**Janssen Research & Development**

**Statistical Analysis Plan**

# A Phase 3 Open-label Study to Assess the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Ustekinumab in the Treatment of Moderate to Severe Chronic Plaque Psoriasis in Pediatric Subjects ≥6 to <12 Years of Age

**Protocol CNTO1275PSO3013; Phase 3**

**CNTO1275 (Ustekinumab)**

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

# TABLE OF CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| CDLQI | Children Dermatology Life Quality Index |
| CI | confidence interval |
| CL/F | apparent clearance |
| CRF | case report form |
| CSR | Clinical Study Report |
| DBL | database lock |
| DMC | Data Monitoring Committee |
| DPS | Data Presentation Specifications |
| eCRF | electronic case report form |
| FDA | Food and Drug Administration |
| IgG1λ | Immunoglobulin G1 lambda |
| IWRS | interactive web response system |
| LTE | long-term extension |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | methotrexate |
| NAb | neutralizing antibodies |
| PASI | Psoriasis Area and Severity Index |
| PD | pharmacodynamic |
| PGA | Physician's Global Assessment |
| PK | pharmacokinetic(s) |
| PK/PD | pharmacokinetic/ pharmacodynamic |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | subcutaneous |
| SD | standard deviation |
| V/F | apparent volume of distribution |

# 1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety and pharmacokinetics for the ustekinumab (CNTO 1275) clinical study CNTO1275PSO3013. Ustekinumab is a fully human immunoglobulin G1 lambda (IgG1κ) monoclonal antibody (mAb) that binds both human interleukin (IL)-12 and IL-23 via a common IL-12/23p40 subunit and has been approved for the treatment for the adult and adolescent subjects (12 years and older) with moderate to severe psoriasis in North America, Europe and other countries based on the CNTO1275PSO3006 (CADMUS) study in 110 subjects. Study CNTO1275PSO3013 evaluates the efficacy, safety and pharmacokinetics of ustekinumab for the treatment of pediatric subjects aged ≥6 to <12 years old with moderate to severe psoriasis.

## 1.1. Trial Objectives

### Primary Objective

The primary objective of this study is:

- To evaluate the efficacy and safety of ustekinumab in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.

### Secondary Objectives

The secondary objectives of this study are:

- To evaluate the pharmacokinetics of ustekinumab in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.
- To evaluate the effect of ustekinumab on the dermatologic health-related quality of life in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.
- To evaluate the immunogenicity of ustekinumab in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.

## 1.2. Trial Design

### Main Study: Week 0 through Week 56

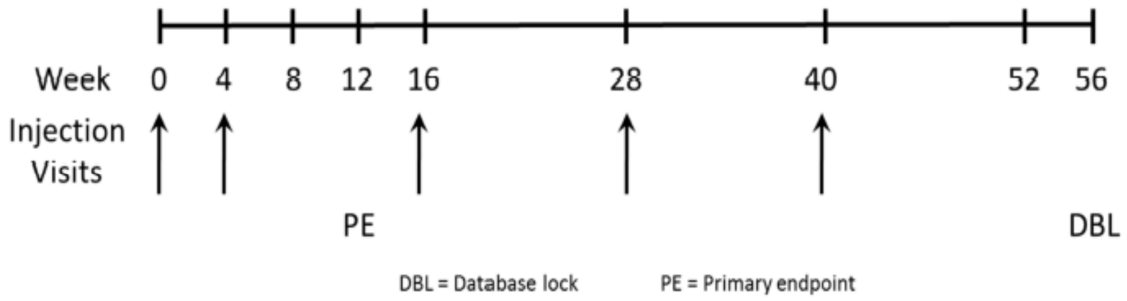
This is an open label multicenter study of ustekinumab in pediatric subjects ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis. The subject population will be comprised of boys and girls who have had a diagnosis of plaque-type psoriasis for at least 6 months prior to first study drug administration and who have moderate to severe disease defined by PASI ≥12, PGA ≥3, and BSA ≥10%.

At least 40 subjects will receive ustekinumab administered subcutaneously at weight-based doses at Weeks 0 and 4 followed by dose administrations every 12 weeks (q12w) through Week 40. Subject weight will be measured at each visit and the dose of ustekinumab will be adjusted accordingly. Expected duration of exposure to study drug during the active treatment period is

52 weeks. Visits will be every 4 weeks (q4w) through Week 16, then q12w through Week 52. Efficacy assessments will be collected through Week 52. Subjects will have a final safety follow-up at Week 56. A database lock (DBL) will occur at the end of the main study (Week 56).

The study schema is presented in Figure 1.

**Figure 1: Study Schema for the Main Study (Week 0 through Week 56)**




For those subjects who do not meet the protocol defined criteria to enter the LTE of the study, Week 56 safety follow-up will be the end of study participation for these subjects.

**Long-term Extension: Week 56 through Week 264**

Following completion of the Week 52 visit, subjects who have had a beneficial response from ustekinumab treatment as determined by the investigator, and who have not yet reached the age of 12 years or older in countries where marketing authorization for ustekinumab has been granted for the treatment of psoriasis in adolescent patients (12-17 years), and are willing to continue ustekinumab treatment, may enter the LTE of the study. For these subjects, the safety follows up for the main study and the first ustekinumab administration of the LTE will be at the Week 56.

Subjects may continue to participate in the LTE until they reach Week 264 or one of the following occurs:

- The subject turns 12 years of age and resides in a country where marketing authorization has been granted for ustekinumab treatment of psoriasis in adolescent patients
- Marketing authorization is obtained for ustekinumab for treatment of plaque psoriasis for patients ≥6 to <12 years of age in the subject's country of residence
- Marketing authorization is denied for ustekinumab for the treatment of plaque psoriasis for patients ≥6 to <12 years of age in the subject's country of residence
- A company decision is made to no longer pursue an indication in plaque psoriasis in the pediatric population (≥6 to <12 years of age) in the subject's country of residence

All assessments will be performed per the Time and Events Schedule for the LTE in the protocol.

During the LTE, consideration should be given to discontinue ustekinumab treatment in subjects who are non-responders (defined by PGA >3 at 2 consecutive visits). A DBL will occur at end of the LTE. The LTE is considered completed when all subjects have either terminated participation according to the above criteria or completed their follow-up at Week 264. Additional DBLs may occur at the Sponsor's discretion.

## 1.3. Statistical Hypotheses for Trial Objectives

There will be no formal hypothesis testing performed. Efficacy and safety of ustekinumab in pediatric subjects ≥6 through <12 years of age with moderate to severe chronic plaque psoriasis will be evaluated using descriptive statistics. The PK of ustekinumab in pediatric subjects will also be evaluated using descriptive statistics of serum ustekinumab concentration and population PK analyses.

## 1.4. Sample Size Justification

The sample size of 40 was determined based on both efficacy and PK assessments. The primary objective is to evaluate the efficacy and safety of ustekinumab for pediatric subjects aged ≥6 to <12 years with moderate to severe chronic plaque psoriasis and one of the major secondary objectives is to evaluate the pharmacokinetics of ustekinumab in this population. To support these objectives, a sample size of 40 subjects was chosen. For the efficacy assessment, no formal hypothesis testing will be performed. The observed response rates and its 95% confidence interval of PGA of cleared (0) or minimal (1) at Week 12 will be provided. A sample size of 40 will provide a 95% confidence interval [50%, 80%], if the observed response rate is 65%.

To assess the pharmacokinetics of ustekinumab in this pediatric population, the sample size evaluation was based on simulations with a population PK model developed from adult Studies C0743T08, C0743T09, and adolescent study CNTO1275PSO3006. The PK in pediatric subjects ≥6 to <12 years of age was simulated using the body weight distribution sampled with replacement from the National Health and Nutrition Examination Survey (NHANES) III growth database. A total of 300 replicates of the planned study, including the PK sampling scheme shown in the Time and Events Schedule, were simulated and subsequently the population PK parameters were re-estimated for each replicate. The precisions to estimate the CL/F and V/F were calculated. The precisions of CL/F estimates with 30 and 40 subjects were 9.4% and 8.1%, respectively, which are lower than 20% and generally considered appropriate. The precisions of V/F estimates with 30 and 40 subjects were 10.4% and 9.2%, respectively. Considering potentially higher variability in pediatric subjects ≥6 to <12 years of age than the adolescent and adult populations, at least 40 subjects are planned to be enrolled to provide adequate data to characterize PK of ustekinumab in the planned study population.

## 1.5. Randomization and Blinding

### Treatment Allocation

This is an open label study. All subjects will be assigned to receive active study drug (ustekinumab).

### Blinding

As this is an open-label study, blinding of study drug is not applicable. However, a blinded efficacy evaluator will be used to assess efficacy during the main study.

# 2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the two planned DBLs.

## 2.1. Imputation Rules for Partial or Missing AE Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

## 2.2. Visit Windows

There are no visit windows for analyses. Nominal visits will be used for all by-visit analyses in the study unless otherwise specified, regardless of the scheduled visit window. The study visits scheduled should occur at the times delineated in the Time and Events Schedule of the protocol.

## 2.3. Pooling Algorithm for Analysis Centers

There is no pooling algorithm for analysis centers.

## 2.4. Analysis Sets

### 2.4.1. Efficacy Analysis Set(s)

#### 2.4.1.1. Full Analysis Set

In this study, the efficacy analyses will be performed on the full analysis set, which is defined as all enrolled and treated subjects who received at least 1 injection of ustekinumab (partial or complete) during the study. The full analysis set will be used for all primary and secondary efficacy analyses.

In addition, the primary endpoint will also be performed using the per protocol analysis set as defined below.

#### 2.4.1.2. Per Protocol Analysis Set

The per protocol population includes subjects in full analysis set except those

- who did not meet the inclusion criteria 2 in the protocol as listed below:
  - Have a PASI ≥12 at screening and at baseline.
  - Have an PGA ≥3 at screening and at baseline.
  - Have an involved BSA ≥10% at screening and at baseline.
- who violated the exclusion diagnosis criteria 1 or 2:
  - Currently have nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
  - Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

- who violated the concomitant or previous psoriasis medical therapies-related exclusion criteria (from 3 through 11) as listed below:
  - Have used any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to ustekinumab, guselkumab, and tildrakizumab.
  - Have used topical medications/treatments that could affect psoriasis or PASI evaluation (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, picrolimus,tacrolimus) within 2 weeks of the first administration of study drug.
  - Have received phototherapy or any systemic medications/treatments that could affect psoriasis or PASI evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens,sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of the first administration of study drug.
  - Have received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil,hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study drug.
  - Have received any biologic agent (eg, ENBREL®, HUMIRA®) within the previous 3 months or 5 times the t1/2 of the agent, whichever is longer.
  - Have received natalizumab, efalizumab, or agents that deplete B or T cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population.
  - Are currently receiving lithium, antimalarials, or intramuscular (IM) gold, or have received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study drug.
  - Have used a topical investigational agent within 4 weeks or 5 times the $t_{1/2}$ of the investigational agent, whichever is longer, before the planned start of treatment or are currently enrolled in a study of a topical agent.
  - Have used a non-topical investigational drug within 3 months or 5 times the $t_{1/2}$ of the investigational agent, whichever is longer, before the planned start of treatment or are currently enrolled in a study of a non-topical investigational agent.
- Subjects enrolled and received ustekinumab at Week 0 but did not receive all scheduled ustekinumab administrations or receive an extra ustekinumab administration prior to Week 12.

However, among subjects who did not receive all scheduled ustekinumab administrations or received an extra ustekinumab administration prior to Week 12, those who discontinued the study agent due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening of psoriasis, or started prohibited medications and continued receiving study agents prior to Week 12 will be included in the per protocol analysis and the treatment failure rules specified in Section 5.1.3.2 will apply.

Subjects who were excluded from the per protocol analyses will also be summarized.

### 2.4.2. Safety Analysis Set

Safety analysis set will be the same as the full analysis set, ie, enrolled subjects who received at least 1 injection of ustekinumab (partial or complete) during the study.

### 2.4.3. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who received at least one injection of ustekinumab and have at least one valid blood sample drawn for PK analysis.

### 2.4.4. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least one injection of ustekinumab and have at least one appropriate sample collected post ustekinumab administration for the detection of antibodies to ustekinumab.

## 2.5. Definition of Subgroups

To evaluate the consistency of efficacy in the primary endpoint over demographic, baseline disease characteristics, and psoriasis medication history, subgroup analyses will be performed when the number of subjects in the subgroups permits.

**Baseline demographics:**

- Sex (male, female)
- Baseline Age (<10 years, ≥10 years)
- Baseline weight (<60 kg, ≥60 to <100 kg, ≥100 kg)

**Baseline disease characteristics:**

- Age at diagnosis (years) (< 6, ≥ 6)
- Psoriasis disease duration (years) (< 3, ≥ 3)
- Baseline PASI (<20, ≥20)
- Baseline PGA (<4, ≥4)
- Baseline BSA (<20%, ≥20%)
- Baseline CDLQI (<10, ≥10)

**Psoriasis medication history:**

- Phototherapy (Ultraviolet B light [UVB] or psoralen-ultraviolet-light [PUVA])
  - Never used
  - Ever used

- Non-biologic systemics (PUVA, MTX, cyclosporine, acitretin, apremilast, or tofacitinib)
  - Never used
  - Ever used
- Biologics (etanercept, infliximab, alefacept, efalizumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab)
  - Never used
  - Ever Used
- Non-biologic systemics or biologics (as defined above)
  - Never used
  - Ever used

In these subgroup analyses, the proportion of subjects achieving a PGA score of cleared (0) or minimal (1) with corresponding 95% CIs will be presented by subgroup. In addition, the proportion of subjects achieving a PGA score of cleared (0) or minimal (1) at Week 12 will also be summarized by investigational site. All above subgroup analyses will also be performed on the proportion of PASI 75 responders at Week 12.

## 2.6. Study Day and Baseline Definition

### 2.6.1. Study Day

Study Day 1 refers to the first study agent administration date. The study day for an event is defined as:

- Event date - (date of Study Day 1) +1, if event date is ≥ date of Day 1
- Event date - date of Day 1, if event date < date of Day 1

### 2.6.2. Baseline

In general, the baseline measurement is defined as the closest measurement taken prior to or at the time of the first study agent administration date unless otherwise specified.

# 3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No formal interim analysis is planned. There is no Data Monitoring Committee (DMC) for this study.

# 4. SUBJECT INFORMATION

The full analysis set will be used for the subject information analyses as specified below unless otherwise noted. In addition, the distribution of subjects by country and site will be presented.

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, subject listings will also be used to present the data.

## 4.1. Demographics and Baseline Characteristics

### 4.1.1. Demographics

Table 1 presents a list of the demographic variables that will be summarized for the full analysis set.

**Table 1: Demographic Variables**

| **Continuous Variables:** | **Summary Type** |
|---|---|
| Age (years) | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range). |
| Weight (kg) | |
| Height (cm) | |
| **Categorical Variables:** | |
| Age (<10 years and ≥10 years) | Frequency distribution with the number and percentage of subjects in each category. |
| Sex (male, female) | |
| Weight (<60 kg, ≥60 to <100 kg, ≥100 kg) | |
| Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple, Unknown, Not reported) | |
| Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown) | |
| BMI (Normal [<25], Overweight [25 -<30], Obese [≥30]) | |

[a]If multiple race categories are indicated, then Race is recorded as "Multiple."

In addition, the histogram plots for the distributions of age at baseline will be provided.

### 4.1.2. Baseline Characteristics

Psoriasis baseline disease characteristics (i.e., psoriasis disease duration [years], age at diagnosis [years], BSA [%], psoriatic arthritis, baseline PGA score, baseline PASI score [0-72], and baseline CDLQI) will be summarized for the full analysis set.

## 4.2. Disposition Information

Screened subjects will be summarized overall.

The number of subjects in the following disposition categories will be summarized:

- Subjects enrolled and treated
- Subjects who completed the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the period of Week 56 and Week 264 if appropriate.

Listings of subjects will be provided for the following categories:

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

## 4.3. Treatment Compliance

Study agent compliance will be summarized descriptively through Week 56 and through Week 248 for the full analysis set.

## 4.4. Extent of Exposure

The exposure data will be summarized through Week 56 and through Week 248. The number and percentage of subjects who receive study agent will be summarized for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of administrations
- Cumulative total dose

In addition, the study agent lots received will be summarized.

## 4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or results of the clinical trial. Subjects with major protocol deviations will be identified prior to database lock and will be summarized by category through Week 56 and through Week 264 for the full analysis set.

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment

- Received a wrong treatment or an incorrect dose
- Other: to be defined in the major protocol deviation criteria document

Subjects with major protocol deviations will also be listed.

## 4.6. Prior and Concomitant Medications

Subjects' prior psoriasis medication history with topical agents, phototherapy, non-biologic systemic therapies, and biologic medications will be summarized. See Section 2.5 for lists of medications in each category. In addition, reasons for which subjects discontinued previous systemic therapies (contraindication, inadequate response, intolerance [ie, AEs], or other) will be summarized.

The number of subjects who received concomitant treatment with a moisturizer for psoriasis will be summarized.

Subjects who received concomitant corticosteroids for indications other than psoriasis will be listed.

# 5. EFFICACY

In general, efficacy data summaries will be provided for the full analysis set.

No formal hypothesis testing will be conducted. Descriptive statistics, such as mean, median, standard deviation, minimum and maximum, interquartile range for continuous variables, and counts and percentages for categorical variables will be used to summarize the data. Graphical data displays and subject listings may also be used to summarize the data.

## 5.1. Analysis Specifications

### 5.1.1. Level of Significance

No formal hypothesis testing will be conducted such that no p-values will be reported. Two-sided exact 95% confidence intervals (CI) will be provided for the primary and major secondary endpoints. The study is designed to provide reasonable precision on the estimation of response rates.

### 5.1.2. Definition of the Efficacy Endpoints and Calculation of the Efficacy Instruments

#### 5.1.2.1. Physician's Global Assessment

The Physician's Global Assessment (PGA) is used to determine the subject's psoriasis at a given time point. Overall lesions are graded for induration, erythema, and scaling. The patient's psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), marked (4), or severe (5).

Efficacy endpoints related to the PGA score are defined below:

**PGA cleared responder**

Subjects who achieve an PGA score of 0 will be considered PGA cleared responders.

**PGA cleared or minimal responder**

Subjects who achieve an PGA score of 0 or 1 will be considered PGA cleared or minimal responders.

**PGA mild or better responder**

Subjects who achieve an PGA score of 0, 1, or 2 will be considered PGA mild or better responders.

#### 5.1.2.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90%-100% involvement), and for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

Efficacy endpoints related to the PASI score are defined below:

**PASI 50 Responder**

Subjects with ≥50% improvement in PASI from baseline will be considered PASI 50 responders.

**PASI 75 Responder**

Subjects with ≥75% improvement in PASI from baseline will be considered PASI 75 responders.

**PASI 90 Responder**

Subjects with ≥90% improvement in PASI from baseline will be considered PASI 90 responders.

**PASI 100 Responder**

Subjects with 100% improvement in PASI from baseline (PASI score=0) will be considered PASI 100 responders.

#### 5.1.2.3. Children Dermatology Life Quality Index

The Children Dermatology Life Quality Index (CDLQI) is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is an adapted version of DLQI. The CDLQI, a 10-item questionnaire has a 4 item response option and a recall period of 1 week. In addition to evaluating overall quality of life, the CDLQI can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, leisure,

school or holidays, personal relationships, sleep, and treatment. The scoring of each question is as follows:

| | |
|---|---|
| Very much | Scored 3 |
| Quite a lot | Scored 2 |
| Only a little | Scored 1 |
| Not at all | Scored 0 |
| Question unanswered | Scored 0 |
| Question 7: ”Prevented school” | Scored 3 |

The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease. The 6 CDLQI components scores are calculated as follows:

| | | |
|---|---|---|
| Symptoms and feelings | Questions 1 and 2 | Score maximum 6 |
| Leisure | Questions 4, 5 and 6 | Score maximum 9 |
| School or holidays | Questions 7 | Score maximum 3 |
| Personal relationships | Questions 3 and 8 | Score maximum 6 |
| Sleep | Questions 9 | Score maximum 3 |
| Treatment | Questions 10 | Score maximum 3 |

### 5.1.3. Data Handling Rules

The following treatment failure rules and data handling rules will be applied to the PASI and PGA-related efficacy analyses in this study.

#### 5.1.3.1. Treatment Failure Criteria

Subjects who discontinue study agent due to lack of efficacy or an adverse event (AE) of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could affect their psoriasis are considered as treatment failures.

The particular protocol-prohibited medications/therapies include:

**Topical Therapies for the Treatment of Psoriasis:**

- Before Week 12, any topical corticosteroid used for treatment of psoriasis.
- After Week 12 through Week 52, any topical corticosteroid used for treatment of psoriasis with the exception of low-potency corticosteroids used on the face and/or groin.
- Non-corticosteroid topical therapies that could affect psoriasis or the PASI evaluation such as tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus and tacrolimus through Week 52 (with the exception of topical moisturizers and shampoos containing tar or salicylic acid only).

Note that in this study, shampoos (containing tar or salicylic acid only) and topical moisturizers are allowed.

**Phototherapy or Systemic Therapies for the Treatment of Psoriasis:**

- Any systemic corticosteroid used for psoriasis with the exception of intra-articular corticosteroids.
- Any other anti-psoriatic systemic therapy or biologic therapy.
- Phototherapy of UVB or PUVA or any other phototherapy for psoriasis.

**Concomitant Therapies for Conditions Other than Psoriasis:**

- Any disease-modifying agents such as MTX, or sulfasalazine.
- Any intramuscular corticosteroid for "Other" indications.

#### 5.1.3.2. Treatment Failure Rules

A subject who meets one or more treatment failure criterion specified in Section 5.1.3.1 will be considered a treatment failure from that point onward through Week 52. The baseline values will be used for all directly measured endpoints regardless of the actual measurements. Zero will be assigned to improvement and percent improvement, and non-responder status will be assigned to binary response variables. No treatment failure rules will be applied after Week 52.

Treatment failure is assumed to have occurred at the earlier of the following dates:

- Date of discontinuation (DC) of study treatment due to lack of efficacy or
- Date of discontinuation of study agent due to an AE of worsening of psoriasis or
- Start date of a protocol-prohibited medication/therapy during the study that could improve psoriasis

#### 5.1.3.3. Additional Data Handling Rules for Children Life Quality Index (CDLQI)

In addition to the data handling rules described in Section 5.1.3.1, the following data handling rules also apply to all the secondary analyses related to Children Dermatology Life Quality Index (CDLQI) before applying the treatment failure rules.

For a partially answered questionnaire (eg, not all 10 answers in the CDLQI questionnaire were available) or incorrectly completed questionnaire:

- If one question is left unanswered, this question will be scored 0. The total score and each of the 6 component scores will then be calculated.
- If two or more questions are left unanswered, the total score and the affected component scores will be set to missing.

If both parts of question 7 are completed, the higher of the two scores should be used.

#### 5.1.3.4. Missing Data Imputation

For the most efficacy analyses (eg, over time summaries), after the treatment failures, no imputation will be performed for missing data (eg, lost to follow-up, missed study visit) and the values will remain as missing except for the following:

The dichotomous endpoints at Week 12:

- PGA score of cleared (0), cleared (0) or minimal (1), and mild or better (≤ 2);
- PASI 100, PASI 90, PASI 75, and PASI 50 responses;
- CDLQI of 0 or 1.

For these types of endpoints, subjects with missing PGA score, PASI score, PASI component, or CDLQI at Week 12 will be considered as not achieving the respective endpoints at Week 12.

### 5.2. Primary Efficacy Endpoint(s)

#### 5.2.1. Definition

The primary endpoint of the study is the proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12. The PGA documents the physician's assessment of the subject's psoriasis status according to the following categories: induration, scaling, and erythema.

#### 5.2.2. Estimand

**Population:** subjects with moderate-to-severe plaque psoriasis who are treated with ustekinumab.

**Endpoint:** the proportion of subjects who achieve a PGA score of cleared (0) or minimal (1) at Week 12 and did not discontinue study agent due to lack of efficacy or AE of psoriasis, or initiate prohibited anti-psoriatic medication/therapy.

**Intercurrent Events:** defined through the endpoint description.

#### 5.2.3. Analysis Methods

In the primary analysis, the number and proportion of subjects achieving a PGA score of cleared (0) or minimal (1) at Week 12 will be summarized. Its two-sided exact 95% confidence intervals (CI) will be provided.

To assess the robustness of the primary endpoint analysis result, the following two sensitivity analyses will be conducted.

**Sensitivity Analysis 1**

For subject who have a missing PGA score at Week12, the score will not be imputed. That is, the analysis will be performed using observed data, after treatment failure rules (as defined in Section 5.1.3.2). Its two-sided exact 95% confidence intervals (CI) will be provided.

**Sensitivity Analysis 2**

The second sensitivity analysis will be performed by using multiple imputations (MI), after applying treatment failure rules (as defined in Section 5.1.3.2). The intermittent missing PGA score through Week 12 will be imputed using the Markov Chain Monte Carlo (MCMC) algorithm with 200 imputed data sets and seed = 123 to make the missing data pattern monotone. The PGA score of cleared (0) or minimal (1) responses will then be derived based on the imputed scores at or before Week 12. The remaining missing data of the PGA score of cleared (0) or minimal (1) will be imputed with monotone logistic regression with baseline PGA score and PGA response status at each visit in the model with one imputed dataset and seed = 789 to fill in the remaining missing items in each of the 200 copies of datasets. Its 95% CI will also be provided under the normal approximation assumption.

### 5.2.4. Data Handling

Subjects who meet treatment failure criteria specified in Section 5.1.3.1 prior to Week 12 will be considered not to have achieved an PGA score of cleared (0) or minimal (1). In addition, subjects with a missing PGA score at Week 12 or who do not return for evaluation at Week 12 will be considered not to have achieved the respective endpoint at Week 12.

## 5.3. Major Secondary Endpoints

The sections below outline the major secondary analyses to be performed, as well as the analysis methods and the data imputation rules.

### 5.3.1. Definition

- The proportions of subjects who achieve a ≥75% improvement in PASI from baseline at Week 12.
- The change in CDLQI from baseline at Week 12.
- The proportions of subjects who achieve a ≥90% improvement in PASI from baseline at Week 12.

### 5.3.2. Analysis Methods

Major secondary analyses for the number and proportion of subjects achieving a PASI 75 and a PASI 90 at Week 12 will be summarized, respectively. Their exact two-sided 95% confidence intervals based on the binomial distribution for the proportion of subjects with PASI 75 and PASI 90 will be provided, respectively. The similar sensitivity analyses with the same number of imputed datasets and the same seeds will be performed for these two endpoints.

For the change from baseline in CDLQI at Week 12, the mean (95% confidence interval) will be computed. Its 95% confidence interval will be based on the normal approximation. A sensitivity analysis will be performed by using multiple imputations (MI), after applying treatment failure rules (as defined in Section 5.1.3.1). The intermittent missing CDLQI score through Week 12 will be imputed using the Markov Chain Monte Carlo (MCMC) algorithm with 200 imputed data sets and seed = 123 to make the missing data pattern monotone. Once the missing pattern is monotone, the remaining missing data of the CDLQI score will be imputed with monotone regression with baseline CDLQI and CDLQI score at each visit in the model with one imputed dataset and seed = 789 to fill in the remaining missing data in each of the 200 copies of datasets. Its 95% CI will then be calculated.

### 5.3.3. Data Handling

Data handling rules specified in Section 5.1.3 will be applied to the major secondary analyses.

## 5.4. Other Efficacy Variable(s)

In addition to the primary and major endpoint analyses, the following efficacy endpoints will be summarized:

- PGA
- PASI
- CDLQI

The analyses of other secondary efficacy analyses outlined in the following sections in general will be carried out for 2 periods

- Analyses through Week 52:
  - Analyses at key time point: Week 12
  - Over time summaries: Through Week 52
- Analyses through Week 248:
  - PGA responses over time summaries

### 5.4.1. Definition

Refer to Section 5.1.2 for the definitions of the other efficacy endpoints described in the following section.

### 5.4.2. Analysis Methods

Most of the other secondary efficacy analyses described in this section below will be based on the full analysis set.

#### 5.4.2.1. Analyses Related to PGA

- The proportions of subjects achieving a PGA score of cleared (0), the proportion of subjects achieving a PGA score of cleared (0) or minimal (1), and the proportion of subjects achieving a PGA score of mild or better (≤2) over time through Week 52 and through Week 248. Line plots will be provided displaying proportions and exact 95% CIs of subjects achieve a PGA score of cleared (0) or minimal (1) through Week 52 and Week 248.

#### 5.4.2.2. Analyses Related to PASI

- The proportions of subjects who achieve PASI 50, PASI 75, PASI 90, and PASI 100 responses over time through Week 52. Line plots will be provided displaying proportions and exact 95% CIs of PASI 75 responders and PASI 90 responders through Week 52.
- The percent improvement from baseline in PASI over time through Week 52 will be provided.
- The proportion of subjects who achieve 100% improvement, ≥90%, ≥75%, or ≥50% improvement from baseline in PASI component (induration, erythema, and scaling) and region component (head, trunk, upper extremities, and lower extremities) will be summarized at Week 12.

#### 5.4.2.3. Analyses Related to CDLQI

- The change from baseline in CDLQI over time through Week 52 will be provided.
- The proportion of subjects with CDLQI = 0 or 1 at Week 12 with a baseline CDLQI score > 1.
- The proportion of subjects with CDLQI = 0 or 1 over time through Week 52 with a baseline CDLQI score > 1 will be provided.
- The change from baseline in CDLQI component scores at Week 12 will be provided.

### 5.4.3. Data Handling

Data handling rules specified in Section 5.1.3 will be applied to all PGA, PASI, and CDLQI related analyses.

## 6. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs, and examining changes in laboratory parameters (hematology and chemistry), and summarizing vital signs, height, weight and BMI if appropriate.

In all the safety analysis, subjects who received at least 1 (partial or complete) dose of ustekinumab will be included. No formal hypothesis testing is planned.

Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods which include through Week 56 for the main study and through Week 264 for the LTE of the study as appropriate.

## 6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE starting at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summary tables will be provided for:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study agent administration
- AEs by severity
- AEs by relationship to study agent
- Infections
- Serious infections
- Infections treated with oral or parenteral antimicrobial treatment parenteral antibiotics
- Injection-site reactions
- AEs of psoriasis

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent administration
- Had AEs of severe intensity
- Had serum sickness-like reactions or anaphylactic reactions
- Had AE of psoriasis

Any unfavorable or unintended sign that occurs at the injection site is an injection site reaction and will be recorded as an injection site reaction by the investigator on the eCRF. An infection is defined as any AE that was recorded as an infection by the investigator on the eCRF.

The treatment-emergent adverse events of psoriasis include any event of erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, and worsening or exacerbation of psoriasis.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average weeks of follow-up and average number of study agent administrations for each treatment group.

## 6.2. Clinical Laboratory Tests

All clinical laboratory reports will be displayed for the subjects included in the safety analysis set. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- **Hematology**: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, and platelets.
- **Chemistry**: blood urea nitrogen/urea, glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, indirect bilirubin, albumin, total protein.

Box plots of laboratory measurements and change from baseline will be provided for selected laboratory analytes.

The proportion of subjects with any markedly abnormal post baseline laboratory values (hematology and chemistry) in selected laboratory measurements will be summarized. Similar to AEs, markedly abnormal clinical laboratory will be summarized through Week 56 for the main study and Week 264 for the LTE of the study, respectively. Markedly abnormal post baseline laboratory values will also be presented in listings.

Markedly abnormal changes from baseline are defined in Table 2. For a laboratory value to be considered markedly abnormal, the corresponding laboratory criteria below must be met. For example, for a platelet value to be markedly abnormal, the platelet value must be $<100 \times 10^9$/L and must be at least 50% decrease from the baseline platelet value. If the baseline value is missing for a parameter, the determination of whether the laboratory value is markedly abnormal will be based solely on the actual value (ie, the criterion for a specific increase or decrease from baseline will not be utilized).

| **Table 2: Markedly Abnormal Criteria for Laboratory Parameters** | |
|---|---|
| **Hematology Test** | **Criteria for Markedly Abnormal Status** |
| Hemoglobin (g/L) | Decrease from baseline > 20 g/L<br>& absolute value < 100 g/L |
| Hematocrit, fraction | absolute value < 0.3 fraction |
| WBC ($x10^9$/L) | Decrease absolute value < 3 x $10^9$/L<br>Increase absolute value > 20 x $10^9$/L |
| Neutrophils ($x10^9$/L) | Percent decrease from baseline ≥ 33%<br>& absolute value < 1.5 x $10^9$/L |
| Lymphocytes ($x10^9$/L) | Percent decrease from baseline ≥ 33%<br>& absolute value < 1.5 x $10^9$/L |
| Eosinophils ($x10^9$/L) | Percent increase from baseline ≥ 100 %<br>& absolute value > 1.0 x $10^9$/L |
| Platelets ($x10^9$/L) | Percent decrease from baseline ≥ 50%<br>& absolute value < 100 x $10^9$/L |
| **Chemistry Test** | |
| ALT/SGPT (U/L) | Percent increase from baseline >= 100<br>& absolute value > 100 U/L |
| AST/SGOT (U/L) | Percent increase from baseline >= 100<br>& absolute value > 100 U/L |
| Total bilirubin (umol/L) | Percent increase from baseline >= 100<br>& absolute value > 41.0 umol/L |
| Non-fasting glucose (mmol/L) | Percent decrease from baseline ≥ 33<br>& absolute value < 3.05 mmol/L<br><br>Percent increase from baseline ≥ 50<br>& value > 8.88 mmol/L |
| Creatinine (umol/L) | Percent increase from baseline >= 66<br>& absolute value > 99 umol/L |
| Albumin (g/L) | Decrease from baseline >= 10 g/L<br>& absolute value < 25 g/L |

## 6.3. Vital Signs and Physical Examination Findings

Box plots of the observed and change from baseline will be provided for the vital signs variables including heart rate, respiratory rate, and blood pressure (systolic and diastolic).

Physical exam findings will not be analyzed except that they are captured as AEs and are included in the analyses of AEs.

### 6.4. Other Safety Parameters

Weight, height and BMI will be summarized at selected points.

## 7. PHARMACOKINETICS/PHARMACODYNAMICS/IMMUNOGENICITY

### 7.1. Pharmacokinetics

Blood samples for measuring serum ustekinumab concentrations (pre-injection if it is injection visit) will be collected from all subjects at scheduled visits as indicated in the Time and Events Schedule in the protocol.

The PK analysis will be based on subjects who received at least 1 administration of ustekinumab and had at least one serum sample for ustekinumab concentration. No imputation of missing concentration data will be performed, that is, data summaries will be based on the observed data.

All concentrations below the lowest quantifiable sample concentration of the assay or missing data will be labeled as such in the concentration data listings or Statistical Analysis Software™ dataset. All BQL serum ustekinumab concentrations below the lowest quantifiable sample concentration in of the assay will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

For analysis of serum ustekinumab concentrations, descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each scheduled sampling time point for the ustekinumab group. The PK concentration data may be displayed graphically.

Serum ustekinumab concentrations will be summarized at each scheduled visit from Week 0 through Week 52. All summaries for serum ustekinumab concentration will exclude data collected after subjects (1) did not receive a scheduled ustekinumab administration within ± 14 days of the protocol scheduled dosing date; (2) discontinued study agent administration; (3) received a partial, incorrect, or an additional ustekinumab administration (ie, subjects received more than 1 ustekinumab injection within the scheduled ustekinumab injection window); or 4) received an increased or decreased dose due to body weight change (eg, from the initial category of <60 kg to the category of ≥60 to ≤100 kg or vice versa) for the concentration summaries by baseline weight. Of note, serum ustekinumab concentrations prior to the first of such events will be included in the summaries.

In addition, invalid concentration data will be excluded from analysis. A concentration will be considered invalid (1) if a pre-injection sample was actually taken after study agent administration (based on date/time); or (2) a concentration value fell outside the predefined statistical range of mean ± 10*SD of the concentration values obtained at the same protocol specified sampling timepoint (refer to SOP-07948-GXP, Version 2.1).

If there were multiple samples collected prior to an injection, the closest sample before the injection will be used. If a sampling time or an injection time was missing, the date will be used. If sampling date was the same as the injection date, the sample will be included in the statistical summary.

Serum ustekinumab concentrations will be summarized as follows:

- Summary of serum ustekinumab concentrations through Week 52 (note: the rule #4 shown above is not applicable to this table).
- Summary of serum ustekinumab concentrations through Week 52 by baseline weight (<60 kg, ≥60 to ≤100 kg, and >100 kg).
- Number of subjects with serum ustekinumab concentrations below the lowest quantifiable sample concentration of the assay (<0.1688 micrograms/mL) through Week 52 (note: the rule #4 shown above is not applicable to this table).
- Number of subjects with serum ustekinumab concentrations below the lowest quantifiable sample concentration of the assay (<0.1688 micrograms/mL) through Week 52 by baseline weight (<60 kg, ≥60 to ≤100 kg, and >100 kg).
- Median (IQ range) serum ustekinumab concentrations over time plot.
- Median (IQ range) serum ustekinumab concentrations over time plot by baseline weight (≤ 60 kg, ≥60 to ≤100 kg, and >100kg).

A population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of ustekinumab in the current study. Data may be combined with those of other selected studies to support a relevant structural model. The CL/F and V/F values will be estimated. The influence of important variables (such as body weight and antibodies to ustekinumab) on the population PK parameter estimates will be evaluated. The results of the population PK analysis will be presented in a separate technical report.

## 7.2. Immunogenicity

Blood samples will be collected for the detection of antibodies to ustekinumab at the specified visits as shown in the Time and Events schedule in the protocol.

The antibodies to ustekinumab analysis will be based on subjects who receive at least 1 dose of ustekinumab and have at least one samples collected post ustekinumab administration for the detection of antibodies to ustekinumab. No imputation of missing data will be performed, that is, data summaries will be based on the observed data.

The following analyses will be performed for ustekinumab group as appropriate:

- Summary of antibodies to ustekinumab status (incidence of antibodies to ustekinumab and antibody titers)
- List of subjects who are positive for antibodies to ustekinumab

In addition, the incidence of neutralizing antibodies (NAbs) to ustekinumab will be summarized for subjects who are positive for antibodies to ustekinumab and have samples evaluable for NAbs.

The effect of antibodies to ustekinumab on PK, efficacy, and safety will be explored, if data permit.

## 7.3. Pharmacokinetic/Pharmacodynamic Relationships

The relationships between serum ustekinumab concentration and efficacy will be analyzed graphically. A suitable pharmacokinetic/ pharmacodynamic (PK/PD) model will be developed to describe the exposure-response relationship. Data may be combined with those of other selected studies to support a relevant structural PK/PD model. The results of the population PK/PD analysis may be presented in a separate technical report.

## 7.4. Biomarker

The goal of the biomarker analyses is to evaluate the pharmacodynamics of ustekinumab by measuring levels of IL-17 and other inflammatory cytokines and aid in evaluating the pharmacodynamic-clinical response relationship. Assessment of IL-17 serum levels will be performed and potential association with ustekinumab response will be explored. Biomarker analyses will be summarized in a separate technical report.

## 7.5. Pharmacogenomic (DNA) Evaluations

The goal of the optional pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow research on the identification of genetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of ustekinumab and to explore genetic factors associated with psoriasis. Genomic analyses will be summarized in a separate technical report.