

Global Medical Affairs - General Medicine

AIN457/secukinumab

Clinical Study Protocol CAIN457A2403 / NCT03553823

A 16-week randomized, open-label, multicenter study to assess the superiority of secukinumab over guselkumab in the complete treatment of ustekinumab-resistant psoriatic plaques – ARROW

Document type:	Clinical Study Protocol
EUDRACT number:	2018-001048-70
Version number:	00 (Original Protocol)
Clinical study phase:	2a
Release date:	22-May-2018

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Clinical Study Protocol Template Version 1.0 (01-Dec-2017)



Table of contents

Table of contents	2
List of tables	5
List of figures	5
List of abbreviations	6
Glossary of terms	7
Protocol summary	9
1 Introduction	12
1.1 Background	12
1.2 Purpose	13
2 Objectives and endpoints	14
3 Study design	14
4 Rationale	15
4.1 Rationale for study design	15
4.2 Rationale for dose/regimen and duration of treatment	16
4.3 Rationale for choice of comparator	16
4.4 Purpose and timing of interim analyses/design adaptations	16
4.5 Risks and benefits	16
4.5.1 Risks	16
4.5.2 Benefits	18
5 Population	18
5.1 Inclusion criteria	18
5.2 Exclusion criteria	18
6 Treatment	21
6.1 Study treatment	21
6.1.1 Investigational and control drugs	21
6.1.2 Additional study treatments	21
6.1.3 Treatment arms	21
6.1.4 Treatment duration	21
6.2 Other treatments	21
6.2.1 Concomitant therapy	22
6.2.2 Prohibited medication	22
6.3 Subject numbering, treatment assignment, randomization	23
6.3.1 Subject numbering	23
6.3.2 Treatment assignment, randomization	23
6.4 Treatment blinding	23

9.1	Discontinuation.....	40
9.1.1	Discontinuation of study treatment.....	40
9.1.2	Withdrawal of informed consent.....	41
9.1.3	Lost to follow up.....	42
9.1.4	Early study termination by the Sponsor.....	42
9.2	Study completion and post-study treatment.....	42
10	Safety monitoring and reporting.....	43
10.1	Definition of adverse events and reporting requirements.....	43
10.1.1	Adverse events.....	43
10.1.2	Serious adverse events.....	44
10.1.3	Serious adverse event reporting.....	45
10.1.4	Pregnancy reporting.....	46
10.1.5	Reporting of study treatment errors including misuse/abuse.....	46
10.2	Additional safety monitoring.....	46
11	Data collection and database management.....	47
11.1	Data collection.....	47
11.2	Database management and quality control.....	47
11.3	Site monitoring.....	48
12	Data analysis and statistical methods.....	48
12.1	Analysis sets.....	49
12.2	Subject demographics and other baseline characteristics.....	49
12.2.1	Demographics and baseline characteristics.....	49
12.2.2	Medical history.....	49
12.3	Treatments.....	49
12.3.1	Study treatments.....	49
12.3.2	Prior and concomitant treatments.....	49
12.4	Analysis of the primary endpoint.....	49
12.4.1	Definition of primary endpoint.....	49
12.4.2	Statistical model, hypothesis, and method of analysis.....	50
12.4.3	Handling of missing values/censoring/discontinuations.....	50
12.4.4	Sensitivity and supportive analyses.....	50
12.5	Analysis of secondary endpoints.....	50
12.6	Analysis of exploratory endpoints.....	50
12.7	Safety analysis.....	51
12.8	Interim analyses.....	52
12.9	Sample size calculation.....	52
12.9.1	Primary endpoint.....	52

13	Ethical considerations and administrative procedures	53
13.1	Regulatory and ethical compliance.....	53
13.2	Responsibilities of the Investigator and IRB/IEC	53
13.3	Publication of study protocol and results.....	54
13.4	Quality control and quality assurance.....	54
14	Protocol adherence	54
14.1	Protocol amendments.....	55
15	References	55
16	Appendices	58
16.1	Appendix 1: Clinically notable laboratory values and vital signs	58
16.2	Appendix 2.....	59
16.2.1	Skin type classification scale	59

List of tables

Table 2-1	Objectives and related endpoints	14
Table 6-1	Investigational and control drug.....	21
Table 6-2	Prohibited medication	22
Table 6-3	Study treatment administration schedule	25
Table 8-1	Assessment schedule.....	27
Table 8-2	Assessments of total clinical score.....	31
		34
		35
Table 8-5	Physical assessments.....	36
Table 8-6	Laboratory assessments.....	37
Table 10-1	Guidance for capturing the study treatment errors including misuse/abuse	46
Table 12-1	Exact 95% confidence intervals for P1 and P2, the corresponding difference P1-P2, and the estimated power of the Fisher's exact test for different P1 and P2 values.....	53

List of figures

Figure 1-1	Central role of IL-17A in psoriasis	12
Figure 3-1	Study design	15



Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), tissue, urine, [REDACTED] etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical study	The end of the clinical study is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Period	The subdivisions of the study design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical study database setup and eventually in analysis
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical study. This data includes subject identifier information, study information, and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
Screen failure	A subject who did not meet one or more criteria that were required for participation in the study
Source data/document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.



Start of the clinical study	The start of the clinical study is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A study participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when the subject does not want to participate in the study any longer, and does not allow any further collection of personal data.



Protocol summary

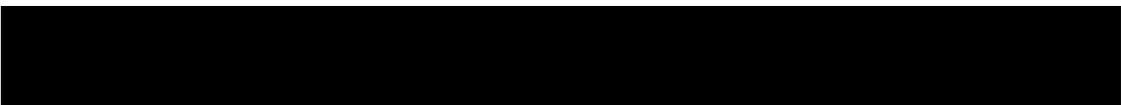
Protocol number	CAIN457A2403
Full title	A 16-week randomized, open-label, multicenter study to assess the superiority of secukinumab over guselkumab in the complete treatment of ustekinumab-resistant psoriatic plaques – ARROW
Brief title	Comparison of secukinumab versus guselkumab in clearing psoriatic plaques refractory to ustekinumab
Sponsor and clinical phase	Novartis Pharma AG Clinical Phase 2a
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The aim of this study is to assess the superiority of direct IL-17A inhibition with secukinumab as compared with the selective inhibition of IL-23 with guselkumab (p19 subunit blocker) in controlling inflammation in psoriatic plaques that remain active despite treatment with the non-selective IL-23 inhibitor ustekinumab (blocker of p40 subunit, shared by IL-12 and IL-23).
Primary objective	To assess the superiority of secukinumab over guselkumab in controlling clinical activity in psoriatic plaques resistant to treatment with ustekinumab.
Secondary objectives	Not applicable.
Exploratory objectives	<p>[REDACTED]</p> <p>2. To compare the effect of secukinumab versus guselkumab on the microscopic morphology of the skin plaque</p> <p>3. To compare the effect of secukinumab versus guselkumab on the number of IL-17A and IL-23R positive immune cells infiltrating the skin plaque</p> <p>4. To compare the effects of secukinumab versus guselkumab on the composition of inflammatory infiltrate in the skin plaque</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Study design	This is a 16-week, randomized, open-label, parallel-group, active-control, Phase 2a study comparing secukinumab 300 mg s.c. versus guselkumab 100 mg s.c. in subjects with plaque psoriasis who had an inadequate response to ustekinumab.
Population	The study population will consist of a total of 40 male and female subjects aged 18 years or older, who have chronic plaque-type psoriasis considered inadequately controlled after treatment with ustekinumab.



Key inclusion criteria	<ol style="list-style-type: none">1. Signed informed consent must be obtained prior to participation in the study2. Men or women \geq 18 years of age at the time of consent3. Chronic plaque-type psoriasis considered inadequately controlled after treatment with ustekinumab according to the following criteria:<ul style="list-style-type: none">o ustekinumab administered at a dose equal or higher than that on the label for at least 24 weeks. The last administration must be at least 12 weeks before randomizationo absolute psoriasis area and severity index (PASI) score of 1-10 at Screening4. Presence of at least 1 refractory skin plaque, defined by a total clinical score (TCS) of at least 6 and severity score of at least 2 or 3 (moderate) for each individual item, with an area \geq 10 cm² at Screening and Baseline (Day 1)
Key exclusion criteria	<ol style="list-style-type: none">1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic, and guttate psoriasis) at Screening or Baseline2. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Screening or Baseline3. Previous treatment with more than one tumor necrosis factor alpha (TNFα) inhibitors or with IL-17A (including secukinumab), IL-17R or IL-23 (including guselkumab) inhibitors
Study treatment	Secukinumab 300 mg s.c and guselkumab 100 mg s.c
Efficacy assessments	<ul style="list-style-type: none">• Total clinical score█ [REDACTED]• Microscopic morphology of the skin plaque• Infiltrating immune cells in the skin plaque• Composition of the inflammatory infiltrate in the skin plaque█ [REDACTED]█ [REDACTED]█ [REDACTED]█ [REDACTED]
Other assessments	<p>Safety:</p> <ul style="list-style-type: none">• Physical examination• Vital signs• Height and weight• Laboratory evaluations (hematology, clinical chemistry, urinalysis)• Pregnancy test• Electrocardiogram (ECG)• Adverse events (AEs) and serious adverse events (SAEs) <p>Additional:</p> <ul style="list-style-type: none">█ [REDACTED]█ [REDACTED]█ [REDACTED]



Data analysis	<p>The number (%) of subjects of subjects whose plaque achieves “clear” or “almost clear” status (TCS = 0-2) by Week 16 treatment with secukinumab or guselkumab (i.e., responders) will be provided based on the full analysis set (FAS) together with the 95% confidence interval using the exact method for the difference in proportions of responders in each arm.</p> <p>Furthermore, a 1-sided Fisher’s exact test for the difference in the proportions of responders in the secukinumab (P1) and gesulkumab (P2) arms, H0: $P1-P2 \leq 0$ versus H1: $P1-P2 > 0$ at a Type I error rate of 0.05 will be performed.</p> <p>Subjects who discontinue between Week 4 and Week 16 will be required to complete the End-of-study Visit assessments. The plaque status based on the TCS at the End-of-study Visit will be used for the primary endpoint assessment i.e., the last observation carried forward approach will be applied.</p>
Keywords	Plaque psoriasis, secukinumab, guselkumab, [REDACTED]



1 Introduction

1.1 Background

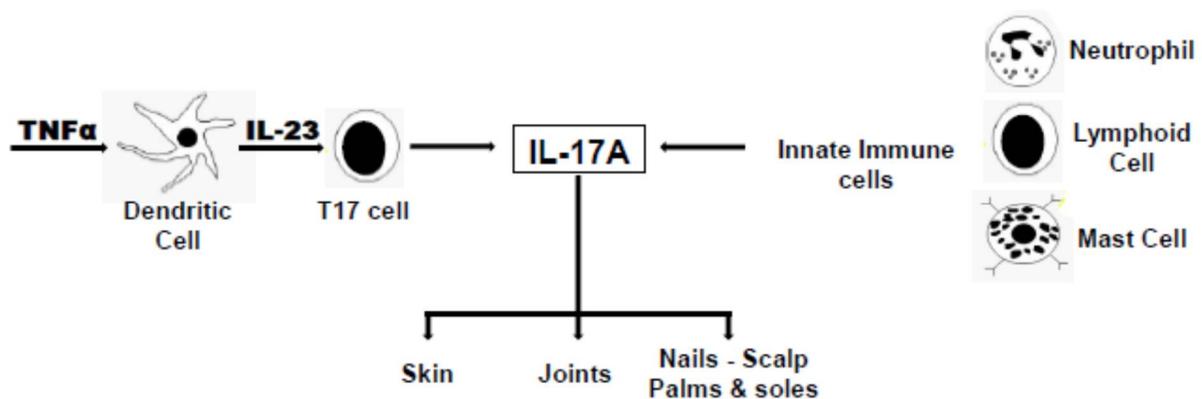
Interleukin17-A (IL-17A) is a key effector cytokine of skin and joint inflammation in psoriasis (Keijsers et al 2014, Lowes et al 2013). It stimulates keratinocytes to release inflammatory molecules that mediate skin damage and recruit neutrophils, monocytes, Th17 cells and other cell types sustaining the inflammatory response through a positive chemotactic feedback loop (Keijsers et al 2014, Reich et al 2015, Hawkes et al 2017). Moreover, IL-17A mediates tissue damage in joints and atherosclerotic plaques (Keijsers et al 2014, Paulissen et al 2013, Cornelissen et al 2013).

The central role of IL-17A is also related to its synergistic activity with many different upstream cytokines and tissue-related factors involved in skin and joint inflammation such as IL-6 (Ogura et al 2008), TNF α (Noack and Miossec 2017, Bosteen et al 2014, Johansen et al 2016), IL-22 (Murakami et al 2011, Dixon et al 2016, Tohyama et al 2009), IFN γ (Simanski et al 2013), BMP-2 (Croes et al 2016), LCN2 (Hau et al 2016), and LL37 (Chen et al 2013), establishing self-reinforcing cycles orchestrated by IL-17A itself.

It has been recently shown in patients with plaque psoriasis that after 52 weeks of treatment with the IL-17A inhibitor secukinumab, the mRNA levels of upstream cytokines along the T17 pathway – including IL-23, IL-12, IL-17A, IL-17F, IL-22, and IL-26 – decreased to the level of healthy controls (Lebwohl et al 2017).

IL-17A production in response to IL-23 is dependent on the presence of the IL-23 receptor in both T17 and innate immune cells (Figure 1-1). However, additional inflammatory cytokines can promote IL-23-independent production of IL-17A in subsets of innate cell populations (Sofen et al 2014, Patel et al 2012). For example, innate immune cells expressing the T-cell receptor (TCR, e.g., $\gamma\delta$ -T cells) can be activated by direct ligation of TCR or pattern recognition receptors (PRR) (Housseau et al 2016) and iNKT cells can be activated by IL-18 or α -GalCer, in turn releasing IL-17A (Cua and Tato 2010, Yoshiga et al 2008).

Figure 1-1 Central role of IL-17A in psoriasis



The availability of biologic drugs in clinical practice gives the unique opportunity to assess the effect of direct blocking of single cytokines in human psoriasis, thus exploring *in-vivo* their role in the pathogenesis of the underlying disorder. Anti-TNF α , anti-IL-12/IL-23p40 and anti-IL-23p19 agents all block the development program of T17 cells (Keijsers et al 2014). These drugs have shown various degrees of efficacy in controlling inflammation in plaque psoriasis and psoriatic arthritis.

It has been recently shown that inadequate response to IL-12/23 inhibition with ustekinumab in psoriatic plaques is related to the persistence of IL-17A produced independently from IL-23 by innate immune cells (Jack et al 2017). Innate immune cells seem to play a prominent role in inducing inflammation in difficult-to-treat areas (namely nails, scalp, palm and soles) and joints (Keijsers et al 2014, Paulissen et al 2013, Cornelissen et al 2013, Bissonette et al 2014, Appel et al 2011). This is consistent with the observation of a suboptimal efficacy of ustekinumab in palmoplantar psoriasis (Bissonette et al 2014) and in axial spondyloarthritis, suggesting disconnect regarding the importance of IL-23 in the skin versus difficult to treat areas and joints.

In addition, it has been shown that the selective inhibition of IL-23 through p19 blockers (guselkumab) is associated with persistence of significant amounts of IL-17A at the site of inflammation and in circulation (Sofen et al 2014). This is possibly due to IL-23-independent release of IL-17A by innate immune cells in the skin and in circulation.

Jack et al (2017) have recently observed that patients treated with ustekinumab can present discrete refractory active plaques despite a good response on other skin locations. They have shown in biopsies of those active plaques the persistence of IL-17A and human β -defensin-2 (hBD2) at the same levels as in plaques from untreated patients. They also showed that IL-23 levels are highly increased in those plaques but not the IL-23 receptor on infiltrating immune cells. Infiltrating cells in those plaques consisted of IL-17A+ T lymphocytes (same levels as untreated plaques) and IL-17A+ cells other than T lymphocytes. Those alternative cells were not further characterized, but the authors postulated that they may include mast cells or innate lymphoid type 3 immune cells (Mashiko et al 2015, Villanova et al 2014). Taken together, these data suggest that psoriatic plaques refractory to ustekinumab are infiltrated with non-T17 cells (likely innate immune cells) which actively produce IL-17A independently of IL-23.

Considering that direct targeting of IL-17A allows inhibition of the activity of this cytokine irrespective of its cellular source, possibly overcoming the issue of IL-23-independent IL-17A release, we hypothesize that secukinumab may be more effective than the selective IL-23p19 inhibitor guselkumab in clearing inflammation in inadequate responders (see [Inclusion criterion 5.1](#)) to ustekinumab since under those conditions IL-17A appears to be produced in an IL-23-independent manner.

1.2 Purpose

The aim of this study is to assess the superiority of direct IL-17A inhibition with secukinumab as compared with the selective inhibition of IL-23 with guselkumab (p19 subunit blocker) in controlling inflammation in psoriatic plaques that remain active despite treatment with the non-selective IL-23 inhibitor ustekinumab (blocker of p40 subunit, shared by IL-12 and IL-23).

Data from this study will help describe which immune cells may drive IL-17A-mediated inflammation that escapes control from IL-12/23p40 inhibition in plaque psoriasis.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	Endpoint for primary objective
To assess the superiority of secukinumab over guselkumab in controlling clinical activity in psoriatic plaques resistant to treatment with ustekinumab	Proportion of subjects whose plaque achieves “clear” or “almost clear” status (TCS = 0-2, see Section 8.3.1) by 16 weeks of treatment with secukinumab or guselkumab
Exploratory objectives	Endpoints for exploratory objectives
[REDACTED]	[REDACTED]
<ol style="list-style-type: none"> 2. To compare the effect of secukinumab versus guselkumab on the microscopic morphology of the skin plaque 3. To compare the effect of secukinumab versus guselkumab on the number of IL-17A and IL-23R positive immune cells infiltrating the skin plaque 4. To compare the effects of secukinumab versus guselkumab on the composition of inflammatory infiltrate in the skin plaque 	<ol style="list-style-type: none"> 2. Change from Baseline to Week 16 in epidermal thickness and in the number of Ki-67 and K16 positive cells of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy (Section 8.3.4) 3. Change from Baseline to Week 16 in the number of infiltrating cells expressing IL-17A and IL-23R of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy (Section 8.3.5) 4. Change from Baseline to Week 16 in the number of different immune cell types in the inflammatory infiltrate of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy (Section 8.3.6)
[REDACTED]	[REDACTED]

3 Study design

This is a 16-week, randomized, open-label, parallel-group, active-control, Phase 2a study comparing secukinumab 300 mg s.c. versus guselkumab 100 mg s.c. in subjects with plaque psoriasis who had an inadequate response to ustekinumab (see [Inclusion criterion 5.1](#)).

[REDACTED]

Inadequate responders are defined as subjects who, after treatment with ustekinumab at a dose equal or higher than that on the label for at least 24 weeks, present a PASI of 1-10 and one or more refractory skin plaques, defined by a TCS of at least 6 and an area ≥ 10 cm² at Baseline.

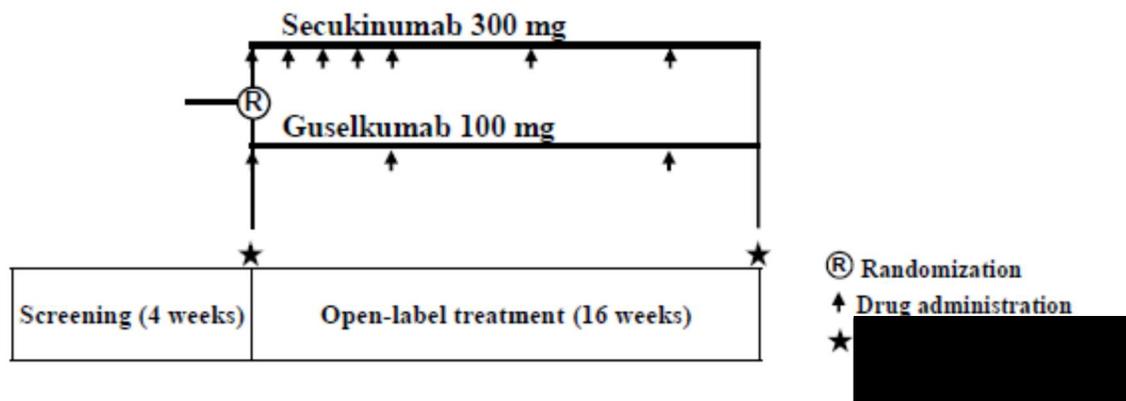
At Baseline (Day 1), subjects will be randomized to treatment with secukinumab or guselkumab in a 1:1 ratio. Secukinumab will be self-administered as two 150-mg s.c. injections at Baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 12 inclusive. Guselkumab will be self-administered as 100-mg s.c. injections at Baseline, Weeks 4, and 12. The initiation of study treatment at Baseline should not happen earlier than 12 weeks after the last administration of ustekinumab.

Forty subjects will be enrolled and treated for 16 weeks. Additional unscheduled visits can be called by the Investigators according to their own judgement and personal clinical experience.

At Baseline, two 6-mm punch biopsies will be taken from all the subjects, one from the identified active plaque (TCS ≥ 6) and one from never-lesional skin. At the End-of-study Visit, one biopsy will be taken from the same area of the active plaque sampled at Baseline. Whenever possible, biopsies should be taken from the trunk to avoid scars in exposed body areas.

The duration of enrollment is expected to be 6 months. The design of the study is outlined in [Figure 3-1](#).

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

Due to the nature of the treatments given, the study will be open label.

In order to ensure full integrity of clinical and molecular observations, the assessment of all endpoints (primary and exploratory) will be performed by blinded independent clinicians, and pathologists/researchers.

4.2 Rationale for dose/regimen and duration of treatment

Secukinumab 300 mg s.c. and the dose regimen with an initial weekly induction at Baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 12 inclusive is based on the approved product label in the United States of America and the European Union.

4.3 Rationale for choice of comparator

The comparator treatment is guselkumab, the first selective IL-23p19 inhibitor that has been approved for use in clinical practice. The dose regimen is based on the approved product label in the United States of America and the European Union.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

4.5.1 Risks

The risk to subjects in this study may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and minimal study duration.

Women of childbearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they must not be entered or continue in the study.

The potential risks for subjects participating in this study are listed below.

4.5.1.1 Risks associated with the administration of secukinumab

The safety data from the completed and ongoing studies including AEs and SAEs, laboratory parameters and immunogenicity demonstrate a favorable safety profile. Observed risks included infections, in particular of the upper respiratory tract, neutropenia and hypersensitivity reactions that can be seen with the administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easy to manage and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient, and did not lead to treatment discontinuation, and only a few cases were temporally associated with non-serious infections.

Subjects with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab, although there is no scientific basis to suggest that secukinumab would increase the risk for malignancies. Indeed, the majority of the preclinical data available in the literature suggest that blocking IL-17A may actually prevent tumor growth ([Fabre et al 2016](#)).

4.5.1.2 Risks associated with the administration of guselkumab

The following side effects have been reported for guselkumab in the approved product label, all usually mild or moderate.

Very common (may affect more than 1 in 10 people):

Upper respiratory infections.

Common (may affect up to 1 in 10 people):

Headache, arthralgia, diarrhea, gastroenteritis, redness at the injection site, hives, fungal infection of the skin (e.g., athlete's foot), herpes simplex infections.

Uncommon (may affect up to 1 in 100 people):

Pain at the injection site.

4.5.1.3 Risks associated with the skin biopsy procedure

A skin biopsy is a routine procedure as part of the diagnostic practice in all dermatology clinics, which may cause bleeding and infections. Subjects may experience bruising, swelling, pain in the area, scarring and fainting caused by a drop in blood pressure. They may also have an allergic response from the anesthetic agent used for the procedure.

Wound healing after the procedure may be compromised in subjects who are smokers or take steroids.

[REDACTED]

4.5.1.5 Other risks

Problems or side effects that are not currently known could also occur.

The procedures done at each visit are standard medical procedures. Blood samples will be taken. The risks of taking blood may include fainting, pain and/or bruising. Rarely, there may

[REDACTED]

be a small blood clot or infection where the needle punctures the skin. The blood pressure cuff may also cause discomfort or bruising of the upper arm.

4.5.2 Benefits

The potential benefits of an intervention with secukinumab may result in quick clearance of psoriatic plaques. Secukinumab has also been shown to be efficacious in clearing inflammation from nails, palms of the hands, soles of the feet, and joints. Subjects may benefit from 16 weeks of treatment that has been proven to be safe and effective.

Subjects randomized to treatment with guselkumab may also benefit from a reduction in psoriasis severity. Guselkumab can improve the condition of the skin and appearance of nails and reduce symptoms, such as scaling, shedding, flaking, itching, pain and burning.

All quality, non-clinical pharmacology and toxicology data, as well as the available clinical efficacy and safety data, are considered sufficient to expect a positive benefit/risk ratio for the treatment of the study subjects.

5 Population

The study population will consist of a total of 40 male and female subjects aged 18 years or older, who have chronic plaque-type psoriasis considered inadequately controlled after treatment with ustekinumab.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Men or women \geq 18 years of age at the time of consent
3. Chronic plaque-type psoriasis considered inadequately controlled after treatment with ustekinumab according to the following criteria:
 - ustekinumab administered at a dose equal or higher than that on the label for at least 24 weeks. The last administration must be at least 12 weeks before randomization
 - absolute PASI score of 1-10 at Screening
4. Presence of at least 1 refractory skin plaque, defined by a TCS of at least 6 and severity score of at least 2 or 3 (moderate) for each individual item, with an area \geq 10 cm² at Screening and Baseline

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic, and guttate psoriasis) at Screening or Baseline
2. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium) at Screening or Baseline
3. Previous treatment with more than one TNF α inhibitor or with IL-17A (including secukinumab), IL-17R or IL-23 (including guselkumab) inhibitors

4. Use of other investigational drugs within 4 weeks before enrolment, or within a period of 5 half-lives of enrollment/initiation of the study treatment, whichever is longer
5. Ongoing use of prohibited treatments (see [Section 6.2.2](#))
6. Known immunosuppression (e.g., AIDS) at Screening or Baseline
7. History of an ongoing, chronic, or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON TB-Gold test In-Tube assay (QFT) at Screening. Subjects with a positive or indeterminate QFT test may participate in the study if a full tuberculosis workup (according to local practice/guidelines) is completed within 12 weeks prior to randomization and conclusively establishes that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local guidelines prior to randomization (see [Section 8.2.4](#))
8. History of hepatitis B, hepatitis C, or HIV infection
9. History of congestive heart failure (NYHA functional classification \geq III) at Screening or Baseline
10. Uncontrolled hypertension (systolic \geq 160 mmHg, diastolic \geq 95 mmHg)
11. History of hypersensitivity to any of the study treatments or its excipients or to any human or humanized biological agents (antibody or soluble receptor) at Screening including reactions to local anesthetics required to perform skin biopsy
12. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before Baseline
13. Any live vaccines (including nasal-spray flu vaccine) starting from 6 weeks prior to initial treatment administration and during the study period
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL)

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study or longer if required by locally-approved prescribing information (e.g., 20 weeks in the European Union and countries where applicable for secukinumab). Effective contraception methods include:

- total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- male sterilization (at least 6 months prior to Screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For countries where applicable, the use of spermicidal foam/gel/film/cream/vaginal suppository will be allowed

- use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form.

15. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed)
16. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the Investigator significantly immunocompromise the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy. In addition, current severe progressive or uncontrolled diseases which render the subject unsuitable for the study or put the subject at increased risk, including any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
17. Inability or unwillingness to undergo study procedures, including venipunctures and skin biopsy

No additional exclusions may be applied by the Investigator in order to ensure that the study population will be representative of all eligible subjects.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ control drug (name and strength)	Pharmaceutical dosage form	Route of administration	Supply type	Sponsor (global or local)
Secukinumab 300 mg	Solution for injection in pre-filled syringe	s.c use	Open label subject packs; pre-filled syringes	Sponsor global
Guselkumab 100 mg	Solution for injection in pre-filled syringe	s.c use	Open label subject packs; pre-filled syringes	Sponsor global

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this study.

6.1.3 Treatment arms

At Baseline, subjects will be randomized to one of the 2 treatment arms in a 1:1 ratio ([Figure 3-1](#)).

Secukinumab treatment arm: 20 subjects with plaque psoriasis with an inadequate response to ustekinumab will self-administer 300 mg secukinumab as two 150-mg s.c. injections at Baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 12 inclusive.

Guselkumab treatment arm: 20 subjects with plaque psoriasis with an inadequate response to ustekinumab will self-administer guselkumab as 100-mg s.c. injections at Baseline, Weeks 4, and 12.

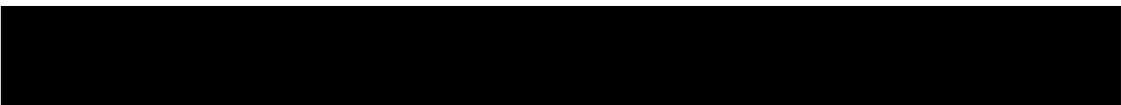
The initiation of secukinumab and guselkumab should not happen earlier than 12 weeks from the last administration of ustekinumab.

6.1.4 Treatment duration

The planned duration of treatment is 16 weeks.

6.2 Other treatments

No additional treatment is included in this study.



6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled in the study must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

Use of topical pharmaceutically active treatment will not be allowed for the entire duration of the study, with the exception of mild topical treatments applied to the face, scalp, and/or genitoanal area.

Use of the treatments displayed in [Table 6-2](#) prior to study start (period specified in the table) or after study start will not be allowed.

Table 6-2 Prohibited medication

Prohibited treatments	Prohibition period before Baseline ^a
Any biologic drug directly targeting IL-17 or any IL-17 receptor or IL-23 (e.g., secukinumab, brodalumab, ixekizumab, guselkumab, risankizumab)	No prior use allowed
TNF α inhibitors (if more than one have been used)	Prior use of one inhibitor allowed. None allowed after Baseline
Any biological immunomodulatory agent other than the above listed (e.g., alefacept, briakinumab, efalizumab)	6 months
Other systemic immunomodulatory treatments ^b (e.g., methotrexate, cyclosporine A, glucocorticosteroids, cyclophosphamide) and any treatment for psoriatic arthritis, except for NSAIDs	4 weeks
Other systemic psoriasis treatments (e.g., retinoids, fumarates, apremilast)	4 weeks
Photo-chemotherapy (e.g., psoralen plus UVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional study	4 weeks or 5 half-lives (whichever is longer)

a) In case of undue safety risk for the subjects, they should discontinue study treatment at the discretion of the Investigator or qualified site staff. If subjects treated with secukinumab receive a live virus vaccination during the study, they must discontinue study treatment

b) Inhalational steroids with only a topical effect (e.g., to treat asthma) are not considered systemic immunomodulatory treatments and are therefore acceptable



NSAID = nonsteroidal anti-inflammatory drug, UVA = ultraviolet light A, UVB = ultraviolet light B

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject will be identified in the study by a subject number, which is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subjects throughout their entire participation in the study. The subject number consists of the study site number (assigned by Novartis to the study site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential subject number available.

6.3.2 Treatment assignment, randomization

At the Baseline Visit, all eligible subjects will be randomized to one of the treatment arms via the Novartis Interactive Response Technology (NIRT). After confirming that the subject fulfills all the inclusion/exclusion criteria, the Investigator or delegate will contact the NIRT and randomize the subject. The NIRT will assign a randomization number to the subject and allocate the subject to a treatment arm. The treatment allocation will be confirmed in the NIRT and communicated to the Investigator or designee, who will dispense the medication accordingly.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased from subjects and Investigator staff. A subject randomization list will be produced by the NIRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to subjects, Investigator staff, and the clinical trial team.

The assessment of all efficacy endpoints (primary and exploratory) will be performed by blinded independent clinicians, and pathologists/researchers.

6.5 Dose escalation and dose modification

Dose adjustments and/or interruptions are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All doses of study treatment administered will be recorded on the appropriate Dosage Administration Record eCRF page. Subject compliance with study treatment should be assessed by qualified study site personnel at each study visit using the study kits and documentation regarding study treatment dispensation and administration.



Compliance will also be assessed continuously by Novartis study personnel during the conduct of the study using medication kits and the corresponding documentation. Study treatment doses and the corresponding dates of self-administration at home should be documented in a self-administration log. Subjects will be required to return the self-administration log as well as all dispensed study treatment at every visit for a compliance check.

The Investigator must promote compliance by instructing the subjects to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

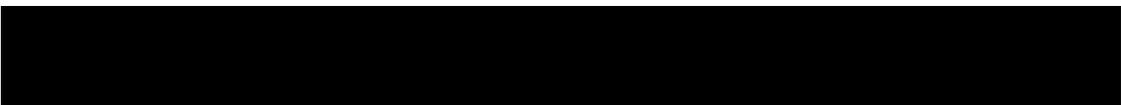
Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the study. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

Study treatments will be administered subcutaneously throughout the study (Table 6-3). The first dose will be administered under supervision at the study site. Self-administration at home will be allowed from the second dose or when the subject, after being instructed and trained, is qualified to self-inject at the discretion of the Investigator.



Study treatments must be injected in never-lesional areas of the skin to one of the following body regions: front of thighs, or lower abdomen (but not the area 2 centimeters around the navel). Investigator/qualified site staff can also inject in the outer upper arms. Study treatment should not be injected into areas where the skin is tender, bruised, red, scaly or hard, and areas with scars or stretch marks should be avoided. As far as possible, the injection site should be changed from administration to administration throughout the study.

Detailed instructions on the self-administration of the study treatment will be described in the instructions for use and provided to each subject.

Subjects will be asked to return all used and unused medication and packaging at each scheduled study visit.

Secukinumab 300 mg s.c.

Secukinumab will be administered at Baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 12 inclusive. After Week 4 (the last weekly administration of secukinumab), the subjects will be contacted by the Investigator or staff and be reminded to start the self-administration every 4 weeks instead of every week until Week 12.

Guselkumab 100 mg s.c.

Guselkumab will be administered subcutaneously at Baseline, Weeks 4, and 12.

Table 6-3 Study treatment administration schedule

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12
Secukinumab	X	X	X	X	X	X	X
Guselkumab	X				X		X

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the subject's representative gives consent (if allowed according to local requirements), the subjects must be informed about the study to the extent possible given their understanding. If the subjects are capable of doing so, they must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by Novartis before submission to the IRB/IEC.



Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

[REDACTED]

[REDACTED]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule ([Table 8-1](#)) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the eCRF.

[REDACTED]

Table 8-1 Assessment schedule

Visit name	Screening	Baseline	End of study	Unscheduled
Visit number	1	2	3	-
Week	-4 to -1	-	16	-
Day	-28 to -1	1	112	-
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Pregnancy test ²	X	X		
Randomization via NIRT		X		
Physical examination	X	X	X	X
Smoking history	X			
Medical history	X			
Relevant family history	X			
Demography	X			
Psoriasis medical and treatment history	X			
QFT	X			
Skin type	X			
Body temperature (°C)	X	X		
Height (cm)	X			
Weight (Kg)	X	X	X	
Vital signs	X	X	X	
Electrocardiogram	X			
Laboratory assessments	X		X	
Adverse events ³	X	X	X	X
Drug administration record		X	X	X
Concomitant medications	X	X	X	X
TCS of target plaque	X	X	X	X
Skin biopsies ██████████ ⁶		X	X	
Information on study completion			X	

Baseline Visit (Visit 2) should be conducted within 28 days of the Screening Visit (Visit 1).



Unscheduled visits can be decided by the Investigators according to their own clinical judgment and practice.

End-of-study assessments (Visit 3) should be conducted only on subjects who complete 4 to 16 weeks of treatment. There will be a \pm 2-day window for Visit 3 (Week 16)

- [REDACTED]
- 2) Performed on serum for women of childbearing potential
 - 3) SAEs collected up to 30 days after the last administration of study treatment

[REDACTED]

6) At Baseline, two 6-mm punch biopsies will be taken, one from the identified active plaque (TCS \geq 6) and one from never-lesional skin. At the End-of-study Visit, one biopsy will be taken from the same area of the plaque sampled at Baseline. Biopsies should be sampled from the trunk whenever possible to avoid scars in exposed areas of the body

8.1 Screening

Subject's eligibility for the study will be assessed at the Screening Visit (Day -28 to Day -1 before Baseline) and at the Baseline Visit (see [Table 8-1](#)).

Subjects who fail screening for any reason may be rescreened. There will be no restriction on the number of times a potential subject may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening. Subjects who are rescreened must sign a new informed consent form and be issued a new subject number before any study-related assessment is performed or any data for the Screening Visit are collected for the subject under the new subject number.

The Investigator or qualified site staff will record all rescreenings on the Rescreening eCRF page and any applicable screening numbers the subject was issued prior to the current screening number. The date of the new informed consent signature must be entered on the Informed Consent eCRF page to correspond with the new screening subject number.

The Withdrawal of Consent eCRF page must be completed if consent was withdrawn during the Screening Visit before the subject was randomized.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently are found to be ineligible prior to randomization will be considered screen failures. The reason for screen failure should be recorded on the appropriate eCRF page. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data will be entered into the clinical database for screen failures, unless the subject experienced an SAE during the Screening Visit (see [Section 10.1.3](#) for reporting details). If the subject fails to be randomized, the NIRT must be notified within 2 days.

Subjects who are randomized and fail to start treatment, e.g., randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate eCRF page.

[REDACTED]

8.2 Subject demographics/other baseline characteristics

Subject demographics and baseline characteristics will be collected at the Screening Visit. Data to be collected on all subjects include: date of birth, age, sex, race, ethnicity, height, weight, and skin type (see [Section 16.2.1](#)).

8.2.1 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be advised to not start smoking during the study.

8.2.2 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions, not including psoriasis or psoriatic arthritis, prior to signing of the informed consent will be recorded in the Medical History eCRF page. Whenever possible, diagnoses and not symptoms will be recorded.

Subjects with inflammatory bowel disease will be eligible for the study but should be closely followed when randomized to secukinumab.

Significant findings that are observed after the subject has signed the informed consent form and that meet the definition of an AE must be recorded in the Adverse Event eCRF page.

8.2.2.1 Psoriasis medical and treatment history

Disease history will be collected at the Screening Visit. The information to be collected and entered in the Psoriasis History eCRF page and Prior Psoriasis Therapies eCRF page will include the following:

1. Date of first diagnosis of plaque psoriasis
2. Previous treatments of psoriasis (including previous use of biologic therapies, as well as phototherapy and/or photo-chemotherapy) and the reason for discontinuation of each therapy
3. Presence of psoriatic arthritis or ankylosing spondylitis (including questions on signs and symptoms captured in the eCRF) and the date of the first diagnosis by a physician

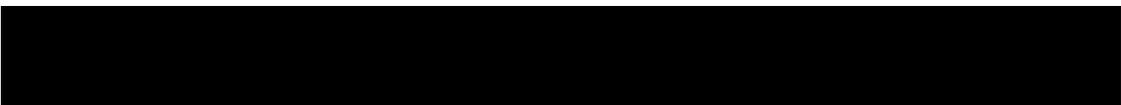
8.2.3 Prior and concomitant medications

Concomitant medications and prior medications taken within the 6 months preceding study enrollment will be captured at the Screening Visit, and updated at the Baseline Visit or subsequent visits.

8.2.4 Determination of tuberculosis status

Determination of TB status will be required at the Screening Visit and should be performed as defined by local guidelines. Tuberculosis status must be determined by medical history, signs, symptoms, and TB testing (QFT).

Any significant findings will be recorded in the Tuberculosis Assessment eCRF page and the Medical History eCRF page, as necessary.



8.2.4.1 QuantiFERON TB-Gold In-Tube assay

This test will only be used to screen the subject population for latent TB infection (Doherty et al 2008) and determine subject's eligibility for the study.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous bacillus Calmette-Guerin vaccination or exposure to other Mycobacteria species. In contrast to the purified protein derivative skin test, it is also insensitive to a booster effect, since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to negative and positive control samples (Manuel and Kumar 2008).

The QFT will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to Investigators in the laboratory manual.

1. If the test result is negative, the subject may be randomized
2. If the test result is positive, the Investigator should perform workup as per local guidelines (if a TB workup was conducted prior to the screening of the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to Randomization)
 - a. subjects positive for active TB per workup are not eligible for the study
 - b. subjects diagnosed with latent TB per workup may be randomized to the study if sufficient treatment has been initiated according to local routine clinical practice or guidelines and will be maintained for the prescribed duration
3. If the test result is indeterminate, it is recommended to repeat the test once
 - a. if the second test is negative, the subject may be randomized
 - b. if the second test is positive or indeterminate, the investigator should perform workup as per local guidelines (if a TB workup was conducted prior to the screening of the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to Randomization)
 - o subjects positive for active TB per workup are not eligible for the study
 - o subjects diagnosed with latent TB per workup may be randomized to the study if sufficient treatment has been initiated according to local routine clinical practice or guidelines and will be maintained for the prescribed duration

8.3 Efficacy

8.3.1 Total clinical score

The TCS will be assessed at all study visits as indicated in Table 8-1. At Baseline, it should be performed before the first administration of study treatment.

The TCS for each plaque will be determined (ideally by the same evaluator) as the sum of 3 scores: erythema (0-3), scaling (0-3) and infiltration (0-3) rated according to their severity as shown in Table 8-2. The TCS can range from 0 (all signs absent) to 9 (all signs severe).



Table 8-2 Assessments of total clinical score

Score	Intensity	Erythema	Scaling	Infiltration
0	No evidence	Normal skin color	No scaling	No infiltration
0.5	Doubtful or very mild			
1.0	Mild	Pink/light red	Slight roughness, mainly fine scales	Slight definite infiltration
1.5	Mild to moderate			
2.0	Moderate	Red	Coarse scaling	Moderate infiltration
2.5	Moderate to severe			
3.0	Severe	Intense red	Coarse, thick scales	Very marked infiltration

8.3.3 Skin biopsies

At Baseline, two 6-mm punch biopsies will be taken, one from the identified active plaque (TCS \geq 6) and one from never-lesional skin. At the End-of-study Visit, one biopsy will be taken from the same area of the active plaque sampled at Baseline.

After collection, biopsies will be transported within 24 hours to the laboratory for further processing using a Novartis delegated service provider.

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date and exact time must be entered on the Sample Collection eCRF page.

8.3.4 Microscopic morphology of the skin plaque

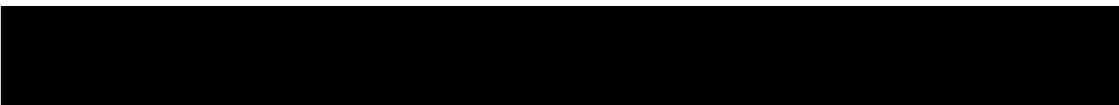
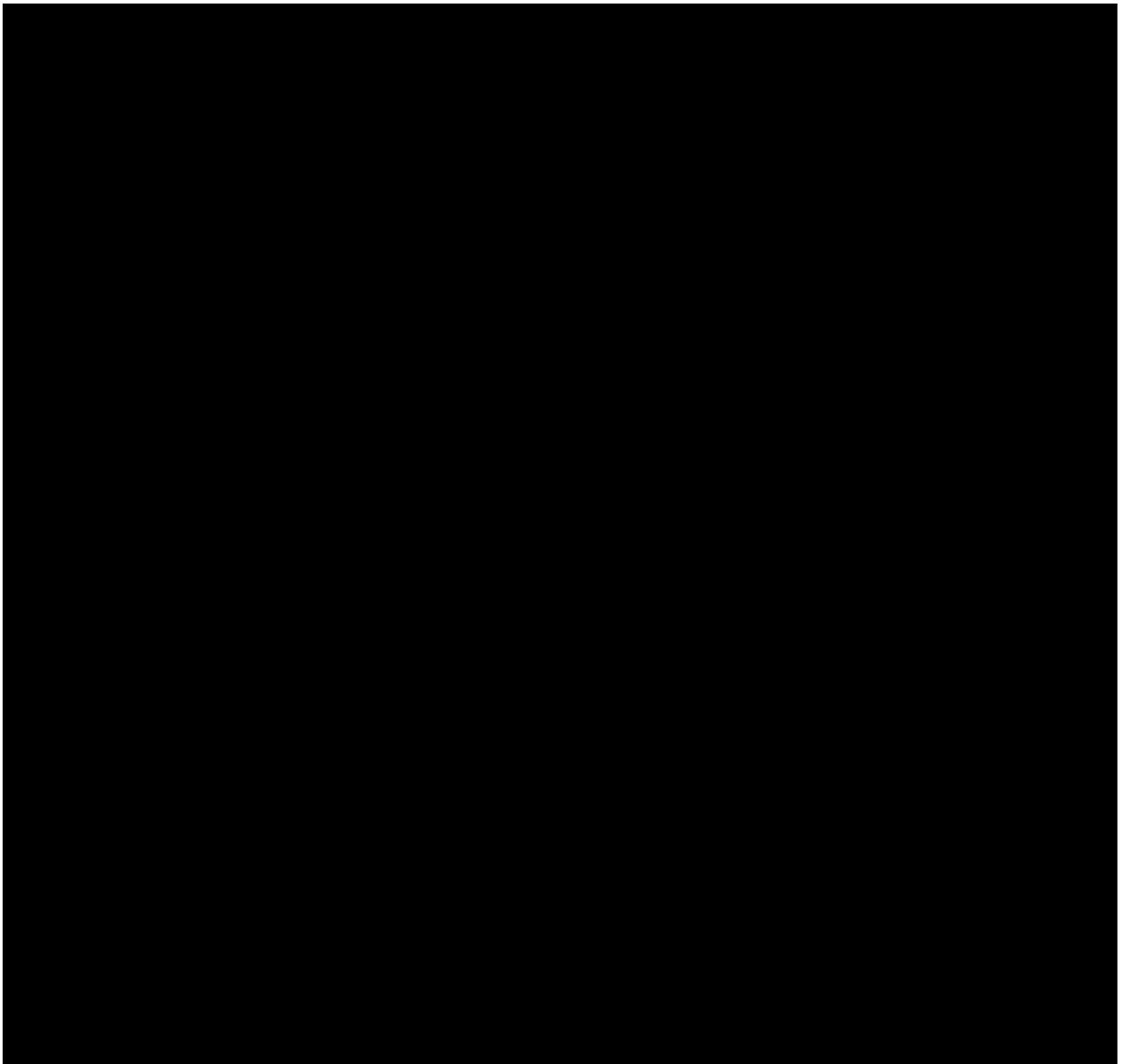
General histopathology of the skin will be assessed by hematoxylin and eosin staining and epidermal proliferation and differentiation by immunohistochemical (IHC) staining of Ki-67 and keratin-16 positive nuclei. The quantification of positive cells will be performed at X 200 magnification and calculated per mm of skin length.

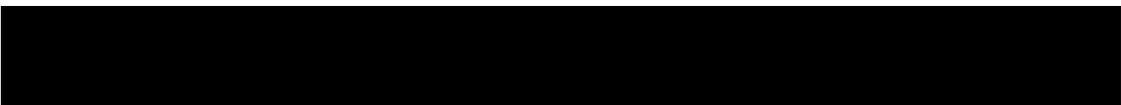
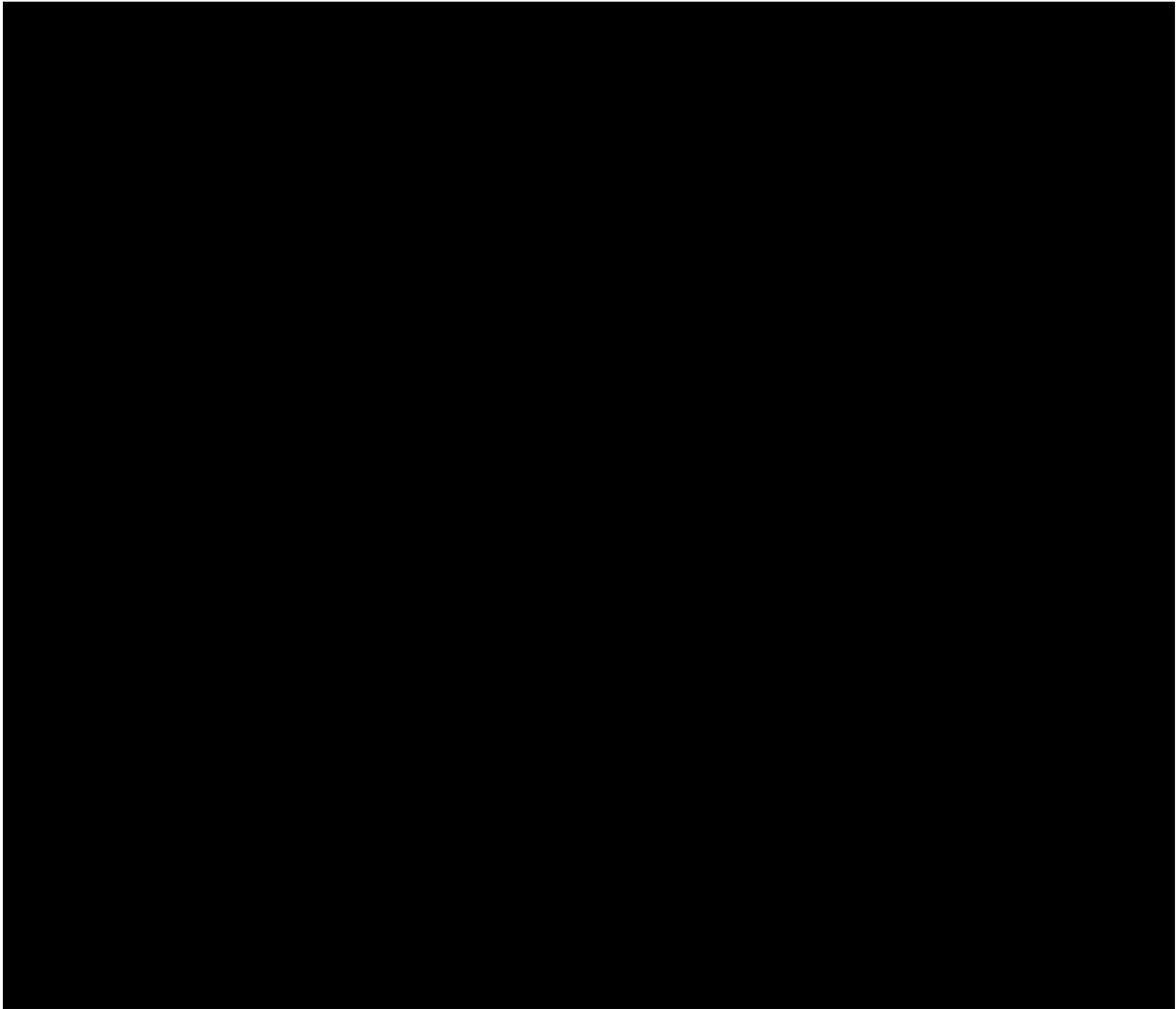
8.3.5 Infiltrating immune cells in the skin plaque

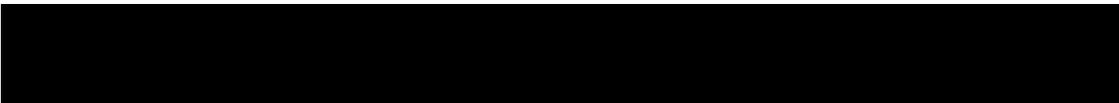
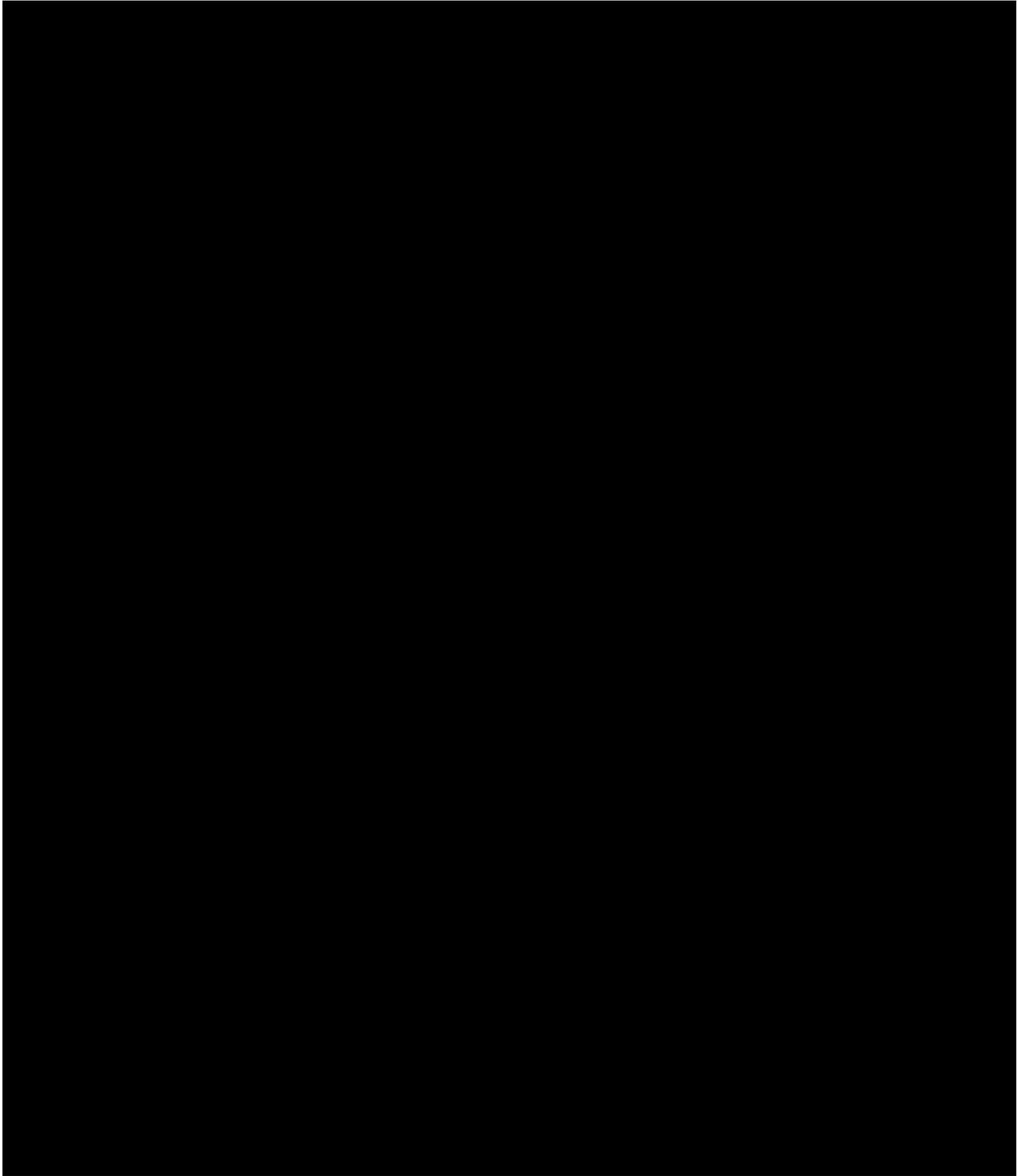
The number of infiltrating cells expressing IL-17A and IL-23R will be assessed by single-staining IF using IHC and immunofluorescence (IF) if needed, and will be counted per mm of skin length.

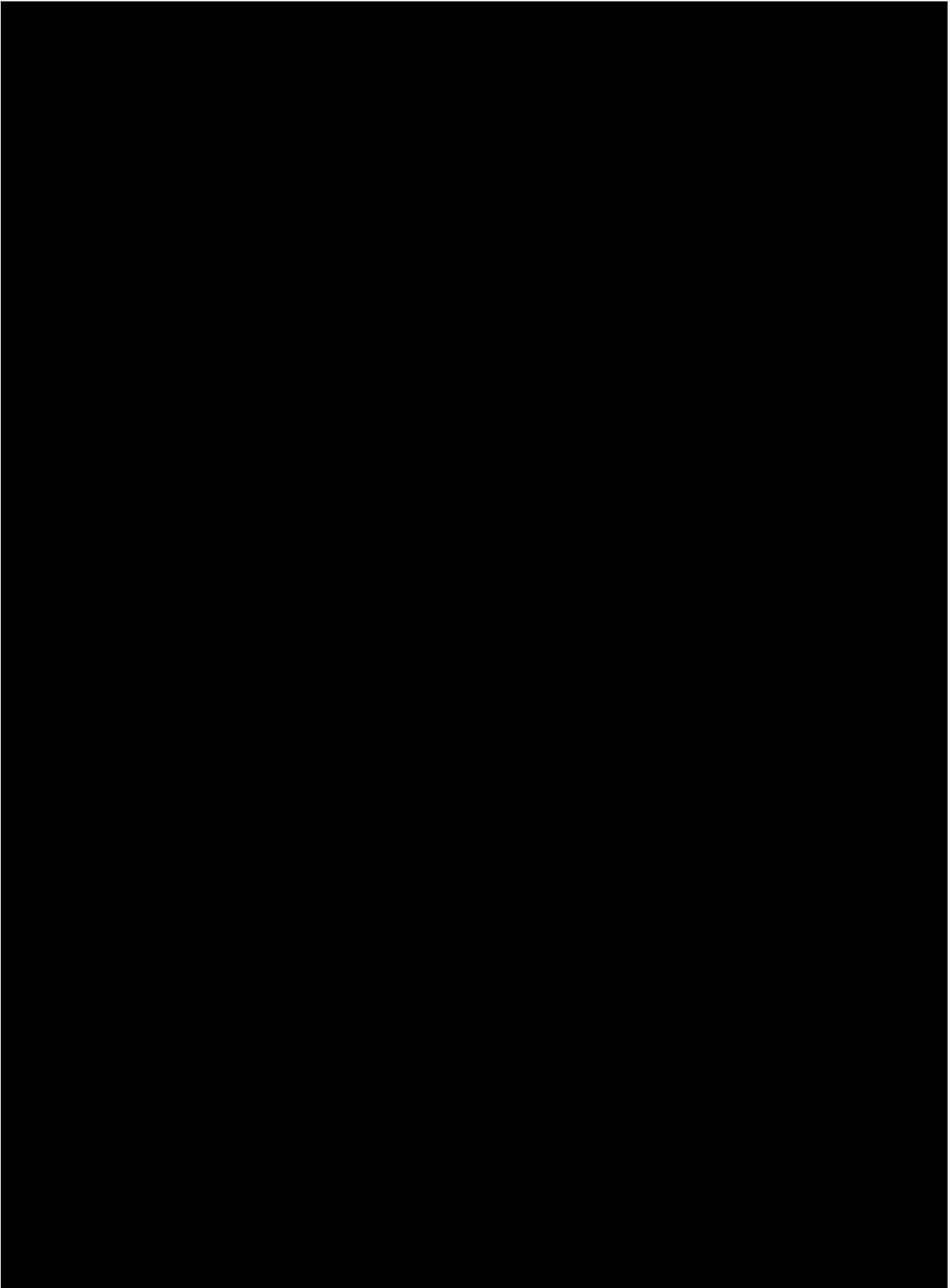
8.3.6 Composition of the inflammatory infiltrate in the skin plaque

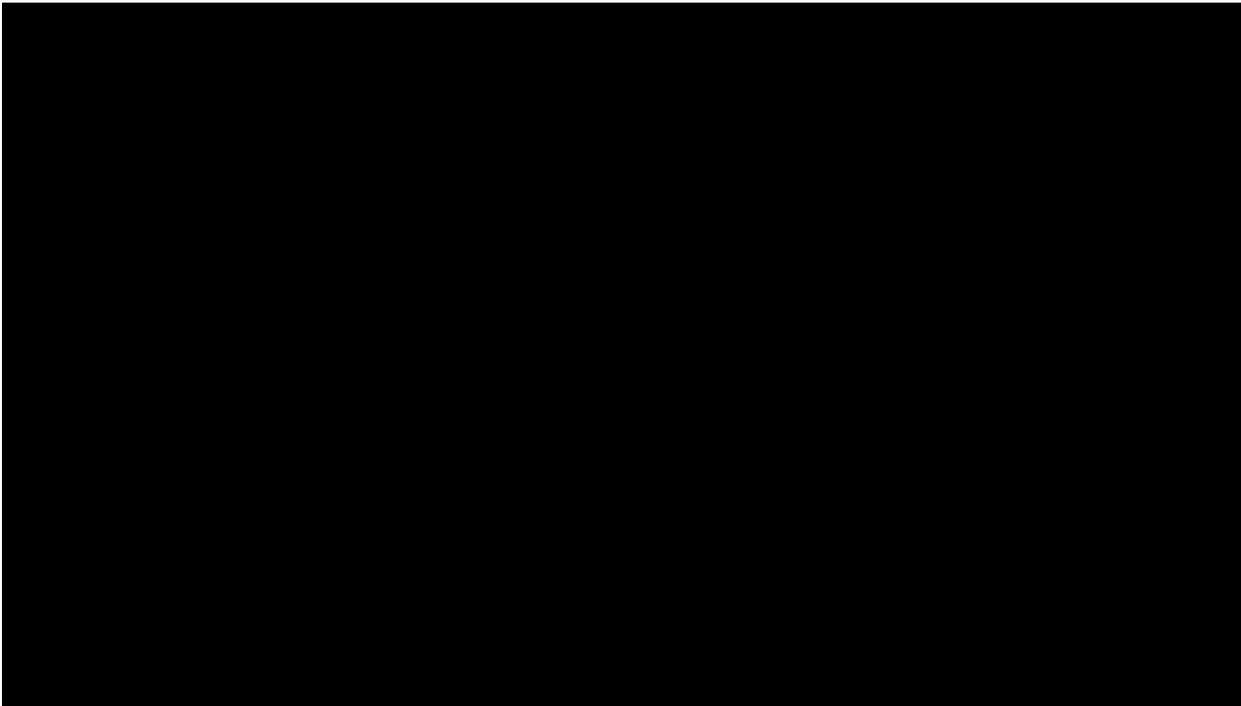
Single or double staining (IHC/IF) will be used to identify different cell types in the immune infiltrate according to the following markers: T-cells (CD3, CD8); neutrophils (elastase); mastocytes (tryptase); dendritic cells (CD11c); macrophages (CD163); NK cells (CD56); NKT cells (CD3, CD56); T-resident memory cells (CD49, CD103). The number of cells per cell type will be counted per mm of skin length.











8.4 Safety

Safety assessments are specified in [Table 8-5](#) and [Table 8-6](#). For details on AE collection and reporting, refer to the AE section.

Table 8-5 Physical assessments

Assessment	Specification
Physical examination	<p>A complete physical examination will include the inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, and the vascular and neurological systems. If indicated based on medical history and/or symptoms, rectum, external genitalia, breast, and pelvic will be examined.</p> <p>In particular, will include recognition of enthesitis, dactylitis, and the patterns of joint, or nail involvement.</p> <p>Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing the informed consent must be included in the Medical History eCRF page. Significant findings made after the first administration of investigational drug, which meet the definition of an AE must be recorded on the Adverse Event eCRF page.</p>
Vital signs	<p>Vital signs include measurements of blood pressure and pulse. After the subject has been sitting for 5 minutes, with the back supported and both feet placed on the floor, systolic and diastolic blood pressures will be measured 3 times using an automated validated device, e.g., OMRON, with an appropriately sized cuff. The repeat-sitting measurements will be made at 1-2 minute intervals and the mean of the 3 measurements will be used. If the available cuff sizes are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.</p> <p>If possible, assessments should be performed by the same study site staff member throughout the study.</p>



Assessment	Specification
	<p>Normal blood pressure will be defined as systolic pressure of 90 to < 120 mmHg, and diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure findings will be hypertension (systolic blood pressure of \geq 140 mmHg and/or diastolic blood pressure of \geq 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or a diastolic blood pressure of < 60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to < 140 mmHg and/or diastolic blood pressure of 80 to < 90 mmHg) will not be regarded as notable (Whelton et al 2017).</p> <p>A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rate will be a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).</p> <p>Whether action needs to be taken to address notable vital signs will be decided by the Investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.</p>
Height and weight	Height in cm and body weight (to the nearest 0.1 Kg in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A central laboratory will be used for the analysis of all specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to Investigators in the laboratory manual.

Clinically notable laboratory findings are defined in [Appendix 1](#).

Table 8-6 Laboratory assessments

Test category	Test name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be quantified.
Chemistry	Blood urea, creatinine, total bilirubin, alkaline phosphatase, international normalized ratio, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, uric acid, and lipid panel will be quantified.
Urinalysis	<p>The central laboratory will provide dipsticks to the sites for local analysis of urine. Dipstick analysis will measure specific gravity, albumin, protein, glucose and blood. Microscopy and white blood cell count and red blood cell count sediments will be assessed in case of an abnormal dipstick test. Only samples with abnormal dipstick will be assessed by the central laboratory and the results provided in loaded data.</p> <p>Study sites should record the results in the source documentation.</p>
Additional tests	
Pregnancy test	<p>A serum β-hCG test will be performed to all pre-menopausal women as shown in Table 8-1.</p> <p>Any woman with a confirmed positive pregnancy test (hCG > 5 mIU/mL) during Screening will not be eligible for randomization.</p> <p>Women of childbearing potential should use an effective method of contraception while on treatment, or longer if required by locally-approved prescribing information (e.g., 20 weeks after the last dose in the EU and countries where applicable for secukinumab).</p>

8.4.2 Electrocardiogram

At the Screening Visit, an ECG must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection at is ECG first, followed by vital signs, and blood sampling for laboratory assessments. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

If the ECG findings are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status and the medication profile), the subject should be recorded as a screen failure, should not be enrolled and should not receive treatment.

Single 12-lead ECGs will be collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing must be labelled with study number, subject initials, subject number, date and time, and filed in the study site source documents. Clinically significant ECG findings at Baseline must be discussed with the Sponsor before administration of study treatment.

For any ECGs with subject safety concerns, 2 additional ECGs must be performed to confirm the safety finding and copies forwarded to the central ECG laboratory for assessment. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at Baseline before administration of study treatment.

Any identifier details must be redacted e.g., subject initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate.

8.4.3 Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

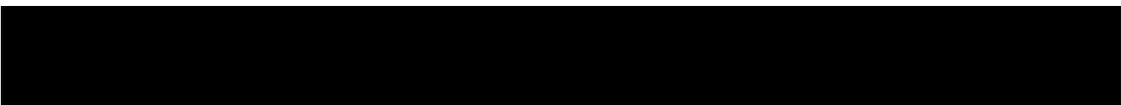
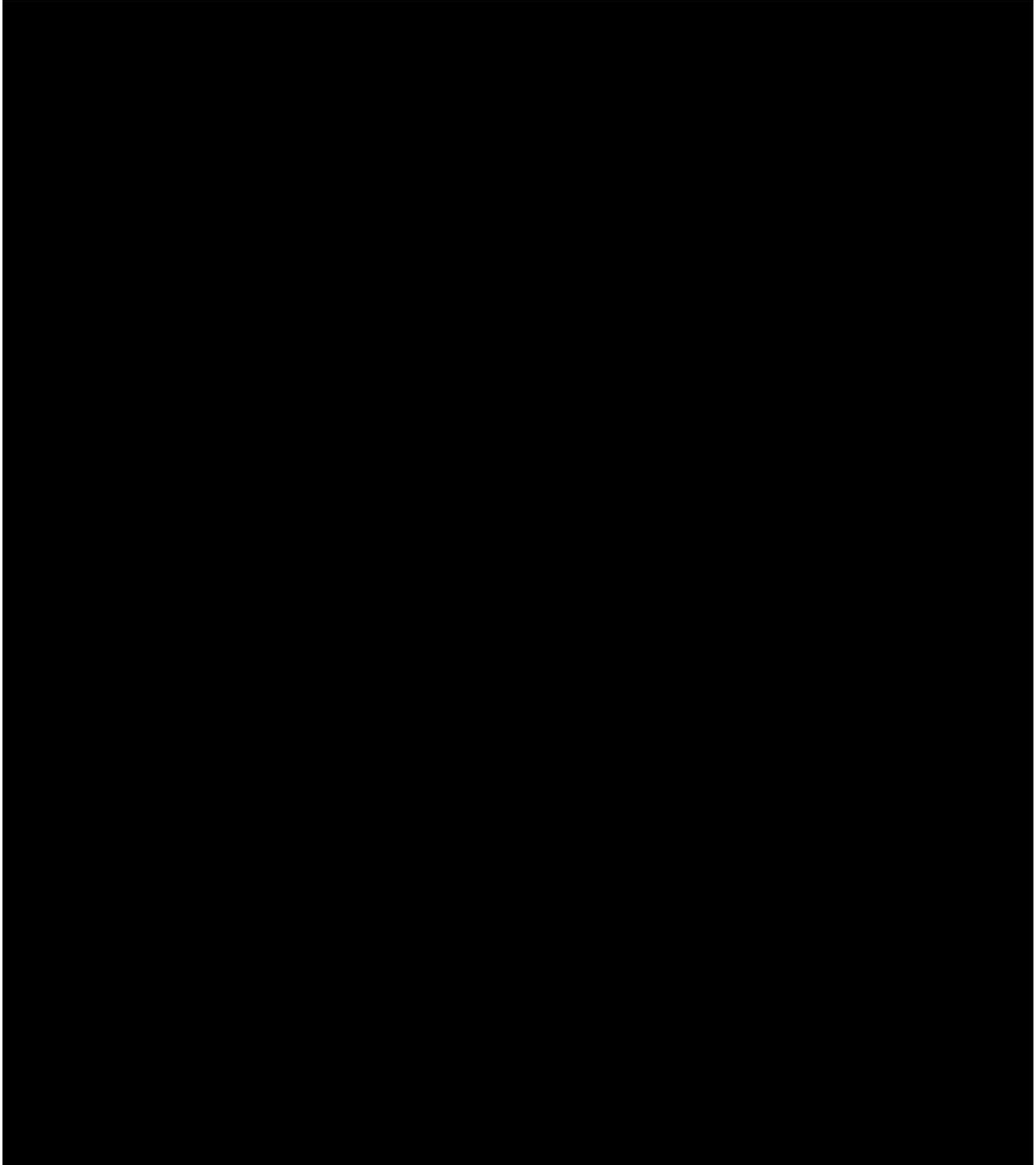
In the absence of the above medical documentation, follicle-stimulating hormone testing is required of any female subject, regardless of reported reproductive/menopausal status at Screening/Baseline.



8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments



9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the Investigator.

The Investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- subject decision
- pregnancy
- use of prohibited treatment as per recommendations in the prohibited treatment section
- any situation in which study participation might result in a safety risk to the subject
- any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 9.1.2](#)). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, or letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at study site visits or via telephone/email contact:

- new/concomitant treatments
- adverse events/SAEs

The Investigator must also contact the NIRT to register the subject's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- does not want to participate in the study anymore

and

- does not allow further collection of personal data

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, or letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to retain and use collected study information (including any data resulting from the analysis of subject's samples until the time of withdrawal) according to applicable law.



For US and Japan: all biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and rest of the world: all biological samples not yet analyzed at the time of withdrawal will no longer be used unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show “due diligence” by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the Sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject’s interests. The Investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the study.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their End-of-study Visit, and any repeat assessments associated with this visit have been documented and followed up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (e.g., each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated subjects should have a safety follow up conducted 30 days after the last administration of study treatment. This will be performed at Week 16 for subjects who complete the study [last administration received at Week 12]. The information collected is kept as source documentation. All SAEs reported during this period must be reported as described in [Section 10.1.3](#). Attempts to contact the subject should be recorded in the source documentation.



10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual subject and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on study related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible, if the event is serious refer to [Section 10.1.2](#)):

1. The Common Toxicity Criteria (CTC) AE grade (version 4.03 or higher). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see [Section 10.1.2](#)) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All AEs must be treated appropriately. Treatment may include one or more of the following:

- dose not changed
 - dose reduced/increased
 - drug interrupted/withdrawn
6. Its outcome, i.e., its recovery status or whether it was fatal

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values that are considered to be non-typical in subjects with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of or worsening of any pre-existing one) undesirable sign, symptom or medical conditions that meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject is at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - a. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (including psoriasis and psoriatic arthritis)
 - b. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - c. social reasons and respite care in the absence of any deterioration in the subject's general condition
 - d. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant”. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred.

10.1.3 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each study site.

Serious adverse events occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow up of the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, an associate from the Novartis Chief Medical Office and Patient Safety (CMO&PS) Department may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment.



10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the CMO&PS. Pregnancy follow up should be recorded on the same form and should include an assessment of the possible relationship to study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Novartis Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database as SAEs within 24 hours of Investigator's awareness ([Table 10-1](#)).

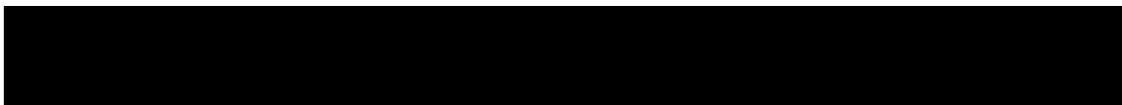
Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional safety monitoring

Not applicable.



11 Data collection and database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, and allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the subject data for archiving at the study site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization [CRO]) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study site via the EDC system. Designated Investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

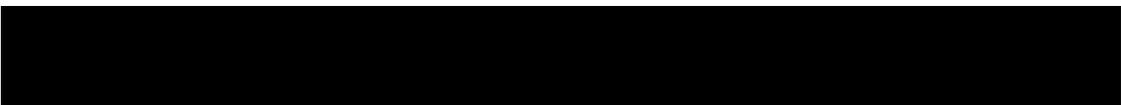
Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the subject and all dosage changes will be tracked using an NIRT system. The randomization list will be generated by a vendor who will transfer it after the RRS has been approved. Later this will be uploaded into the NIRT system.

Each occurrence of a code break via NIRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.



11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e., eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with study oversight.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for the primary endpoint. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

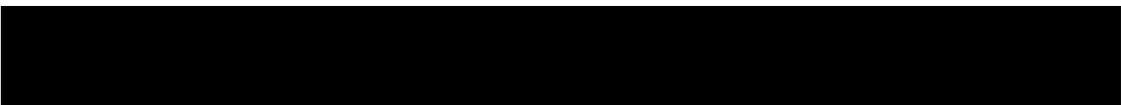
12 Data analysis and statistical methods

All analyses will be performed by Novartis or a designated CRO. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Continuous variables will be summarized by number of subjects, mean, standard deviation, minimum, median, and maximum. For selected parameters, 25th and 75th percentiles will also be presented. Categorical variables will be summarized by frequencies and percentages.

In addition to the statistical methods outlined below, further details and any additional exploratory analyses that may be performed will be described in the Statistical Analysis Plan.

The last available assessment on or before the start date of study treatment (i.e., secukinumab or guselkumab) is taken as the baseline assessment.



12.1 Analysis sets

The following analysis sets will be used in this study:

The FAS comprises all subjects to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all subjects who receive at least one dose of study treatment. Subjects will be analyzed according to the study treatment received.

12.2 Subject demographics and other baseline characteristics

12.2.1 Demographics and baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS.

12.2.2 Medical history

Relevant medical histories and current medical conditions at Screening will be listed and summarized by system organ class and preferred term for each treatment arm for the FAS.

12.3 Treatments

The Safety Set will be used for the analyses below.

12.3.1 Study treatments

The duration of exposure to secukinumab and guselkumab (in weeks), will be summarized by means of descriptive statistics. In addition, the number and percentage of subjects with cumulative exposure levels (e.g., any exposure, ≤ 1 week, ≤ 2 weeks, ≤ 3 weeks, ≤ 4 weeks, ≤ 8 weeks, etc.) will be presented.

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons thereof will be summarized. All dosing data will be listed.

12.3.2 Prior and concomitant treatments

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment arm.

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

The primary objective is to assess the superiority of secukinumab over guselkumab in controlling clinical activity in psoriatic plaques resistant to treatment with ustekinumab.

The primary endpoint is the proportion of subjects whose plaque achieves “clear” or “almost clear” status (TCS = 0-2) by 16 weeks of treatment with secukinumab or guselkumab.



12.4.2 Statistical model, hypothesis, and method of analysis

The number (%) of subjects whose plaques achieve “clear” or “almost clear” status (TCS = 0-2) at Week 16 (i.e., responders) will be provided based on the FAS together with the 95% confidence interval using the exact method for the difference in proportions of responders in each arm.

Furthermore, a 1-sided Fisher’s exact test for the difference in the proportions of responders in the secukinumab (P1) and gesulkumab (P2) arms, $H_0: P_1 - P_2 = 0$ versus $H_1: P_1 - P_2 > 0$ at a Type I error rate of 0.05 will be performed.

12.4.3 Handling of missing values/censoring/discontinuations

Subjects who discontinue between Week 4 and Week 16, will be required to complete the End-of-study Visit assessments as shown in [Table 8-1](#). The plaque status based on the TCS at the End-of-study Visit will be used for the primary endpoint assessment i.e., the last observation carried forward approach will be applied. Subjects discontinued before Week 4 will be treated as failures.

12.4.4 Sensitivity and supportive analyses

Analysis of the primary endpoint as observed i.e., without missing data imputation (as described in [Section 12.4.3](#)) will be performed as a sensitivity analysis for the primary endpoint.

12.5 Analysis of secondary endpoints

Not applicable.

12.6 Analysis of exploratory endpoints

The following exploratory endpoints will be analyzed:

- [REDACTED]
2. Change from Baseline to Week 16 in epidermal thickness and in the number of Ki-67 and K16 positive cells of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy ([Section 8.3.4](#)) will be provided based on the FAS. Box plots and bar plots will also be provided
 3. Change from Baseline to Week 16 in the number of infiltrating cells expressing IL 17A and IL-23R of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy ([Section 8.3.5](#)) will be provided based on the FAS
 4. Change from Baseline to Week 16 in the number of different immune cell types in the inflammatory infiltrate of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy ([Section 8.3.6](#)) will be provided based on the FAS
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED] Values below the lower limit of quantification and above the upper limit of quantification will be flagged.

12.7 Safety analysis

The Safety Set will be used for all safety analyses. All summary tables and listings will be presented by treatment arm.

Safety summary tables will include only data from the on-treatment period (from first administration of study treatment to 30 days after the last administration of study treatment) with the exception of baseline data which will also be summarized where appropriate.

Adverse events

All information obtained on AEs will be displayed by treatment arm.

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the *treatment-emergent* AEs (TEAEs).

The incidence of TEAEs will be summarized by system organ class and/or preferred term, severity based on the Common Terminology Criteria of Adverse Events (CTCAE) grades, type of AE and relation to study treatment.

Serious adverse events, AEs leading to discontinuation, and AEs leading to dose adjustment during the on-treatment period will be tabulated.

All on-treatment deaths will be summarized.

All AEs and SAEs will be listed.

A subject with multiple AEs within a primary SOC will only be counted once towards the total of the primary SOC.

[REDACTED]

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per the CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for key hematology and biochemistry laboratory tests:

- shift tables comparing baseline to the worst on-treatment value. Each subject will be counted only once for the worst grade observed post-baseline.
- for laboratory tests where grades are not defined shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value will be used.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example summary tables, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the Statistical Analysis Plan. Listings will be provided for all data.

Other safety evaluations

Data on ECG, vital sign, height, and weight will be summarized descriptively, listed and flagged as appropriate. Any significant findings will be documented as AEs and reported as such.

12.8 Interim analyses

Not applicable.

12.9 Sample size calculation

12.9.1 Primary endpoint

A total of 40 subjects will be enrolled in this study i.e., 20 subjects per treatment arm. Based on the feedback from dermatologists with experience in prescribing biologic treatments for psoriasis (there is no historical data in the literature), the response rates to treatment are assumed to be 35% for guselkumab and 75% for secukinumab.

Table 12-1 presents the 95% exact confidence interval for different P1 (proportion of responders in the secukinumab arm) and P2 (proportion of responders in the guselkumab arm) and their corresponding difference P1-P2, together with the estimated power of a 1-sided Fisher's exact test at the target 1-sided Type I error rate of 5%.

For the favorable P1 = 0.75 and P2 = 0.35 values, the Fisher's exact test at the target Type I error of 5% will correctly reject H0: P1-P2 ≤ 0 with the power of 0.72%.



Table 12-1 Exact 95% confidence intervals for P1 and P2, the corresponding difference P1-P2, and the estimated power of the Fisher's exact test for different P1 and P2 values

Proportion (number) of responders in the secukinumab arm at Week 16: P1	Proportion (number) of responders in the guselkumab arm at Week 16: P2	95% exact confidence interval for P1	95% exact confidence interval for P2	95% exact confidence interval for P1-P2	Power of a 1-sided Fisher's exact test: H1: P1-P2 > 0
0.60 (12)	0.20 (4)	(0.36, 0.80)	(0.05, 0.43)	(0.10, 0.66)	75%
0.65 (13)	0.25 (5)	(0.40, 0.84)	(0.08, 0.49)	(0.06, 0.66)	72%
0.70 (14)	0.30 (6)	(0.45, 0.88)	(0.11, 0.54)	(0.09, 0.64)	71%
0.75 (15)	0.30 (6)	(0.50, 0.91)	(0.11, 0.54)	(0.13, 0.70)	82%
0.75 (15)	0.35 (7)	(0.50, 0.91)	(0.15, 0.59)	(0.06, 0.66)	72%
0.75 (15)	0.40 (8)	(0.50, 0.91)	(0.19, 0.63)	(0.01, 0.62)	61%
0.80 (16)	0.40 (8)	(0.56, 0.94)	(0.19, 0.63)	(0.10, 0.66)	75%

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.



13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicalstudies.gov and as required in EudraCT. In addition, after study completion (e.g., defined as last patient last visit) and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results, such as the Novartis clinical study results website and all required Health Authority websites (e.g., Clinicalstudies.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the study Investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

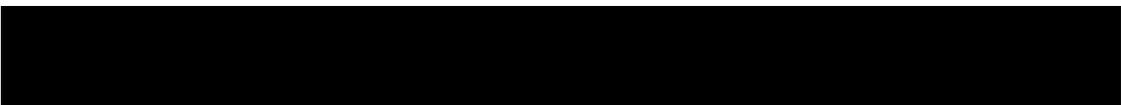
Audits of Investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical study. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.



14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Appel H, Maier R, Wu P et al (2011) Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. *Arthritis Res Ther*; 13(3):R95

Bissonnette R, Nigen S, Langley RG et al (2014) Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. *J Eur Acad Dermatol Venereol*; 28(10):1298-305

Bosteen MH, Tritsaris K, Hansen AJ et al (2014) IL-17A potentiates TNF α -induced secretion from human endothelial cells and alters barrier functions controlling neutrophils rights of passage. *Pflugers Arch*; 466(5):961-72

Chen X, Takai T, Xie Y et al (2013) Human antimicrobial peptide LL-37 modulates proinflammatory responses induced by cytokine milieu and double-stranded RNA in human keratinocytes. *Biochem Biophys Res Commun*;433(4):532-7

Cornelissen F, Asmawidjaja PS, Mus AM et al (2013) IL-23 dependent and independent stages of experimental arthritis: no clinical effect of therapeutic IL-23p19 inhibition in collagen-induced arthritis. *PLoS One*;8(2):e57553

Croes M, Öner FC, van Neerven D et al (2016) Proinflammatory T cells and IL-17 stimulate osteoblast differentiation. *Bone*;84:262-70

Cua DJ, Tato CM (2010) Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol*; 10(7):479-89

Dixon BR, Radin JN, Piazuolo MB et al (2016) IL-17a and IL-22 Induce Expression of Antimicrobials in Gastrointestinal Epithelial Cells and May Contribute to Epithelial Cell Defense against *Helicobacter pylori*. *PLoS One*; 11(2):e0148514

Doherty SD, Van Voohes A, Lebwohl MG et al (2008) National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents. *J Am Acad Dermatol*; 59(2): 209-17

Fabre J, Giustiniani J, Garbar C et al (2016) Targeting the tumor microenvironment: The protumor effects of IL-17 related to cancer type. *Int. J. Mol. Sci.*; 17(9): 1433

[REDACTED]

Gottlieb AB, Griffiths CE, Ho VC (2005) Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol*; 152(6):1219-27

Hau CS, Kanda N, Tada Y et al (2016) Lipocalin-2 exacerbates psoriasiform skin inflammation by augmenting T-helper 17 response. *J Dermatol*; 43(7):785-94

Hawkes JE, Chan TC, Krueger JG (2017) Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol*; 140(3):645-53

Housseau F, Wu S, Wick EC et al (2016) Redundant Innate and Adaptive Sources of IL17 Production Drive Colon Tumorigenesis. *Cancer Res*; 76(8):2115-24

Jack C, Mashiko S, Arbour N et al (2017) Persistence of interleukin (IL)-17A+ T lymphocytes and IL-17A expression in treatment-resistant psoriatic plaques despite ustekinumab therapy. *Br J Dermatol*; 177(1):267-270

Johansen C, Bertelsen T, Ljungberg C et al (2016) Characterization of TNF- α - and IL-17A-mediated synergistic induction of DEFB4 gene expression in human keratinocytes through I κ B ζ . *J Invest Dermatol*; 136(8):1608-16

Keijsers RR, Joosten I, van Erp PE et al (2014) Cellular sources of IL-17 in psoriasis: a paradigm shift? *Exp Dermatol*; 23(11):799-803

[REDACTED]

Lebwohl M, Iversen L, Eidsmo L et al (2017) Long-term psoriasis control following secukinumab discontinuation indicates disease modification of moderate to severe psoriasis: clinical and mechanistic results. P1747 at the EADV2017 congress

Lowes MA, Russell CB, Martin DA et al (2013) The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends Immunol*;34(4);174-81

Manuel O, Kumar D (2008) QuantiFERON-TB gold assay for the diagnosis of latent tuberculosis infection. *Expert Rev Mol Diagn*; 8(3):247-56

Mashiko S, Bouguermouh S, Rubio M et al (2015) Human mast cells are major IL-22 producers in patients with psoriasis and atopic dermatitis. *J Allergy Clin Immunol*; 136:351-9

[REDACTED]

Murakami M, Hagforsen E, Morhenn V et al (2011) Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. *Exp Dermatol*; 20(10):845-7

Noack M, Miossec P (2017) Selected cytokine pathways in rheumatoid arthritis. *Semin Immunopathol*;39(4):365-383

Ogura H, Murakami M, Okuyama Y et al (2008) Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity*; 29(4):628-36

Patel DD, Lee DM, Kolbinger F et al (2013) Effect of IL-17A blockade with secukinumab in autoimmune diseases. *Ann Rheum Dis*; 72 Suppl 2:ii116-23

Paulissen SM, van Hamburg JP, Davelaar N et al (2013) Synovial fibroblasts directly induce Th17 pathogenicity via the cyclooxygenase/prostaglandin E2 pathway, independent of IL-23. *J Immunol*; 191(3):1364-72

Reich K, Papp KA, Matheson RT et al (2015) Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol*; 24(7):529-35

Simanski M, Rademacher F, Schröder L et al (2013) IL-17A and IFN- γ synergistically induce RNase 7 expression via STAT3 in primary keratinocytes. *PLoS One*; 8(3):e59531

Sofen H, Smith S, Matheson RT et al (2014) Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol*; 133(4):1032-40

Tohyama M, Hanakawa Y, Shirakata Y et al (2009) IL-17 and IL-22 mediate IL-20 subfamily cytokine production in cultured keratinocytes via increased IL-22 receptor expression. *Eur J Immunol*; 39(10):2779-88

Villanova F, Flutter B, Tosi I et al (2014) Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44+ ILC3 in psoriasis. *J Invest Dermatol*; 134(4):984-91

Whelton PK, Carey RM, Aronow WS et al (2017) ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*; S0735-1097(17):41519-1

Yoshiga Y, Goto D, Segawa S et al (2008) Invariant NKT cells produce IL-17 through IL-23-dependent and -independent pathways with potential modulation of Th17 response in collagen-induced arthritis. *Int J Mol Med*; 22(3):369-74

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in [Table 8-5](#).

Liver function and related variables

Total bilirubin:	> 2 x upper limit of normal (ULN)
Alkaline phosphatase:	> 2.5 x ULN

Renal function and electrolyte variables

Creatinine (serum):	> 1.5 x ULN
Potassium:	> 6 mmol/L or < 3 mmol/L
Sodium:	> 160 mmol/L or < 115 mmol/L

Urinalysis variable

Protein urine dipstick:	2+ (100 mg/dL)
-------------------------	----------------

Hematology variables

Hemoglobin:	≥ 20 g/L decrease from Baseline
Platelet count:	< lower limit of normal (LLN)
White blood cell count:	< 0.8 x LLN
Neutrophils:	< 0.9 x LLN
Eosinophils:	> 1.1 x ULN
Lymphocytes:	> 1.1 x ULN

16.2 Appendix 2

16.2.1 Skin type classification scale

Fitzpatrick Classification Scale			
Skin Type	Skin Color	Characteristics	Score
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans	(scores 0–6)
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty	(scores 7–13)
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans	(scores 14–20)
IV	Brown; typical Mediterranean caucasian skin	Rarely burns, tans with ease	(scores 21–27)
V	Dark Brown; mid-eastern skin types	very rarely burns, tans very easily	(scores 28–34)
VI	Black	Never burns, tans very easily	(scores 35–36)