NOVARTIS

Clinical Development

AIN457A/Secukinumab/Cosentyx®

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 Statistical Analysis Plan (SAP)


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| 22-Aug-2018 | Prior to FPFV | Creation of final version | N/A - First version | NA |
| 15-Apr-2019 | Before DBL | A few updates needed due to implementation of SAPLeaning principles and to correct the description of prior psoriasis therapy summaries | Amendment 1 | 2.3.3 Baseline disease characteristics<br>2.4.1 Study treatment / compliance<br>[redacted]<br>2.7.1.2 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<br>2.8.3 Laboratory data<br>2.8.4.1 ECG data |

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical therapeutic classification |
| CSR | Clinical study report |
| CTCAE | Common terminology criteria for adverse events |
| DBL | Database lock |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EOS | End of study |
| FAS | Full Analysis Set |
| IF | Immunofluorescence |
| [redacted] | [redacted] |
| IHC | Immunohistochemical |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| PDS | Programming datasets specifications |
| SD | Standard deviation |
| SOC | System organ class |
| TCS | Total clinical score |
| TEAE | Tretment-emergent adverse event |
| TFLs | Tables, Figures, Listings |
| [redacted] | [redacted] |
| WHO | World Health Organization |

# 1 Introduction

This document describes the detailed statistical methodology to be used for the Clinical Study Report (CSR) for the analysis of ARROW study CAIN457A2403, 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.

The content of this SAP is based on protocol CAIN457A2403 version 00.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specifications (PDS), respectively.

## 1.1 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.

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 psoriasis area and severity index (PASI) of 1-10 and one or more refractory skin plaques, defined by a total clinical score (TCS) of at least 6 and an area $\geq 10$ $cm^2$ 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.

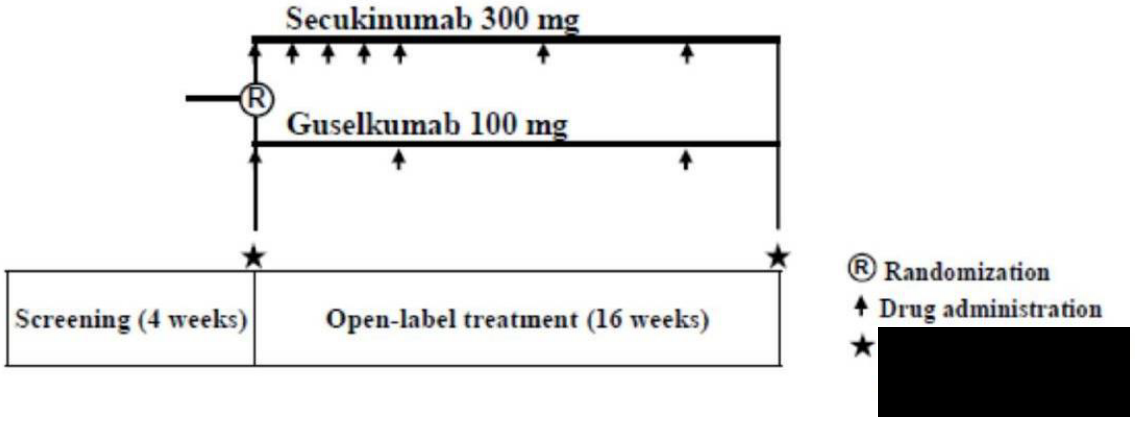
The initiation of study treatment at Baseline should not happen earlier than 12 weeks after the last administration of ustekinumab.

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 $\geq 6$) 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.

There will be no interim analysis. The CSR analysis will be performed after final database lock (DBL). The duration of enrollment is expected to be 6 months. The design of the study is outlined in Figure 1-1.

**Figure 1-1 Study design**



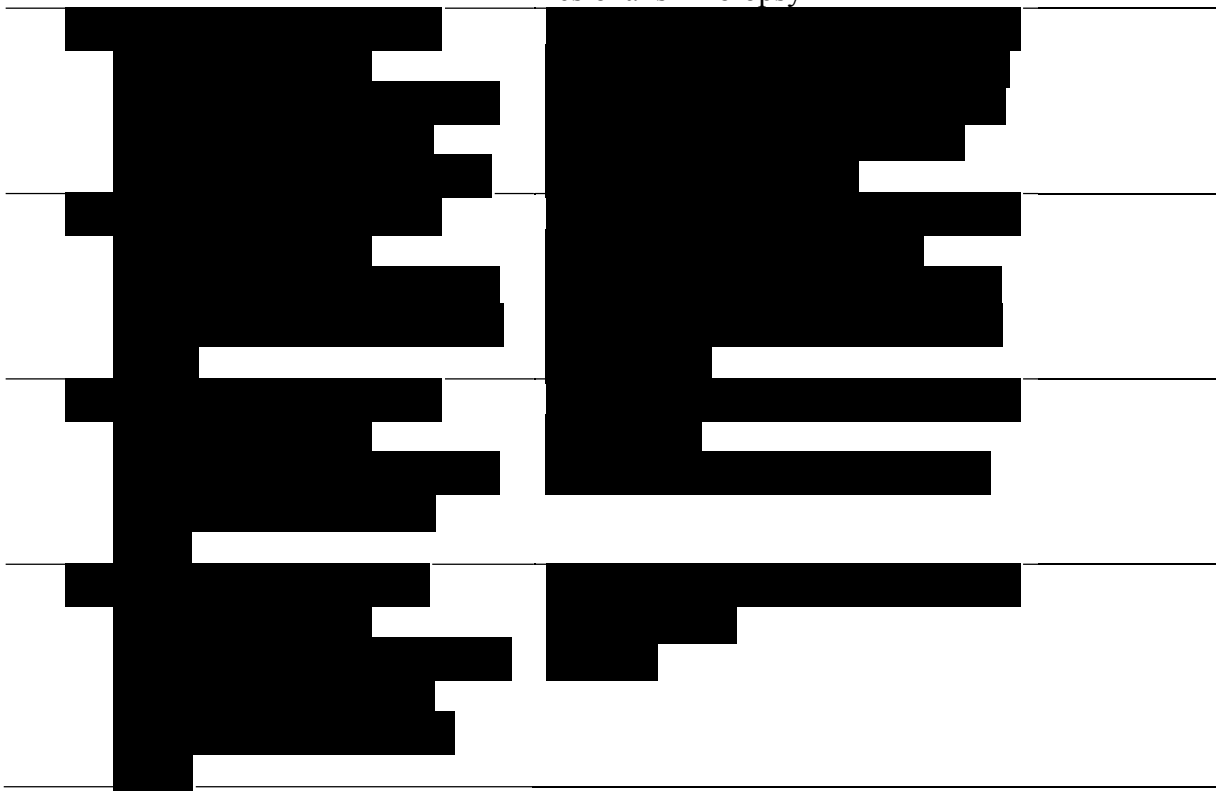

## 1.2 Study objectives and endpoints

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 1-1.

**Table 1-1 Study objective**

| Objectives | Endpoint | Analysis |
|---|---|---|
| **Primary objective:**<br>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) by 16 weeks of treatment with secukinumab or guselkumab | |
| **Exploratory objective:** [redacted] | [redacted] | |
| 2. To compare the effect of secukinumab versus guselkumab on the microscopic morphology of the skin plaque | 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 | |
| 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 | 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 | |

| | | |
|---|---|---|
| 4. | To compare the effects of secukinumab versus guselkumab on the composition of inflammatory infiltrate in the skin plaque | 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 |



# 2 Statistical methods

## 2.1 Data analysis general information

Data will be analyzed by Novartis statistical and programming team. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

SAS (version 9.4 or higher) will be used for generating study outputs used for clinical reports.

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

### 2.1.1 General definitions

**Study treatment** is defined as secukinumab or guselkumab.

**Date of first administration** of study treatment is defined as the first date when a nonzero dose of study treatment is administered and recorded on the dose administration eCRF page. The date of first administration of study treatment will also be referred to as start of study treatment.

**Date of last administration** of study treatment is defined as the last date when a nonzero dose of study treatment is administered and recorded on the dose administration eCRF page.

**Study day** will be calculated as:

- If event is on or after the start of study treatment: the date of the event (visit date, onset date of an event, assessment date etc.) – date of first administration of study treatment + 1;
- If event is before the start of study treatment: the date of the event (visit date, onset date of an event, assessment date etc.) – date of first administration of study treatment.

Study Day 1 is defined as the date of the first administration of study treatment.

**Baseline assessment** is defined as the last available assessment on or before the start date of study treatment.

**On-treatment assessment/event** is defined as any assessment/event in the period after the first dose of study medication and on or before last administration of study treatment plus 30 days.

### 2.1.2 Visit windows for data analysis

As it is a short term study with only one post-baseline scheduled visit, visit-windows will not be used for data analysis. The following visits will be used for the efficacy and safety data that is summarized by visit:

- Baseline - the last available assessment before the first study treatment administration will be used;
- Week 16 – the post-baseline assessment of subjects that completed 16 weeks of planned treatment will be used;
- EOS - the post-baseline assessment of all subjects taken study treatment for at least 4 weeks and with assessment at EOS Visit will be used.

In case of more than one post-baseline assessment due to unscheduled visits, the assessment closest to the scheduled day of EOS Visit at Week 16 (Day 112) will be used for the analysis. For the summary of notable laboratory abnormalities, the most extreme post-baseline measurement will be used for the analysis in case of more than one post-baseline assessment.

## 2.2 Analysis sets

The following analysis sets will be used in this study:

The **Full Analysis Set (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.

[redacted]

## 2.3 Subject disposition, demographics and other baseline characteristics

Subject disposition, background and demographic characteristics, and psoriasis baseline disease characteristics will be summarized by treatment arm for the FAS.

### 2.3.1 Subject disposition

Summary for all screened subjects will be presented and will include the number of screened and rescreened subjects and the number and percentage of subjects who completed or discontinued during the Screening, along with the primary reason for discontinuation. Data collected on the rescreen eCRF page and Screening completion eCRF page will be used to summarize this information.

The number and percentage of subjects that were treated, the number and percentage of subjects who complete or prematurely discontinue study will be presented, along with the primary reason for discontinuation. Data collected on the Study completion eCRF page will be used to summarize this information. The summary will be on the FAS.

### 2.3.2 Background and demographic characteristics

Demographic and background characteristics (age, sex, race, ethnicity and country as collected on the Demographics eCRF page), Fitzpatrick classification score, smoking history, relevant family history, height (as collected at Screening Visit) and baseline body weight will be summarized by treatment arm for the FAS using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median, and maximum (for continuous variables).

### 2.3.3 Baseline disease characteristics

Psoriasis medical and treatment history will be summarized by treatment arm for the FAS.

The summary of psoriasis medical history will include duration of plaque psoriasis, the number and percentage of active lesions at Screening per lesion location (head, trunk, upper and lower limbs, genitals), along with the number and percentage of subjects with active lesion affecting the nails, the scalp, the palms, and the soles. Data collected on the Active Psoriasis Plaques eCRF pages will be used to summarize this information.

The summary of psoriatic arthritis at Screening will include duration of psoriatic arthritis, the number and percentage of subjects with different types of the disease and the number and percentage of subjects with actively inflamed joints per lesion location (shoulders, elbows, wrists, fingers, hips, knees, ankles, toes). Data collected on the Psoriasis Arthritis History eCRF page and the Psoriasis Arthritis Joint Detailse eCRF page will be used for these summaries. In addition, duration of ankylosing spondylitis will be summarized for subjects with present disease at Screening.

Duration of disease since diagnosis (in years) will be derived as [(start date of study treatment –diagnosis start date +1)/365.25]. In these calculations, partial dates if any will be imputed according to the rules specified in Section 5.1.

Duration of exposure in months, time since discontinuation of the ustekinumab and the reason for discontinuation of the therapy will be summarized by treatment arm. Time since discontinuation of the therapy (in months) will be derived as [(start date of study treatment – last date of use +1)/30.4375]. In these calculations, partial dates if any will be imputed according to the rules specified in Section 5.1. The type of prior psoriasis therapies other than ustekinumab (including previous use of biologic therapies, non-biologic systemic therapies and topical therapies, as well as phototherapy and/or photo-chemotherapy) and total duration of exposure in months to the therapies will be summarized by treatment arm. Total exposure to the therapies (in months) will be derived as a sum of the exposures to all prior therapies other that ustekinumab. Exposure to each of the prior psoriasis therapy (in months) will be derived as [(start date of therapy – last date of use +1)/30.4375]

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Study treatment / compliance

Analyses described in this section will be performed on the Safety Set.

The duration to the study treatment in weeks will be defined as (date of last dose – date of first dose +1)/7 and summarized using descriptive statistics (number of subjects, mean, SD, minimum and maximum).

In addition, the treatment duration will be summarized by treatment with the number and percentage of subjects and by cumulative exposure level (e.g., any exposure, ≤ 1 week, ≤ 2 weeks, ≤ 3 weeks, ≤ 4 weeks, ≤ 8 weeks, etc.) will be presented.

On-treatment exposure in weeks to the study treatment will be defined as [(date of last dose date + 30 days) – date of first dose +1]/7.

The number of subjects with dose changed or dose interrupted and the reasons for dose change will be summarized by treatment using the information collected on Secukinumab and Guselkumab Dose Administration Record eCRF pages.

All dosing data will be listed.

### 2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the FAS.

Medications and non-drug therapies/procedures administered 6 months prior to or concomitantly with treatment will be coded using the WHO Drug Reference List version September 2017, which employs the Anatomical Therapeutic Chemical (ATC).

Prior and concomitant medication and non-drug therapies/procedures are defined as folows:

- Prior medications and prior non-drug therapies/procedures are those started and stopped prior to the first dose of treatment.

- Concomitant medications and concomitant non-drug therapies/procedures are those with start date on or after the first dose of treatment, or those with a start date before the first dose of treatment and stop date after the first dose of treatment.

Prior medications, concomitant medications, prior non-drug therapies/procedures and concomitant non-drug therapies/procedures will be listed and summarized by treatment arm, ATC code and preferred term. ATC level 1 and level 3 will be used.

### 2.4.3 Medical history

Medical history/current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) version 20.1.

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.

The tuberculosis assessments at Screening for subjects has 1 positive or 2 indeterminate QuantFERON TB - Gold test results will be listed by treatment arm and subject.

## 2.5 Analysis of the primary objective

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

### 2.5.1 Primary endpoint

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.

### 2.5.2 Statistical hypothesis, model, 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 treatment 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, H0: P1-P2 = 0 versus H1: P1-P2 > 0 at a type I error rate of 0.05 will be performed.

The TCS will be assessed at all study visits as indicated in Table 2-1. 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 2-1. The TCS can range from 0 (all signs absent) to 9 (all signs severe).

**Table 2-1 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 |

### 2.5.3 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 required in the protocol. 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 non-responders (failures).

### 2.5.4 Sensitivity and supportive analyses

Analysis of the primary endpoint as observed i.e., without missing data imputation (as described in Section 2.5.3) will be performed as a sensitivity analysis for the primary endpoint.

## 2.6 Analysis of the secondary objective

Not applicable.

## 2.7 Analysis of exploratory objective(s)

The exloratory objectives are presented in Table 1-1.

### 2.7.1 Exploratory endpoints

Analyses described in this section will be performed on the FAS and will be summarized by visit (Baseline, Week 16 Visit and EOS Visit) as specified in Section 2.1.2.

[redacted]

#### 2.7.1.2 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

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 EOS (End-of-study) Visit, one biopsy will be taken from the same area of the active plaque sampled at Baseline.

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.

Change from Baseline to Week 16 in epidermal thickness and in the number of Ki-67 and K16 positive cells of lesional skin biopsies will be summarized. In addition, the epidermal thickness differences at Baseline and Week 16 between the lesion biopsy and the Baseline non-lesional skin biopsy will be calculated. Similarly, the number of Ki-67 and K16 positive cells differences for Baseline and Week 16 will be derived. The change from Baseline to Week 16 in epidermal thickness differences and in the number of Ki-67 and K16 positive cells differences will be summarized by treatment.

#### 2.7.1.3 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

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

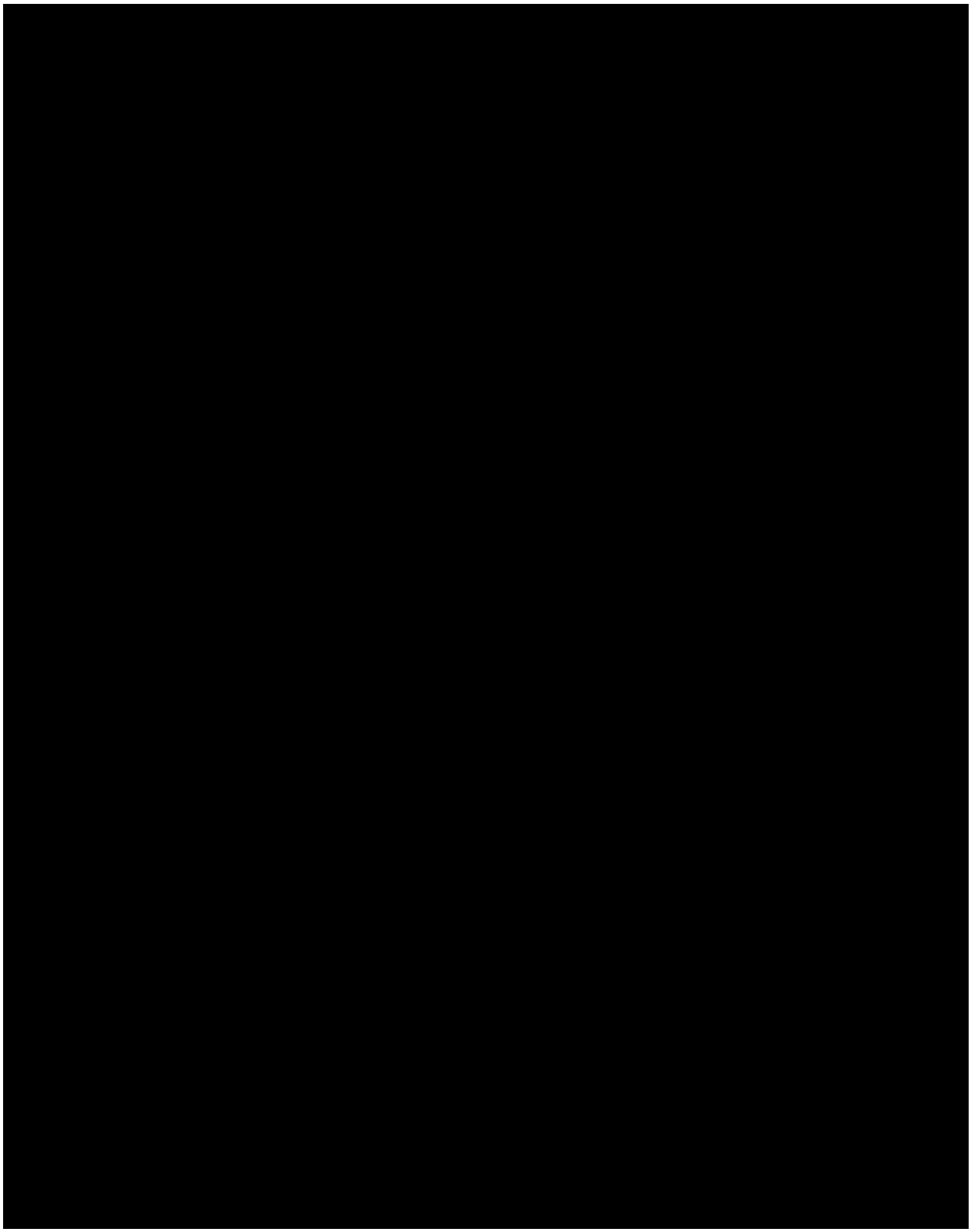
Change from Baseline to Week 16 in the number of infiltrating cells expressing IL-17A and IL-23R of lesional skin biopsies will be summarized. In addition, the number of infiltrating cells expressing IL-17A and IL-23R differences at Baseline and Week 16 between the lesion biopsy and the Baseline non-lesional skin biopsy will be calculated. The hange from Baseline to Week 16 in the number of infiltrating cells expressing IL-17A and IL-23R differences will be summarized by treatment.

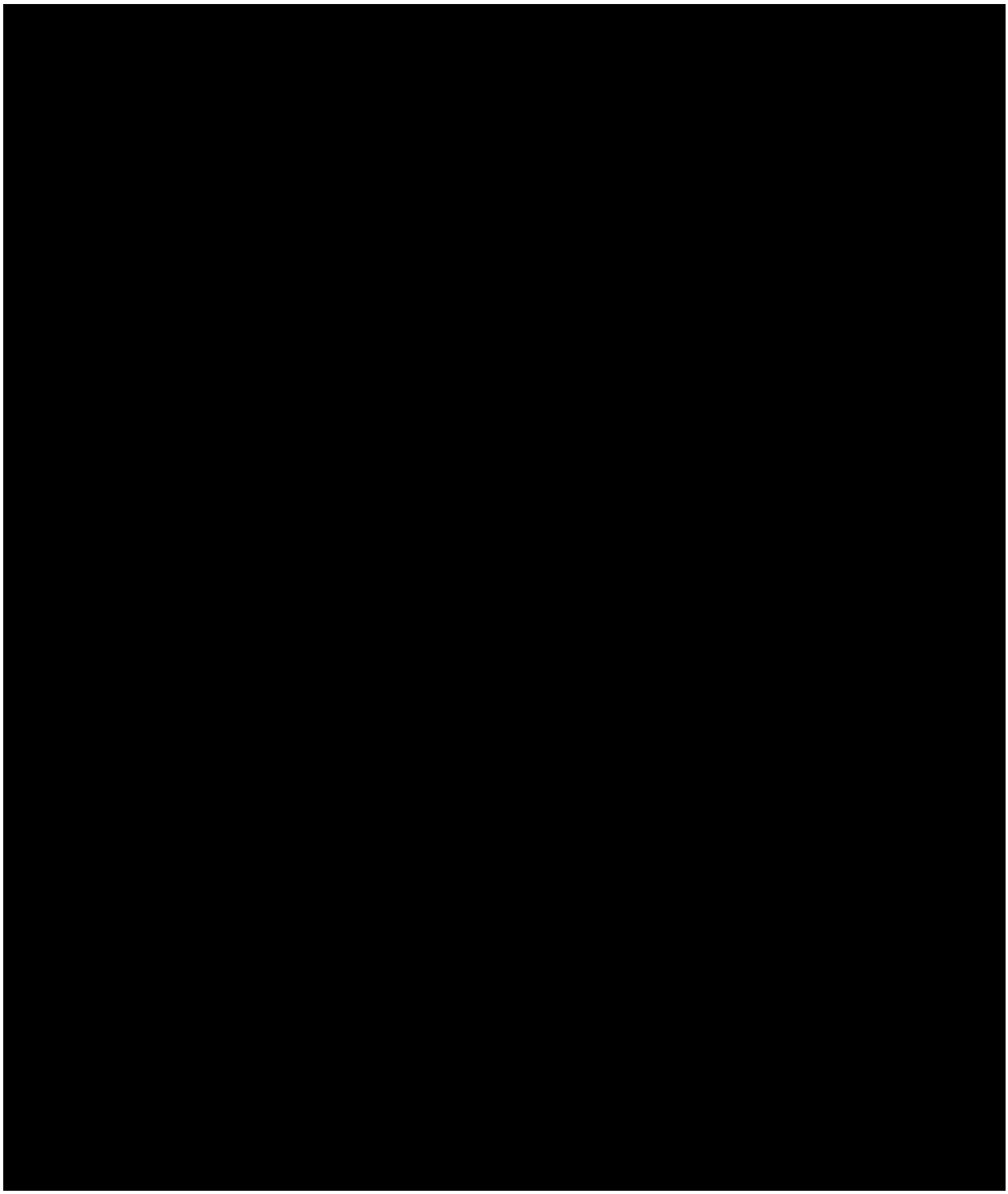
#### 2.7.1.4 Change from Baseline to Week 16 in the number of different immune cell types in the inflammatory infiltrate of lesional skin biopsies and difference from the Baseline non-lesional skin biopsy

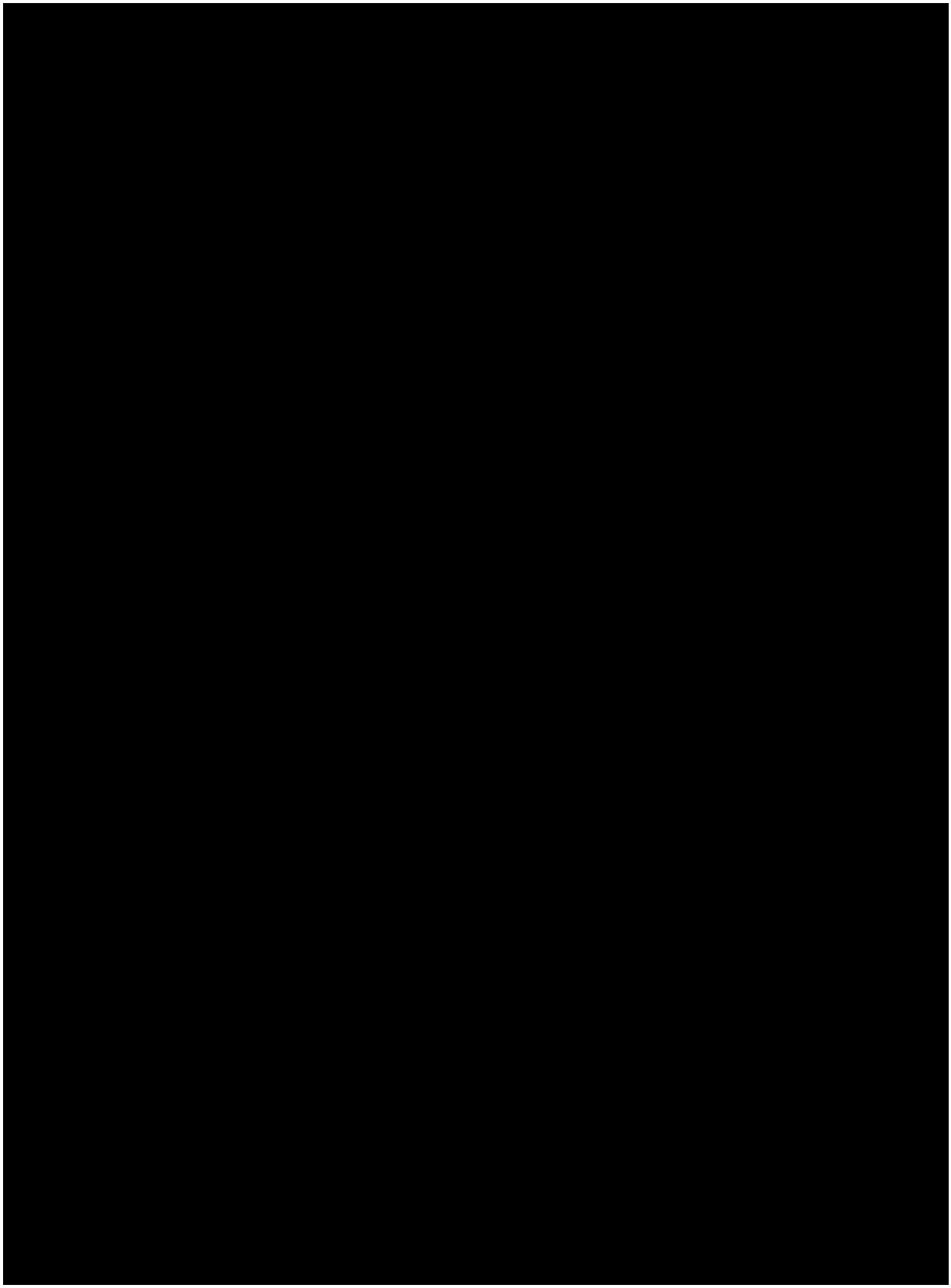
Single or double staining (IHC/IF) will be used to identify different cell types in the immune infiltrate according to the following markers: T-cells (CD3, CD8); neutrophils (elastase); mastocytes (tryptase); dendritic cells (CD11c); macrophages (CD163); NK cells (CD56); NKT cells (CD3, CD56); T-resident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

Change from Baseline to Week 16 in the number of different immune cell types in the inflammatory infiltrate of lesional skin biopsies will be summarized. In addition, the number of different immune cell types in the inflammatory infiltrate differences at Baseline and Week 16 between the lesion biopsy and the Baseline non-lesional skin biopsy will be calculated. The

change from Baseline to Week 16 in the number different immune cell types in the inflammatory infiltrate differences will be summarized by treatment.







### 2.7.2 Handling of missing values/censoring/discontinuations

The LOCF technique as described in Section 2.5.3 for the primary endpoint will be used for all the explorarory analysis.

## 2.8 Safety analyses

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. All safety events/assessments will be listed and those collected outside of the on-treatment window will be flagged.

### 2.8.1 Adverse events (AEs)

***Treatment-emergent*** AE (TEAE) is defined as any adverse event which start on or after the day of the first dose of study drug and up to 30 days after date of last dose of study treatment or event with start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment.

TEAE will be summarized by primary system organ class and preferred term according to the MedDRA terminology.

Incidence of TEAEs will be summarized (number of subjects reporting any cases and the percentage of number of subjects at risk) by primary system organ class (SOC), preferred term (PT), and treatment arm. Serious TEAEs, drug related TEAEs, TEAEs leading to premature discontinuation from study drug and most common TEAEs (>=10% in any of the treatment arms) will be presented by primary SOC, PT, and treatment arm. In addition, incidence of TEAEs will be summarized by SOC, PT, and maximum grade with respect to Common Terminology Criteria for Adverse Events (CTCAE). Missing CTCAE grade will not be imputed. The CTCAE version 4.03 will be used.

If a subject reports more than one adverse event within the same primary SOC, the subject will be counted only once with the maximum CTCAE grade at the SOC level, where applicable.

All AEs will be presented in listings.

#### 2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

### 2.8.2 Deaths

Death, if any, will be listed by treatment arm. All deaths as recorded in the database will be included.

### 2.8.3 Laboratory data

Data summaries will be provided in SI units. Laboratory data up to 30 days after study treatment discontinuation will be summarized.

Descriptive summary statistics for the change from baseline to each study visit will be presented by laboratory test and treatment arm. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

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 presented for hematology and biochemistry laboratory tests for subjects with both baseline and post-baseline value:

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

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectevely.

For liver function, urinalysis and hematology abnormalities, the number of subjects with newly occurring abnormalities will be summarized by treatment arm. Newly occurring abnormalities are defined in Section 5.3. In case of renal events, the overall frequency of events and percentage of subjects with renal events during the treatment period will be summarized and detailed.

Individual subject data listings will be provided for subjects with abnormal laboratory data using low and high classification. Data of subjects with newly occurring liver function, renal function, urinalysis and hematology abnormalities will be listed in additional listings.

Listings will be provided for the Quantiferon Gold, the serum pregnancy, [redacted]

### 2.8.4 Other safety data

#### 2.8.4.1 ECG data

ECG data will be listed and flagged as appropriate.

#### 2.8.4.2 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment arm. Change from baseline will only be summarized for subjects with both baseline and postbaseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of subjects with newly occurring notable vital signs will be

presented for the entire treatment period. Criteria for notable vital sign abnormalities are provided in Section 5.4.

## 2.9 Pharmacokinetic endpoints

Not applicable.

## 2.10 PD and PK/PD analyses

Not applicable.

## 2.11 Subject-reported outcomes

Not applicable.

## 2.12 Biomarkers

## 2.13 Not applicable.Other Exploratory analyses

Not applicable.

## 2.14 Interim analysis

Not applicable.

# 3 Sample size calculation

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 3-1 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 3-1 95% exact 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% |

# 4 Change to protocol specified analyses

Not applicable.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Missing or partial dates are not allowed in completing the study drug administration eCRF pages. The end date of study drug will be the last date of dose administration.

### 5.1.2 AE date imputation

For the start and end dates of the adverse event records, when incomplete or missing, dates will be imputed according to Novartis standards (details will be given in PDS document).

### 5.1.3 Concomitant medication date imputation

For the start and end dates of the concomitant medication records, when incomplete or missing, dates will be imputed according to Novartis standards (details will be given in PDS document).

#### 5.1.3.1 Prior therapies date imputation

Same as above.

#### 5.1.3.2 Post therapies date imputation

Same as above.

#### 5.1.3.3 Other imputations

For the calculation of duration or time since relevant history events as specified in section 2.3.3 (psoriasis disease baseline characteristics), partial dates will be imputed for the diagnosis start date, the first symptom date, the most recent relapse onset date via below imputation rules.

- If the year is missing or impossible (e.g. 12-Jan-1911), then the date will be imputed as missing.
- If the year is not missing and possible, but the month is impossible or missing (e.g. 17-XXX-2010), then the year will be kept and date will be imputed as July 1st (e.g., 1-July-2010).
- If the year and the month are not missing and possible, but the day is impossible or missing (e.g., 31-FEB-2009), then the year and month will be kept, and date will be imputed as 15th (e.g., 15-FEB-2009).
- The imputed dates should be prior to the screening visit date. That is, if imputed dates are on or after the screening visit date, the dates will be imputed to be one day before the screening visit date.

## 5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. The MedDRA version 20.1 will be used and will be described in the footnote of relevant outputs.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, “fatal” is collected as AE outcome and death information is also collected on a separate eCRF page.

## 5.3 Laboratory parameters derivations

The table below shows all laboratory parameters that will be presented.

## Table 5-1 Laboratory Tests

| Order | Laboratory Group<br>Subgroups | Tests [SI unit] |
|---|---|---|
| 1 | Hematology | |
| | Red Blood Cells | Hematocrit [%]<br>Hemoglobin [mmol/L]<br>Platelet count [10E9/L]<br>Red cell count [10E12/L] |
| | White Blood Cell Differential | Absolute Basophils [10E9/L]<br>Absolute Eosinophils [10E9/L]<br>Absolute Lymphocytes [10E9/L]<br>Absolute Monocytes [10E9/L]<br>Basophils [%]<br>Eosinophils [%]<br>Lymphocytes [%]<br>Monocytes [%]<br>Neutrophils [%]<br>White Cell Count [10E9/L] |
| 2 | Chemistry | |
| | Renal Function | Creatinine [umol/L]<br>Blood urea [mmol/L] |
| | Liver Function Test | Albumin [g/L]<br>Alkaline Phosphatase [U/L]<br>Total Bilirubin [umol/L]<br>Total protein [g/L] |
| | Lipids | Cholesterol HDL [mmol/L]<br>Cholesterol LDL [mmol/L]<br>Triglycerides [mmol/L]<br>Total Cholesterol [mmol/L] |
| | Other | International normalized ratio<br>Uric acid |
| | Electrolytes / Metabolism Tests | Bicarbonate [mmol/L]<br>Calcium [mmol/L]<br>Chloride [mmol/L]<br>Magnesium [mmol/L]<br>Phosphate [mmol/L]<br>Potassium [mmol/L]<br>Sodium [mmol/L] |

| Order | Laboratory Group<br>Subgroups | Tests [SI unit] |
|---|---|---|
| 3 | Urinalysis | Blood<br>Glucose<br>Specific gravity<br>Albumin<br>Protein |

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

**Liver function and related variables:**

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

**Renal function and electrolyte variables:**

- Creatinine (serum): > 1.5 × 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 × LLN
- Neutrophils: < 0.9 × LLN
- Eosinophils: > 1.1 × ULN
- Lymphocytes: > 1.1 × ULN

## 5.4 Clinically notable vital signs

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic blood pressure of ≥ 140 mmHg (hypertension)
- Diastolic blood pressure of ≥ 90 mmHg (hypertension)
- Pulse rate ≥ 100 bpm (tachycardia).

Clinically notable below normal values

- Systolic blood pressure of < 90 mmHg (hypotension)
- Diastolic blood pressure of < 60 mmHg (hypotension)
- Pulse rate < 60 bpm (bradycardia)

## 5.5 Statistical models

### 5.5.1 Primary analysis

The null hypothesis is that there is no difference in the proportions of responders (subject with TCS=0-2 at Week 16) in the secukinumab (P1) and gesulkumab (P2) arms. The alternative hypothesis is that there is a difference between the two treatment arms (P1 greater than P2).
$H_0$: P1-P2 = 0 versus $H_A$: P1-P2 > 0

The null hypothesis will be tested using 1-sided Fisher's exact test for difference in the proportion of responders at the target 1-sided Type I error rate of 5% (using the FISHER option in the SAS procedure FREQ).

The Clopper-Pearson formula will be used to derive exact 95% confidence intervals for the proportion of responders using the BINOMIAL(EXACT) option in the SAS procedure FREQ.

### 5.5.2 Key secondary analysis

Not applicable

### 5.5.3 Exploratory endpoints

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment arm.

## 5.6 Rule of exclusion criteria of analysis sets

**Table 5-2 Subject Classification**

| Analysis Set | PD ID that cause subjects to be excluded | Non-PD criteria that cause subjects to be excluded |
|---|---|---|
| FAS | NA | Not randomized<br>Mistakenly randomized and no study treatment taken |
| SAF | NA | No study treatment taken |

# 6 Reference

Fredriksson T, Pettersson U (1978) Severe psoriasis--oral therapy with a new retinoid. Dermatologica; 157(4):238-44

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