II. Pregnancy tests must be completed and negative at the study visit prior to administration of study drug (guselkumab or FAE). All pregnancy test results must be recorded in study source documents.

Vital Signs

Blood pressure and pulse measurements will be done according to the TES. If any clinically significant changes in vital signs are noted, they must be reported as AEs (see Section 12) and followed to resolution, or until reaching a clinically stable endpoint.

Physical Examination

Physical examinations will be performed as part of safety evaluation by the investigator or designated physician at visits specified in the TES. Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document and recorded in the eCRF.

Height and weight

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

9.4. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. Details on timing and frequency of sample collections are listed in the TES.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

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

10.1. Completion

A subject will be considered to have completed Study Part I if he or she has completed assessments at Week 24 of the open-label phase. For subject who completed Study Part I but do not enter Study Part II the reason for not entering the extension phase will be documented in the eCRF and in source documents.

A subject will be considered to have completed Study Part IIa when he or she has completed assessments at Week 32. 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. Subjects who prematurely discontinue study treatment for any reason before completion of the corresponding treatment phase (Study Part I through Week 24 or Study Part II through Week 56) will not be considered to have completed this study part (discontinuation before Week 24), respectively the entire study.

A subject will be considered to have completed Study Part III when he or she has completed last assessments after loss of response, withdrawal from study participation or at Week 100 at the latest.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

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

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated without evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
  - A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive IGRA, eg QuantiFERON®-TB Gold Plus test result (and/or a positive tuberculin skin test result), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study drug and continued to completion. Indeterminate IGRA, eg QuantiFERON®-TB Gold Plus test results should be handled as described in Section 9.1.2.
  - A subject treated with guselkumab receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The subject initiates a protocol-prohibited medication for his/her psoriasis (unless previously agreed to by the sponsor).
- The subject withdraws consent for administration of study drug.
- The subject is unable to adhere to the study visit schedule or to comply with protocol requirements.
- The subject develops an allergic reaction like bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study drug administration.
- The subject has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study drug. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The subject treated with FAE develops a laboratory finding that requires termination of treatment according to SmPC.

Discontinuation of study treatment should be considered, and discussed with the sponsor for subjects who develop a serious or opportunistic infection, congestive heart failure, demyelinating disease, lupus-like syndrome, cytopenias (including pancytopenia) and liver abnormalities.

If a subject discontinues study treatment for any reason before the end of the open-label phases of Study Part I or, when continuing to Study Part II, of Study Part II, end-of-treatment (Early Termination Visit) and post-treatment assessments (safety follow-up for 12 weeks after the last administration of study drug) should be obtained as indicated in the TES. However, regular safety follow-up ends for all subjects not entering Study Part III at Week 64.

Subjects who decide to discontinue study drug administration must be interviewed by the investigator to determine if a specific reason for discontinuing study drug can be identified. Subjects should be explicitly asked about the contribution of possible AEs to their decision to discontinue study drug; investigators should confirm that any AE information elicited has been documented.

If a subject elects to discontinue study drug due to an AE, the event should be recorded as the reason for study drug discontinuation, even if the investigator's assessment is that the AE would not require study drug discontinuation. The reason for study drug discontinuation must be documented in the eCRF and in

source documents. Study drug assigned to a subject who discontinues may not be assigned to another subject.

Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Start of a protocol-prohibited medication/therapy during Study Part III

If a subject discontinues study drug and withdraws from the study before the end of the open-label treatment phases of Study Part I or, when continuing to Study Part II, of Study Part II, end-of-treatment (Early Termination Visit) and post-treatment assessments (Safety Follow-up) should be obtained as indicated in the TES.

A subject's study participation from Study Part III must be discontinued if a protocol-prohibited medication/therapy (for his/her psoriasis or another indication) is started before completion of the final study visit after loss of response or at Week 100.

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

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

For subjects not completing Study Part I, ie, who withdraw from study participation before or at Week 24 as for subjects entering but not completing Study Part II, ie, who withdraw from study participation after Week 24 but before or at Week 56 every effort should be made to conduct the final assessments (Early Termination Visit) as indicated in the TES. For subjects who are not eligible for Study Part II and withdraw from the safety follow-up before Week 32 and for subjects enter Study Part II but withdraw from study participation after Week 56, every effort should be made to conduct the safety follow-up visit (Week 32 for Study Part I or Week 64 for Study Part II), as indicated in the TES. Similarly, for subjects who are not eligible for Study Part III, the Study Part II safety follow-up visit (Week 64) should be performed, as indicated in the TES. For subjects not completing Study Part III, every effort should be made to conduct a final study visit (FSV Part III) as indicated in the TES.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the study, final study assessments should be obtained (Early Termination Visit, as outlined in TES).

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP). The SAP will be divided in three separate documents describing analyses for the three study parts. Additional analyses may be performed for evaluations on health technology assessment (HTA). These analyses are not included in this clinical protocol and will be specified in a separate HTA SAP, if applicable.

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

Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Graphical data displays may also be used to summarize the data. The chi-square test will be used to compare the proportion of subjects responding to treatment. Continuous response parameters will be compared using an analysis of variance model with baseline value as a covariate. 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).

11.1. Subject Information

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

11.2. Sample Size Determination

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 (ie, $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive. 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 7: 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				

11.3. Efficacy Analyses

Analysis Data Set

For all efficacy analyses to compare guselkumab vs. FAE in Study Part I (Week 24 analysis), all randomized subjects will be included. For all the efficacy analyses, subjects will be analyzed according to the treatment group to which they were randomized regardless of the treatment they actually received ("intent-to-treat" principle). Additionally, all efficacy analyses will be performed with all randomized subjects that received at least one dose of study drug. For all efficacy analyses to compare guselkumab vs. FAE in Study Part II (Week 64 analysis), subjects will be analyzed according to the treatment they actually received. For all efficacy analyses in the follow-up extension phase (Study Part III, Week 100 analysis), subjects who entered Study Part III and received guselkumab from Week 0 and subjects who received FAE from Week 0 to Week 32 and switched to guselkumab will be analyzed.

The confirmatory statistical analysis of the primary and major secondary endpoints will be performed after all subjects have completed the Week 24 visit or have terminated the study prematurely. First data base lock (DBL) will be after the Week 24 visit data are ready for statistical analysis (ie, clean data). All analyses including all primary and secondary analyses as well as additional analyses as described in detail in the SAP for Week 24 analysis will be performed after DBL.

The second statistical analysis will be performed after all subjects have completed the Week 64 visit or have terminated the study prematurely. Second data base lock (DBL) will be after the Week 64 visit data are ready for statistical analysis (ie, clean data). All analyses will be performed after DBL and will be described in detail in the SAP for Week 64 analysis. Following the rationale for Study Part II, the Week 64 analysis will focus on PASI 75 responders and PASI 75 non-responders taking into account the switch decision.

The third statistical analysis will be performed after all subjects have completed the Week 100 visit or have terminated the study prematurely or lost their response. Third data base lock (DBL) will be after the Final Study Visit/Week 100 visit data are ready for statistical analysis (ie, clean data). All analyses will be performed after DBL and will be described in detail in the SAP for Week 100 analysis. Following the rationale for Study Part III, the Week 100 analysis will focus on PASI 90 responders at Week 56 taking into account baseline disease characteristics and study treatment to explore prediction parameters of disease modification.

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) 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. Subjects who discontinue study treatment or who started a protocol-prohibited medication/therapy during the study (Section 11.4, Section 8.1.1) before Week 24 will be considered non-responders for the primary endpoint at Week 24. In addition, subjects who do not return for evaluation at Week 24 will be considered non-responders at Week 24.

To address the primary objective, a two-sided ($\alpha = 0.05$) 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 group and for the difference between the two groups.

Major Secondary Endpoints

The major secondary endpoints will comprise the endpoints as defined in Section 9.2.2. For the major secondary analyses, the chi-square test will be used to compare the proportion of subjects responding to treatment. Summary tabulation and analyses will be performed analogously to the primary endpoint. 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 (ie, $p < 0.05$), and the second major secondary endpoint will be tested only if the first major secondary endpoint is positive.

Other Secondary Endpoints

The other secondary endpoints will comprise the endpoints as defined in Section 9.2.2. For the other secondary analyses including Study Part II and Part III analyses, the chi-square test will be used to compare the proportion of subjects responding to treatment. Summary tabulation will be performed analogously to the primary endpoint. Continuous response parameters will be compared using an analysis of variance model with baseline value as covariate. Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to-event. All statistical tests will be performed two-sided and are to be interpreted in the exploratory sense only.

Subgroup and Sensitivity Analyses

Subgroup analyses will be performed to evaluate consistency of the primary endpoint and selected major secondary endpoints over demographics and baseline disease characteristics. Additional subgroup and sensitivity analyses may be performed and will be documented in the SAPs.

Handling of Missing Data

All available data will be included in the analyses and will be summarized as far as possible. In general, there will be no substitution of missing data, ie, missing data will not be replaced, missing data will be handled as 'missing' in the statistical evaluation ('observed cases analysis'). Subjects who discontinue study treatment or who do not return for evaluation at Week 24 or 56 will be considered non-responders at Week 24 and 56, respectively.

In case of premature termination, the last available observation after baseline will be calculated and used for analysis for continuous response parameters (LOCF = Last Observation Carried Forward approach). LOCF will also be used as sensitivity analysis for binary response parameters. Additional sensitivity analyses may be done by applying different imputation rules for missing data. A more detailed description of the handling of missing data will be provided in the SAPs.

11.4. Criteria for Endpoints

PASI 75 Responders: Subjects with ≥75% improvement in PASI from baseline.

PASI 90 Responders: Subjects with ≥90% improvement in PASI from baseline.

PASI 100 Responders: Subjects with 100% improvement in PASI from baseline

Loss of Response, Study Part III: Increase in absolute PASI >5

11.5. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, ADRs, SADRs, infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. A general description of the planned safety analyses is provided below. Details will be specified in the SAPs.

Analysis Data Set

For all safety analyses to compare guselkumab vs. FAE, all randomized subjects treated with at least one dose of study drug (guselkumab or FAE) will be included. For all the safety analyses, subjects will be analyzed according to the treatment they actually received. A main safety analysis will be performed after all subjects have completed their visit 24 weeks after randomization or discontinued earlier (with the confirmatory analysis). Safety analyses covering the time until Week 64 and until Week 100 safety visits will be performed separately with the Week 64 and Week 100 analyses.

Adverse Events/Adverse Drug Reactions

The verbatim terms used in the eCRF by investigators to identify adverse events (AEs) or adverse drug reactions (ADRs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. (S)ADRs documented during Study Part III will be treated correspondingly.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious adverse event (SAE) or serious adverse drug reaction (SADR). The incidence of injection site reactions, SAEs, SADRs and premature discontinuations due to AEs/ADRs will be summarized separately.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAPs) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory item at baseline and 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). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory result (eg, CTCAE grade 3 or higher) will also be provided.

Vital Signs

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

Physical Examination

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

11.6. Interim and Final Analyses

The confirmatory analysis is planned to be performed at the end of Study Part I, ie, after all subjects have completed their visit at 24 weeks after randomization or discontinued earlier. This analysis will include the confirmatory analysis of the primary endpoint, the major secondary endpoints and all other predefined efficacy and safety analyses until Week 24.

The second exploratory analysis will occur after all subjects have completed their visit at 64 weeks after randomization or discontinued earlier. This analysis will include the safety analysis and all efficacy measures after Week 24 and will cover the time until the Week 64 safety visit.

The third and final exploratory analysis will occur after all subjects have completed their visit at 100 weeks after randomization or discontinued earlier. This analysis will include the safety analysis and all efficacy measures after Week 64 and will cover the time until the Week 100 safety visit.

12. ADVERSE EVENT/ADVERSE DRUG REACTION REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event/Adverse Drug Reaction Definitions and Classifications

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition of International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor will collect adverse events starting with signing of the ICF (see Section 12.3.1).

Adverse Drug Reaction

An ADR is defined as all untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered. 'Response to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is possible, probable, or very likely. Thus, an ADR is characterized by the fact that a causal relationship between the medicinal product and the occurrence of the event is suspected. All adverse events judged by either the investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

Serious Adverse Event/Serious Adverse Drug Reaction

A serious adverse event (SAE)/serious adverse drug reaction (SADR) based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event/adverse drug reaction occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/ Adverse Drug Reaction/ Reference Safety Information

An adverse event is considered unlisted, if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For Fumaderm® initial/ Fumaderm® with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the prescribing information.

Adverse Event Associated With the Use of the Drug/ Adverse Drug Reaction

An adverse event is considered an Adverse Drug Reaction if it is associated with the use of the drug meaning if the attribution is possible, probable, or very likely by the definitions listed in the following Section 12.1.2.

12.1.2. Attribution Definitions

Not Related: An adverse event that is not related to the use of the drug.

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

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

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

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

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation; prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded in the Serious Adverse Event section of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events/Adverse Drug Reactions

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure of Study Part II, which may include contact for follow-up of safety.
Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study drug, must be reported using the Serious Adverse Event Form. During follow-up extension phase (Study Part III), all adverse events suspected to be related to the use of the drug (Adverse Drug Reactions, ADRs, Section 12.1.1) and deaths are recorded until final study visit of Study Part III. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, and all adverse drug reactions regardless of seriousness and severity must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events/adverse drug reactions to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs).

The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study.

The wallet card indicates the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events/Serious Adverse Drug Reactions

All serious adverse events/adverse drug reactions occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events/adverse drug reactions will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event/adverse drug reactions should be made by facsimile (fax).

All serious adverse events/adverse drug reactions that have not resolved by end of the study, or that have not resolved upon discontinuation of the subject's study participation, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event/adverse drug reaction (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study within 12 weeks of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event. During participation in Study Part III, the cause of death of a subject is also considered a serious adverse event and must be reported using the Serious Adverse Event Form.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be

reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

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

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study drug in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3. Investigators are also advised that active TB is considered a reportable disease in Germany. These events are to be considered serious only if they meet the definition of a serious adverse event.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (see Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The guselkumab supplied for this study is a sterile liquid for SC injection in a single-use PFS assembled in an UltraSafe PLUS™ Passive Needle Guard (PFS-U). Each single-use PFS-U contains 100 mg (1 mL fill

of liquid) guselkumab in a 1 mL glass syringe with a 27 gauge, 1/2 inch fixed needle and a latex-free rigid needle shield. No preservatives are present. The guselkumab solution should be essentially free of visible particulate matter. The PFS-U is a passive safety needle guard that is permanently assembled on the syringe and incorporates a spring driven shield that automatically extends beyond the PFS needle following complete injection of the guselkumab PFS contents. Guselkumab will be manufactured and provided under the responsibility of the sponsor. A list of excipients can be found in the Investigator's Brochure.

Commercially available Fumaderm® initial/ Fumaderm® blisters will be repackaged and supplied as an active comparator to the study sites. Details on the drug can be found in the Fumaderm® initial/ Fumaderm® SmPC, and details regarding the Fumaderm® initial/ Fumaderm® drug product are available in the Site Investigational Product Manual.

14.2. Packaging

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

Fumaderm® initial/ Fumaderm® is sourced as blisters in a commercial carton. The sponsor will take the Fumaderm® blisters out of the commercial cartons and will place them in a new package to ensure child resistant packaging for the take home Fumaderm® medication.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Guselkumab must be stored at controlled temperatures ranging from 2°C to 8°C, and protected from light. Vigorous shaking of the product should be avoided. The sterile product does not contain preservatives and is designed for single use only. Protection from light is not required during administration.

Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used. Study drug in PFS will be ready to use. Aseptic procedures must be used during the preparation and administration of the study material.

Further details regarding the storage of guselkumab will be provided in the Site Investigational Product Manual.

Further details regarding the preparation and storage of FAE can be found in the Fumaderm® initial/ Fumaderm® SmPC.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drugs received at the site are inventoried and accounted throughout the study. The dispensing of FAE to the subject, and the return of FAE from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. Guselkumab administered to the subject must also be documented on the drug accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with protocol and container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return of unused study drug to the sponsor, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under supervision of the investigator or a qualified member of the site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Counting remaining FAE tablets during the study visits for compliance check is not considered as a return and re-dispense. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator’s Brochure for guselkumab
- SmPC (“Fachinformation”) for Fumaderm® initial/Fumaderm®
- Site investigational product manual
- Laboratory manual
- Paper PRO questionnaires including completion guideline section
  - DLQI
  - PSSD (7-days)
  - SF-36
- Electronic Data Capture (EDC) Manual
- Trial Center File
- Sample ICFs
- Paper forms to document efficacy assessment by blinded efficacy assessor (BSA, IGA, ss-IGA and PASI)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Thorough scientific evaluation of a new therapy is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to compare new drugs with those already established on the market. This study is being conducted to compare SC administration of guselkumab with orally taken FAE tablets as treatment of moderate or severe psoriasis.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the study status at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

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

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. To meet the scope of this amendment three separate ICFs have been developed to cover Study Parts I, II and III. The ICF(s) must be signed before performance of any study-related activity (ICF I at screening, ICF II at Week 24 at the latest, ICF III at Week 64 at the latest). The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study or in Parts II or III of the study, if applicable, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent

to participate at any time. They will be informed that choosing not to participate will not affect any care the subject will receive for treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also re-contact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before study entry, consent will be appropriately recorded by means of the subject's personally dated signature. After having obtained consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to the subject's original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. If the changes involve only logistic or administrative aspects of the study, the IEC/IRB (where required) will only be notified.

During the study course, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the Paul-Ehrlich Institute (PEI).

A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICFs, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/ license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification number and year of birth.

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

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. The author of an entry in the source documents should be identifiable. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly in the eCRF and will be considered source data:

- Blood pressure and pulse
- Height and weight
- Investigator-completed scales and assessments

The minimum source documentation requirements for Section 4.1 and Section 4.2 specifying the documentation of medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be used, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

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

All subjective measurements (eg, questionnaires) will be completed by the same individual (ie, blinded efficacy assessor) who made the initial baseline determinations whenever possible. Results of efficacy assessments performed by the blinded efficacy assessor (in Study Part I and II) will be entered in the eCRF by unblinded study personnel as described in Section 9.2.3. Corresponding documentation (separate forms) is part of the source data.

If necessary, queries will be generated in the EDC tool. If corrections to data are needed after the initial entry in the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- Sponsor or sponsor delegate can generate queries for resolution by the investigator and site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples. Guidelines for eCRF completion will be provided and reviewed with study-site personnel before start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable

regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor. If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (remote and on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered in the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on study progress at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

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

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator.

The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews

will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication.

Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose existence of and results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Investigator´s Global Assessment (IGA)

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)
0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, > 1 mm

Erythema (E) (averaged over all lesions)
0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration

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

Total Average = (I + E + S) / 3
(Average will be calculated in the device but not displayed. Numeric result will be included in data transfer.)

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

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

Attachment 2: Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

$$PASI = 0.1 (E_h + I_h + S_h) A_h + 0.3 (E_t + I_t + S_t) A_t + 0.2 (E_u + I_u + S_u) A_u + 0.4 (E_l + I_l + S_l) A_l$$

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

Attachment 3: QuantiFERON TB Gold Plus Test

The QuantiFERON®-TB Gold Plus (QFT®-Plus) test is one of the interferon-γ (IFN-γ) based blood assays for TB screening. It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 to detect in vitro cell-mediated immune responses in infected individuals. The QFT®-Plus assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic M. *tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QFT®-Plus test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii, M. marinum*, and *M. szulgai.* Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of a precursor of the QFT®-Plus test (QuantiFERON®-TB Gold test, QFT® test) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QFT® assay in immunosuppressed populations suggest that the sensitivity of the QFT® test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QFT® test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QFT® test result (Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004).

Performing the QuantiFERON® TB Gold Plus Test (according to QFT®-Plus ELISA Package Insert 02/2015)

The QuantiFERON® TB Gold Plus test uses specialized blood collection tubes, which include a Nil tube (gray), TB1 tube (green), TB2 tube (yellow), and a Mitogen tube (purple). The Mitogen tube is used with the QFT®-Plus test as a positive control and as a control for correct blood handling and incubation. The Nil tube adjusts for background (e.g., excessive levels of circulating IFN-γ or presence of heterophile antibodies). The IFN-γ level of the Nil tube is subtracted from the IFN-γ level for the TB Antigen tubes and Mitogen tube.

To perform the test, blood is drawn through standard venipuncture into supplied tubes. A total of 4 tubes will be needed per subject, each requiring 1 mL of blood. Tubes should be between 17°C to 25°C at the time of blood filling. Antigens have been dried onto the inner wall of the blood collection tubes so it is essential that the contents of the tubes be thoroughly mixed with blood (shake them 10 times). The QFT®-Plus tubes should be incubated at 37°C as soon as possible, and within 16 hours of collection.

Following a 16 to 24 hour incubation period at 37°C, the tubes are shipped (ambient temperature) to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

If available, test results from local laboratory can be accepted.

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Attachment 4: Hepatitis B Virus (HBV) Screening with HBV DNA

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

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

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+
* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

Attachment 5: Scalp-specific IGA (ss-IGA)

Subjects with psoriasis of the scalp will be assessed using the 5-point ss-IGA presented below.

Only subjects with an ss-IGA score ≥2 at baseline will be included in the subset of subjects analyzed for efficacy.

Details of the Scalp-Specific Investigator Global Assessment (ss-IGA)

Score	Category	Description
0	Absence of Disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp.
1	Very Mild Disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild Disease	The overall clinical picture consists of lesions with mild erythema, slight, but definite, thickness, and a thin scale layer
3	Moderate Disease	The overall clinical picture consists of lesions with moderate erythema, a moderate thickness, and a moderate scaled layer
4	Severe Disease	The overall clinical picture consists of lesions with bright erythema, severe thickness and a severe, coarse thick scale

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator:

Name (typed or printed): Prof. Dr. med. Diamant Thaci

Institution and Address: Uni[redacted]tein, Campus Lübeck
Exz[redacted]in
[redacted]

Telephone Number: [redacted]

Signature: [redacted] Date: 25-JAN-2018

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed):

Institution and Address:

Telephone Number:

Signature: Date:

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Sven Wegner, MD, PhD

Institution: Janssen-Cilag GmbH, Neuss
Johnson & Johnson Platz 1,
[redacted] Germany

Telephone Number: [redacted]

Signature: [redacted] Date: 23/01/2018

(Day Month Year)

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

LAST PAGE