Janssen Research & Development *

Clinical Protocol

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
AMENDMENT 1

STELARA® (ustekinumab)

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	22 January 2016
Amendment 1	18 May 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (17 May 2017)

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

The overall reason for the amendment: The overall reason for this amendment is to allow pediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. Additionally, longer-term safety and efficacy data in this patient population will be collected.

Applicable Section(s)	Description of Change(s)
Rationale: Update the study design and other applicable sections to add a long-term extension (LTE) to the study.	
Synopsis; 3.1. Overview of Study Design; Long-term Extension: Week 56 through Week 264	Main Study: Week 0 through Week 56 A database lock (DBL) will occur at end of the main study (Week 56; Section 17.9.1). 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 follow-up for the main study and the first ustekinumab administration of the LTE will be completed at the Week 56 visit. At the Week 52 visit, subjects who have not had a beneficial response from ustekinumab treatment as determined by the investigator, or who have 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), will not enter the LTE of the study. The Week 56 safety-follow-up will be the end of study participation. 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

Applicable Section(s)	Description of Change(s)
	All assessments will be performed per the Time and Events Schedule (see Table 2). 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 (Week 264; Section 17.9.1). Additional DBLs may occur at the Sponsor's discretion.
Rationale: The overall reason for this amendment is to allow pediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. Additionally, longer-term safety and efficacy data in this patient population will be collected.	
3.2 Study Design Rationale; Study Phases	The addition of the LTE is to allow pediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. Additionally, longer-term safety and efficacy data in this patient population will be collected.
Rationale: Table 2 has been added to the Time and Events Schedule to summarize the frequency and timing of study drug administration, ongoing subject reviews, and safety and efficacy assessments in subjects who enter the LTE starting at the Week 56 study visit.	
Time and Events Schedule; Table 2: Time and Events Schedule for the LTE Phase (Week 56 to Week 264) (new table)	Table 2 has been added to the Time and Events Schedule and includes the following parameters to be completed during the LTE: • Study drug administration/site visit every 12 weeks • Body weight measured every 12 weeks • A urine pregnancy test for female subjects performed every 12 weeks • Adverse events and concomitant medications collected every 12 weeks • Subject vital signs to be taken every 12 weeks • Efficacy evaluation (PGA only) every 6 months • A complete physical examination once per year • Height measured once per year • Full chemistry and hematology test results obtained once per year
Rationale: To update the footnotes from the main study (Table 1) to accommodate instructions for the LTE (Table 2), for details related to subjects who enter the LTE of the study and receive ustekinumab treatment.	
Time and Events Schedule; Table 2: Time and Events Schedule for the LTE Phase (Week 56 to Week 264); Footnotes a, d, f, and g	[a] All procedures and evaluations are to be completed prior to study drug injection. For subjects in the LTE who decide to withdraw from study participation, or who discontinue treatment, the assessments (excluding study drug injection) for the Week 248 study visit will be performed. [d] Efficacy assessments (PGA) should be performed by the investigator or any qualified healthcare provider at the study site. [f] Subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit for the LTE prior to Week 248, the procedures and evaluations (excluding study drug injection) for Week 248 will be followed. If a subject discontinues study drug and terminates study participation, the procedures and evaluations (excluding study drug injection) for Week 248 will be performed at the current visit. [g] Final LTE visit. The Week 264 visit is a follow-up safety visit that will be handled as a phone call.

Applicable Section(s)	Description of Change(s)
Rationale: To update the dosing and administration of ustekinumab to subject during the LTE of the study.	
6 Dosage and Administration	All subjects enrolled in the study will receive ustekinumab at Weeks 0 and 4 followed by q12w dosing. Subjects who enter the LTE will receive ustekinumab q12w beginning at Week 56 and continue according to criteria defined in Section 3.1.
Rationale: Update rules for use of topical medications as concomitant medication for psoriasis treatment during the LTE.	
8.3 Concomitant Therapies for Conditions Other Than Psoriasis	During the LTE, the medication rules outlined above still apply except that all topical therapies, with the exception of ultra-high potency corticosteroids are permitted for treatment of psoriasis.
Rationale: To update total blood volume collected from subjects during the LTE.	
9.1.1 Overview	For subjects participating in the LTE, a maximum of 4 additional hematology samples and 4 additional serum chemistry samples (2 mL per hematology sample and 2.5 mL per serum chemistry sample; total blood volume of 18 mL) will be collected.
9.1.1 Overview: Table 3: Volume of Blood to be Collected From Each Subject in the Main Study	Table 2 has been renumbered to Table 3 with the addition of the new Time and Events Schedule for the LTE (new Table 2). Additionally, the table title has been updated to reflect that the table covers blood volumes collected during the main study.
Rationale: Update study design and other applicable sections to add an LTE to the study.	
9.1.5 Open-label Long-term Extension (Week 56 to Week 264) (new section)	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 follow up for the main study and the first ustekinumab administration of the LTE will be completed at the Week 56 visit. 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 During the LTE, consideration should be given to discontinue ustekinumab treatment in any subjects who are non-responders (defined by PGA >3 at 2 consecutive visits). A DBL will occur at end of the LTE (Week 264; Section 17.9.1). Additional DBLs may occur at the Sponsor's discretion.).
Rationale: To update performance of PGA assessments during the LTE.	
9.2.1 Blinded Efficacy Evaluation	During the LTE, PGA assessments should be performed by the investigator or any qualified healthcare provider at the study site. When possible, all PGA assessments for a subject should be performed by the same assessor.

Applicable Section(s)	Description of Change(s)
Rationale: To add the determination of study completion/withdrawal and discontinuation of study treatment for subjects who received ustekinumab during the LTE of the study.	
10.2 Completion of Long-term Extension (new section)	A subject will be considered to have completed the LTE if he or she has completed all assessments up through Week 264. For subjects in the LTE who decide to withdraw from study participation, who discontinue treatment for any reason, or who become ineligible to continue to receive study drug (ie, due to the occurrence of one of the criteria listed in Section 3.1), the assessments (excluding study drug injection) for the Week 248 study visit will be performed.
10.3 Discontinuation of Study Treatment; Long-term extension (new section)	During the LTE, subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit for the LTE, the procedures and evaluations (excluding study drug injection) for Week 248 will be followed. If a subject discontinues study drug and terminates study participation, the procedures and evaluations for Week 248 will be performed at the current visit. During the LTE, consideration should also be given to discontinue ustekinumab treatment in any subjects who are non-responders (ie, defined by PGA >3 at 2 consecutive visits).
Rationale: To update the assessments that should be obtained for subjects who withdraw or discontinue early and received ustekinumab during the LTE of the study.	
10.4 Withdrawal from Study	If a subject withdraws from the study prior to Week 52, the Week 52 assessments will be obtained. If a subject withdraws from the study before the end of the LTE, the Week 248 assessments (excluding study drug injection) will be performed.
Rationale: To update the data handling rules regarding treatment failures or missing data for PGA scores after Week 52.	
11.3.1 Data-Handling Rules	After Week 52, treatment failure rules or missing data imputations will not be applied for PGA scores.
Rationale: To update the volume of blood collected during the study phases.	
16.1 Study-Specific Design Considerations	The total blood volume to be collected during the main study will be approximately 69.5 mL and during the LTE will be approximately 18 mL, which is considered to be within the normal range allowed for the pediatric population.
Rationale: To update the determination of study completion for subjects who entered the LTE of the study and received ustekinumab treatment.	
17.9.1. Study Completion	• The main study is considered completed when the safety follow-up for the last subject is completed at Week 56. • The LTE is considered completed when all subjects have either terminated participation according to Section 3.1 or completed their follow-up at Week 264.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa monoclonal antibody (mAb) that binds both human interleukin (IL)-12 and IL-23 via a common IL-12/23p40 subunit. Ustekinumab neutralizes the activities of IL-12 and IL-23 by preventing these cytokines from binding to the IL-12 receptor beta-1 receptor protein, which is expressed on the surface of immune cells. The first approval of ustekinumab for the treatment of adult patients with chronic moderate to severe plaque psoriasis occurred in Canada (12 December 2008) and was based primarily on data from 2 global Phase 3 pivotal studies (C0743T08 [PHOENIX 1] and C0743T09 [PHOENIX 2]), comprising 1,996 subjects. Both studies had long-term extensions for up to 5 years. Ustekinumab was subsequently approved in numerous other countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients with chronic moderate to severe plaque psoriasis and/or psoriatic arthritis (PsA). Ustekinumab has also been approved for the treatment of pediatric moderate to severe psoriasis in patients ≥12 years to <18 years in Europe and other countries, based primarily on data from the completed Phase 3 CADMUS study. Extensive postmarketing experience also supports the favorable safety profile of ustekinumab established to date.

OBJECTIVES AND HYPOTHESIS

The primary and major secondary objectives of this study are:

Primary Objective

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

Major Secondary Objectives

- To evaluate the pharmacokinetics (PK) of ustekinumab in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.
- 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.
- Evaluate the immunogenicity of ustekinumab in pediatric subjects aged ≥6 through <12 years with moderate to severe chronic plaque psoriasis.

Hypothesis

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.

OVERVIEW OF STUDY DESIGN

Main Study

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. At least 40 subjects will receive a weight-based dose of ustekinumab administered subcutaneously 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. 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 telephone follow-up at Week 56. A single database lock (DBL) will occur at Week 56.

All assessments will be performed according to the Time and Events Schedule. Unblinded safety data will be routinely evaluated by the study medical monitor.

Long -term Extension

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 follow up for the main study and the first ustekinumab administration of the LTE will be completed at the Week 56 visit.

At the Week 52 visit, subjects who have not had a beneficial response from ustekinumab treatment as determined by the investigator, or who have 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), will not enter the LTE of the study. The Week 56 safety-follow-up will be the end of study participation.

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 (see Table 2).

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 (Week 264; Section 17.9.1). Additional DBLs may occur at the Sponsor's discretion.

SUBJECT POPULATION

The subject population will comprise boys and girls ≥6 to <12 years of age with moderate to severe chronic plaque psoriasis. Subjects must have had a diagnosis of plaque psoriasis for at least 6 months prior to first study drug administration and have moderate to severe disease defined by Psoriasis Area and Severity Index score (PASI) ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) ≥10%.

DOSAGE AND ADMINISTRATION

All subjects enrolled in the study will receive ustekinumab at Weeks 0 and 4 followed by q12w dosing with the last dose at Week 40. Subject weight will be measured at each visit and the dose of ustekinumab will be adjusted accordingly. Subjects will receive 1 of the following dose levels:

- Weight <60 kg: 0.75 mg/kg
- Weight ≥60 kg to ≤100 kg: 45 mg
- Weight >100 kg: 90 mg

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations chosen for this study are consistent with applicable US and EU regulatory guidance and precedent established in previous studies of therapeutic biologic agents for the treatment of psoriasis. Patient-reported outcomes (PROs) chosen for this study are also consistent with clinically relevant measurements that are accepted in the medical literature for other studies in psoriasis and applicable US/EU regulatory guidance documents. Psoriasis response evaluations include:

- Physician's Global Assessment (PGA)
- Psoriasis Area and Severity Index (PASI)
- Children's Dermatology Life Quality Index (CDLQI; PRO)

Given the open-label study design, PASI and PGA assessments will be performed by a blinded evaluator.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for the measurement of serum ustekinumab concentrations and detection of antibodies to ustekinumab at the timepoints presented in the Time and Events Schedule. Serum samples will also be collected at the final visit from subjects who terminate study participation early.

BIOMARKER EVALUATIONS

Biomarker assessments will include the evaluation of relevant serum markers.

PHARMACOGENOMIC (DNA) EVALUATIONS

A one-time swab collection for genetic and epigenetic analyses will be collected from those subjects (or their legally acceptable guardian) who sign a separate consent form to participate in the pharmacogenomics assessment.

SAFETY EVALUATION

Safety and tolerability will be assessed by monitoring AEs, clinical laboratory tests, vital signs, physical examinations, concomitant medication review, injection site evaluations, observations for allergic reactions, and assessments for early detection of active tuberculosis.

STATISTICAL METHODS

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, range, and interquartile range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Graphical data displays may also be used to summarize the data.

Subject baseline data, demographic and baseline clinical disease characteristics will be summarized. The baseline measurement is defined as the closest measurement taken at or before Week 0.

Safety and efficacy analysis will include enrolled subjects who receive at least 1 dose administration of ustekinumab.

Sample Size Determination

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 1 of the major secondary objective is to evaluate the pharmacokinetics of ustekinumab for 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. However, 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 Studies C0743T08, C0743T09, and CADMUS. The PK in pediatric subjects 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 design, 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.

Efficacy Analyses

Efficacy results will be summarized for all subjects enrolled in the study and 95% confidence intervals will be calculated for the primary and major secondary efficacy endpoints.

Primary Endpoints

- The proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12.

Major Secondary Endpoints

- Serum ustekinumab concentrations will be summarized over time to assess the PK of ustekinumab.
- 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.

Other Endpoints

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

- 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.

- The proportions of subjects who achieve PASI 50, PASI 75, PASI 90, and PASI 100 responses over time.
- The percent improvement from baseline in PASI over time.
- The change from baseline in CDLQI over time.
- The proportion of subjects with CDLQI = 0 or 1 over time.

Other Analyses

The incidence and titers of antibodies to ustekinumab will be summarized by treatment group over time.

Safety Analyses

Safety will be assessed by analyses of rates and type of adverse events (AEs), serious AEs, reasonably related AEs, injection-site reactions, infections, and AEs of psoriasis. Safety assessments will also include analyses of laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) and rates of markedly abnormal laboratory parameters (hematology and chemistry).

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for the Main Study (Week 0 to Week 56)

	Screening	Treatment Period[k]								Safety Follow up
Week	≤10 Weeks	0	4	8	12	16	28	40	52	56[a]
Study Procedures										
Screening/Administrative										
Informed consent/assent	X									
Demographics	X									
Medical History	X									
Inclusion/exclusion criteria[b]	X	X								
Body surface area (BSA)% psoriasis skin involvement	X	X								
Study Drug Administration										
Study drug administration[c]		X	X			X	X	X		
Safety Assessments										
Physical examination	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	
Height		X				X	X	X	X	
Weight		X	X			X	X	X	X	
QuantiFERON-TB® Gold testing[d]	X									
Tuberculosis Intradermal Skin Test[d]	X									
Urine pregnancy test, qualitative[e]	X	X	X			X	X	X		
Full chemistry	X				X		X	X	X	
Hematology	X				X		X	X	X	
Serum varicella and measles antibody titers	X									
Hep B Surf Ab (HBsAb)	X									
Hepatitis B Core Antibody (HBcAb)	X									
Hepatitis C Antibody (HCVAb)	X									
HIV	X									
Ongoing Subject Review										
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Adverse event (AE) review[f]	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments										
Physician's Global Assessment (PGA)[g]	X	X	X	X	X	X	X	X	X	
Psoriasis Area and Severity Index (PASI)[g]	X	X	X	X	X	X	X	X	X	
Children's Dermatology Life Quality Index (CDLQI)[h]		X	X		X		X		X	
Pharmacokinetics/Immunogenicity[i]										
Serum ustekinumab concentration	X		X		X	X	X	X	X	
Antibodies to ustekinumab	X				X		X		X	
Biomarkers										
Serum sample (eg, for IL-17 quantification)	X				X				X	

Table 1: Time and Events Schedule for the Main Study (Week 0 to Week 56)

	Screening	Treatment Period[k]								Safety Follow up
Week	≤10 Weeks	0	4	8	12	16	28	40	52	56[a]
Study Procedures										
Pharmacogenomics (DNA)[j]										
Buccal swab sample collection		X								

[a] Telephone follow-up (only for subjects who will not enter the LTE phase).
[b] Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation.
[c] All procedures and evaluations are to be completed prior to study drug injection. For subjects who withdraw from study participation, every effort should be made to conduct final efficacy and safety assessments at Week 52.
[d] All subjects will receive QuantiFERON-TB® Gold testing and those subjects who are positive or have 2 indeterminate results will be excluded from the study. In countries where QuantiFERON-TB Gold test is not registered/approved, tuberculin skin testing will also be required.
[e] Urine pregnancy test to be conducted for girls of childbearing potential.
[f] Includes TB evaluation. Refer to the Early Detection Of Active Tuberculosis text in Section 9.6 for a complete description of this TB evaluation and the subsequent actions required based upon the results of this evaluation.
[g] PASI and PGA to be performed by a blinded efficacy evaluator.
[h] Performed prior to any tests, procedures, or other consultations (PASI, PGA) for that visit.
[i] All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled. Details will be provided in the Laboratory Manual.
[j] Buccal swab for pharmacogenomics or epigenomics analysis will be collected only from subjects from whom separate informed consent indicating willingness to participate in this optional component of the study has been obtained.
[k] Subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit prior to Week 52, the procedures and evaluations for Week 52 should be followed. If a subject discontinues study drug and terminates study participation prior to Week 52, the procedures and evaluations for Week 52 should be performed at the last visit.

Table 2: Time and Events Schedule for the Long-term Extension (Week 56 to Week 264)

	Long-term Extension[f]																	
Week	56	68	80	92	104	116	128	140	152	164	176	188	200	212	224	236	248	264[g]
Study Procedures																		
Study Drug Administration																		
Study drug administration[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments																		
Physical examination					X				X				X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height					X				X				X				X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test, qualitative[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full chemistry[e]					X				X				X				X	
Hematology[e]					X				X				X				X	
Ongoing Subject Review																		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE) review[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																		
Physician's Global Assessment (PGA)[d]			X		X		X		X		X		X		X		X	

[a] All procedures and evaluations are to be completed prior to study drug injection. For subjects in the LTE who decide to withdraw from study participation, or who discontinue treatment, the assessments (excluding study drug injection) for the Week 248 study visit will be performed.

[b] Urine pregnancy test to be conducted for girls of childbearing potential.

[c] Includes TB evaluation. Refer to the Early Detection Of Active Tuberculosis text in Section 9.6.

[d] Efficacy assessments (PGA) should be performed by the investigator or any qualified healthcare provider at the study site.

[e] All blood samples must be collected before study drug administration at visits when a study drug administration is scheduled. Details will be provided in the Laboratory Manual.

[f] Subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit for the LTE prior to Week 248, the procedures and evaluations (excluding study drug injection) for Week 248 will be followed. If a subject discontinues study drug and terminates study participation, the procedures and evaluations (excluding study drug injection) for Week 248 will be performed at the current visit.

[g] Final LTE visit. The Week 264 visit is a follow-up safety visit that will be handled as a phone call.

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacille Calmette-Guerin vaccine
BQL	below the lowest quantifiable sample concentration of the assay
BSA	body surface area
CADMUS	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of ADolescent Subjects with Moderate to Severe Plaque-type psoriasis
CDLQI	Children's Dermatology Life Quality Index
CL/F	apparent clearance
CRF	case report form
eDC	electronic data capture
EudraCT	European Clinical Trials Database
FVP	final vialed product
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1k	immunoglobulin G1 kappa
IL	interleukin
IL-12Rb1	interleukin-12 receptor beta 1
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LTE	Long-term extension
mAb	monoclonal antibody
MTX	methotrexate
NAbs	neutralizing antibodies
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics(s)
PGA	Physician's Global Assessment
PHOENIX 1	A Phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension
PHOENIX 2	A Phase 3 multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension 2
PK	pharmacokinetic(s)
PO	by mouth (per OS)
PQC	product quality compliant
PRO	patient-reported outcome(s)
PsA	psoriatic arthritis
q12w	every 12 weeks
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
TB	tuberculosis
V/F	apparent volume of distribution

1. INTRODUCTION

STELARA® (ustekinumab) is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds both human interleukin (IL)-12 and IL-23 via a common IL-12/23p40 subunit. Ustekinumab neutralizes the activities of IL-12 and IL-23 by preventing these cytokines from binding to the IL-12 receptor beta-1 receptor protein, which is expressed on the surface of immune cells. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases, including psoriasis, and binding the shared IL-12/23p40 subunit may provide effective therapy in psoriasis. Ustekinumab is being developed by Janssen Research & Development.

The first approval of ustekinumab for the treatment of adult patients with chronic moderate to severe plaque psoriasis occurred in Canada (12 December 2008) and was based primarily on data from 2 global Phase 3 pivotal studies (C0743T08 [PHOENIX 1] and C0743T09 [PHOENIX 2]), comprising 1,996 subjects. Both studies had long-term extensions for up to 5 years. Ustekinumab was subsequently approved in numerous other countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients with chronic moderate to severe plaque psoriasis and/or psoriatic arthritis (PsA). Extensive postmarketing experience also supports the favorable benefit-risk profile of ustekinumab established to date. Ustekinumab is also approved for the treatment of pediatric psoriasis in patients ≥12 years to <18 years in Europe and other countries based on the CNTO1275PSO3006 (CADMUS) study in 110 subjects.

For the most accurate and current information regarding the efficacy and safety of ustekinumab, refer to the latest version of the Investigator's Brochure for ustekinumab.

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

1.1. Background

Psoriasis is a common chronic skin disease, characterized by the infiltration of inflammatory cells into the skin and excessive keratinocyte cellular proliferation, producing raised, well-demarcated erythematous lesions/plaques that significantly impacts patient quality of life.[6,16] The pathogenesis of psoriasis involves environmental factors and immune dysregulation in genetically-predisposed individuals.[10] The proinflammatory IL-12/T-helper (Th)1 and IL-23/ Th17 pathways are upregulated in psoriatic lesions.[20,13] Ustekinumab is a fully human immunoglobulin G1 kappa monoclonal antibody to human IL-12/23p40 that binds with specificity to human IL-12 and IL-23 and neutralizes their bioactivity by preventing these cytokines from binding to specific receptors expressed on the surface of immune cells. Ustekinumab has been shown to be an effective treatment and has a favorable benefit risk profile for adult[11,15]and pediatric psoriasis patients age 12 and older.[9]

To assess potential risks in pediatric patients, toxicity studies in juvenile cynomolgus monkeys and developmental toxicity studies using pregnant monkeys have been performed. Ustekinumab was well tolerated in these studies following weekly intravenous (IV) injection or twice weekly SC injection at doses up to 45 mg/kg. No ustekinumab related adverse effects were noted in

clinical pathology and histopathology evaluations and no evidence of immunotoxicity was observed. Additionally, there was no evidence of teratogenicity or developmental toxicity in fetuses or newborn monkeys who were exposed to ustekinumab as a result of ustekinumab administration in utero.

1.2. Overall Rationale for the Study

Ustekinumab has been approved for the treatment of adult psoriasis in numerous countries beginning in 2008, and was recently approved for use in adolescent psoriasis patients age 12 and older in the EU and Canada based primarily on the results from the completed CADMUS study. The objectives of this clinical study are to evaluate the efficacy and safety of ustekinumab in pediatric subjects aged ≥6 to <12 years, and to determine if the weight based standard dosage being studied provides appropriate ustekinumab exposure in this age group. Determining that pediatric patients aged ≥6 to <12 receiving a weight based standard dosage are exposed to comparable levels of ustekinumab as adults is important for extrapolating the extensive and longer term safety data already available from the adult ustekinumab clinical experience to this pediatric population.

Clinical studies of adult and adolescent patients with moderate to severe psoriasis completed to date have demonstrated consistently low and predictable placebo response rates, suggesting that the efficacy of ustekinumab can be accurately assessed in the absence of a placebo control group. Therefore, this clinical study will utilize an open-label design. This approach accomplishes the scientific objectives of assessing ustekinumab efficacy, safety and pharmacokinetics (PK) in the population of interest, while also allowing all subjects to benefit from active treatment for the entire 52-week planned treatment duration. To help improve objectivity, given the open-label design, efficacy assessments will be performed by a blinded evaluator.

1.3. Clinical Studies

As of 31 December 2014, a total of 30 clinical interventional studies of ustekinumab have been completed or are ongoing in the following indications, psoriasis, PsA, Crohn's disease, rheumatoid arthritis, multiple sclerosis, sarcoidosis, primary biliary cirrhosis, axial spondyloarthritis, ulcerative colitis, systemic lupus erythematosus as well as in healthy subjects. The development in rheumatoid arthritis, multiple sclerosis, sarcoidosis, and primary biliary cirrhosis are no longer being pursued due to a lack of efficacy.

The details of completed clinical studies or ongoing blinded clinical studies of ustekinumab can be found in the latest version of the Investigator's Brochure for ustekinumab.

1.3.1. Efficacy and Safety in Adult Psoriasis Studies

Two placebo controlled Phase 3 studies, PHOENIX 1 (C0743T08)[11] and PHOENIX 2 (C0743T09)[15] evaluated the efficacy of 2 dosages for the treatment of moderate to severe psoriasis:

- 45 mg at Week 0 and Week 4, followed by every 12 weeks (q12w) dosing;
- 90 mg at Week 0 and Week 4, followed by q12w dosing.

These dosages led to a statistically significant, rapid onset of efficacy. High proportions of subjects (66.4% to 75.7% across ustekinumab groups in each study) achieved a Psoriasis Area and Severity Index (PASI) 75 response at Week 12 (the primary endpoint). With maintenance dosing, response rates continued to improve with consistent results across both studies at Week 28. While the 45 mg and 90 mg regimens both resulted in high levels of efficacy, the 90 mg dosing regimen achieved approximately 8% to 10% higher PASI 75 response rates than the 45 mg dosing regimen by Week 28, which generally persisted over time.

In both PHOENIX 1 and PHOENIX 2, subjects were followed in an open-label long-term extension for up to 5 years. In the overall population, PASI 50, PASI 75, and PASI 90 response rates were generally stable from Week 76 (PHOENIX 1) and Week 52 (PHOENIX 2) through Week 244 in both dose groups. Results suggested that with continuous maintenance treatment (ie, q12w or q8w), clinical response is sustained through the final treatment visit in the overall population treated with ustekinumab.

In both studies, ustekinumab was generally well tolerated. Through Week 12, adverse event (AE) rates, AE profiles, and rates of AEs leading to study drug discontinuation in each of the ustekinumab treatment groups were generally comparable to those observed in the placebo group. Through the controlled and uncontrolled portions of the study, ustekinumab continued to be generally well tolerated with no apparent dose effect on safety evident between the 45 mg group and the 90 mg group.

Analyses of the 5-Year Psoriasis Safety Experience showed that follow-up-adjusted rates of serious infections, malignancies (nonmelanoma skin cancer [NMSC] and malignancies other than NMSC), and major adverse cardiovascular event (MACE) did not appear to increase over time in the by-year analysis. The rates of these events were also lower than or consistent with what would be expected from the general US population and/or the psoriasis population. These observations suggest that rates of these targeted AEs remain stable over time, and do not reveal evidence of risks associated with increasing duration of ustekinumab exposure.

1.3.2. Efficacy and Safety in Pediatric Psoriasis Subjects ≥12 to <18 Years of Age

The first of 2 planned Phase 3 clinical studies of ustekinumab in pediatric psoriasis (CNTO1275PSO3006, [CADMUS]) has been completed. The CADMUS study was a randomized, double-blind, placebo-controlled, parallel group, multicenter 3-arm study conducted at sites in Europe and Canada. Subjects were randomized 2:2:1:1 to receive SC injections of the ustekinumab half-standard dosage, the ustekinumab standard dosage, or placebo and received their assigned treatment at Week 0 and Week 4 followed by q12w doses with the last dose at Week 40. Subjects in the placebo group were randomized at baseline to later crossover to either ustekinumab half-standard dosage or ustekinumab standard dosage at Weeks 12 and 16 followed by q12w dosing with the last dose at Week 40. The subject population was comprised of 110 adolescent subjects ≥12 to <18 years of age who had a diagnosis of plaque-type psoriasis for at least 6 months prior to first study drug administration and who had moderate to severe disease

defined by PASI ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) involvement ≥10%.

CADMUS studied 2 distinct weight-based ustekinumab dosages: a "standard dosage", and a "half-standard dosage". For the "standard dosage", fixed doses of 45 mg for pediatric subjects weighing >60 kg to ≤100 kg and 90 mg for those weighing >100 kg, identical to adults, were utilized. For subjects weighing ≤60 kg, a weight adjusted dose of 0.75 mg/kg (obtained by adjusting the 45 mg adult dose by a body weight of 60 kg [45/60 = 0.75]) was utilized. Additionally, a "half-standard" dosage (ie, weight-based dose of 0.375 mg/kg for subjects weighing ≤60 kg, fixed dose of 22.5 mg for those weighing >60 kg to ≤100 kg, and a fixed dose of 45 mg for those weighing >100 kg) was also included, to allow for a more robust characterization of the dose-response relationship of ustekinumab in pediatric subjects and identification of an appropriate dosage for pediatric use.

Baseline demographics and disease characteristics were well-balanced across the CADMUS treatment groups. Mean age at baseline was 15 years and mean body weight was 65 kg. All of the CADMUS primary and major secondary efficacy endpoints were met. Significantly greater proportions of subjects in the half-standard and standard dosage groups achieved PGA scores of cleared (0) or minimal (1) at Week 12 (67.6% and 69.4%, respectively) compared with subjects in the placebo group (5.4%; $p<0.001$ for both ustekinumab dosage groups versus placebo).[9] Significantly greater proportions of subjects in each of the ustekinumab dosage groups achieved PASI 75 and PASI 90 response, as well as a meaningful improvement in the Children's Dermatology Life Quality Index (CDLQI) at Week 12. During the 12-week placebo controlled period, outcomes were generally comparable between the ustekinumab half-standard and standard dosage groups, and each ustekinumab dosage group was significantly better than placebo. However, differences in responses between the 2 ustekinumab dosage groups, favoring the standard dosage, were observed with more stringent efficacy criteria, including PGA scores of 0 and PASI 90 response at Week 12. Through Week 52, efficacy results were generally better with the standard dosage group relative to the half standard dosage group across most endpoints. Responses were better sustained through Week 52 over the 12-week dose interval in the standard dosage group whereas, a modest loss of efficacy was more frequently observed toward the end of the dose interval in the half-standard dosage group.

Overall, dose-proportionality in serum ustekinumab concentration was observed when comparing mean or median serum ustekinumab concentrations through Week 52 between the half-standard dosage and standard dosage groups. A higher proportion of subjects with trough serum ustekinumab concentrations below the lowest quantifiable sample concentration of the assay (BQL; <0.1688 µg/mL) was observed in the half-standard dosage group (range: 21.7% to 54.2%) compared with the standard dosage group (range: 6.3% to 16.1%). In addition, the standard dosage of ustekinumab in pediatric subjects produced comparable systemic drug exposure to that in adult subjects with body weight ≤100 kg who received the approved 45 mg fixed dose, whereas pediatric subjects treated with half-standard dosage had generally lower systemic exposure than adults. The comparability of exposure and efficacy responses between

the standard dosage in pediatric subjects and the approved adult dosage in adults confirms the similarity in the exposure-response relationship of ustekinumab in the 2 populations.

Relative to the safety profile observed in the adult psoriasis and PsA populations treated with ustekinumab, no new safety issues were identified in the adolescent subjects studied in CADMUS. The proportions of treated subjects reporting AEs and the AE terms were similar across the ustekinumab dosage groups and the placebo group through Week 12. No subject discontinued study drug due to an AE during the 12-week placebo-controlled period. The proportions of treated subjects reporting serious adverse event (SAEs) were low in all treatment groups during the placebo-controlled period; there was 1 SAE of worsening of psoriasis in a subject in the half-standard dosage group. Through Week 60, 6 SAEs were reported (including leukopenia, injury, psoriasis, pyelonephritis, dermatitis contact, ear infection), 5 were in the half-standard dosage group. Two of the SAEs (1 each in the half-standard dosage group and the standard dosage group) were considered infections. There was 1 death associated with injuries sustained in a motor vehicle accident. There were no cases of tuberculosis (TB), opportunistic infection, malignancy or major adverse cardiovascular events reported through Week 60. In addition, the safety profile of ustekinumab at the standard and half-standard dosages in pediatric subjects ≥12 years of age was comparable with that shown for adults, and there were no demonstrable differences in safety or tolerability between the 2 pediatric dosages studied.

2. OBJECTIVES AND HYPOTHESIS

2.1. 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.

2.2. Hypothesis

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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study 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%.

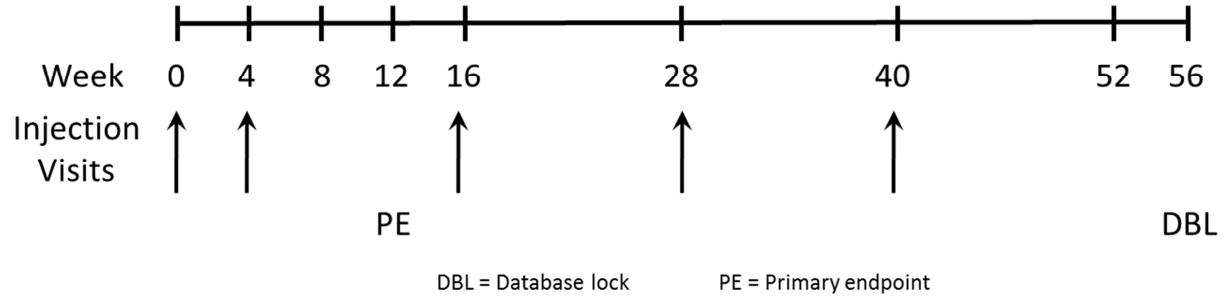
At least 40 subjects will receive ustekinumab administered subcutaneously at weight-based doses at Weeks 0 and 4 followed by dose administrations every 12 weeks (q12w) through Week 40. Subject weight will be measured at each visit and the dose of ustekinumab will be adjusted accordingly. Expected duration 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; Section 17.9.1).

Efficacy assessments (PGA, PASI, and CDLQI) will be performed per the Time and Events Schedule (see Table 1). Serum samples for PK and immunogenicity analyses will be collected at the timepoints shown in the Time and Events Schedule. Buccal swab samples for pharmacogenomic analysis will be collected at Week 0 from all subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

Safety and tolerability will be assessed by monitoring AEs, SAEs, clinical laboratory tests, vital signs, physical examinations, concomitant medication review, injection site evaluations, observations for allergic reactions, immunogenicity, and assessments for early detection of TB.

All assessments will be performed per the Time and Events Schedule (see Table 1). The study schema is presented in Figure 1.

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



At the Week 52 visit, subjects who have not had a beneficial response from ustekinumab treatment as determined by the investigator, or who have 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), will not enter the LTE of the study. The Week 56 safety follow-up will be the end of study participation.

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 follow up for the main study and the first ustekinumab administration of the LTE will be completed at the Week 56 visit.

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 (see Table 2).

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 (Week 264; Section 17.9.1). Additional DBLs may occur at the Sponsor's discretion.

3.2. Study Design Rationale

Dosing Rationale

In the completed CADMUS study, the standard dosage group was demonstrated to be the more effective dose through Week 52 and had a similar safety profile as the half-standard dosage (Section 1.3.2).

In addition, as noted in Section 1.3.2, results for CADMUS demonstrated that the PK of ustekinumab in children ≥12 to <18 years of age receiving a body weight adjusted dosage (0.75 mg/kg for subjects weighing ≤60 kg, 45 mg for subjects weighing >60 kg to ≤100 kg, and 90 mg for subjects weighing >100 kg) was comparable to that of adults receiving the standard ustekinumab psoriasis dosage (45 mg for subjects weighing ≤100 kg and 90 mg for subjects weighing >100 kg). The safety and tolerability in pediatric subjects was no different from that extensively established in adults with psoriasis. Moreover, efficacy observed for psoriasis with this dosing approach in pediatric subjects from ≥12 to <18 years of age was also comparable to adults, suggesting that the exposure-response relationship of ustekinumab for psoriasis is similar between adult subjects and pediatric subjects ≥12 to <18 years of age.

Therefore, a body weight adjusted dosing approach identical to the standard dose shown to be safe and effective for pediatric subjects ≥12 to <18 years of age in CADMUS will be utilized in this clinical study of subjects ≥6 and <12 years of age.

Study Phases

The screening phase of up to 10 weeks will allow for sufficient time to perform screening study evaluations and determine study eligibility. Open label active treatment will continue through Week 52 (last ustekinumab injection at Week 40) and safety evaluations through Week 56 will provide adequate time to demonstrate the efficacy and safety of ustekinumab as maintenance therapy for psoriasis.

The addition of the LTE is to allow pediatric subjects who have demonstrated clinical benefit through Week 52 of the main study to continue receiving ustekinumab. Additionally, longer-term safety and efficacy data in this patient population will be collected.

Efficacy evaluations chosen for this study are consistent with applicable US and EU regulatory guidance and precedent established in previous studies of therapeutic agents for the treatment of psoriasis.

Patient reported outcomes (PROs) chosen for this study are consistent with clinically relevant measurements that are accepted in the medical literature for other studies in psoriasis and applicable US/EU regulatory guidance documents. Health-related quality of life impairment in dermatologic diseases like psoriasis has been shown to be as or even more burdensome than other chronic diseases like diabetes and asthma in the pediatric population.[1] Skin disease in the pediatric population specifically impacts physical, social, and emotional health with the potential for school functioning.[18] Effective treatment of psoriasis may allow for improvements in physical, social, emotional, and school functioning and health. Data collected directly from the subject can best capture these concepts.

Psoriasis response evaluations include:

- PGA
- PASI
- CDLQI

To help improve objectivity, given the open-label design, clinical efficacy assessments (PGA and PASI) will be performed by a blinded evaluator.

Pharmacokinetic Evaluations

To assess the pharmacokinetics of ustekinumab in pediatric subjects ≥6 and <12 years of age with psoriasis, serum samples will be collected at selected visits in this study.

Immunogenicity Evaluations

Serum samples for immunogenicity assessment will be collected at selected visits in this study. Samples that test positive for antibodies to ustekinumab will be further characterized to determine if antibodies to ustekinumab could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies [NAbs] to ustekinumab).

Biomarker Evaluations

Serum samples for biomarker analyses will be collected to evaluate the mechanism of action of ustekinumab or help to explain inter-individual variability in clinical outcomes or help to identify population subgroups that respond differently to ustekinumab. 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. There is currently no accepted laboratory biomarker used to diagnose or monitor psoriasis therapy. However, emerging evidence from the literature and from our own research group suggest that IL-17 proteins, a family of effector cytokines partly downstream of IL-23, are increased in lesional skin and blood of patients with psoriasis[7,8,21] and respond to IL-23 targeted therapies.[17] Accumulating data from sensitive IL-17 assays utilized in previous psoriasis clinical studies of IL-23 directed therapies demonstrate that serum levels of IL-17A and IL-17F correlate with psoriasis severity based on PASI score (Zhang et al, 2010; unpublished data).[22] Therefore, assessment of IL-17 serum levels will be performed and will be used as an additional biomarker of ustekinumab response.

Pharmacogenomic (DNA) Evaluations

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of ustekinumab and to identify genetic factors associated with psoriasis.

Two buccal swab samples will be collected for pharmacogenomic assessments at Week 0 from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

4. SUBJECT POPULATION

Screening for eligible subjects must be performed within a maximum of 10 weeks before administration of the study drug can occur.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study.

4.1. Inclusion Criteria

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

1. Subject must be a boy or girl ≥6 and <12 years of age.

2. Have a diagnosis of plaque-type psoriasis with or without PsA for at least 6 months prior to first administration of study drug, with widespread lesions defined by PASI ≥12, PGA ≥3, and involved BSA ≥10%.

3. Are candidates for phototherapy or systemic treatment of psoriasis (either naive or history of previous treatment) or have psoriasis considered by the investigator as poorly controlled with topical therapy after an adequate dose and duration of therapy.

4. Before enrollment, a girl must be either:

   a. Not of childbearing potential: premenarchal; permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy,

   b. Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, true abstinence (when this is in line with the preferred and usual lifestyle of the subject); established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject).

      Note: If the childbearing potential changes after start of the study (eg, girl who is not heterosexually active becomes active, premenarchal girl experiences menarche) a girl must begin a highly effective method of birth control, as described above.

5. A girl of childbearing potential must have a negative urine pregnancy test at screening and at all visits when study drug is to be administered.

6. A boy who is sexually active with a female of childbearing potential must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

7. Are considered eligible according to the following TB screening criteria:

   – Have no history of latent or active TB prior to screening.

   – Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

   – Have had no recent close contact with a person with active TB.

   – Within 10 weeks prior to the first administration of study drug, have a negative QuantiFERON®-TB Gold test result (see Attachment 1). Within 10 weeks, a negative tuberculin skin test prior to the first administration of study drug is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

   – Indeterminate results should be handled as outlined in Section 9.1.2.

8. Must have positive protective antibody titers to varicella and measles prior to the first administration of study drug. In the absence of positive protective antibody titers, the subject must have documentation of age-appropriate vaccination for varicella and/or measles (that includes both doses of each vaccine) or verification of past varicella and/or measles infection documented by a health care provider.

9. Must agree not to receive a live virus or live bacterial vaccination at least 2 weeks (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of study drug, during the study, or within 15 weeks after the last administration of study drug.

10. Must agree not to receive a bacille Calmette-Guérin (BCG) vaccination within 12 months of screening, during the study, or within 12 months after the last administration of study drug.

11. Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.

12. Have screening laboratory test results within the following parameters:

- Hemoglobin ≥10 g/dL (SI: ≥100 g/L)
- White blood cells ≥3.0 x 10^3 cells/µL (SI: ≥3.0 x 10^9cells/L)
- Neutrophils ≥1.5 x 10^3 cells/µL (SI: ≥1.5 x 10^9 cells/L)
- Platelets ≥150 x 10^9/L
- Serum creatinine ≤0.7 mg/dL (SI: 62 µmol/L; 6 to 10 years of age)
- ≤1.0 mg/dL (SI: 88 µmol/L; 11 to 12 years of age)
- Aspartate aminotransferase (AST) ≤72 IU/L (girls and boys, 2 to 11 years of age)
- Alanine aminotransferase (ALT) ≤54 IU/L (girls and boys, 2 to 18 years of age)

13. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Section 16.2.3, Informed Consent.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

Disease Characteristics:

1. Currently have nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).

2. Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).

Concomitant or previous medical therapies received:

3. Have used any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to ustekinumab, guselkumab, and tildrakizumab.

4. 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.

5. 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.

6. 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.

7. Have received any biologic agent (eg, ENBREL®, HUMIRA®) within the previous 3 months or 5 times the $t_{1/2}$ of the agent, whichever is longer.

8. 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.

9. 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.

10. 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.

11. 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.

12. Have received, or are expected to receive, any live virus or bacterial vaccination at least 2 weeks (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of study drug, during the study, or within 15 weeks after the last administration of study drug.

13. Have had a BCG vaccination within 12 months of screening.

Infections or predispositions to infections:

14. Have a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.

15. Have had a serious infection (eg, hepatitis, pneumonia, or pyelonephritis), have been hospitalized for an infection, or have been treated with IV antibiotics for an infection within 2 months prior to first administration of study drug or have had multiple (≥2) serious infections requiring hospitalization or treatment with parenteral antibiotics within the past year. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

16. Have a history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to screening.

17. Have ever had a nontuberculous mycobacterial infection or systemic opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

18. Is infected with human immunodeficiency virus (HIV; positive serology for HIV antibody).

19. Tests positive for antibodies to hepatitis C virus (HCV) at screening.

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

a. Subjects who test **positive** for surface antigen (HBsAg+) **are not eligible** for this study, regardless of the results of other hepatitis B tests.

b. Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) **and** surface antibody (anti-HBs+) **are eligible** for this study.

c. Subjects who test **positive only for surface antibody** (anti-HBs+) **are eligible** for this study.

d. Subjects who test **positive only for core antibody** (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject is **not eligible** for this study. If the HBV DNA test is **negative**, the subject is **eligible** for this study. In the event the HBV DNA test cannot be performed, the subject is **not eligible** for this study.

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

21. Have a documented history of immune deficiency syndrome (eg, severe combined immunodeficiency syndrome, T cell deficiency syndromes, B cell deficiency syndromes and chronic granulomatous disease).

Malignancy or increased potential or malignancy:

22. Have any known malignancy or have a history of malignancy.

23. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

Coexisting medical conditions or past medical history

24. Have a history of or current signs or symptoms of moderate or severe progressive or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances.

25. Have shown a previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (eg, plasma derived or recombinant mAb).

26. Known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients.

27. Have a transplanted organ (with exception of a corneal transplant >3 months prior to the first administration of study drug).

28. Is currently undergoing or has previously undergone allergy immunotherapy for a history of anaphylactic reactions.

29. Have been hospitalized in the past 1 year for asthma, ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or required more than one short-term (≤2 weeks) course of oral corticosteroids for asthma within the previous year.

30. Be known to have had a substance abuse (drug or alcohol) problem.

31. Are pregnant, or nursing.

Other

32. Are unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.

33. Are participating in another interventional study using an investigational agent or procedure during participation in the study.

34. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

35. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Investigators are encouraged to enroll subjects as soon as they become eligible and should not wait for the maximum of the 10-week screening period. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. Must not receive a live virus or live bacterial vaccination during the study or within 15 weeks after the last administration of study drug.

2. Must not receive a BCG vaccination during the study or within 12 months after the last administration of study drug.

3. Must agree not to plan a pregnancy or father a child within 6 months following the last administration of study drug.

4. If sexually active, girls must remain on a highly effective method of birth control during the study and for 6 months after receiving the last administration of study drug.

5. Refer to Section 8 (PRESTUDY AND CONCOMITANT THERAPY) for details regarding prohibited and restricted therapy during the study.

6. Agree to follow the contraceptive requirements as noted in the inclusion criteria.

7. Subjects must avoid prolonged sun exposure and avoid use of tanning booths or other UV light sources during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Randomization will not be used in this 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 as described in Section 9.2.1.

6. DOSAGE AND ADMINISTRATION

The ustekinumab for this study will be supplied as final vialed product (FVP), single-use 2 mL Schott Type I glass vial closed with a Daikyo D777-1 FluroTec®-coated stopper and a West 13 mm aluminum seal and plastic light green flip-off button. The FVP formulation is composed of 90 mg/mL ustekinumab with excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, and 0.004% (w/v) polysorbate 80, pH 6.0. There is 1 dose strength (ie, 45 mg in 0.5 mL volume). No preservatives are present.

All subjects enrolled in the study will receive ustekinumab at Weeks 0 and 4 followed by q12w dosing. Eligible subjects who enter the LTE will receive ustekinumab q12w beginning at Week 56 and continue treatment according to criteria defined in Section 3.1. At each dosing visit, subject weight will be measured and the dose of ustekinumab will be adjusted accordingly. Subjects will receive 1 of the following dose levels depending on their weight:

- Weight <60 kg: 0.75 mg/kg
- Weight ≥60 kg to ≤100 kg: 45 mg
- Weight >100 kg: 90 mg

7. TREATMENT COMPLIANCE

Compliance with the treatment schedule and study visit is strongly encouraged, although it is acknowledged that treatment may need to be interrupted for various reasons. The following visit windows must be adhered to: ±1 week for the Week 4, Week 8 and Week 12 (primary endpoint) visits and ±2 weeks for all visits after Week 12. For any reason, if the subject deviates from the scheduled visits, the rescheduled visit should occur as soon as possible, preferably within 2 weeks. The subject should then resume the normal study schedule relative to the baseline visit (Week 0). The Sponsor must be contacted for any significant deviation in a visit or dosing.

All subject case report forms (CRFs) will be monitored by a site monitor designated by the sponsor. During these monitoring visits, all procedures will be evaluated for compliance with the protocol. Subject charts will be reviewed and compared with the data entries on the CRFs to ensure accuracy.

8. PRESTUDY AND CONCOMITANT THERAPY

All concomitant therapies must be recorded throughout the study beginning when the first dose of study drug is administered.

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

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Topical Therapies for Psoriasis

The use of any topical corticosteroid preparations for the treatment of psoriasis is prohibited within 2 weeks prior to the first study drug administration and during the first 12 weeks of the study period.

After the Week 12 evaluation, low potency topical corticosteroids may be used on the face and groin only. Acceptable low potency corticosteroids include 2.5% concentration or less of hydrocortisone cream or equivalent.

Other non-corticosteroid topical therapies that could affect psoriasis or the PASI evaluation, such as tar, anthralin, calcipotriene, tazarotene, methoxsalen, picrolimus, or tacrolimus, are prohibited through Week 52 of the study.

Through Week 52, shampoos (containing tar or salicylic acid only) and topical moisturizers are allowed. Subjects should not use these topical agents during the morning prior to a study visit. Nonmedicated shampoos may be used on the day of a visit.

8.2. Phototherapy or Systemic Therapies for Psoriasis

The use of phototherapy (psoralen with ultraviolet light A [PUVA] and/or ultraviolet light B [UVB]), systemic antipsoriatic medications targeted for reducing tumor necrosis factor (including but not limited to etanercept or adalimumab), drugs targeted for reducing IL-12 or IL-23 (including but not limited to guselkumab and tildrakizumab), alpha-4 integrin antagonists (including but not limited to natalizumab), any conventional systemic antipsoriatic therapy (including but not limited to MTX, cyclosporine, acitretin), and any other systemic agent that could affect psoriasis or the PASI evaluation are not allowed at any time during the study. Subjects taking these drugs must be discontinued from study drug and be followed for an additional 16 weeks.

8.3. Concomitant Therapies for Conditions Other Than Psoriasis

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

The use of stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs) is allowed. However, disease-modifying agents such as MTX, sulfasalazine, or IM gold must be discontinued within 4 weeks of the first study drug administration and are prohibited during the study. Antimalarial agents, except for chloroquine, may be used after Week 12.

Corticosteroids should be used only as follows:

- **Topical Corticosteroids**: Topical corticosteroids for indications other than psoriasis should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks.
- **Systemic Corticosteroids**: (oral or IV only; IM steroids are prohibited): Short term use (≤2 weeks) of oral or IV systemic corticosteroids for indications other than psoriasis should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. If feasible, the medical monitor or designee should be contacted prior to initiation.
- **Intralesional Corticosteroids**: Intralesional corticosteroids are not allowed for use in the treatment of psoriasis. Intralesional corticosteroids for indications other than psoriasis should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis.
- **Intra-articular Corticosteroids**: Subjects may receive no more than 2 intra-articular, tendon sheath, or bursal corticosteroid injections through Week 52 of the study.
- **Epidural Corticosteroids**: Epidural corticosteroids are prohibited through Week 52 of the study.
- **Other Corticosteroids**: Inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed.

During the LTE, the medication rules outlined above still apply except that all topical therapies, with the exception of ultra-high potency corticosteroids are permitted for treatment of psoriasis.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1 and Table 2) summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study. The visit-specific CLDQI PRO assessment should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

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

The total blood volume to be collected from each subject will be 69.5 mL. Table 3 summarizes the estimated blood volume to be drawn during the study.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 3: Volume of Blood to be Collected From Each Subject in the Main Study

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Hematology	2	5	10
Serum chemistry[b]	2.5	5	12.5
Serology (HIV, hepatitis)	8.5	1	8.5
Pharmacokinetic only[b]	2.5	3	7.5
Pharmacokinetics and immunogenicity[c]	3.5	4	14
Serum antibody titers for varicella and measles	2.5	1	3.5
Biomarkers[d]	3.5	3	10.5
QuantiFERON®-TB Gold testing	3	1	3
Approximate Total			69.5

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Blood samples collected for pharmacokinetics only evaluation (approximately 2.5 mL each): each serum sample will be split into 2 aliquots (approximately 0.5 mL each).
[c] Blood samples collected for pharmacokinetic and immunogenicity evaluations (approximately 3.5 mL each): each serum sample will be split into 3 aliquots (approximately 0.5 mL each).
[d] Blood samples collected for serum biomarkers (approximately 3.5 mL each): each serum sample will be split into 3 aliquots (approximately 0.5 mL each).

For subjects participating in the LTE, a maximum of 4 additional hematology samples and 4 additional serum chemistry samples (2 mL per hematology sample and 2.5 mL per serum chemistry sample; total blood volume of 18 ml), will be collected.

9.1.2. Screening Phase

After written informed consent has been obtained and within a maximum period of 10 weeks before enrollment into the study, all screening evaluations establishing subject eligibility must be performed. Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study as soon as practically possible. There is no need to wait for the maximum 10-week screening period. Every effort should be made to adhere to the study Time and Events Schedule for each subject (see Table 1).

Girls of childbearing potential must have a negative urine β-human chorionic gonadotroptin (β−hCG) pregnancy test at screening and before enrollment. Girls and boys who are sexually active must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study and for 6 months after the last dose of study drug. The method(s) of contraception used by each subject must be documented.

Subjects must undergo testing for TB (see Attachment 1 and Attachment 2) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON®-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities) are eligible to continue with procedures. Subjects with a newly identified positive QuantiFERON®-TB Gold (or tuberculin skin) test result must be excluded from the study.

A subject whose first QuantiFERON®-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON®-TB Gold test result is also indeterminate, the subject must be excluded from the study.

Subjects that do not have positive protective antibody titers to varicella and measles based on screening laboratory test results or appropriate documentation of prior immunization or documentation of prior infection from a health care provider can be immunized during the 10-week screening period prior to receiving study drug. These subjects should receive both an initial immunization and a booster 4 weeks later. Also note that if a live attenuated viral vaccine is utilized, it is also necessary for 2 weeks to elapse between the booster shot and receipt of study drug.

9.1.3. Open-Label Treatment Period (Week 0 to Week 52)

After screening, subjects will have clinic visits at Weeks 0, 4, 8, 12, and 16 then every 12 weeks through Week 52. The last injection of study drug will be administered at Week 40, the final efficacy assessments will be performed at Week 52.

9.1.4. Safety Follow-up (Week 52 to Week 56)

A final safety assessment at Week 56 will be obtained via telephone contact for those subjects not entering LTE.

9.1.5. Long-term Extension (Week 56 to 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 follow up for the main study and the first ustekinumab administration of the LTE will be completed at the Week 56 visit.

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 (see Table 2).

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 (Week 264; Section 17.9.1). Additional DBLs may occur at the Sponsor's discretion.

9.2. Efficacy

Efficacy evaluations are consistent with those used to evaluate other therapies for psoriasis and will include the following:

- PGA
- PASI
- CDLQI

9.2.1. Blinded Efficacy Evaluator

During the main study, an independent, blinded efficacy evaluator, approved by the Sponsor, will be designated at each study site to perform all PASI and PGA efficacy assessments, including the screening visit. The blinded efficacy evaluator should have no contact with the subject during the study other than the efficacy assessments, should not discuss the subject's

treatment with the subject, subject's caregiver, or other site personnel at any time, and will not be permitted to review the subject's medical records, questionnaires, or the electronic CRF prior to each assessment. The blinded efficacy evaluator should be documented in the source documents at each visit.

During the LTE, PGA assessments should be performed by the investigator or any qualified healthcare provider at the study site. When possible, all PGA assessments for a subject should be performed by the same assessor.

The Sponsor will provide PASI and PGA training for each site's designated efficacy evaluator prior to the screening of the first subject at each site. If the efficacy evaluator was trained by the Sponsor in a previous clinical study within the last 3 years and there is adequate documentation of this training (certification), that training will be considered adequate for this study; however, repeat training prior to start of the study is encouraged. Training documentation of each efficacy evaluator should be maintained at the study site.

All efficacy evaluators at a site must be listed on the Delegation Log at the study.

9.2.2. Physician's Global Assessment

The PGA is a static evaluation of the subject's current psoriasis status based on a qualified healthcare provider's assessment of the following categories: induration, scaling, and erythema. A description of the PGA is provided in Attachment 3.

9.2.3. 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 (Fredriksson and Pettersson, 1978).[5] For the PASI assessment, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that can range from 0 to 72. A PASI 50 response is defined as ≥50% improvement in PASI score from baseline; PASI 75 and PASI 90 are similarly defined. A description of the PASI is provided in Attachment 4.

9.2.4. Children's Dermatology Life Quality Index

The CDLQI is an adapted version of the DLQI for the pediatric population. The adaption and validation of the CDLQI was undertaken by the original developer of the DLQI to ensure it addressed the specific needs of the pediatric population.[12] The CDLQI questionnaire is frequently used to assess the patient's perspective on the impact of skin disorders on daily living.[12,14] The development of the instrument included a wide variety of dermatologic conditions (Finlay and Khan, 1994).[4] The content validity and other psychometric properties were further assessed in a subsequent study in patients with psoriasis.[3] Additional validation work was completed on the children's version.[12] The CDLQI, a 10-item instrument, has 4 item response options and a recall period of 1 week. The instrument is designed for use in children (ie, subjects from 4 to 16 years of age), is self-explanatory and can be simply handed to the subject

who is asked to fill it in with the help of the child's parent or guardian. A sample CDLQI is provided in Attachment 5.

9.2.5. Endpoints

Primary Endpoint

- The proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12.

PGA results will be summarized along with 95% confidence intervals for all subjects enrolled in the study.

Major Secondary Endpoints

- Serum ustekinumab concentrations will be summarized over time to assess the PK of ustekinumab.
- 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.

The major secondary efficacy endpoints will be summarized along with 95% confidence intervals for all subjects enrolled in the study.

Applicable data handling rules for the efficacy endpoints are defined in Section 11.3.1.

Other Endpoints

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

- 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
- The proportions of subjects who achieve PASI 50, PASI 75, PASI 90, and PASI 100 responses over time
- The percent improvement from baseline in PASI over time
- The change from baseline in CDLQI over time.
- The proportion of subjects with CDLQI = 0 or 1 over time

Safety data will be summarized using descriptive statistics

9.3. Pharmacokinetics and Immunogenicity

Blood samples will be collected for the measurement of serum ustekinumab concentrations and evaluation of antibodies to ustekinumab at the timepoints presented in the Time and Events

Schedule (Table 1). Serum samples will also be collected at the final visit from subjects who terminate study participation early.

Serum ustekinumab concentrations will also be used for population PK modelling to characterize the PK of ustekinumab in this pediatric population and for exposure-response modeling and simulation analysis. These analyses will be presented in a separate technical report (see Section 11.5).

9.3.1. Evaluations

Venous blood samples will be collected for measurement of serum ustekinumab concentrations and antibodies to ustekinumab at the timepoints shown in the Time and Events Schedule (Table 1).

Venous blood samples of approximately 2.5 mL for pharmacokinetics only evaluations will be collected and each serum sample will be divided into 2 aliquots (1 for serum ustekinumab concentration and 1 for back-up). Venous blood samples of approximately 3.5 mL for both pharmacokinetics and immunogenicity evaluations will be collected and each serum sample will be divided into 3 aliquots (1 for serum ustekinumab concentration, 1 for antibodies to ustekinumab, and 1 for back-up). Samples collected for analyses of ustekinumab serum concentration and antibodies to ustekinumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for further characterization of immunogenicity. Samples must be collected before study drug administration at visits when a study drug administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form. See the Laboratory Manual for further information regarding collection, handling, and shipment of biological samples. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine serum ustekinumab concentrations using a validated, specific, and sensitive immunoassay method by the sponsor’s bioanalytical facility or under the supervision of the Sponsor. The Sponsor, or its designee, under conditions in which the subjects’ identity remains blinded, will assay these samples.

9.3.3. Immunogenicity Assessments (Antibodies to Ustekinumab)

Antibodies to ustekinumab will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule (Table 1). Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Samples that test positive for antibodies to ustekinumab will be further characterized to determine if antibodies to ustekinumab could neutralize the biological effects of ustekinumab in vitro (ie, NAbs to ustekinumab). All samples will be tested by the Sponsor or Sponsor's designee.

9.4. Biomarker Evaluations

Serum will be collected from all subjects for assay of IL-17 according to the Time and Events Schedule (Table 1). Serum may also be analyzed for levels of specific proteins including but not limited to cytokines such as IL-12p40, IL-17, IL-21, IL-22, IL-23p19, and other inflammation-related molecules.

9.5. Pharmacogenomic (DNA) Evaluations

Two buccal swab samples will be collected for pharmacogenomic assessments at Week 0 from subjects who consent separately to this component of the study (where local regulations permit). Subject participation in pharmacogenomic research is optional.

DNA samples will be used for research related to ustekinumab or psoriasis. They may also be used to develop tests/assays related to ustekinumab and psoriasis. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to ustekinumab or psoriasis clinical endpoints.

Subjects have the option to withdrawal consent from the phramcogenomic assessment or to withdraw their consent for their samples to be stored for research (refer to Sections 10.4 and 16.2.5).

9.6. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule (Table 1):

Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. AEs will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. The following tests will be performed by the central laboratory. Use of local laboratories is only allowed in cases where safety follow-up is time-critical and the central laboratory results are not expected to be available if actions need to be taken for safety reasons. These laboratory results will not be entered in the CRF but should be retained with the source documents.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -lymphocytes
  -monocytes
  -neutrophils
  -bands
  -eosinophils
  -basophils
  -platelet count

- Serum Chemistry Panel

  -blood urea nitrogen
  -creatinine
  -glucose
  -AST
  -ALT
  -total bilirubin
  -indirect bilirubin
  -albumin
  -total protein

- Urine pregnancy testing for girls of childbearing potential only.
- Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody; serum antibody titers to varicella, measles)

During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.

Vital Signs

Heart rate, respiratory rate, and blood pressure will be collected.

Physical Examination

Physical examinations will be performed. Total body skin examination will be performed to evaluate for any suspected malignant skin lesions including basal cell carcinoma, squamous cell carcinoma, and melanoma. Height and weight will be collected.

Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

Injection-site Reactions

A study drug injection-site reaction is any adverse reaction at an SC study drug injection site. The injection sites will be evaluated for reactions and any injection-site reactions will be recorded as an AE.

Allergic Reactions

All subjects must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives) for at least 30 minutes after the injection. If mild or moderate allergic reaction is observed, acetaminophen 650 mg by mouth (PO) or NSAIDs and diphenhydramine 25 mg PO or IV may be administered.

Subjects with reactions following an injection resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm mercury (Hg) will not be permitted to receive any additional study drug injections. In the case of such reactions, appropriate medical treatment should be administered.

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at each scheduled visit (refer to Time and Events Schedule) or by telephone contact approximately every 4 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Has your child had a new cough of > 14 days' duration or a change in a chronic cough?"
- "Has your child had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Has your child had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat QuantiFERON® TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON® TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2.

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, no additional study drug should be given, and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form.

Refer to the Time and Events Schedule (Table 1) for the timing and frequency of all sample collections.

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

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion of Main Study

A subject will be considered to have completed the main study if he or she has completed assessments at Week 56. Subjects who prematurely discontinue study treatment for any reason before completion of the main study will not be considered to have completed the study.

10.2. Completion of Long-term Extension

A subject will be considered to have completed the LTE if he or she has completed all assessments up through Week 264. For subjects in the LTE who decide to withdraw from study participation, who discontinue treatment for any reason, or who become ineligible to continue to receive study drug (ie, due to the occurrence of one of criteria listed in Section 3.1), the assessments (excluding study drug injection) for the Week 248 study visit will be performed.

10.3. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if any of the following occur:

- The investigator or Sponsor’s medical monitor believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment;
- An AE temporally associated with study drug injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure;
- The subject or their legally acceptable representative withdraws consent/assent for administration of study drug;
- Pregnancy, or pregnancy planned within the study period or within 6 months after the last study drug injection;
- The initiation of protocol-prohibited medications or treatments as outlined in Section 8;
- Malignancy;
- An opportunistic infection;
- A recurrent or chronic serious infection;
- A severe study drug injection-site reaction;

- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB.
  - A subject undergoing evaluation has a positive QuantiFERON®-TB Gold test result and/or an indeterminate QuantiFERON®-TB Gold test result on repeat testing (refer to Section 9.1.2) and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities.

Main Study

Subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. In addition to the procedures and evaluations listed for the corresponding visit, the Week 52 visit assessments should also be performed 16 weeks after the last dose of study drug.

If a subject discontinues study drug and terminates study participation prior to week 52, the procedures and evaluations for the current study visit will be completed. In addition, the Week 52 visit assessments should be performed in the subject's current (final) visit.

All procedures and evaluations must be conducted prior to a subject's withdrawal of consent.

Long-term Extension

During the LTE, subjects who discontinue study drug but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 16 weeks (4 months) following the last dose of study drug. At the subject's last study visit for the LTE, the procedures and evaluations (excluding study drug injection) for Week 248 will be followed. If a subject discontinues study drug and terminates study participation, the procedures and evaluations for Week 248 excluding study drug injection will be performed at the current visit.

During the LTE phase, consideration should also be given to discontinue ustekinumab treatment in any subjects who are non-responders (ie, defined by PGA >3 at 2 consecutive visits).

10.4. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study prior to Week 52, the Week 52 assessments will be obtained. If a subject withdraws from the study before the end of the LTE, the Week 248 assessments (excluding study drug injection) will be performed.

11. STATISTICAL METHODS

Statistical analysis will be done by the Sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, range, and interquartile range appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Graphical data displays may also be used to summarize the data.

Subject baseline data, demographic and baseline clinical disease characteristics will be summarized. The baseline measurement is defined as the closest measurement taken at or before Week 0.

Safety and efficacy analysis will include enrolled subjects who receive at least 1 dose administration of ustekinumab.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug, descriptive statistics will be provided.

11.2. Sample Size Determination

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 1 of the major secondary objective is to evaluate the pharmacokinetics of ustekinumab for 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. However, 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 Studies

C0743T08, C0743T09, and CADMUS. The PK in pediatric subjects was simulated using the body weight distribution sampled with replacement from the National Health and Nutrition Examination Survey (NHANES) III growth database.[2] A total of 300 replicates of the planned study design, 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.[19] 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.

11.3. Efficacy Analyses

Efficacy results will be summarized for all subjects enrolled in the study and 95% confidence intervals will be calculated for the primary and major secondary efficacy endpoints.

Primary Endpoints

- The proportion of subjects with a PGA of cleared (0) or minimal (1) at Week 12.

Major Secondary Endpoints

- Serum ustekinumab concentrations will be summarized over time to assess the PK of ustekinumab.
- 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.

Other Endpoints

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

- 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
- The proportions of subjects who achieve PASI 50, PASI 75, PASI 90, and PASI 100 responses over time
- The percent improvement from baseline in PASI over time
- The change from baseline in CDLQI over time.
- The proportion of subjects with CDLQI = 0 or 1 over time

11.3.1. Data-Handling Rules

The following treatment failure rules and data-handling rules will be applied to the efficacy analyses through Week 52 in this study.

Treatment Failure Criteria and Rules

- Subjects are considered as treatment failures if they discontinue study treatment due to lack of efficacy, an AE of worsening of psoriasis, or start a protocol-prohibited medication/therapy during the study that could affect their psoriasis.

  A subject who meets one or more treatment failure criteria specified above will be considered as a treatment failure from that point onward. The baseline values will be used for all directly measured endpoints regardless of the actual measurements. Zeros will be assigned to improvements and percent improvements, and nonresponder status will be assigned to binary response variables.

- 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.

After Week 52, treatment failure rules or missing data imputations will not be applied for PGA scores.

11.4. Pharmacokinetic Analyses

Serum ustekinumab concentrations over time will be summarized for treated subjects. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each nominal sampling timepoint. All BQL concentrations or missing data will be labeled as such in the concentration data listing or Statistical Analysis System (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

A population PK analysis with nonlinear mixed effects modeling (NONMEM) 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. Details will be given in a population PK analysis plan, and results of the population PK analysis may be presented in a separate technical report.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

A suitable population PK/pharmacodynamic (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. Details will be given in a population PK/PD analysis plan, and results of the population PK/PD analysis may be presented in a separate technical report.

11.6. Immunogenicity Analyses

The incidence and titers of antibodies to ustekinumab will be summarized for all subjects who receive at least 1 dose of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (ie, subjects with at least 1 sample obtained after their first dose of ustekinumab). A listing of subjects who are positive for antibodies to ustekinumab will be provided in the Clinical Study Report (CSR).

The incidence of NAbs to ustekinumab will be summarized for subjects who are positive for antibodies to ustekinumab and have samples evaluable for NAbs.

11.7. Biomarker Analyses

Results will be presented in a separate report.

11.8. Pharmacogenomic Analyses

Results will be presented in a separate report.

11.9. Safety Analyses

All subjects who receive at least 1 administration of study drug will be included in the safety analyses.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

The following analyses will be used to assess the safety of subjects in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of reasonably related AEs.
- The incidence and type of injection site reactions.
- The incidence of infections.
- The incidence AEs of psoriasis.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the markedly abnormalities will be presented. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics of heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

11.10. Data Monitoring Committee

This is an open-label study. Therefore, the investigators, who have primary responsibility for monitoring the safety of individual subjects under their care, will know that all subjects are receiving a weight-adjusted standard dosage of active ustekinumab throughout the duration of the study. Moreover, the available aggregate unblinded safety data will be routinely evaluated by experienced clinical trial medical monitors while the study is ongoing. Therefore, an external Data Monitoring Committee will not be utilized.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

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

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an AE will be determined by whether it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

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

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

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

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

Note that seriousness and severity should not be confused. A subject could experience a severe headache that would not qualify as an SAE, while another might experience a mild stroke that, while not severe, would be considered serious.

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject (or their designees, if appropriate) must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

Adverse Events Associated with the Study Population

Worsening of psoriasis is considered common for the study population defined in this protocol and, when determined to be serious, should be reported by the investigator as described in Section 12.3.2. For safety reporting, single occurrences of the event, when serious, may be excluded from expedited reporting. If aggregate analyses of this event indicate that it occurs more frequently with study drug, an expedited safety report may be submitted.

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

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

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study within 16 weeks of the last dose of study drug, whether the event is expected or associated with the study drug, is considered a SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form and report it as AE in CRF. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form and report as partner pregnancy in CRF.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study drug(s) in subjects participating in this clinical study must be reported by the investigator according to procedures in Section 12.3.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The ustekinumab for this study will be supplied as FVP, single-use 2 mL Schott Type I glass vial closed with a Daikyo D777-1 FluroTec®-coated stopper and a West 13 mm aluminum seal and plastic light green flip-off button. The FVP formulation is composed of 90 mg/mL ustekinumab with excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, and 0.004% (w/v) polysorbate 80, pH 6.0. There is 1 dose strength (ie, 45 mg in 0.5 mL volume). No preservatives are present.

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). The ustekinumab product should not be frozen and should be protected from light. Vigorous shaking of the ustekinumab product should be avoided. The formulation does not contain preservatives. Prior to administration, the drug product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Refer to the Site Investigational Product Procedures Manual for additional guidance on study drug preparation and handling.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Site Investigational Product Procedures Manual
- Online access to electronic CRFs and Electronic Data Capture (eDC) Manual
- Trial Center File
- Laboratory Manual
- Interactive Web Response System (IWRS) Manual
- Subject study participation card
- STELARA (ustekinumab) IB
- Sample ICF

The following assessments are included as attachments to the protocol;

- Physician's Global Assessment
- Psoriasis Area and Severity Index
- Children's Dermatology Life Quality Index

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected during the main study will be approximately 69.5 mL and during the LTE will be approximately 18 mL, which is considered to be within the normal range allowed for the pediatric population.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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

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

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

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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

16.2.3. Informed Consent

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used

must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

A separate ICF will be used for the optional DNA component of the study.

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

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically

subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent and/or legally acceptable representative.

16.2.4. Privacy of Personal Data

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

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

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

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

Exploratory DNA research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand psoriasis, to understand differential drug responders, and to develop tests/assays related to ustekinumab and psoriasis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Previous vaccination (measles and varicella) history and previous infection history (specifically for subjects in which the screening blood test results do not demonstrate positive protective antibody titers to varicella and measles)
- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries

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

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electric Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual (ie, the blinded efficacy evaluator) who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

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

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote, and/or on-site monitoring to monitor this study.

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

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

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

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion

- The main study is considered completed when the last follow-up for the last subject participating is completed at Week 56.
- The LTE is considered completed when all subjects have either terminated participation according to Section 3.1 or completed their follow-up at Week 264.

The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject telephone follow-up at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

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

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

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

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. If issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information.

For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: QuantiFERON®-TB Gold Testing

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

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

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

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

Adherence to Local Guidelines

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

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Attachment 2: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

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Attachment 3: Physician's Global Assessment

The PGA is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain a final PGA score.

Induration (I) (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = marked plaque elevation, = 1 mm
5 = severe plaque elevation, = 1.25 mm or more

Erythema (E) (averaged over all lesions)

0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration
5 = dusky to deep red coloration

Scaling (S) (averaged over all lesions)

0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion
2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = marked; thick, nontenacious scale dominates
5 = severe; very thick tenacious scale predominates

Add I + E + S =_____ / 3 =_____(Total Average)

Physician's Static Global Assessment based upon above Total Average

0 = Cleared, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1
2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3
4 = Marked - majority of lesions have individual scores for I + E + S / 3 that averages 4
5 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 5

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

Attachment 4: Psoriasis Area and Severity Index

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

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

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

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

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

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

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

The PASI formula is:

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

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

Attachment 5: Children's Dermatology Life Quality Index

1. Over the last week, how **itchy, "scratchy", sore or painful** has your skin been?		Very much Quite a lot Only a little Not at all	o o o o
2. Over the last week, how **embarrassed or self conscious, upset or sad** have you been because of your skin?		Very much Quite a lot Only a little Not at all	o o o o
3. Over the last week, how much has your skin affected your **friendships?**		Very much Quite a lot Only a little Not at all	o o o o
4. Over the last week, how much have you changed or worn **different or special clothes/shoes** because of your skin?		Very much Quite a lot Only a little Not at all	o o o o
5. Over the last week, how much has your skin trouble affected **going out, playing, or doing hobbies?**		Very much Quite a lot Only a little Not at all	o o o o
6. Over the last week, how much have you avoided **swimming, or other sports** because of your skin trouble?		Very much Quite a lot Only a little Not at all	o o o o
7. Last week, was it **school time?** →	**If school time:** Over the last week, how much did your skin problem affect your **school work?**	Prevented school Very much Quite a lot Only a little Not at all	o o o o o
OR was it **holiday time?** →	**If holiday time:** How much over the last week, has your skin problem interfered with your enjoyment of the **holiday?**	Very much Quite a lot Only a little Not at all	o o o o
8. Over the last week, how much trouble have you had because of your skin with other people **calling you names, teasing, bullying, asking questions or avoiding you?**		Very much Quite a lot Only a little Not at all	o o o o
9. Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all	o o o o
10. Over the last week, how much of a problem has the **treatment** for your skin been?		Very much Quite a lot Only a little Not at all	o o o o

INVESTIGATOR AGREEMENT

STELARA® (ustekinumab)
Clinical Protocol CNTO1275PSO3013 Amendment 1

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Philippe Szapary, MD, MSCE, Vice President, Clinical Development, Immunology

Institution: Janssen Research & Development

Signature: PPD PPD Date: 18-MAY-2017
(Day Month Year)

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

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Approved, Date: 18 May 2017