Janssen Research & Development*

Clinical Protocol

Protocol Title

A Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Pediatric Participants (≥6 To <18 Years of Age)

PROTOSTAR

Short Title

A Study of Efficacy, Safety, and Pharmacokinetics of Guselkumab in the Treatment of Chronic Plaque Psoriasis in Pediatric Participants

Protocol CNTO1959PSO3011; Phase 3
AMENDMENT 5
CNTO 1959 (guselkumab)

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This compound has been investigated in adult Phase 3 clinical studies.
US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).
Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

EU Trial Number: 2023-503378-19
EudraCT NUMBER: 2017-003053-42

Status: Approved
Date: 29 August 2024
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-138623051, 13.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	29 August 2024
Amendment 4	24 February 2022
Amendment 3	19 Feb 2020
Amendment 2	08 May 2019
Amendment 1	09 May 2018
Original Protocol	21 Dec 2017

Amendment 5 (29 August 2024)

Overall Rationale for the Amendment: The changes in this protocol amendment are implemented for compliance with EU CTR.

The changes made to the clinical protocol CNTO1959PSO3011 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.23 Appendix 23: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Title page	Added the following sentence: Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.	For compliance with EU CTR
Title page	Added EU Trial number	
Synopsis	Added a section on Benefit-Risk Assessment	
Synopsis	Added EU Trial number	
Section 6.1	Added IMP/NIMP/AxMP table	
Section 7.3	Revised to allow site (rather than sponsor) to engage a third party to search public sources for participant information.	
Section 8.3.3 Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events	Added anticipated events requirements.	
Appendix 2 RECRUITMENT STRATEGY	Added section, explaining that a recruitment strategy is not applicable as enrollment for this study has stopped.	
Appendix 2 DATA PROTECTION	Updated text on Privacy of Personal data.	
Appendix 2 PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA	Added clarification on disclosure of the study results.	
Appendix 2 RECORD RETENTION	Added text regarding record retention under EU regulation.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Pediatric Participants (≥6 To <18 Years of Age)

EU TRIAL NUMBER: 2023-503378-19

Protocol Number: CNTO1959PSO3011

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

BENEFIT-RISK ASSESSMENT

Guselkumab has a well-defined long-term safety profile and has been extensively studied for the following approved indications: adults with moderate to severe psoriasis and active psoriatic arthritis. Taking into account the measures taken to minimize risk to pediatric participants in this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to pediatric participants with moderate to severe psoriasis. More detailed information about the known and expected benefits and risks of guselkumab can be found in the IB.

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objectives

The primary objective of this study is to evaluate the efficacy and safety of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the pharmacokinetics (PK) and immunogenicity of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate the effect of guselkumab on the dermatologic health-related quality of life in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate maintenance of response in participants who have active treatment withdrawn.
- To evaluate the efficacy and safety of retreatment with guselkumab.
- To generate clinical usability data and use experience with the CCI in pediatric participants with chronic plaque psoriasis and a body weight <70 kg.

Hypotheses

The primary hypothesis is that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) and the proportion of participants achieving a Psoriasis Area and Severity Index (PASI) 75 response at Week 16.

The major secondary hypotheses are that guselkumab treatment is:

- superior to placebo as assessed by the proportion of participants achieving a PASI 90 response at Week 16.
- superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) at Week 16.
- superior to placebo as assessed by the proportion of participants achieving a PASI 100 response at Week 16.
- superior to placebo in improving the dermatologic health-related quality of life in pediatric participants as assessed by the change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16.

OVERALL DESIGN

This is a Phase 3, multicenter, randomized, placebo- and active comparator-controlled study evaluating the efficacy, safety, and PK of subcutaneously (SC) administered guselkumab for the treatment of chronic plaque psoriasis in pediatric participants ≥6 to <18 years of age that cannot be adequately controlled with phototherapy and/or topical agents.

The main study will be conducted in 2 parts. In Part 1, the efficacy, safety, and PK of a weight-based dose regimen of guselkumab will be evaluated in pediatric participants during a 16-week randomized, placebo- and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. Etanercept (active comparator) will be administered in an open-label fashion during the controlled period of the study and efficacy will be assessed by a blinded efficacy evaluator. Part 1 of the study will be divided into Part 1a (≥12 to <18 years of age [ie, adolescents]) and Part 1b (≥6 to <12 years of age). Enrollment of participants ≥6 to <12 years of age in Part 1b will commence only after all participants ≥12 to <18 years of age in Part 1a have completed Week 16, all available safety data have been reviewed by an independent Data Monitoring Committee (DMC), with no important safety concerns identified, and all available guselkumab PK data for the ≥12 to <18-year-old participants through Week 16 have been evaluated via PK modeling and simulation to confirm that the body weight-based dose used in Part 1a provided systemic exposure comparable to adults.

Part 2 of the study will be an open-label, single-arm study to collect additional efficacy, safety, and PK data for pediatric participants with a weight-based dose regimen of guselkumab through Week 52. Part 2 will begin after the reviews of safety and PK data through Week 16 for all participants ≥12 to <18 years of age in Part 1a have been completed and will enroll enough additional participants to achieve a total of at least 100 participants exposed to guselkumab in this study. Enrollment of participants ≥6 to <12 years of age in Part 2 will commence only after all participants in Part 1b have completed 16 weeks of treatment, all available safety data have been reviewed by an independent DMC, and all PK data through Week 16 from Part 1b have been evaluated via PK modeling and simulation to confirm that the body weight-based dose used in Part 1b provided systemic exposure comparable to adults. Clinical usability data of the to-be-marketed CCI [redacted] will be collected in Part 2 of the study.

A long-term extension (LTE) of the study will be initiated at Week 52.

There are 3 database locks (DBL) planned for this study at Week 16, Week 52 (end of the main study), and at the end of the study (end of the LTE). The Week 16 database lock will occur after all participants in Part 1 of the study complete their Week 16 visit and will include only data from Part 1. The sponsor will

be unblinded after the Week 16 database lock for Part 1 has occurred. The Week 52 database lock will occur after all participants in both Part 1 and Part 2 of the study complete their Week 52 visit. Additional database locks may be performed if deemed necessary.

NUMBER OF PARTICIPANTS

At least 100 boys and girls, ≥6 and <18 years of age, with a diagnosis of plaque-type psoriasis (with or without psoriatic arthritis [PsA]) for at least 6 months before the first administration of study intervention will be enrolled. Participants must have chronic plaque-type psoriasis defined as having an IGA ≥3, a PASI ≥12, a ≥10% BSA involvement, and at least one of the following: very thick lesions, clinically relevant facial, genital, or hand/ foot involvement, PASI≥20, >20% BSA involvement, or IGA=4. Participants are also required to be a candidate for phototherapy or systemic treatment of plaque psoriasis and have plaque psoriasis considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy.

In Part 1a, a minimum of 60 participants will be randomized in a 2:1:1 ratio to guselkumab, placebo, and etanercept. In Part 1b, a minimum of 30 participants will be randomized in a 1:1:1 ratio to guselkumab, placebo, and etanercept. In Part 2, at least 10 participants will be enrolled to achieve a total of at least 100 participants exposed to guselkumab in this study.

INTERVENTION GROUPS AND DURATION

Guselkumab and placebo for guselkumab will be provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) or a CCI [redacted] Commercially available etanercept will be provided in a prefilled syringe or as a powder and solvent for solution for injection.

Participants randomized to guselkumab will receive a dose based on body weight. Participants will receive 1 of the following dose levels depending on their weight:

- Weight <70 kg: CCI [redacted] administered CCI [redacted]
- Weight ≥70 kg: CCI [redacted] administered using the PFS-U

Participants randomized to placebo will receive injections with a volume determined using the same weight based dose calculation for guselkumab.

Commercially available etanercept will be supplied and participants will receive a dose based on body weight:

- <63 kg: 0.8 mg/kg once weekly using a powder and solvent for solution for injection.
- ≥63 kg: 50 mg once weekly administered using a prefilled syringe.

Dose Regimen:

Participants in Part 1 will be randomized to 1 of 3 treatment groups to receive:

- Group I: Weight-based guselkumab dose CCI [redacted] SC at Weeks 0, 4, and 12.
- Group II: Weight-based placebo for guselkumab dose administered SC at Weeks 0, 4, and 12.
- Group III: Weight-based etanercept dose up to 50 mg SC weekly through Week 15.

From Week 16 through Week 52:

- Group Ia: Participants randomized to guselkumab who are PASI 90 responders at Week 16 will not receive any additional doses of guselkumab until they lose ≥50% of their Week 16 PASI response, at which time they will receive a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and every 8 weeks (q8w) thereafter through Week 52.
- Group Ib: Participants randomized to guselkumab who are PASI 90 nonresponders at Week 16 will receive a placebo injection at Week 16 and continue treatment with guselkumab q8w from Week 20 through Week 52.
- Group IIa: Participants randomized to placebo who are PASI 90 responders at Week 16 will not receive any additional doses of study intervention until they lose ≥50% of their Week 16 PASI response, at which time they will receive a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and q8w thereafter through Week 52.
- Group IIb: Participants randomized to placebo who are PASI 90 nonresponders at Week 16 will receive a weight-based guselkumab dose at Weeks 16 and 20, followed by q8w dosing thereafter through Week 52.
- Group III: Participants randomized to etanercept who elect to continue in the study will receive a weight-based guselkumab dose at Weeks 20 and 24, followed by q8w dosing thereafter through Week 48.

Participants enrolled in Part 2 of the study will receive a weight-based dose of open-label guselkumab SC at Weeks 0, 4 and q8w thereafter through Week 52.

Participants who complete Week 52 of the main study and who have had a beneficial response from guselkumab treatment as determined by the investigator, will have the option of continuing with a weight-based guselkumab q8w regimen until one of the following occurs: 1) they have reached 18 years of age and reside in a country where guselkumab is approved for treatment of plaque psoriasis in adults, and have had the opportunity to complete up to 1 year in the LTE, 2) marketing authorization is obtained for guselkumab for treatment of plaque psoriasis for patients ≥6 to <18 years of age, 3) marketing authorization is denied for guselkumab for the treatment of plaque psoriasis in pediatric patients, or 4) the company decides to no longer pursue an indication in plaque psoriasis in the pediatric population.

EFFICACY EVALUATIONS

Efficacy evaluations include:

- Investigator's Global Assessment (IGA)
- Psoriasis Area and Severity Index (PASI)
- Body Surface Area (BSA)
- Children's Dermatology Life Quality Index (CDLQI)
- Family Dermatology Life Quality Index (FDLQI)

ENDPOINTS

The co-primary and major secondary endpoints for Part 1, with the primary comparisons between the guselkumab and placebo groups, include:

Co-primary Endpoints

- The proportion of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16.
- The proportion of participants with a PASI 75 response at Week 16.

Major Secondary Endpoints

- The proportion of participants achieving a PASI 90 response at Week 16.
- The proportion of participants achieving an IGA score of cleared (0) at Week 16.
- The proportion of participants achieving a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16.

Other Secondary Endpoints

Secondary endpoints for Part 1 of the study include:

- The proportion of retreated participants that achieve a PASI 90 response over time after retreatment.
- The proportion of retreated participants that achieve PASI responses (PASI 50, 75, 90, and 100) or IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) over time after retreatment.
- The time to loss of 50% of the Week 16 PASI improvement (ie, time to retreatment) after withdrawal.
- The time to loss of PASI 90 response after withdrawal.
- The proportion of participants achieving a PASI 50 response at Week 16.
- The proportion of participants who achieve an IGA score of mild or better (≤2) at Week 16.
- The percent improvement from baseline in PASI over time through Week 16.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) over time through Week 16.
- The proportion of IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) over time through Week 16.
- The proportion of participants with CDLQI=0 or 1 at Week 16 among randomized participants with a baseline CDLQI>1
- Body surface area involved (BSA) and change from baseline in BSA at Week 16 will be compared between the guselkumab group and the placebo group.
- BSA and change from baseline in BSA will be summarized over time through Week 16.
- The proportion of participants with FDLQI=0 or 1 at Week 16 among randomized participants with a baseline FDLQI>1.
- The change from baseline in FDLQI at Week 16.

For Part 2 of the main study, PASI responses, IGA responses, PASI percent improvement, change from baseline in CDLQI and FDLQI, the proportion of participants achieving a CDLQI of 0 or 1, and the proportion of participants achieving a FDLQI of 0 or 1 will be summarized over time through Week 52.

USABILITY ASSESSMENTS

The usability of the CCI [redacted] will be assessed using a CCI [redacted].

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for the measurement of serum guselkumab concentrations and detection of antibodies to guselkumab at the time points presented in the Schedule of Activities. Serum samples will also be collected at the final visit from participants who terminate study participation early.

SAFETY EVALUATIONS

Safety evaluations include assessments of the following: adverse events (AEs, including injection site and allergic reactions), clinical laboratory tests (hematology, chemistry, liver function, and pregnancy testing), physical examinations, vital sign measurements, concomitant medication review, Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaires, and early detection of tuberculosis.

STATISTICAL METHODS

Sample Size Determination

In Part 1 of the main study, a minimum of 90 participants, including at least 60 in Part 1a, randomized in a 2:1:1 ratio, and at least 30 in Part 1b, randomized in a 1:1:1 ratio to guselkumab (n=40), placebo (n=25), and etanercept (n=25) will have at least 99% power to detect differences for each co-primary endpoint for the guselkumab versus placebo comparison at a significance level of 0.05. This sample size was also chosen to provide adequate power for the major secondary endpoint comparisons between the guselkumab and placebo groups. The number of participants enrolled in Part 2 will be at least 10, and depend on the number of participants actually exposed to guselkumab in Part 1, so that a total of at least 100 participants from Part 1 and Part 2 will be exposed to guselkumab.

Efficacy Analyses

All randomized participants will be included in the efficacy analyses for Part 1. Participants will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

The binary endpoints will be compared between the guselkumab group or the active comparator and the placebo group using a Fisher's exact test, stratified by age and region. Continuous response parameters will be compared using a Mixed effect Model Repeat Measurement (MMRM) approach, or an analysis of covariance (ANOVA) model, adjusting for baseline value, age group, and region. All statistical testing will be performed 2 sided at a significance level of 0.05. In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses will be tested in a fixed sequence for the comparison between the guselkumab and placebo groups. That is, the first major secondary endpoint will be tested only if both co-primary endpoints are positive. Similarly, the second major secondary endpoint will be tested only if the first major secondary endpoint is positive. In addition, the comparison between etanercept and placebo for the co-primary and major secondary endpoints will be performed and nominal p-values will be reported.

Analyses for other efficacy endpoints will be performed and nominal p-values will be provided.

In addition, efficacy will be summarized over time through Week 52 for participants in Part 2 of the study.

Usability Analyses

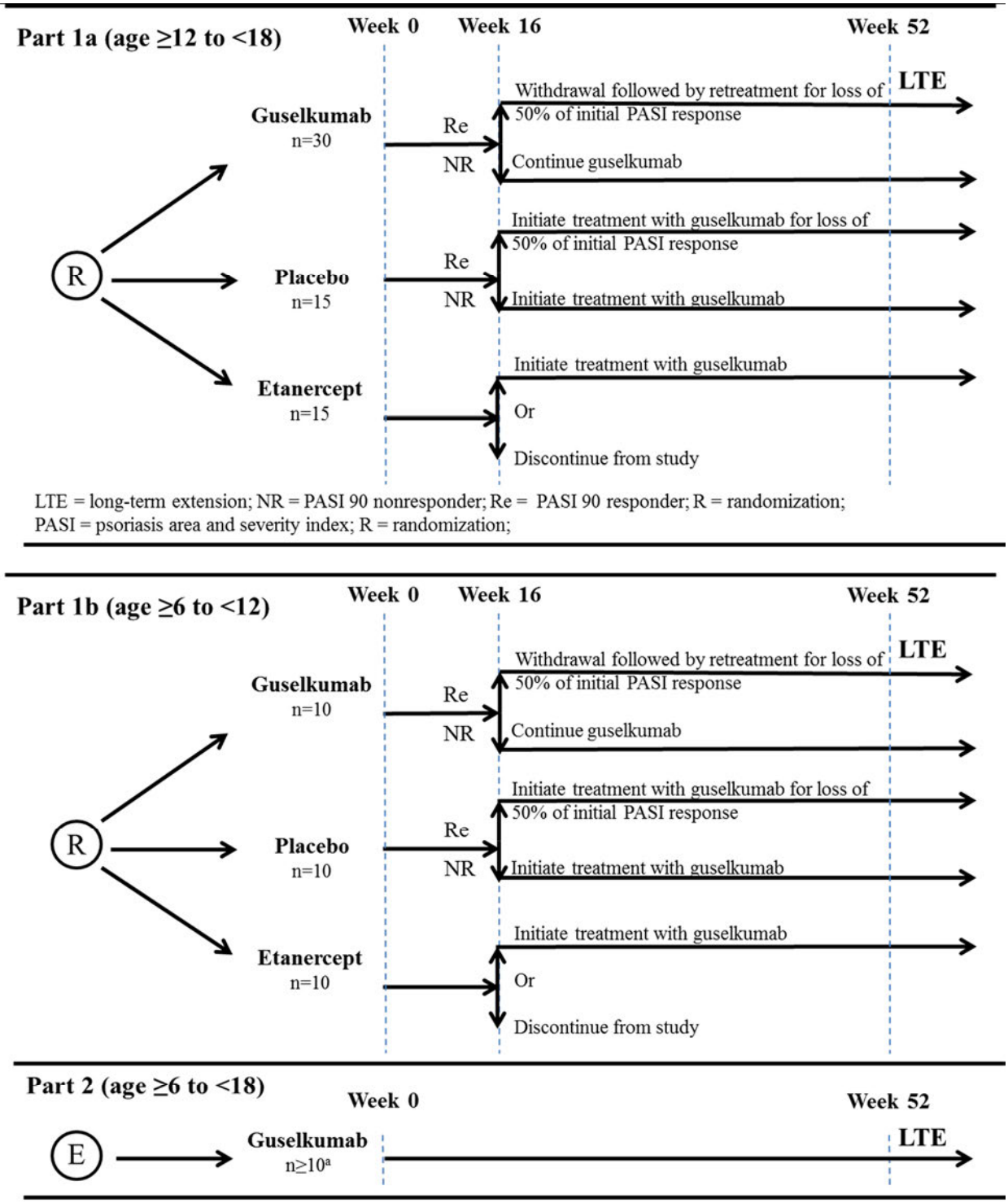
Endpoints related to usability of the[redacted] will be summarized for participants or their caregivers who self-administer guselkumab in Part 2 of the study.

Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, changes in vital signs, and suicidal ideation and behavior based on C-SSRS and AEs will be summarized. Treatment emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

1.3.1. Screening Through Week 52 – Part 1a and 1b

Phase	Screening[a]	Placebo-controlled					Withdrawal and Retreatment[b]									Study Termination Visit[c]
Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52[d]	
Study Procedures[e]																
Screening/Administrative																
Informed consent/assent[f]	X															
Medical history and demographics	X															
Inclusion/ exclusion criteria	X	X														
Study Intervention Administration																
Randomization		X														
Administration[b,g,h,i,j]		X----------														
Safety Assessments																
Physical examination (including skin exam and Tanner staging)	X						X								X	X
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[l]	X	X	X	X	X	X	X----------								-X	X
Height		X			X		X				X				X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Head circumference[m]		X													X	X
Assessment of injection pain[n]		X	X		X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Phase	Screening[a]	Placebo-controlled					Withdrawal and Retreatment[b]									Study Termination Visit[c]
Week		0	4	8	12	16	20	24	28	32	36	40	44	48	52[d]	
Study Procedures[e]																
Efficacy Assessments																
IGA[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body surface area (BSA)%[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Children's Dermatology Life Quality Index (CDLQI)[q]		X		X		X			X		X			X	X	X
Family Dermatology Life Quality Index (FDLQI)[r]		X		X		X			X		X			X	X	X
Clinical Laboratory Assessment																
QuantiFERON-TB test[s]	X															
Hepatitis B and C serology	X															
HIV antibody test	X															
Serum varicella, measles, mumps, and rubella antibody titers[t]	X															
Serum IgG, IgM, and IgA		X				X									X	X[u]
Hematology[v]	X	X[x]		X		X			X		X		X		X	X
Chemistry[v,w]	X	X[x]		X		X			X		X		X		X	X
Pharmacokinetics and Immunogenicity[y]																
Serum guselkumab concentration		X[z]	X[z]		X[z]	X	X		X		X		X			X
Antibodies to guselkumab		X[z]	X[z]		X[z]	X			X				X			X

BSA=body surface area; C-SSRS=Columbia-Suicide Severity Rating Scale; HIV=human immunodeficiency virus; Ig=immunoglobulin; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; TB=tuberculosis.

Footnotes:

a. The screening visit should occur within approximately 10 weeks before the Week 0 visit.
b. Participants randomized to guselkumab or placebo who are PASI 90 responders at Week 16 will be withdrawn from treatment. Upon loss of ≥50% of the improvement in PASI achieved at Week 16, these participants will initiate guselkumab, followed by a second dose 4 weeks later followed by q8w administration through Week 52.
c. A participant who discontinues study intervention but does not terminate study participation will continue to return for protocol-specified procedures and evaluations for at least 12 weeks following the last dose of study intervention (see Section 7.1) and complete all procedures and evaluations listed under the Study Termination Visit at the final visit. If a participant discontinues study intervention and terminates study participation, the procedures and evaluations for the Study Termination Visit should be performed at the last visit (Section 7.2).
d. Participants who choose not to continue in the long-term extension of this study will not receive any administration of study intervention at Week 52 and will be asked to return for a study termination visit 12 weeks after their last administration of study intervention.
e. All study procedures and evaluations are to be completed before study intervention administration.
f. Must be signed before first study-related activity.
g. Participants randomized to guselkumab who are PASI 90 nonresponders at Week 16 will receive a placebo injection at Week 16 to maintain the blind and continue guselkumab q8w dose regimen from Week 20 through Week 52.
h. Participants randomized to placebo who are PASI 90 nonresponders at Week 16 will initiate guselkumab at Week 16 and Week 20 followed by q8w administration through Week 52.
i. Participants randomized to etanercept will receive an etanercept dose weekly from Week 0 through Week 15. Participants will have the option of returning to the study site weekly for dose administration or the option to self-administer at home for the weeks when no regular site visit is scheduled (ie, Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, and 15). Participants who decide to administer etanercept at home will record study drug administration information on a paper questionnaire. Participants randomized to etanercept will then have the option to initiate a weight-based guselkumab dose regimen with injections at Week 20 and 24 followed by q8w administration through Week 48 **or** terminate study participation after a study termination visit at Week 28.
j. PASI 90 responders withdrawn from treatment at Week 16 who have not met loss of response criteria prior to Week 52 and are continuing into the long-term extension of the study will receive guselkumab at Week 52 followed by q8w administration beginning at Week 60 in the long-term extension. Participants withdrawn from treatment at Week 16 who met loss of response criteria prior to Week 48 and received a guselkumab dose at Week 48 and continue into the long-term extension will receive their next administration of guselkumab at Week 60 followed by q8w thereafter. Participants who meet loss of response criteria at Week 48 will receive a weight-based dose of guselkumab at Week 48 followed by a dose at Week 52 and q8w administration starting at Week 60.
k. Vital signs include heart rate, blood pressure, and temperature.
l. Girls of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits through Week 16. After Week 16 a negative urine pregnancy test is required at all visits at which study intervention is to be administered.
m. Head circumference will be measured for participants ≥6 to <12 years of age
n. Pain experienced with each placebo or guselkumab injection will be assessed at each study visit at which an injection is administered. Pain will be assessed using the Faces Pain Scale-Revised for injection pain in children ≥6 to <12 years of age (Appendix 17 [Section 10.17]), and the linear Injection Pain Visual Analog Scale for adolescents ≥12 to <18 years of age (Appendix 18 [Section 10.18]).
o. The C-SSRS should be completed as the first assessment at screening after signing informed consent and at all post-baseline visits after the CDLQI assessment and before any other tests, procedures, or other consultations to prevent influencing participant perceptions (Section 8.2.4). There are 4 versions of the C-SSRS; a Baseline version to be completed at screening by children ≥6 to <12 years of age (Appendix 13 [Section 10.13]), a Baseline/Screening version to be completed by adolescents ≥12 years of age (Appendix 14 [Section 10.14]), a Children's Since Last Visit version to be completed at all other visits (Appendix 15 [Section 10.15]), and a Since Last Visit version for adolescents (Appendix 16 [Section 10.16]).
p. PASI, IGA, and BSA to be performed by a blinded efficacy evaluator until the Week 16 database lock is completed for all participants in Part 1 of the study.

q. Performed prior to any tests, procedures, or other consultations (PASI, IGA, BSA) for that visit.
r. The FDLQI should be completed by a participant's primary caregiver.
s. A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this study is being conducted.
t. Titers for measles, mumps, rubella, and varicella only required if adequate documentation of complete vaccination schedule or healthcare provider verification of previous infection is unavailable.
u. Serum IgG, IgM, and IgA sample should not be collected at study termination visit if a sample was collected at Week 52.
v. Laboratory tests are listed in Section 8.2.3 and Appendix 11 (Section 10.11).
w. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.12).
x. Not required if participant is randomized within 4 weeks of blood draws for chemistry and hematology at screening.
y. All blood samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. Details will be provided in the Laboratory Manual.
z. Participants randomized to etanercept will not require a blood draw for pharmacokinetics and/or immunogenicity assessments at these visits.

1.3.2. Screening Through Week 52 – Part 2

Phase	Screening[a]	Open-label treatment										
Week		0	4	8	12	16	20	28	36	44	52[b]	Study Termination Visit[c]
Study Procedures[d]												
Screening/Administrative												
Informed consent/assent[e]	X											
Medical history and demographics	X											
Inclusion/exclusion criteria	X	X										
Study Intervention Administration												
Administration[f]		X	X		X		X	X	X	X	X	
[redacted] CCI		X										
CCI [redacted]			X		X		X	X	X	X		
Safety Assessments												
Physical examination (including skin exam and Tanner staging)	X						X				X	X
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[j]	X	X	X		X		X	X	X	X	X	X
Height		X			X		X		X		X	X
Weight[k]	X	X	X		X		X	X	X	X	X	X
Head circumference[l]		X									X	X
Assessment of injection pain[m]		X	X		X		X	X	X	X	X	
C-SSRS[n]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments												
IGA[o]	X	X	X	X	X	X	X	X	X	X	X	X
PASI[o]	X	X	X	X	X	X	X	X	X	X	X	X
Body surface area (BSA)%[o]	X	X	X	X	X	X	X	X	X	X	X	X
Children's Dermatology Life Quality Index (CDLQI)[p]		X		X		X		X	X		X	X

Phase	Screening[a]	Open-label treatment										
Week		0	4	8	12	16	20	28	36	44	52[b]	Study Termination Visit[c]
Study Procedures[d]												
Family Dermatology Life Quality Index (FDLQI)[q]		X		X		X		X	X		X	X
Clinical Laboratory Assessment												
QuantiFERON-TB test[r]	X											
Hepatitis B and C serology	X											
HIV antibody test	X											
Serum measles, mumps, rubella, and varicella antibody titers[s]	X											
Serum IgG, IgM, and IgA		X				X					X	X[t]
Hematology[u]	X	X[v]		X		X		X	X	X	X	X
Chemistry[u,v]	X	X[v]		X		X		X	X	X	X	X
Pharmacokinetics and Immunogenicity[x]												
Serum guselkumab concentration		X	X		X	X	X	X	X	X		X
Antibodies to guselkumab		X	X		X			X		X		X

BSA=body surface area; C-SSRS=Columbia-Suicide Severity Rating Scale; HIV=human immunodeficiency virus; Ig=immunoglobin; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; TB=tuberculosis.

Footnotes:

a. The screening visit should occur within approximately 10 weeks before the Week 0 visit.

b. Participants who choose not to continue in the long-term extension of this study will not receive any administration of study intervention at Week 52 and will be asked to return for a study termination visit 12 weeks after their last administration of study intervention.

c. A participant who discontinues study intervention but does not terminate study participation will continue to return for protocol-specified procedures and evaluations for at least 12 weeks following the last dose of study intervention (see Section 7.1) and complete all procedures and evaluations listed under the Study Termination Visit at the final visit. If a participant discontinues study intervention and terminates study participation, the procedures and evaluations for the Study Termination Visit should be performed at the last visit (Section 7.2).

d. All study procedures and evaluations are to be completed before study intervention administration.

e. Must be signed before first study-related activity.

f. In Part 2, caregivers and participants ≥12 years of age will be given the option to self-administer study injections at the study site using the appropriate study intervention presentation (PFS-U or CCI). Participants or their caregiver will be trained on proper use of the device(s). Study staff will complete the CCI CCI , (Appendix 20 [Section 10.20]) which will be used in conjunction with study staff judgment to determine if the participant or caregiver is eligible for self- or caregiver administration for the CCI . The judgment of the study staff alone will be used to determine of the participant or caregiver is eligible for self- or caregiver administration for the PFS-U. If not eligible, injections will continue to be performed by study staff.

g. To be completed by the study staff in order to determine that the user (participant or caregiver) is able to correctly administer the injection using the CCI only.

h. To be completed by the participant or their caregiver who performs self-administration using the CCI only.

i. Vital signs include heart rate, blood pressure, and temperature.
j. Girls of childbearing potential must have a negative urine pregnancy test before randomization and at all study visits at which study intervention is to be administered.
k. Weight should be measured at all study visits at which study intervention is to be administered.
l. Head circumference will be measured for participants ≥6 to <12 years of age
m. Pain experienced with each placebo or guselkumab injection will be assessed at each study visit at which an injection is administered. Pain will be assessed using the Faces Pain Scale-Revised for injection pain in children ≥6 to <12 years of age (Appendix 17 [Section 10.17]), and the linear Injection Pain Visual Analog Scale for adolescents ≥12- to <18 years of age (Appendix 18 [Section 10.18]).
n. The C-SSRS should be completed as the first assessment at screening after signing informed consent and at all post-baseline visits after the CDLQI assessment and before any other tests, procedures, or other consultations to prevent influencing participant perceptions Section 8.2.4). There are 4 versions of the C-SSRS; a Baseline version to be completed at screening by children ≥6 to <12 years of age (Appendix 13 [Section 10.13]), a Baseline/Screening version to be completed by adolescents ≥12 years of age (Appendix 14 [Section 10.14]), a Children's Since Last Visit version to be completed at all other visits (Appendix 15 [Section 10.15]) and a Since Last Visit version for adolescents (Appendix 16 [Section 10.16]).
o. PASI, IGA, and BSA to be performed by a blinded efficacy evaluator for all participants until completion of the Week 16 database lock for all participants in Part 1 of the study.
p. Performed prior to any tests, procedures, or other consultations (PASI, IGA, BSA) for that visit.
q. The FDLQI should be completed by a participant's primary caregiver.
r. A tuberculin skin test is additionally required if the QuantiFERON-TB test is not approved/registered in the country in which this study is being conducted.
s. Titers for measles, mumps, rubella, and varicella only required if adequate documentation of complete vaccination schedule or healthcare provider verification of previous infection is unavailable.
t. Serum IgG, IgM, and IgA sample should not be collected at study termination visit if a sample was collected at Week 52.
u. Laboratory tests are listed in Section 8.2.3 and Appendix 11 (Section 10.11).
v. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.2).
w. Not required if participant is randomized within 4 weeks of blood draws for chemistry and hematology at screening.
x. All blood samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. Details will be provided in the Laboratory Manual.

1.3.3. Long-term Extension Phase (Week 60 Through Study Completion/Termination)

Phase	Long-term Extension				Study Completion/Termination Visit[c]
	Week 60	q8w visit	q24w visit[a]	q48w visit[b]	
Study Procedures[d]					
Study Intervention Administration					
Administration[e]	X	X	X	X	
Safety Assessments					
Physical examination (including skin exam)				X	X
Vital signs[f]	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X
Urine pregnancy test[g]	X	X	X	X	X
Height				X	X
Weight	X	X	X	X	X
C-SSRS[h]	X	X	X	X	X
Concomitant therapy	X	X	X	X	X
Adverse events	X	X	X	X	X
Efficacy Assessments					
IGA[i]	X		X	X	X
PASI[i]	X		X	X	X
Body surface area (BSA)%[i]	X		X	X	X
Clinical Laboratory Assessment					
Hematology[j]	X		X	X	X
Chemistry[j,k]	X		X	X	X
Pharmacokinetics and Immunogenicity					
Serum guselkumab concentration					X
Antibodies to guselkumab					X

BSA=body surface area; C-SSRS=Columbia-Suicide Severity Rating Scale; IGA=Investigator's Global Assessment; LTE=long-term extension; PASI=Psoriasis Area and Severity Index.

Footnotes:

a. Procedures listed in this column should be completed every 24 weeks in addition to those procedures noted for the q8w visit.
b. Procedures listed in this column should be completed every 48 weeks in addition to those procedures noted for the q8w and q24 visits.
c. Study completion/termination visit procedures should be performed 12 weeks after a participant receives their final administration of study intervention.
d. All study procedures and evaluations are to be completed before study intervention administration.
e. Participants (or their caregiver) enrolled in Part 2 of the main study who were self-administering study intervention at the study site may continue self-administration in the LTE. Participants will be able to begin self-administration in the LTE after participants or their caregiver have been trained on proper use of the device(s).
f. Vital signs include heart rate, blood pressure, and temperature.
g. Girls of childbearing potential must have a negative urine pregnancy test before study intervention administration.
h. The C-SSRS should be completed as the first assessment before any other tests, procedures, or other consultations to prevent influencing participant perceptions.
i. PASI, IGA, and BSA to be performed by a blinded efficacy evaluator for all participants until completion of the Week 16 database lock for all participants in Part 1 of the study.
j. Laboratory tests are listed in Section 8.2.3 and Appendix 11 (Section 10.11).

k. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.12).

2. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin (Ig) G1 lambda (G1λ) monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab has been approved in the United States of America (USA), the European Union (EU) and Canada for the treatment of adult patients with moderate to severe plaque and Marketing Authorization Applications (MAA) are currently under review in other regions. Data supporting the approval of the plaque psoriasis indication in adults included safety and efficacy data from 2,700 participants from 3 global Phase 3 studies (CNTO1959PSO3001 [VOYAGE 1], CNTO1959PSO3002 [VOYAGE 2], and CNTO1959PSO3003 [NAVIGATE]). Studies CNTO1959PSO3001 and CNTO1959PSO3002 have ongoing long-term extensions (LTE).

The approved dosage in the adult plaque psoriasis indication is 100 mg administered by SC injection at Week 0, Week 4, and every 8 weeks (q8w) thereafter. Guselkumab is not currently approved for use in pediatric patients in any country.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) for guselkumab.

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.

2.1. Study Rationale

This study will evaluate the efficacy and safety of guselkumab for the treatment of chronic plaque psoriasis in pediatric participants aged ≥6 through <18 years using a placebo control and an active comparator (ENBREL® [etanercept]) through Week 16 by means of:

- comparison of guselkumab to placebo to establish the efficacy of guselkumab.
- utilization of etanercept as a benchmark for efficacy.
- collection of safety and tolerability data for guselkumab in the pediatric plaque psoriasis population.

This study will also provide an evaluation of safety and the ability to recapture response with retreatment following withdrawal from guselkumab.

In addition, the pharmacokinetics (PK) of guselkumab will be evaluated in this study to determine whether the proposed weight-based dose in children with plaque psoriasis achieves PK exposure comparable to that established in adults with the approved dose regimen. Furthermore, evaluations will be done to assess whether, with comparable exposure, the observed clinical response in pediatric participants treated with guselkumab is consistent with that observed in adults.

2.2. Background

Plaque psoriasis is a chronic, immunologically-mediated, inflammatory skin disease of unknown etiology affecting 2% to 4% of the general population.[14,17,22,24,26,28] The pathogenesis of plaque psoriasis involves environmental factors and immune dysregulation in genetically-predisposed individuals.[10,19] Substantial evidence indicates that IL-23 plays an important role in innate and adaptive immune responses, and may play a pivotal role in the pathogenesis of psoriasis vulgaris.[1,15,34]

Adult and pediatric plaque psoriasis share similar clinical manifestations, histological features, genetic factors, and treatment options.[6] Taken together, the data demonstrate that a complex network of immune mediators (cells and cytokines) drive the inflammatory skin processes of plaque psoriasis in adults and children.

Plaque psoriasis is characterized by symmetrically distributed, well-defined, sharply demarcated, indurated, erythematous plaques that are covered by friable, dry, white-silvery scale and is reported to account for up to 84% of psoriasis in pediatric patients.[5,21,29] Areas of the body that are frequently involved include the scalp, elbows, knees, buttocks, and genitalia. Definitions of plaque psoriasis severity differ depending on the source, but are generally related to the extent of the body surface involved, although the extent of exposed skin involved is also often considered.

Studies addressing the age of onset of psoriasis have suggested that 2 subgroups exist: early onset disease (before 30 years of age, including pediatric onset) and late onset disease (after age 30).[8] Generally, the clinical manifestations of plaque psoriasis in patients with pediatric onset and those with adult or late onset disease are similar, and not clinically distinguishable.[21,29] Therefore, the consensus of the literature is essentially that plaque psoriasis is a life-long chronic disease with a variable age of onset, and that pediatric plaque psoriasis is probably most accurately characterized as early onset disease rather than as an entity distinct from adult plaque psoriasis.

The traditional paradigm for the treatment of plaque psoriasis follows a stepwise approach to treatment starting with topical agents, followed by phototherapy, and then systemic agents.[5,7] Recently, several biologic psoriasis treatments have been approved for use in patients with pediatric plaque psoriasis. Currently, etanercept (ENBREL®), adalimumab (HUMIRA®) and ustekinumab (STELARA®) are approved for various pediatric age groups in some jurisdictions. Among these biologics, etanercept is currently approved in a broad pediatric age range and the largest number of geographic regions.

Although stepwise therapy is mentioned frequently in the literature, the optimal treatment approach for pediatric patients with chronic plaque psoriasis is far less clear than for adults due to the practical scheduling issues of phototherapy in school aged children, the known, often cumulative, toxicities of traditional systemic therapies and the paucity of rigorous clinical data or approved therapeutic options for this age group. For these reasons, a proportion of pediatric patients with plaque psoriasis are currently undertreated, and could benefit from additional safe, effective, and convenient therapies. Based on currently available data, guselkumab could offer efficacy, safety and convenience advantages compared with available therapies.

2.2.1. Clinical Studies

The clinical development program to support use of guselkumab in the treatment of moderate to severe plaque-type psoriasis included two Phase 1 studies (CNTO1959PSO1001, CNTO1959PSO1002), one Phase 2 study (CNTO1959PSO2001), and three Phase 3 global studies (CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003). The two Phase 1 studies and the Phase 2 study have been completed and formed the basis to proceed to Phase 3. Details about these 3 individual studies are provided in the IB. The Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002 were both conducted using placebo and an active comparator, adalimumab (HUMIRA®). In these studies, guselkumab demonstrated superior efficacy to both placebo and adalimumab. Results for studies CNTO1959PSO3001 and CNTO1959PSO3002 are most relevant to the design of the pediatric studies and are presented below. Study CNTO1959PSO3003 evaluated efficacy and safety in participants who were inadequate responders to 16 weeks of treatment with ustekinumab and results for this study are presented in the guselkumab IB.

Phase 3 Study (CNTO1959PSO3001, VOYAGE 1)

Study CNTO1959PSO3001 (VOYAGE 1) is a multicenter, Phase 3, randomized, double-blind, placebo- and active-comparator-controlled study in participants with moderate to severe plaque-type psoriasis with 3 parallel treatment groups: placebo, guselkumab 100 mg, and adalimumab. In this study, 837 adult participants were randomized to receive guselkumab (n=329) or adalimumab (n=334) or placebo (n=174). Participants in the placebo group crossed over to guselkumab 100 mg beginning at Week 16.

At Week 16, a significantly greater proportion of participants randomized to guselkumab achieved the co-primary endpoints of an Investigator's Global Assessment (IGA) score of cleared (0) or minimal (1) and Psoriasis Area and Severity Index (PASI) 90 response (85.1% and 73.3%, respectively; $p<0.001$ for both endpoints) compared with placebo (6.9% and 2.9%, respectively). At Week 24, a significantly higher proportion of participants achieved an IGA score of cleared (0), an IGA score of cleared (0) or minimal (1), and a PASI 90 response in the guselkumab group than in the adalimumab group. Similar to the observations at Week 24, a significantly higher proportion of participants achieved an IGA score of cleared (0), an IGA score of cleared (0) or minimal (1), and a PASI 90 response in the guselkumab group than in the adalimumab group at Week 48.

Treatment with guselkumab was well-tolerated through Week 48. The frequency of adverse events (AE) was comparable between the guselkumab, placebo, and adalimumab groups through Week 16 and between the guselkumab and adalimumab groups through Week 48. The most common AEs were nasopharyngitis and upper respiratory tract infection. Through Week 16, the percentage of participants with 1 or more serious adverse events (SAEs) was 1.7% (n=3) in the placebo group, 2.4% (n=8) in the guselkumab group and 1.8% (n=6) in the adalimumab group, and was comparable between the guselkumab (4.9% [n=16]) and adalimumab (4.5% [n=15]) groups through Week 48. The incidence of infections was comparable between placebo, guselkumab and adalimumab groups through Week 16, and between the guselkumab group (52.3%) and the adalimumab group (50.2%) through Week 48. No opportunistic infections or active tuberculosis (TB) were reported. No anaphylactic or serum sickness-like reactions were

reported in the guselkumab group, and the incidence of injection site reactions was lower in the guselkumab group than the adalimumab group.

Phase 3 Study (CNTO1959PSO3002, VOYAGE 2)

Study CNTO1959PSO3002 (VOYAGE 2) is a multicenter, Phase 3, randomized, double-blind, placebo- and active-comparator-controlled study in participants with moderate to severe plaque-type psoriasis with 3 treatment groups: placebo, guselkumab 100 mg, and adalimumab. In this study, 992 adult participants were randomized to either the placebo (n=248), guselkumab (n=496), or adalimumab (n=248) treatment groups at Week 0. Participants in the placebo group crossed over to guselkumab 100 mg beginning at Week 16. This study evaluated the benefit of maintenance therapy using a randomized withdrawal design starting at Week 28.

At Week 16, a significantly greater proportion of participants randomized to guselkumab achieved the co-primary endpoints of an IGA score of cleared (0) or minimal (1) and a PASI 90 response (84.1% and 70.0%, respectively; $p<0.001$ for both endpoints) compared with placebo (8.5% and 2.4%, respectively). In addition, a significantly greater proportion of participants achieved an IGA score of cleared (0), an IGA score of cleared (0) or minimal (1), and a PASI 90 response in the guselkumab group than in the adalimumab group at Week 24.

Treatment with guselkumab was well tolerated. Through Week 16, the proportion of participants experiencing 1 or more AEs was comparable between treatment groups. Nasopharyngitis and upper respiratory tract infection were the most common AEs. The percentage of participants with 1 or more SAEs was comparable between the placebo and guselkumab groups, and slightly higher in the adalimumab group. The incidence of infections was comparable between placebo, guselkumab, and adalimumab groups through Week 16. Through Week 28, the proportion of participants experiencing 1 or more AEs was comparable between the guselkumab and adalimumab groups. Two adalimumab-treated participants reported active TB. No opportunistic infections were reported. No anaphylactic or serum sickness-like reactions were reported and the incidence of injection site reactions was lower in the guselkumab group than the adalimumab group.

2.2.2. Comparator

ENBREL® (etanercept)

Etanercept (ENBREL®) is a dimeric fusion protein genetically engineered by fusing the extracellular ligand binding domain of human tumor necrosis factor (TNF) receptor-2 (TNFR2/p75) to the Fc domain of the human immunoglobulin G1 (IgG1). Etanercept binds specifically to TNF and blocks its interaction with cell surface TNF receptors.

Etanercept was selected as the active comparator because it has demonstrated efficacy in pediatric patients with moderate to severe plaque psoriasis and serves as a useful efficacy benchmark.[25] Etanercept has been approved for treatment of moderate to severe plaque psoriasis in the pediatric population in the United States of America, and severe plaque psoriasis in Canada, the European Union, and the Asia-Pacific region. Pediatric participants randomized to etanercept will receive a

weekly dose of 0.8 mg/kg body weight (up to a maximum of 50 mg/dose) administered subcutaneously as per the approved label.

For further information regarding etanercept, refer to the product labeling applicable to the local country in which the study is being conducted.

2.3. Benefit/Risk Assessment

2.3.1. Guselkumab

A large global Phase 3 program consisting of 3 studies (CNT1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003) has been conducted to investigate the efficacy and safety of SC guselkumab in participants with moderate to severe plaque psoriasis (Section 2.2), and the longer-term efficacy and safety of guselkumab is being assessed in 4-year extensions of studies CNTO1959PSO3001 and CNTO1959PSO3002 (ie, both studies will have an overall study duration of 5 years).

The data through Week 48 from these studies demonstrate high levels of efficacy for guselkumab 100 mg administered SC at Weeks 0, 4, and q8w thereafter. Guselkumab treatment led to an onset of clinical responses as early as 2 weeks after initiating treatment. Significant improvements were observed within 16 weeks of treatment that were maintained through 1 year, as assessed by IGA scores, PASI response, regional measures of psoriasis and patient-reported outcome (PRO) measures such as the DLQI and Psoriasis Symptom and Sign Diary (PSSD). Benefits were demonstrated across all subpopulations representing the full spectrum of moderate to severe plaque psoriasis.

Guselkumab was well-tolerated. Rates of AEs, SAEs, and discontinuations due to AEs, among participants who received guselkumab were comparable to those reported for the placebo group through Week 16, or for the adalimumab group through 48 weeks of treatment. Events identified as possible adverse drug reactions (IB, Section 5) were generally mild, nonserious events that did not require treatment discontinuation. Rates of serious infections, MACE, malignancies, and SIB were low, not demonstrably different between treatment groups, and appeared to be generally consistent with rates expected in the psoriasis population. The rate of development of antibodies to guselkumab was low and did not appear to impact response rates or the frequency of injection-site reactions. Overall, the safety profile for guselkumab was similar to that for placebo through 16 weeks of treatment and comparable with adalimumab through 48 weeks of treatment.

In conclusion, the Phase 3 psoriasis data in adults demonstrate a favorable benefit:risk profile for guselkumab when administered subcutaneously as a 100 mg dose at Weeks 0, 4, and q8w thereafter in participants with moderate to severe plaque psoriasis who are candidates for systemic therapy, and support evaluation of guselkumab in pediatric patients with chronic plaque psoriasis.

More detailed information about the known and expected benefits and risks of guselkumab can be found in the guselkumab IB.

2.3.2. Etanercept

The benefit:risk profile of etanercept in pediatric participants as young as 4 years of age was established in a Phase 3 study,[25] which was the basis of global approvals for etanercept in the treatment of psoriasis in the pediatric population. More detailed information about the known and expected benefits and risks of etanercept can be found in the etanercept product labeling.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the PK and immunogenicity of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate the effect of guselkumab on the dermatologic health-related quality of life in pediatric participants aged ≥6 through <18 years with chronic plaque psoriasis.
- To evaluate maintenance of response in participants who have active treatment withdrawn.
- To evaluate the efficacy and safety of retreatment with guselkumab.
- To generate clinical usability data and use experience with the CCI in pediatric participants with chronic plaque psoriasis and a body weight <70 kg.

ENDPOINTS

The co-primary and major secondary endpoints for Part 1 of the study, with the primary comparisons between the guselkumab and placebo groups, include:

Co-primary Endpoints

- The proportion of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16.
- The proportion of participants with a PASI 75 response at Week 16.

Major Secondary Endpoints

- The proportion of participants achieving a PASI 90 response at Week 16.
- The proportion of participants achieving an IGA score of cleared (0) at Week 16.
- The proportion of participants achieving a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16.

Other Secondary Endpoints

Secondary endpoints for Part 1 of the study include:

- The proportion of retreated participants that achieve a PASI 90 response over time after retreatment.
- The proportion of retreated participants that achieve PASI responses (PASI 50, 75, 90, and 100) or IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) over time after retreatment.
- The time to loss of 50% of the Week 16 PASI improvement (ie, time to retreatment) after withdrawal.
- The time to loss of PASI 90 response after withdrawal.
- The proportion of participants achieving a PASI 50 response at Week 16.
- The proportion of participants who achieve an IGA score of mild or better (≤2) at Week 16.
- The percent improvement from baseline in PASI over time through Week 16.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) over time through Week 16.
- The proportion of IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) over time through Week 16.
- The proportion of participants with CDLQI=0 or 1 at Week 16 among randomized participants with a baseline CDLQI>1
- The proportion of participants with Family Dermatology Life Quality Index (FDLQI)=0 or 1 at Week 16 among randomized participants with a baseline FDLQI>1
- The change from baseline in FDLQI at Week 16.

For Part 2 of the study, PASI responses, IGA responses, PASI percent improvement, change from baseline in CDLQI and FDLQI, the proportion of participants achieving a CDLQI of 0 or 1, and the proportion of participants achieving a FDLQI of 0 or 1 will be summarized over time through Week 52.

In addition, efficacy in the LTE period for participants who continue in the LTE of the study will be summarized.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis is that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) or minimal (1) and the proportion of participants achieving a PASI 75 response at Week 16.

The major secondary hypotheses are that guselkumab treatment is:

- superior to placebo as assessed by the proportion of participants achieving a PASI 90 response at Week 16.

- superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) at Week 16.
- superior to placebo as assessed by the proportion of participants achieving a PASI 100 response at Week 16.
- superior to placebo in improving the dermatologic health-related quality of life in pediatric participants as assessed by the change from baseline in CDLQI at Week 16.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, placebo- and active comparator-controlled study evaluating the efficacy, safety, and PK of subcutaneously administered guselkumab for the treatment of chronic plaque psoriasis in pediatric participants ≥6 to <18 years of age. The participant population will be comprised of boys and girls who have had a diagnosis of chronic plaque-type psoriasis, defined as having an IGA ≥3, a PASI ≥12, a ≥10% BSA involvement, and at least one of the following: very thick lesions, clinically relevant facial, genital, or hand/ foot involvement, PASI≥20, >20% BSA involvement, or IGA=4. Participants must also be a candidate for phototherapy or systemic treatment of plaque psoriasis and have plaque psoriasis considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy.

The main study will be conducted in 2 parts. In Part 1, the efficacy, safety, and PK of guselkumab will be evaluated in pediatric participants during a 16-week randomized, placebo- and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52.

Part 1 of the study will be divided into Part 1a (≥12 to <18 years of age [ie, adolescents]) and Part 1b (≥6 to <12 years of age) and enroll a minimum of 90 participants. Part 1a will enroll at least 60 participants randomized in a 2:1:1 ratio to guselkumab (n=30), placebo (n=15), and etanercept (n=15). Part 1b will enroll at least 30 participants randomized in a 1:1:1 ratio to guselkumab (n=10), placebo (n=10), and etanercept (n=10). Enrollment of participants ≥6 to <12 years of age in Part 1b will commence only after:

1) All participants ≥12 to <18 years of age in Part 1a will have completed Week 16, and all available safety data have been reviewed by an independent Data Monitoring Committee (DMC), with no important safety concerns identified.

2) All available guselkumab PK data for the ≥12 to <18-year-old participants through Week 16 have been evaluated to determine if the body weight-based dose used in Part 1a has provided systemic exposure comparable to adults, or whether a revised body weight-based dose should be instituted in Part 1b.

Participants randomized to guselkumab or placebo will receive a weight-based dose of study intervention at Weeks 0, 4, and 12. Participants randomized to etanercept will receive a weight-based etanercept dose up to 50 mg SC weekly through Week 15. Participants randomized

to etanercept will be given the option to self-administer or have their caregiver administer at home or have the study intervention administered at the study site.

At Week 16:

- Participants initially randomized to guselkumab will be treated as follows:
  - PASI 90 responders at Week 16 will not receive any additional doses of guselkumab until they lose ≥50% of their Week 16 PASI response, at which time they will be retreated with guselkumab followed by a dose 4 weeks later, and then guselkumab q8w thereafter through Week 52.
  - PASI 90 nonresponders at Week 16 will receive a placebo injection at Week 16 to maintain the blind and continue treatment with guselkumab q8w from Week 20 through Week 52.
- Participants initially randomized to placebo will be treated as follows:
  - PASI 90 responders at Week 16 will not receive any additional doses of study intervention until they lose ≥50% of their Week 16 PASI response, at which time they will initiate treatment with guselkumab SC followed by a dose 4 weeks later, and q8w thereafter through Week 52.
  - PASI 90 nonresponders will initiate treatment with guselkumab at Weeks 16 and 20, and q8w thereafter through Week 52.
- Participants initially randomized to etanercept will receive their last administration of etanercept at Week 15. Irrespective of PASI response at Week 16, participants or their legally acceptable representative will be given the option, in consultation with the investigator, to initiate treatment with guselkumab at Week 20 followed by a dose 4 weeks later, and then q8w thereafter through Week 48, **or** discontinue from study intervention administration. This option allows for participants receiving etanercept who have not attained an adequate level of efficacy or have poor tolerance for weekly injections to switch to guselkumab.

Part 2 of the main study will be an open-label, single-arm study to collect additional efficacy, safety, and PK data for pediatric participants with a continuous weight-based dose regimen of guselkumab at Weeks 0, 4, and q8w thereafter through Week 52. Participants ≥12 to <18 years of age will begin enrollment in Part 2 after the reviews of safety and PK data through Week 16 for all participants ≥12 to <18 years of age in Part 1a have been completed, and an appropriate body weight-based dose that matches adult exposure has been confirmed, or a revised body weight-based dose has been determined. Enrollment of participants ≥6 to <12 years of age into Part 2 will not occur until all participants in Part 1b have completed 16 weeks of treatment and all efficacy data through Week 16 from Part 1 have been evaluated by the sponsor, and all available safety data have been reviewed by an independent DMC. Part 2 will enroll enough additional participants to achieve a total of at least 100 participants exposed to guselkumab (ie, at least 10 participants in Part 2, with the total number dependent on the number of participants randomized in Part 1 who are exposed to guselkumab).

In Part 2 of the main study, participants will be given the option to self-administer or have their caregiver administer study injections at the study site using the appropriate presentation (either a

prefilled syringe (PFS) assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) device, designed to deliver a single, fixed dose of CCI [redacted] Participants must be at least 12 years of age to self-administer study injections. Participants or their caregivers will be trained on proper use of the device(s) and deemed capable, as determined by study staff. Otherwise injections will continue to be performed by study staff.

All participants who complete either Part 1 or Part 2 of the main study through Week 52 will be offered the opportunity to participate in an open-label LTE. Participants will be required to return to the study site every 8 weeks for safety and efficacy assessments in addition to study intervention administration. Additional details on the LTE can be found in Section 8.

Efficacy assessments (IGA, PASI, BSA, CDLQI, and FDLQI) will be performed according to the Schedules of Activities. Serum samples for PK and immunogenicity analyses will be collected at the timepoints shown in the Schedules of Activities.

Rescue Treatment

In Part 1 of the study, participants with a PASI score increase of ≥50% from their baseline PASI score at Week 8 or Week 12 will be allowed to use a topical steroid as rescue treatment, with the exception of ultra-high potency topical steroids (eg, clobetasol propionate, halobetasol propionate) which are not allowed at any time. It is recommended that participants use no more than 60 grams of topical steroids per week. In addition, participants should be managed using the lowest possible potency and frequency of rescue topical steroid. Participants must discontinue the use of rescue topical steroids by Week 20 (should not initiate rescue topical steroids at or after Week 16).

Safety and tolerability will be assessed by monitoring AEs, SAEs, clinical laboratory tests, vital signs, physical examinations, growth, development and sexual maturity, concomitant medication review, injection site evaluations, collection of Columbia-Suicide Severity Rating Scale (C-SSRS) data, measurement of serum immunoglobulins, observations for allergic reactions, immunogenicity, and assessments for early detection of TB.

An independent DMC will be commissioned for this study. Refer to Committees Structure in Appendix 2 (Section 10.2), Regulatory, Ethical, and Study Oversight Considerations for details.

An interim analysis of the PK data will occur when all participants in Part 1a of the study complete their Week 16 visit (Section 9.5, Interim Analysis). All available guselkumab PK data for participants ≥12 to <18 years of age through Week 16 will be evaluated via modeling and simulation, to determine if the body weight-based dose used in Part 1a provided exposure comparable with the exposure observed in adults, or whether a revised body weight-based dose should be instituted in Part 1b and Part 2 of the study.

There are 3 database locks (DBL) planned for this study at Week 16, Week 52 (end of the main study), and at the end of the study. The Week 16 DBL will occur after all participants in Part 1 of the study complete their Week 16 visit and will include only data from Part 1. The sponsor will be

unblinded for Part 1 after the Week 16 DBL for Part 1 has occurred. The Week 52 DBL will occur after all participants in both Part 1 and Part 2 of the study complete their Week 52 visit. The investigators, participants, and site monitors can be unblinded after the Week 52 DBL has occurred. Additional database locks may be performed if deemed necessary.

The end of the main study is defined as the timepoint when the last participant completes the Week 52 visit. The end of the complete study is defined as the timepoint when the last participant completes the last follow-up visit after guselkumab receives regulatory approval for use in pediatric patients or the sponsor discontinues development of guselkumab for the treatment of plaque psoriasis in pediatric patients.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

The screening phase of up to 10 weeks will allow for sufficient time to perform screening study evaluations, determine study eligibility, and allows time for immunization of participants requiring them for eligibility. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. In addition to placebo control, an active control will be used to determine the sensitivity of the clinical endpoints in this study. Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. In Part 1, treatment for participants randomized to guselkumab or placebo will be blinded through Week 16 and since etanercept will be open-label, a blinded efficacy evaluator will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Participants in Part 1 randomized to guselkumab or placebo who are PASI 90 responders at Week 16 will be withdrawn from treatment. Upon loss of ≥50% of the improvement in PASI achieved at Week 16, participants will receive guselkumab SC, followed by a dose 4 weeks later, and then guselkumab q8w thereafter through Week 52.

Open label treatment with guselkumab in Part 2 will continue through Week 52 (last guselkumab injection at Week 44) and will provide adequate time to demonstrate the efficacy and safety of guselkumab as maintenance therapy for pediatric plaque psoriasis.

Participants who continue with the LTE will receive a weight-based guselkumab SC dose q8w until they have reached 18 years of age and reside in a country where guselkumab is approved for treatment of plaque psoriasis in adults and have had the opportunity to complete up to 1 year in the LTE, marketing authorization is obtained for guselkumab for treatment of plaque psoriasis for patients ≥6 to <18 years of age, marketing authorization is denied for guselkumab for the treatment of plaque psoriasis in pediatric patients, or the company decides to no longer pursue an indication in plaque psoriasis in the pediatric population.

Efficacy Evaluations

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

Patient-reported outcomes (PROs) chosen for this study are consistent with clinically relevant measurements that have been described in the medical literature for other studies in pediatric plaque psoriasis. Health-related quality of life impairment in dermatologic diseases like plaque psoriasis has been shown to be as, or even more, burdensome than other chronic diseases like diabetes and asthma in the pediatric population.[4] Skin disease in the pediatric population specifically impacts physical, social, and emotional health with the potential for negatively affecting school functioning.[32] Effective treatment of plaque psoriasis may allow for improvements in physical, social, emotional, and school functioning and overall health. Data collected directly from the participant can best capture these concepts.

Psoriasis response evaluations include:

- Investigator's Global Assessment (IGA)
- Psoriasis Area and Severity Index (PASI)
- Percent of body surface area with psoriasis skin involvement (BSA)
- Children's Dermatology Life Quality Index (CDLQI)
- Family Dermatology Life Quality Index (FDLQI)

To help improve objectivity, given the open-label active-comparator study design, clinical efficacy assessments (IGA, PASI, and BSA) will be performed by blinded efficacy evaluators until all participants in Part 1 of the study complete their Week 16 visit and the Week 16 database lock is complete.

Pharmacokinetic Evaluations

To assess the PK of guselkumab in pediatric participants ≥6 and <18 years of age with plaque psoriasis and to evaluate the similarity in exposure-response relationship between pediatric participants and adult participants, 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 guselkumab will be further characterized to determine if antibodies to guselkumab could neutralize the biological effects of guselkumab in vitro (ie, neutralizing antibodies [NAbs] to guselkumab).

4.2.1. Study-Specific Ethical Design Considerations

Potential participants (and their caregivers) will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the informed consent form (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 participant, his or her parent(s) (preferably both parents, if available) or 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 participants 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to participants who have provided consent (and assent as applicable) refers to the participants and his or her parent(s) or the participant'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 parent(s) still want them to participate.

The total blood volume to be collected is considered to be within the normal range allowed for the pediatric population.

4.3. Justification for Dose

In the guselkumab Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002 in adult participants with moderate to severe plaque psoriasis, the dose and dosing regimen of guselkumab CCI SC at Weeks 0, 4, and q8w thereafter, produced high levels of efficacy and a favorable benefit:risk profile across the entire adult study population. In addition, an association between systemic exposure to guselkumab and clinical responses (IGA and PASI) was observed. Since adult and pediatric plaque psoriasis share similar clinical manifestations, histological features, genetic factors, and treatment options, it is reasonable to assume that pediatric participants who attain similar systemic exposure to guselkumab will likely exhibit similar clinical responses as observed in the adult population. Therefore, the goal for selection of the dose and dosing regimen in the proposed guselkumab pediatric plaque psoriasis study was to achieve exposure in the pediatric population similar to the exposure attained in the adult plaque psoriasis study population.

CCI [redacted]. Therefore, dose selection for this pediatric study was based on body weight only, typical for systemic therapeutic biologics administered in pediatric patients.[16,18,25]

Pharmacokinetic simulations were performed to select an appropriate dose for pediatric participants that would achieve similar systemic exposure to guselkumab as seen in the adult Phase 3 studies. The results from these simulations suggested that the dose regimen of guselkumab CCI SC at Week 0, 4, and q8w thereafter, which has been approved for use in adults with moderate to severe plaque psoriasis, would achieve a guselkumab exposure in pediatric participants with body weight ≥70 kg similar to that achieved in adult participants. For pediatric participants with a body weight <70 kg, several weight-based dose regimens (in mg/kg) were simulated to identify the regimen that would achieve consistent guselkumab exposures across age groups and weight ranges in the pediatric population. The results from these simulations suggested that a dose regimen of guselkumabCCI at Weeks 0, 4, and q8w thereafter in pediatric participants weighing <70 kg would achieve an exposure comparable to that observed for adult participants.

In summary, the proposed weight-based dose regimen selected for the Phase 3 plaque psoriasis study in pediatric (≥6 to <18 years of age) participants is expected to achieve a guselkumab exposure comparable to that established in the adult plaque psoriasis Phase 3 studies.

4.4. End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the Schedule of Activities for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement. The end of the complete study is defined as the timepoint when the last participant completes the last follow-up visit after guselkumab receives regulatory approval for use in pediatric patients or the sponsor discontinues development of guselkumab for the treatment of plaque psoriasis in pediatric patients.

The end of the main study is defined as the timepoint when the last participant completes the Week 52 visit.

5. STUDY POPULATION

Screening for eligible participants will be performed within 10 weeks prior to administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

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

5.1. Inclusion Criteria

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

1. Participant must be a boy or girl ≥6 to <18 years of age.

2. Have a diagnosis of chronic plaque-type psoriasis for at least 6 months (with or without PsA), prior to first administration of study intervention, defined as having at screening and baseline:

   - IGA ≥3 **and**
   - PASI ≥12 **and**
   - ≥10% BSA involvement **and**

   at **least one** of the following:

     - very thick lesions **or**
     - clinically relevant facial, genital, or hand/ foot involvement **or**
     - PASI≥20 **or**
     - >20% BSA involvement **or**
     - IGA=4

3. Be a candidate for phototherapy or systemic treatment of plaque psoriasis (either naive or history of previous treatment).

4. Have plaque psoriasis considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy.

5. Be considered, in the opinion of the investigator, a suitable candidate for etanercept (ENBREL) therapy according to their country's approved ENBREL product labeling.

6. Be otherwise healthy on the basis of physical examination, medical history, and vital signs performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

7. Contraceptive use by boys or girls should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

   Before randomization, a girl must be either:

   Not of childbearing potential defined as:

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

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

   or otherwise be incapable of pregnancy.

   Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose - the end of relevant systemic exposure. Examples of highly effective methods of contraception are in Appendix 3 (Section 10.3); however, the method selected must meet local/regional regulations/guidelines for highly effective contraception

   Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

   Note: If the childbearing potential changes after start of the study (eg, a premenarchal girl experiences menarche) or the risk of pregnancy changes (eg, a girl who is not heterosexually active becomes active), a girl must begin a highly effective method of contraception, as described above and in Appendix 3 (Section 10.3).

   If reproductive status is questionable, additional evaluation should be considered

8. A girl must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 12 weeks following the last dose of study intervention.

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

10. A boy who is sexually active with a female of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of study intervention. All boys must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention.

11. Criterion modified per Amendment 4.

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

- Have no history of latent or active TB before 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 before the first administration of study intervention, have a negative QuantiFERON®-TB test result (Appendix 5 [Section 10.5]). Within 10 weeks before the first administration of study intervention, a negative tuberculin skin test (Appendix 5 [Section 10.5]) is additionally required if the QuantiFERON-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

Indeterminate or suspected false-positive QuantiFERON®-TB test results should be handled as outlined in Section 8.

12. Must have acceptable evidence of immunity to measles, mumps, rubella, and varicella, which includes any one of the following:

a. Documentation of age-appropriate vaccination for measles, mumps, rubella, and varicella that includes both doses of each vaccine (unless local guidelines specify otherwise).

OR

b. Documentation of past measles, mumps, rubella, and varicella infection by a healthcare provider.

OR

c. In the absence of (a) or (b) above, must have positive protective antibody titers to measles, mumps, rubella, and varicella prior to the first administration of study intervention.

For participants who have not completed the recommended vaccination schedule for varicella and measles, mumps, and rubella (MMR), and the subsequent vaccination falls within the next 4 years, an accelerated vaccination schedule must be completed prior to

study enrollment if available and required or strongly recommended for the location. If varicella or MMR vaccines are utilized, it is necessary for 2 weeks to elapse between the vaccination and receipt of study intervention.

13. Must agree not to receive a live virus or live bacterial vaccination at least 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of study intervention (except for varicella and MMR vaccines), during the study, or within 3 months after the last administration of study intervention.

14. 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 intervention.

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

16. Must have screening laboratory test results within the following parameters:

- Hemoglobin ≥10 g/dL (SI: ≥100 g/L; 6 to 11 years of age)
  ≥12 g/dL (SI: ≥120 g/L; ≥12 years of age)
- White blood cells ≥3.0 x 10^3 cells/µL (SI: ≥3.0 x 10^9 cells/L; 6 to 11 years of age)
  ≥4.5 x 10^3 cells/µL (SI: ≥4.5 x 10^9 cells/L; ≥12 years of age)
- 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)
  <1.5 mg/dL (SI: <133 µmol/L; >12 years of age)
- Aspartate aminotransferase (AST) ≤72 IU/L (6 to 11 years of age)
  <1.5 x ULN for the laboratory conducting the test (≥12 years of age)
- Alanine aminotransferase (ALT) ≤54 IU/L (6 to <18 years of age)

If one or more of the above laboratory parameters is out of range, a single retest of laboratory values is permitted.

17. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

18. Must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to

participate in the study. Parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study, as per local requirements. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Informed Consent Process in Appendix 2 (Section 10.2), Regulatory, Ethical, and Study Oversight Considerations.

5.2. Exclusion Criteria

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

Medical history-related exclusion criteria

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

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

3. Is pregnant, nursing, or planning a pregnancy or fathering a child while enrolled in the study or within 12 weeks after receiving the last administration of study intervention.

4. Has a history of or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.

5. Has a transplanted organ (with exception of a corneal transplant > 3 months prior to the first administration of study intervention).

6. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or will not have fully recovered from such surgery, or has such surgery planned during the time the participant is expected to participate in the study.

   Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

7. Has unstable suicidal ideation or suicidal behavior:

   - Participants ≥12 to <18 years of age may not be randomized if they have:
     - a C-SSRS rating at screening of: suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or non-suicidal self-injurious behavior ***within the past 6 months***, OR

- a C-SSRS rating at screening of suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) ever (***lifetime***)

- Participants ≥6 to <12 years of age may not be randomized if they have:
  - a C-SSRS rating at screening of: suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), or suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) or any self-injurious behavior ever (***lifetime***)

- Participants with a C-SSRS rating at screening of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), or Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3") may not be randomized if:
  - ***participants ≥12 to <18 years of age*** have one of the above C-SSRS ratings ***within the past 6 months*** and are determined to be at risk by the investigator after being discussed with the medical monitor or designee.
  - ***participants ≥6 to <12 years of age*** have one of the above C-SSRS ratings ever (***lifetime***) and are determined to be at risk by the investigator after being discussed with the medical monitor or designee.

8. Is known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.

Medical therapies-related exclusion criteria

9. Has previously received guselkumab or etanercept.

10. Has any contraindications to the use of etanercept per local prescribing information.

11. Has received any anti-TNFα biologic therapy (with the exception of etanercept, see exclusion 9) within the previous 3 months before the first administration of study intervention.

12. Is not a suitable candidate for anti-TNFα therapy for the following reasons:

- Has a history of known demyelinating diseases such as multiple sclerosis or optic neuritis.
- Has known or suspected intolerance or hypersensitivity to anti-TNFα medications (eg, clinical lupus-like syndrome, serum sickness-like reaction).
- Has a history of, or concurrent congestive heart failure (CHF), including medically controlled CHF.

13. Has received any therapeutic agent directly targeted to IL-12/23, IL-17, or IL-23 within 6 months of the first administration of study intervention (including but not limited to ustekinumab, tildrakizumab, secukinumab, ixekizumab, risankizumab, or brodalumab).

14. Has received natalizumab, efalizumab, or agents that deplete B or T cells (eg, rituximab, alemtuzumab, abatacept, anakinra, 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.

15. Has 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 intervention.

16. Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study intervention.

17. Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study intervention.

18. Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or has received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study intervention.

19. Has received an experimental antibody or biologic therapy within the previous 6 months or received any other experimental therapy or new investigational agent (topical or systemic) within 30 days or 5 half-lives (whichever is longer) of any study intervention administration or is currently enrolled in another study using an investigational agent or procedure.

20. Has received, or is expected to receive, any live virus or bacterial vaccination (with the exception of varicella or MMR vaccines; see inclusion criterion 12) within 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of study intervention, during the study, or within 12 weeks after the last administration of study intervention.

21. Has had a BCG vaccination within 12 months of screening.

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

23. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure) or etanercept or its excipients.

24. Has known allergy or sensitivity to latex.

Infections or predisposition to infections

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

26. Has or has had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening.

27. Has or has had herpes zoster within the 2 months before screening.

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

29. Has had a nontuberculous mycobacterial infection.

30. Has ever had an opportunistic infection (eg, cytomegalovirus colitis or retinitis, pneumocystosis pneumonia, or invasive aspergillosis).

31. Has persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB test results. Indeterminate results should be handled as described in Section 8, Study Assessments and Procedures.

32. Is infected with human immunodeficiency virus (HIV, positive serology for HIV antibody).

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

34. Tests positive for hepatitis B virus (HBV) infection (Appendix 6 [Section 10.6]).

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

Note: For COVID-19-related exclusion, see Exclusion Criterion 42.

Malignancy or increased potential for malignancy

36. Has a known history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

37. Has any known malignancy or a history of malignancy.

Other exclusion criteria

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

39. Lives in an institution on court or authority order.

40. Has any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the participant or that could prevent, limit, or confound the protocol-specified assessments.

41. 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.

42. COVID-19 infection:

During the 6 weeks prior to baseline, has had **any** of the following (regardless of vaccination status): (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive) **OR** (b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results) **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test
  - i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, dyspnea])

  AND

  - ii) with absence of all conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

Note on COVID-related exclusion:

- The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator

and in accordance with current regulations/guidance from authorities/standards of care.

Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 2 (Section 10.2), Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

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

1. a girl of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 5) during the study and for at least 12 weeks after receiving the last administration of study intervention.

2. all girls must agree not to donate eggs (ova, oocytes) during the study and for a period of at least 12 weeks following the last administration of study intervention.

3. a boy who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom, Inclusion Criterion 8) during the study and for at least 12 weeks after receiving the last administration of study intervention.

4. all boys must agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention.

5. participants must not receive a live virus or bacterial vaccination (except for varicella and MMR vaccines prior to first administration of study intervention), during the study and for 3 months after the last administration of any study intervention. See Lifestyle Consideration 6 for information regarding BCG vaccination.

6. participants must not receive a BCG vaccination during the study and for 12 months after the last administration of any study intervention.

7. participants must comply with restrictions on concomitant medications and therapies specified in the protocol (refer to Section 6.5, Concomitant Therapy for details).

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

9. participants are recommended to be up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (including emergency use-authorized) COVID-19 vaccination regimen at least 2 weeks prior to study-related visits or procedures. Study participants should follow applicable local vaccine labelling, guidelines, and standards-of-care for participants receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section5.2).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

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

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

In general, if a participant is a screen failure, but at some point in the future meets all of the participant eligibility criteria, the participant may be rescreened after a new informed consent has been obtained. Participants who are rescreened will be assigned a new participant number and will restart a new screening phase. Rescreening will be permitted once.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Guselkumab
Authorization status in the EU/EEA:<table><tr><td>Authorized</td><td></td></tr><tr><td>Unauthorized</td><td>X</td></tr></table>
Placebo
Authorization status in the EU/EEA:<table><tr><td>Authorized</td><td></td></tr><tr><td>Unauthorized</td><td>X</td></tr></table>
Etanercept
Authorization status in the EU/EEA:<table><tr><td>Authorized</td><td>X</td></tr><tr><td>Unauthorized</td><td></td></tr></table></td></tr>
</table>

Guselkumab or placebo will be administered SC using a sponsor-supplied, single use administration device. This will be either the CCI PFS assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U) device, designed to deliver a single, fixed dose of CCI, or a CCI Identical devices containing placebo will be used to deliver a volume equivalent to that of active treatment for participants randomized to the placebo arm. Guselkumab will be supplied as a CCI solution of guselkumab in a single-use CCI CCI or CCI PFS. The PFS-U is assembled with a PFS containing 1.0 mL of study intervention and the CCI

Participants will receive a dose based on body weight. At each dosing visit, participant weight will be measured and the dose of guselkumab will be adjusted accordingly. Participants will receive 1 of the following dose levels depending on their weight:

- Weight <70 kg: CCI administered CCI
- Weight ≥70 kg: CCI administered using the PFS-U

Placebo for guselkumab will also be supplied in a PFS assembled with either the UltraSafe Plus™ Passive Needle Guard or the CCI. Participants who weigh <70 kg will receive 1 or 2 injections of either guselkumab or placebo with a volume(s) determined using the weight-based dose calculation for guselkumab. In Part 2 of the study, participants or their caregiver will be given the option to self-administer guselkumab at the study site. Participants must be ≥12 years of age to self-administer guselkumab.

Commercially available etanercept (25 mg powder and solvent for solution for injection and 50 mg prefilled syringes) will be supplied and administered subcutaneously based on body weight:

- <63 kg: 0.8 mg/kg once weekly using powder and solvent for solution for injection.
- ≥63 kg: 50 mg once weekly administered using a prefilled syringe.

Participants receiving etanercept or their caregiver will also be given the option to self-administer study injections either at the study site when a visit is scheduled or at-home for doses required between regular visits. Participants who weigh <63 kg will receive 1 or 2 injections with a volume(s) determined using the weight-based calculation for etanercept.

Study staff will receive training on study intervention administration using either PFS-U or CCI, which must be documented. For participants/caregivers who will self-administer, training on study intervention administration will be provided by study staff. This will include education regarding instructions for use (IFU), proper handling and storage of devices, guidance on study intervention injection, and proper handing and accounting for used devices. Required storage conditions and expiration date are indicated on the label.

At any time, if participants or caregivers are uncertain about how to administer the study intervention or have questions regarding self-administration, the sponsor recommends that study staff review the IFU with the participant/caregiver along with practice injections with a training device if necessary. Patients or caregivers may be retrained at any time during the study, including if there is a use issue reported by the patient or caregiver. If at any time there is a change in the device required for dosing (eg, CCI to PFS-U) due to a change in a participant's body weight, and the participant/caregiver wishes to continue with self-administration, they must receive training on the new device and the participant/caregiver using the device must be witnessed self-administering a successful injection by study staff prior to performing self-administration.

Different sites should be used for consecutive injections or for two injections administered on the same day. Sites that are tender for any reason should be avoided. Study intervention and injections of other concomitant medications should be given at different anatomic sites.

Details on dose preparation and administration can be found in the Study Site Investigational Product Procedures Manual.

Part 1

Week 0 to Week 16 (Placebo-Controlled Period)

The guselkumab and placebo administrations will be administered by site personnel at the study site. Etanercept will be administered at the study site at Week 0. Subsequent weekly doses of etanercept through Week 15 may be administered at the study site or be self-administered at home by the participant or caregiver on weeks without a site visit. The dose regimens are as follows:

- **Group I:** Weight-based guselkumab dose up to CCI SC at Weeks 0, 4, and 12.
- **Group II:** Weight-based placebo for guselkumab dose administered SC at Weeks 0, 4, and 12.
- **Group III:** Weight-based etanercept dose up to 50 mg SC weekly through Week 15.

Week 16 through Week 52 (Withdrawal and Retreatment Period)

- **Group Ia:** Participants randomized to guselkumab who are PASI 90 responders at Week 16 will not receive any additional doses of guselkumab until they lose ≥50% of their Week 16 PASI improvement, at which time they will receive a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and q8w thereafter through Week 52.
- **Group Ib:** Participants randomized to guselkumab who are PASI 90 nonresponders at Week 16 will receive a placebo SC injection at Week 16 and continue treatment with guselkumab SC q8w from Week 20 through Week 52.
- **Group IIa:** Participants randomized to placebo who are PASI 90 responders at Week 16 will not receive any additional doses of study intervention until they lose ≥50% of their Week 16 PASI improvement, at which time they will receive a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and q8w thereafter through Week 52.
- **Group IIb:** Participants randomized to placebo who are PASI 90 nonresponders at Week 16 will receive a weight-based guselkumab SC dose at Weeks 16 and 20, followed by q8w dosing thereafter through Week 52.
- **Group III:** Participants randomized to etanercept who elect to continue in the study will receive a weight-based guselkumab SC dose at Weeks 20 and 24, followed by q8w dosing thereafter through Week 48.

Participants in any of the treatment groups who elect to end study participation at Week 52 and not participate in the LTE will not receive any administration of study intervention at Week 52 and should return to the site 12 weeks after receiving the last administration of study intervention for a safety follow-up visit.

Part 2

Participants enrolled in Part 2 of the study will receive a weight-based dose of open-label guselkumab SC at Weeks 0, 4 and q8w thereafter through Week 52. Participants in Part 2 of the study who elect to end study participation at Week 52 and not participate in the LTE will not receive any administration of study intervention at Week 52 and should return to the site 12 weeks after receiving the last administration of study intervention for a safety follow-up visit.

In Part 2 of the main study, participants or their caregiver will be given the option to self-administer study injections at the study site using the appropriate presentation (either PFS-U or CCI Participants must be at least 12 years of age to self-administer study injections. Participants or their caregivers will be trained on proper use of the device(s) and deemed capable, as determined by study staff. Otherwise injections will continue to be performed by study staff.

Long-term Extension (From Week 52 until study termination)

Following completion of the Week 52 visit, participants who have had a beneficial response from guselkumab treatment as determined by the investigator, and are willing to continue guselkumab treatment, may enter the LTE of the study. Participants who decide to participate in the LTE will continue to receive guselkumab at Week 52 and q8w thereafter until one of the following occurs:

- The participant turns 18 years of age and resides in a country where marketing authorization has been granted for guselkumab treatment of plaque psoriasis in adult patients, and have had the opportunity to complete up to 1 year in the LTE.
- Marketing authorization is obtained for guselkumab for treatment of plaque psoriasis for patients ≥6 to <18 years of age in the participant's country of residence.
- Marketing authorization is denied for guselkumab for the treatment of plaque psoriasis for patients ≥6 to <18 years of age in the participant's country of residence.
- A company decision is made to no longer pursue an indication in plaque psoriasis in the pediatric population (≥6 to <18 years of age) in the participant's country of residence.

Participants in Part 1 who continue in the LTE portion of the study will receive guselkumab as follows:

- Participants withdrawn from guselkumab or placebo at Week 16 who meet loss of response criteria and are retreated with or initiated guselkumab prior to Week 52 and receive guselkumab at Week 48 will not receive study intervention administration at Week 52 and will resume guselkumab administration at Week 60 and q8w thereafter.
- Participants who meet loss of response criteria at Week 48 will receive guselkumab at Weeks 48 and 52 followed by q8w administration beginning at Week 60.
- Participants withdrawn from treatment at Week 16 who have not been retreated with guselkumab prior to Week 52 will receive a weight-based guselkumab dose at Week 52 and q8w thereafter.

Physical Description of Study Intervention(s)

Guselkumab

The guselkumab supplied for this study is a sterile liquid for SC injection in a single-use PFS. Each single-use PFS is 1 mL glass syringe with a 27 gauge, 1/2 inch fixed needle and a latex-free rigid needle shield and contains CCI of guselkumab with either a 1 mL fill of liquid for the PFS-U (CCI No preservatives are present. Guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the guselkumab IB for a list of excipients in the drug product.

Placebo is supplied as a sterile liquid for SC injection at a fill volume of 1.0 mL in single-use PFS-U or CCI Each placebo PFS contains the same excipients as the drug product.

ENBREL (etanercept)

Commercial etanercept (ENBREL) will be supplied as an active comparator to the study sites. Details on etanercept are available in the etanercept (ENBREL) package insert in the Site Investigational Product Procedures Manual.

Packaging

Two dosage forms for guselkumab and placebo will be used in this study, PFS-U and CCI assembled with a PFS. Both dosage forms will be packaged in individual participant kits in tamper evident packaging.

Etanercept (ENBREL) will be provided in commercial primary packaging. Secondary packaging may be changed to facilitate clinical labeling.

Study intervention administration must be captured in the source documents and the case report form (CRF). Study-site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol.

For details on rescue medications, refer to Section 6.5.1, Rescue Medication. For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

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

All study intervention must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C), not frozen, and protected from light. Vigorous shaking of the product should be avoided. The sterile product does not contain preservatives and is designed for single use only. Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used. Study intervention in PFS-U and CCI will be ready to use. Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during preparation and administration.

Further details regarding the preparation and storage of guselkumab and placebo will be provided in the Site Investigational Product Procedures Manual. Further details regarding the preparation and storage of etanercept can be found in the ENBREL package insert in the Site Investigational Product Procedures Manual.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the drug accountability form. Participants, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study intervention. The study intervention administered to the participant must be documented on the drug accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention 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 intervention 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 intervention will be documented on the drug return form. When the study site is an authorized destruction unit and study intervention 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 intervention 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 intervention will be supplied only to participants participating in the study. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees to neither dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants in Part 1a (≥12 to <18 years of age) will be randomized in a 2:1:1 ratio to guselkumab, placebo, or etanercept and participants in Part 1b (≥6 to <12 years of age) will be randomized separately in a 1:1:1 ratio to 1 of same 3 treatment groups using computer-generated randomization schedules, prepared before the study by, or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by region. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study intervention kit(s) for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Randomization will not be used in Part 2 of this study. All participants in Part 2 will receive open-label guselkumab.

Blinding

For Part 1 of the main study, the investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment assignment (eg, treatment allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until the Week 52 database lock is completed. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In such cases, the investigator may in an emergency determine the identity of the treatment using the IWRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the CRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their treatment assignment unblinded should continue to return for scheduled evaluations. The decision to continue or discontinue study treatment for these participants will be based upon consultation of the investigator with the medical monitor.

One interim PK analysis is planned for this study after all participants ≥12 to <18 years of age in Part 1a have completed Week 16. This evaluation will be conducted by sponsor personnel who are otherwise not participating in the conduct of this study. Efficacy data will not be analyzed in this interim analysis.

The Sponsor will be unblinded after the last participant in Part 1 has completed their Week 16 visit and the Week 16 DBL has occurred. The investigators, participants, and sponsor site monitors can be unblinded after the last participants in Part 1 and Part 2 have completed the Week 52 visit, and the Week 52 DBL has occurred.

Blinding procedures are not applicable for participants in Part 1 who are randomized to open-label etanercept, with the exception of the blinded efficacy evaluator (see Section 8.1.6), and all participants in Part 2 of the main study who will receive open-label guselkumab and will not be blinded in this study.

6.4. Study Intervention Compliance

Because guselkumab and placebo will be administered at the investigational site by trained study staff or self-administered by the participant or their caregiver, treatment compliance for these study interventions will be controlled by site personnel.

From Week 0 through Week 52, it is expected that all visits will occur within a range of ±7 days of the scheduled visit. Any visits outside of these ranges should be discussed with the sponsor. If a study visit occurs outside the specified visit window, the participant should then resume his or her normal dose schedule relative to the baseline visit (Week 0) as soon as possible. All other follow-up study visits should occur within ±14 days of the scheduled study visit. Any out-of-range visit should be documented in the participant's source notes. Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Appendix 22 (Section 10.22).

Study-site personnel will maintain a log of all study intervention administered. Drug supplies for each participant will be inventoried and accounted for. Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Participant charts and worksheets may be reviewed and compared with the data entries on the CRFs to ensure accuracy. Although it is understood that treatment may be interrupted for many reasons, compliance with the treatment schedule is strongly encouraged.

When etanercept is administered by the participant or caregiver away from the site, the amount of study intervention dispensed will be recorded and compared with the amount returned and the participant or caregiver will be asked to record administration information on a paper questionnaire. Etanercept dosing should occur within a range of ±3 days of the scheduled date. Participants (and parent/caregiver) will receive instructions on compliance with study treatment when they begin self-administration of etanercept at home. During the course of the study, the investigator or designated study research personnel will be responsible for providing additional instruction to reeducate any participant who is not compliant with taking the study intervention.

6.5. Concomitant Therapy

Concomitant therapies must be recorded throughout the study from screening and continuing until 12 weeks after the last dose of study intervention. Concomitant therapies should also be recorded beyond that point only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study intervention, as well as all shampoos used to treat plaque psoriasis, moisturizers, or emollients, must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

If a prohibited therapy is administered during the active treatment phase including the LTE, unless agreed to by the medical monitor, the participant should be discontinued from study treatment. If a prohibited therapy is initiated during the safety follow-up period (12 weeks between last administration of study intervention and final site visit), the participant should still complete his or her final study visit, and the medication should be recorded as a concomitant medication.

6.5.1. Rescue Medication

In Part 1 of the study, participants with a PASI score increase of ≥50% from their baseline PASI score at Week 8 or Week 12 will be allowed to use a topical steroid as rescue treatment, with the exception of ultra-high potency topical steroids (eg, clobetasol propionate, halobetasol propionate) which are not allowed at any time. It is recommended that participants use no more than 60 grams of topical steroid per week. In addition, participants should be managed using the lowest possible potency and frequency of rescue topical steroid. Participants must discontinue the use of rescue topical steroids by Week 20 (should not initiate rescue topical steroids at or after Week 16).

6.5.2. Topical Therapies for Psoriasis

With the exception of the use of topical steroids by participants who qualify for rescue therapy (see Section 6.5.1, Rescue Medication), topical therapies that could affect psoriasis or the IGA evaluation (eg, corticosteroids, tar, anthralin, calcipotriene, tazarotene, methoxsalen, pimecrolimus, tacrolimus, and traditional Taiwanese, Korean, or Chinese medicines) are not permitted at any time during the study. The only allowable concomitant treatments on areas affected by plaque psoriasis throughout the study are shampoos (containing tar or salicylic acid only) and topical moisturizers. Participants should not use these topical agents (shampoos, moisturizers) on the day of a study visit. Nonmedicated shampoos may be used on the day of the study visit.

6.5.3. Phototherapy or Systemic Therapies for Psoriasis

The use of phototherapy or systemic antipsoriatic medications is not permitted at any time during the study. These medications include those targeted for reducing TNFα (including but not limited to infliximab or adalimumab), drugs targeted for reducing IL-12, IL-17A, IL-17R, or IL-23 (including but not limited to ustekinumab, tildrakizumab [MK3222], risankizumab [BI-655066], ixekizumab [LY2439821], or brodalumab [AMG827]), alpha-4 integrin antagonists (including but not limited to natalizumab), apremilast, steroids, any conventional systemic therapy that could affect psoriasis or the IGA evaluation (including but not limited to MTX, cyclosporine, acitretin), herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines, and any other biological agent or other systemic medication that could affect psoriasis or the IGA evaluation.

6.5.4. Concomitant Therapies for Conditions Other Than Psoriasis

Every effort should be made to keep participants 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 participant's medical record.

The use of stable doses of nonsteroidal anti-inflammatory drugs is allowed. However, disease modifying agents such as MTX, sulfasalazine, or IM gold are prohibited during the study. Lithium and antimalarial agents may not be used.

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

6.5.5. Concomitant Therapies After Week 52

After the Week 52 visit, the medication rules outlined above still apply except that most topical therapies are permitted for treatment of psoriasis; ultra-high potency corticosteroids are still prohibited during this period.

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

6.5.6. Vaccinations (including COVID-19)

When considering use of locally-approved non-live vaccines (including emergency use-authorized COVID 19 vaccines) in study participants, follow applicable local vaccine labelling, guidelines, and standards-of-care for participants receiving immune-targeted therapy.

For study participants receiving a locally-approved (including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

6.6. Dose Modification

Participants will receive a dose based on body weight as described in Section 6.1, Study Interventions Administered.

6.7. Intervention After the End of the Study

The LTE is described in Section 4.1, Overall Design. There are no plans for post-study provision of study intervention.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

A participant will be considered to have completed the main study if he or she has completed assessments at Week 52. Participants who prematurely discontinue study treatment for any reason before completion of the study will not be considered to have completed the study.

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if any of the following occur:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- An AE temporally associated with study intervention injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension (defined as systolic BP < [70 + (2 x age in years])[30].
- The participant or their legally acceptable representative withdraws consent/assent for administration of study intervention.
- Pregnancy, or pregnancy planned within the study period or within 12 weeks after the last study intervention injection.
- The initiation of protocol-prohibited medications or treatments as outlined in Section 6.5, Concomitant Therapy, unless agreed to by the sponsor medical monitor.
- The participant is diagnosed with a malignancy.

- An opportunistic infection.
- A recurrent or chronic serious infection.
- A severe study intervention injection-site reaction.
- The participant meets one of the following TB criteria:
  - A diagnosis of active or latent TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
  - A participant undergoing evaluation has chest imaging with evidence of TB and/or a positive IGRA test result and/or 2 indeterminate/borderline IGRA test results. Indeterminate/borderline or suspected false-positive tests should be handled as outlined in Section 8.
- The participant has liver test abnormalities as described in Section 8.2.3 and Appendix 12 (Section 10.2). Such abnormalities would include the following:
  - ALT or AST >8 x ULN
  - ALT or AST >5 x ULN for more than 2 weeks
  - ALT or AST >3 x ULN **and** (total bilirubin >2 x ULN or international normalized ratio [INR] >1.5)
  - ALT or AST >3 x ULN **and** symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

Discontinuation of a participant's study intervention should be considered for:

- Participants with any type of suicidal ideation or behavior, or any self-injurious behavior, who are deemed to be at risk by the investigator. Discussion of such participants with the medical monitor or designee is required. For participants who report suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) or any self-injurious behavior on a post-baseline C-SSRS assessment, the investigator risk assessment must be based upon evaluation by a mental health professional.
- Participants who have shown insufficient improvement in their psoriasis with up to 28 weeks of treatment.

Participants who decide to discontinue study intervention administration for reasons other than those outlined above must be interviewed by the investigator to determine if a specific reason for discontinuing study intervention can be identified. Participants should be explicitly asked about the possible contribution of AEs to their decision to discontinue study intervention; investigators should confirm that any AE information elicited has been documented. If a participant elects to discontinue study intervention due to an AE, the event should be recorded as the reason for study intervention discontinuation, even if the investigator's assessment is that the AE would not require study intervention discontinuation. The reason for study intervention discontinuation must be documented in the CRF and in source documents. Study intervention assigned to a participant who discontinues may not be assigned to another participant.

A participant will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. Participants who discontinue study intervention but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for at least 12 weeks following the last dose of study intervention. The procedures and evaluations listed for the Study Termination Visit, should also be performed 12 weeks after the last dose of study intervention.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

To ensure access for participant follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from participants (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the participant, before randomization. For participants who withdraw from study participation, every effort should be made to conduct the Study Termination Visit assessments, as indicated in the Schedule of Activities.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good participant relationships to avoid withdrawals of consent. For participants who truly request withdrawal of consent, it is recommended that the participant withdraw consent in writing; if the participant or the participant's representative refuses to do so or is physically unavailable, the study site should document the reason for the participant's failure to withdraw consent in writing, sign the documentation, and maintain it with the participant's source records. When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will not be replaced.

7.2.1. Withdrawal From the Use of Research Samples

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 2 (Section 10.2), Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, attempts should be made to obtain contact information from each participant, such as home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant and/or their parent or legal guardian (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address), or local equivalent methods. These contact attempts should be documented in the participant's medical records.
- Should the participant and/or their parent or legal guardian continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, immunogenicity, and safety measurements applicable to this study.

Patient-reported assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions and the CDLQI should be completed before the C-SSRS (except at screening where C-SSRS is the first assessment after signing informed consent). Investigator-reported efficacy assessments (ie, IGA, PASI, and BSA) should

be completed before any study intervention administrations and will be performed by an assessor trained by the sponsor, as outlined in the Schedule of Activities.

The CDLQI and FDLQI will be completed at appropriate visits, as outlined in the Schedule of Activities.

A urine pregnancy test will be performed for girls of child-bearing potential to confirm the absence of pregnancy at every study intervention administration visit. Additional 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 participant's participation in the study.

The approximate total volume of blood per type of sample to be collected through Week 52 is presented in Table 1. The total blood volume to be collected from each participant per visit through Week 52 of the study will be approximately 79.5 mL with maximum volume of 17.5 mL at screening and 10.5 mL at other study visits (Table 2).

Where possible, tests are combined to allow for fewer draw tubes and in the interest of keeping blood volumes to a minimum. Therefore, the total volume is less than that presented in Table 1. The annual blood volume to be collected from each participant participating in the LTE of the study will be approximately 9 mL (Table 3). In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

Table 1: Approximate Total Volume of Blood Per Type of Sample to be Collected Through Week 52 from Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Hematology	2	8	16
Serum chemistry	2.5	8	20
Serology (HIV, hepatitis)	6.5	1	6.5
Serum antibody titers for varicella, measles, mumps, and rubella[b]	2.5	1	2.5
QuantiFERON®-TB testing	4	1	4
Pharmacokinetic samples only[c]	2.5	2	5
Pharmacokinetics and immunogenicity samples[d]	3.5	6	21
Serum immunoglobulin levels[e]	2.5	3	7.5
Approximate Total[f]			82.5

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Titers for measles, mumps, rubella, and varicella only required if adequate documentation of complete vaccination schedule or healthcare provider verification of previous infection is unavailable.
c. 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).
d. 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).
e. IgG, IgM, IgA
f. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Table 2: Approximate Volume of Blood to be Collected per Visit Through Week 52

Weeks	Screening	0[a]	4	8	12	16[a]	20	28	36	44	52[a]	Total[b]
Volume (mL)	17.5	10.5	3.5	4.5	3.5	9.0	2.5	8.0	7.0	8.0	5.5	79.5

a. Where possible, tests are combined to allow for fewer draw tubes and in the interest of keeping blood volumes to a minimum. Therefore, the total volume is less than that presented in Table 1.

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

Table 3: Approximate Volume of Blood to be Collected Annually from Each Participant in the Long-term Extension

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Hematology	2	2	4
Serum chemistry	2.5	2	5
Approximate Total[b]			9

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples

Screening Phase

Each participant's legally acceptable representative will be asked to sign the consent form at the screening visit before any study-related procedures are conducted. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Appendix 2 (Section 10.2), Regulatory, Ethical, and Study Oversight Considerations.

After written informed consent has been obtained and within a maximum period of approximately 10 weeks before enrollment into the study, all screening evaluations establishing participant eligibility must be performed. Participants who meet all of 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 Schedule of Activities for each participant.

Girls of childbearing potential must have a negative urine β-human chorionic gonadotroptin (β–hCG) pregnancy test at screening and before enrollment. Girls 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 12 weeks after the last dose of study intervention. The method(s) of contraception used by each participant must be documented. A boy who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control and continue to use contraception for the duration of the study and for 12 weeks after the last dose of study intervention.

As outlined in the eligibility criteria, participants must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

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

A suspected false-positive initial IGRA test must be repeated. If the repeat testing is negative, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation and final decision must be discussed with the sponsor and adequately documented prior to the first administration of study intervention. If the repeat testing is positive or indeterminate, however, it will be considered a true-positive and the participant must be excluded from the study.

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

Participants that do not have positive protective antibody titers to measles, mumps, rubella, and varicella 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 intervention. These participants should receive both an initial immunization and a booster 4 weeks later. If local guidelines specify otherwise, local guidelines may be followed. 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 intervention.

Participants will undergo screening for HBV (see Appendix 6 [Section 10.6]) and antibodies to HCV and HIV.

Screen Failure/Rescreening

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

In general, if a participant is a screen failure, but at some point in the future meets all of the participant eligibility criteria, the participant may be rescreened after a new informed consent has been obtained. Participants who are rescreened will be assigned a new participant number and will restart a new screening phase. Rescreening will be permitted once.

Part 1: Placebo-controlled and Withdrawal/Retreatment Periods

Week 0/Randomization

At Week 0, participants who meet all inclusion criteria and do not demonstrate any exclusion criteria will be randomized.

Randomization visit procedures will be performed as specified on the Schedule of Activities. After completion of required study procedures, participants will be administered study intervention according to their randomization assignment (guselkumab, placebo, or etanercept).

Week 1 to Week 15 (Placebo-controlled Period)

All visit procedures will be performed as specified in the Schedule of Activities. All study procedures and evaluations should be completed before the participant is administered study intervention. Participants randomized to receive etanercept and who elect to self-administer at home will receive 3 dose kits at site visits through Week 12 to accommodate self-administration of etanercept at home between site visits through Week 15.

Week 16 to Week 52 (Withdrawal/Retreatment Period)

Participants will return to the study site for q4w visits until the Week 52 visit. All visit procedures will be performed as specified in the Schedule of Activities.

Participants randomized to guselkumab or placebo who are PASI 90 responders at Week 16 will be withdrawn from treatment. Upon loss of ≥50% of the improvement in PASI achieved at Week 16, participants will receive a weight-based guselkumab SC dose, followed by a dose 4 weeks later with subsequent q8w dosing through Week 52.

Participants randomized to guselkumab who are PASI 90 nonresponders at Week 16 will receive a placebo injection at Week 16 to maintain the blind and continue guselkumab SC q8w beginning at Week 20.

Participants randomized to placebo who are PASI 90 nonresponders at Week 16 will initiate weight-based guselkumab SC at Week 16 and 20 followed by q8w thereafter through Week 52.

Participants randomized to etanercept who elect to continue in the study will receive a weight-based guselkumab dose at Weeks 20 and 24, followed by q8w dosing thereafter through Week 48.

Part 2: Open-Label Treatment from Week 0 through Week 52

All visit procedures for participants participating in Part 2 of the study will be performed as specified in the Schedule of Activities. Participants in Part 2 will receive guselkumab treatment through Week 52. This phase of the study will begin for participants ≥12 years of age after the safety and PK reviews in Part 1a have been completed, and an appropriate body weight-based dose that matches adult exposure has been confirmed. Enrollment of participants ≥6 to <12 years of age into Part 2 will not occur until all participants in Part 1b have completed 16 weeks of treatment and all efficacy data through Week 16 from Part 1 have been evaluated by the sponsor after the Week 16 DBL, and all available safety data have been reviewed by the independent DMC.

In Part 2 of the main study, participants or their caregiver will be given the option to self-administer study injections at the study site using the appropriate presentation (PFS-U or CCI). Participants must be at least 12 years of age to self-administer study injections. Participants or their caregivers

will be trained on proper use of the device(s) and deemed capable, as determined by study staff. Otherwise injections will continue to be performed by study staff.

Long-Term Extension Phase

Following completion of the Week 52 visit, participants who have had a beneficial response from guselkumab treatment as determined by the investigator, and are willing to continue guselkumab treatment, may enter the LTE of the study. Participants who decide to participate in the LTE will continue to receive guselkumab q8w until one of the following occurs:

- The participant turns 18 years of age and resides in a country where marketing authorization has been granted for guselkumab treatment of plaque psoriasis in adult patients, and have had the opportunity to complete up to 1 year in the LTE.
- Marketing authorization is obtained for guselkumab for treatment of plaque psoriasis for patients ≥6 to <18 years of age in the participant's country of residence.
- Marketing authorization is denied for guselkumab for the treatment of plaque psoriasis for patients ≥6 to <18 years of age in the participant's country of residence.
- A company decision is made to no longer pursue an indication in plaque psoriasis in the pediatric population (≥6 to <18 years of age) in the participant's country of residence.

All participants will begin q8w administration of guselkumab at Week 52, except for participants who have initiated or been retreated with guselkumab prior to Week 48 and receive a guselkumab injection at Week 48. Those participants will receive their first dose of guselkumab in the LTE at Week 60 and q8w thereafter. Participants who are retreated with or initiate guselkumab treatment at Week 48 will also receive a guselkumab dose at Week 52 followed by q8w administration beginning at Week 60. The same guidance for self-administration in Part 2 applies to the LTE.

Safety Follow-Up

Participants should return to the study site at least 12 weeks after their last dose of study intervention for a safety follow-up visit. This includes participants who discontinue study intervention administration in the main study or the LTE, and participants who receive their final dose of guselkumab at the final dosing visit of the LTE (see Section 8, Study Assessments and Procedures). Assessments listed in the study termination visit entry of the Schedule of Activities should be completed.

Sample Collection and Handling

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

Refer to the Schedule of Activities 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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for guselkumab
- Package Leaflet for etanercept
- Site Investigational Product Procedures Manual
- Laboratory Manual
- IWRS Manual
- Electronic Data Capture (eDC) Manual
- Sample ICF
- iPad® and site user guide, if the study site is participating in electronic informed consent
- PFS-U and CCI Instructions for Use
- Participant Study Participation Card
- Investigative Site File
- Recruitment materials, as needed

The following assessments are included as appendices to the protocol.

- Faces Pain Scale-Revised for Injection Pain
- Injection Pain Visual Analog Scale
- Investigator's Global Assessment
- Psoriasis Area and Severity Index
- Children's Dermatology Life Quality Index
- Family Dermatology Life Quality Index
- Columbia-Suicide Severity Rating Scale (Children's Baseline)
- Columbia-Suicide Severity Rating Scale (Baseline/Screening)
- Columbia-Suicide Severity Rating Scale (Children's Since Last Visit)
- Columbia-Suicide Severity Rating Scale (Since Last Visit)
- CCI
- CCI

8.1. Efficacy Assessments

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

- IGA

- PASI
- BSA
- CDLQI
- FDLQI

8.1.1. Investigator's Global Assessment

The IGA documents the investigator's assessment of the participant's plaque psoriasis at a given timepoint (Appendix 7 [Section 10.7]). Overall lesions are graded for induration, erythema, and scaling. The patient's plaque psoriasis is assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4). A higher score indicates more severe disease.

8.1.2. Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Appendix 8 [Section 10.8]).[13] In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities. Each of these areas is assessed separately for the percentage of the area involved, which translates to a numeric score that ranges from 0 (indicates no involvement) to 6 (90% to 100% involvement), and for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The PASI produces a numeric score that could range from 0 (no psoriasis) to 72. A higher score indicates more severe disease.

8.1.3. Body Surface Area

The percentage of a participant's total body surface area affected by psoriasis will be assessed.

8.1.4. Children's Dermatology Life Quality Index

The CDLQI is an adapted version of the Dermatology Life Quality Index (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.[20] The CDLQI questionnaire is frequently used to assess the patient's perspective on the impact of skin disorders on daily living.[20,25] The development of the instrument included a wide variety of dermatologic conditions.[12] The content validity and other psychometric properties were further assessed in a subsequent study in patients with plaque psoriasis.[11] Additional validation work was completed on the children's version.[20] 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, participants from 4 to 16 years of age), is self-explanatory and can be simply handed to the participant who is asked to fill it in with the help of the child's parent or caregiver. A sample CDLQI is provided in Appendix 9 (Section 10.9).

8.1.5. Family Dermatology Life Quality Index

The FDLQI is a dermatology-specific QoL instrument for the family members of patients having any skin disease.[2,3] It has 10 items asking the family members/partners about the impact of a patient's skin disease on different aspects of their QoL (e.g. emotional, physical well-being, relationships, social life, leisure activities, burden of care, job/study, housework and expenditure).

The frame of reference for items is over the last 1 month. Each item has a four-point response option, where Not at all/Not relevant = 0; A little = 1; Quite a lot = 2; and Very much = 3. The scores of individual items (0–3) are added to give a total scale score that ranges from 0 to 30; a higher score indicates greater impairment of QoL. The FDLQI is designed to be used as an additional outcome measure in conjunction with the DLQI or any other patient-completed questionnaire. This instrument should be completed by a participant's primary care-giver.

A sample FDLQI is provided in Appendix 10 (Section 10.10).

8.1.6. Blinded Efficacy Evaluator

A blinded efficacy evaluator, qualified by the sponsor, will be designated at each study site to perform all PASI, IGA, and BSA efficacy assessments, including the screening visit. Blinded efficacy evaluation will be performed in both Part 1 and Part 2 of the study until all participants in Part 1 complete their Week 16 visit and the Week 16 database lock is completed.

The blinded efficacy evaluator should have no contact with the participant during the study other than the efficacy assessments, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant'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.

The sponsor will provide PASI, IGA, and BSA training for each site's designated efficacy evaluator(s) prior to the screening of the first participant at each site. If the efficacy evaluator was trained by the Sponsor in a previous clinical study 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.

8.2. Safety Assessments

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or the participant's legally acceptable representative) for the duration of the study and will be followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event 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 Schedule of Activities:

8.2.1. Physical Examination

Physical Examination

Physical examinations, including Tanner staging every 12 months for sexual maturity, and a skin examination, will be performed according to the Schedule of Activities. Review of systems will be performed at all visits to evaluate for new symptomatology and if necessary, full physical examination may be performed at investigator discretion. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Height and Weight

Height and weight will be measured as specified in the Schedules of Activities. Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.2. Vital Signs

Heart rate, blood pressure, and temperature will be measured.

8.2.3. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 11 (Section 10.11), Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

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.

If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN, see Appendix 12 (Section 10.12; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease) for information on monitoring and assessment of abnormal liver function tests.

8.2.4. Columbia-Suicide Severity Rating Scale (C-SSRS)

In light of the recent reports concerning suicidal ideation and behavior in adult patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab),[9] the C-SSRS will be used as a screening tool to prospectively evaluate the potential of guselkumab to induce suicidal ideation and behavior in children and adolescents ≥6 to <18 years of age. The C-SSRS is an investigator-administered questionnaire that defines 5 subtypes of suicidal ideation and four possible suicidal behaviors, as well as non-suicidal self-injurious behavior (NSSIB) and completed suicide.[23,27] Four versions of the C-SSRS will be used in this study, a Baseline version to be completed at screening by children ≥6 to <12 years of age (Appendix 13, Section 10.13), a Baseline/Screening version to be completed by adolescents ≥12 years of age (Appendix 14, Section 10.14), a Children's Since Last Visit version to be completed at all other visits (Appendix 15, Section 10.15), and a Since Last Visit

version for adolescents (Appendix 16, Section 10.16). The children's version should be used for participants ≥6 to <12 years of age and the standard version for adolescents ≥12 years of age. The 'Baseline' and 'Baseline/Screening' versions of the C-SSRS will be conducted during the screening visit followed by the 'Since Last Visit' versions of the C-SSRS at all other visits through the end of the study. Participants who are <12 years of age when enrolled in the study should continue using the children's 'Since Last Visit' version of the C-SSRS for the entire duration of the study.

The investigator or trained study site personnel will interview the participant and complete the C-SSRS. The investigator and study site personnel will be trained to administer the C-SSRS. The C-SSRS will be provided in the local languages in accordance with local guidelines.

The C-SSRS will be performed during each evaluation visit according to the assessment schedule and should be performed after the CDLQI and before any other study procedure (except at screening where C-SSRS is the first assessment after signing informed consent). Participants will be interviewed by the investigator or study site personnel in a private, quiet place.

At the conclusion of each assessment, the trained personnel administering the C-SSRS will determine the level of suicidal ideation or behavior, if any. They will then determine the next course of action if any level of suicidal ideation or behavior is reported. The participant should not be released from the site until the C-SSRS has been reviewed and the participant's risk has been assessed and follow-up determined, as appropriate.

At screening, the necessary course of action is indicated below by age category and C-SSRS result:

- Participants ≥12 to <18 years of age who have one of the following C-SSRS ratings may **not** be randomized into the study:
  - a C-SSRS rating at screening of: Suicidal ideation with intention to act ("Ideation level 4"), Suicidal ideation with specific plan and intent ("Ideation level 5"), or non-suicidal self-injurious behavior ***within the past 6 months***, OR
  - a C-SSRS rating of suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) ever (***lifetime***)
- Participants ≥6 to <12 years of age who have one of the following C-SSRS ratings may **not** be randomized into the study:
  - a C-SSRS rating at screening of: Suicidal ideation with intention to act ("Ideation level 4"), Suicidal ideation with specific plan and intent ("Ideation level 5"), or any self-injurious behavior ever (***lifetime***), OR
  - a C-SSRS rating of suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) ever (***lifetime***)

- For C-SSRS ratings of Wish to be Dead ("Ideation level 1"), Non-Specific Active Suicidal Thoughts ("Ideation level 2"), or Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act ("Ideation level 3"):
    - ***a participant ≥12 to <18 years of age who has had one of the above C-SSRS ratings*** within ***the past 6 months*** must be determined not to be at risk by the investigator and discussed with the medical monitor or designee in order to be randomized.
    - ***a participant ≥6 to <12 years of age who has had one of the above C-SSRS ratings ever (lifetime)*** must be determined not to be at risk by the investigator and discussed with the medical monitor or designee in order to be randomized.

At Week 0, the above guidance applies with the time frame of "since last visit". Any questions regarding eligibility of participants should be discussed with the medical monitor or designee.

For each assessment after Week 0, the following actions should be taken for all age groups, if applicable:

- No suicidal ideation, suicidal behavior, or other self-injurious behavior: No further action is needed.
- Suicidal ideation levels 1-3: Participant risk is assessed by the investigator.
- Suicidal ideation levels 4 or 5 or any suicidal or self-injurious behavior: Participant risk is assessed and referral is made to a mental health professional.

Interruption or discontinuation of study treatment should be considered for any participant with any type of suicidal ideation or behavior, or any self-injurious behavior, who is deemed to be at risk by the investigator. Participants with any type of ideation or behavior reported during treatment with the study intervention must be discussed with the medical monitor or designee to determine if study intervention can be continued (see Section 7.1, Discontinuation of Study Intervention). For participants who report suicidal ideation with intention to act ("Ideation level 4"), suicidal ideation with specific plan and intent ("Ideation level 5"), suicidal behavior (actual suicide attempt, interrupted suicide attempt, aborted suicide attempt, or preparatory behaviors for making a suicide attempt) or any self-injurious behavior on a post-baseline C-SSRS assessment, the investigator risk assessment must be based upon evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse). For participants who are referred to a mental health professional for evaluation, if that participant can be adequately treated with psychotherapy and/or pharmacotherapy based on the judgment of the mental health professional, then the participant, at the discretion of the investigator, may continue to receive study treatment if agreed to by the medical monitor or designee.

Any C-SSRS finding, which in the opinion of the investigator is new or considered to be a worsening and clinically significant, should be reported on the AE CRF (see Appendix 4 [Section 10.4], Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.2.5. Immunogenicity Assessments

Anti-guselkumab antibodies will be evaluated in serum samples collected from all participants according to the Schedule of Activities. Additionally, serum samples should also be collected at the final visit from participants who are discontinued from intervention or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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

8.2.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.2.7. Injection-site Reactions

A study intervention injection-site reaction is any adverse reaction at an SC study intervention injection site. The injection sites will be evaluated for reactions and any injection-site reactions will be recorded as an AE. In addition, the duration of adverse events of injection site reactions, including injection-site pain, will be captured with the standard AE information which includes information on the start and end date, as well as the start and end time of the AE. Discontinuations due to injection-site reactions, including injection-site pain, will also be recorded.

8.2.8. Injection Pain

Pain experienced during study intervention injection will be assessed using the Faces Pain Scale-Revised for children ≥6 to <12 years of age (Appendix 17, Section 10.17), and the linear Injection Pain Visual Analog Scale for children ≥12 to <18 years of age (Appendix 18, Section 10.18).[31,33]

8.2.9. Allergic Reactions

All participants must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives) for at least 30 minutes after study intervention injection for all injections performed at the study site.

Participants with reactions following an injection resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension (defined as a systolic BP < [70 + (2 x age in years])[30], will not be permitted to receive any additional study intervention injections.

8.2.10. Early Detection of Active Tuberculosis

To aid in the early detection of new active TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at each scheduled visit (refer to Schedule of Activities). 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.)

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat QuantiFERON®-TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB 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 participant's risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON®-TB test result is indeterminate or suspected false-positive, the test should be repeated (with expert consultation, as applicable) as outlined under Screening Phase in Section 8, Study Assessments and Procedures.

If the evaluation raises suspicion that a participant may have TB reactivation or new (active or latent) TB infection, no additional study intervention 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 participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or the participant's legally acceptable representative) for the duration of the study.

Anticipated events will be recorded and reported as described in Appendix 19, Section 10.19.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information

8.3.1.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, 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 a serious adverse event will be reported as serious adverse events. Anticipated events will be recorded and reported as described in Appendix 19, Section 10.19.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

All SAEs and nonserious AEs that represent events of suicidal ideation or suicidal behavior, including any of the following diagnoses, must be reported to the sponsor following the procedures outlined in Section 8.3.1.2:

- Suicidal ideation
- Suicidal behavior, including completed suicide
- Self-injurious behavior

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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
- Participant number

- Any other information that is required to do an emergency breaking of the blind

8.3.1.2. Serious Adverse Events

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

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

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

- Hospitalizations not intended to treat an acute illness or adverse event (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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

Any possible Hy's law case (AST or ALT ≥ 3X ULN together with bilirubin ≥ 2X ULN or INR >1.5 if measured) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event form, even before all other possible causes of liver injury have been excluded (INR criterion is not applicable to participants receiving anticoagulants).

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

8.3.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of the Safety Information to the regulatory authorities/IECs/IRBs in each respective country/territory, as applicable. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. 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. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 reported as an adverse event in the CRF. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

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

8.3.5. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study intervention(s) in participants participating in this clinical study must be reported by the

investigator according to the procedures in Section 8.3.1.2. 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.

8.4. Treatment of Overdose

For this study, any dose of guselkumab or etanercept greater than twice the weight-based dose of study intervention described in Section 6.1, Study Interventions Administered, within a 24-hour time period will be considered an overdose.

As all blinded study interventions will be administered at the study site, overdoses are unlikely to occur. In the event of an overdose, the investigator or treating physician should closely monitor the participant for any signs or symptoms of adverse reaction(s) and administer appropriate symptomatic treatment immediately.

8.5. Pharmacokinetics

Blood samples will be collected for the measurement of serum guselkumab concentrations and evaluation of antibodies to guselkumab at the timepoints presented in the Schedules of Activities. Serum samples will also be collected at the final visit from participants who terminate study participation early. Blood samples collected for serum guselkumab concentrations may also be used for exploratory biomarker analyses.

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

Evaluations

Samples of approximately 2.5 mL for PK only evaluations will be collected and each serum sample will be divided into 2 aliquots (1 for serum guselkumab concentration and 1 for back-up). Venous blood samples of approximately 3.5 mL for both PK and immunogenicity evaluations will be collected and each serum sample will be divided into 3 aliquots (1 for serum guselkumab concentration, 1 for antibodies to guselkumab, and 1 for back-up). Samples collected for analyses of guselkumab serum concentration and antibodies to guselkumab 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 intervention administration at visits when a study intervention 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. Participant confidentiality will be maintained.

Pharmacokinetic Analytical Procedures

Serum samples will be analyzed to determine serum guselkumab 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 participants' identity remains blinded, will assay these samples.

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study. However, blood samples collected for serum guselkumab concentrations may be used for exploratory biomarker analyses.

8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10. Usability Assessment

In Part 2 of the main study and in the LTE, pediatric participants ≥12 years of age and caregivers of pediatric participants of any age will be given the option to administer study intervention.

For participants or caregivers using the CCI [redacted] a CCI [redacted] will be completed by study staff to assess whether the user is able to correctly administer the injection. Based on this information, the study staff will determine whether the participant (≥12 years of age) or their caregiver is able to administer the injection in a home-like setting at the site.

Following subsequent independent self- or caregiver- administrations with the CCI [redacted], all study participants performing the injection will be asked to complete a CCI [redacted] If the injections have been performed by the caregiver, the questionnaire will be completed by the caregiver. If the injections have been performed by the participant, the participant will complete the questionnaire with parent or caregiver assistance, if needed.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Descriptive statistics will include counts and proportions for categorical data, and median, mean, interquartile range, and range for continuous data. Life table estimates will be provided for the time to event variables. Graphical data displays may also be used to summarize the data.

Fisher's exact test, stratified by age and region, will be used to compare the proportion of participants responding to treatment. Continuous response parameters will be compared using a Mixed effect Model Repeat Measurement (MMRM) analysis or an analysis of covariance (ANOVA) model, adjusting for baseline value, age group, and region. All statistical testing will be performed 2-sided at a significance level of 0.05.

In general, the baseline measurement is defined as the closest measurement taken at or before Week 0.

9.1. Statistical Hypotheses

The primary hypothesis is that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) or minimal (1) and the proportion of participants achieving a PASI 75 response at Week 16.

The major secondary hypotheses are that guselkumab treatment is:

- superior to placebo as assessed by the proportion of participants achieving a PASI 90 response at Week 16.
- superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) at Week 16.
- superior to placebo as assessed by the proportion of participants achieving a PASI 100 response at Week 16.
- superior to placebo in improving the dermatologic health-related quality of life in pediatric participants as assessed by the change from baseline in CDLQI at Week 16.

9.2. Sample Size Determination

The assumptions for the sample size calculations for Part 1 of the study are based on the historical response rates from the adults and/or pediatric studies for placebo, guselkumab and the active comparator, etanercept. A power of at least 99% is targeted for the guselkumab versus placebo comparisons for the co-primary endpoints while a power of at least 81% is targeted for the etanercept versus placebo comparisons. Hereby, it is to be acknowledged that etanercept has already been established as an efficacious therapeutic agent for the treatment of pediatric plaque psoriasis. The etanercept active comparator arm is thus included as a "benchmark" (ie, assessment of the efficacy of etanercept compared to placebo is intended to help internally validate the overall results of the pediatric psoriasis study). No formal efficacy comparisons between etanercept and guselkumab will be performed because the relatively small number of participants does not provide sufficient power to detect a difference between these two active treatment groups.

Assumptions for Placebo Response Rates

Across completed adult studies in moderate to severe plaque psoriasis, the placebo response rates for the endpoint of PGA (0 or 1) have varied between 3.9% and 8.5%, and PASI 75 rates have varied between 3.1% and 8.1% for clinical studies of ENBREL, STELARA, guselkumab, and HUMIRA. In the completed pediatric plaque psoriasis studies (ENBREL, STELARA), the placebo

response rates were slightly higher. The PGA responder (0 or 1) rates were 13% and 5.4%, while the PASI 75 rates were 11% and 10.8%, respectively.[18,25] Therefore, based on consideration of all the available data, an assumption of a 13% placebo response rate for both IGA 0/1 and PASI 75 was utilized for the proposed guselkumab pediatric study.

Assumptions for Guselkumab Response Rates

The IGA responder (0 or 1) rates in the active treatment arm of the adult guselkumab Phase 3 studies (CNTO1959PSO3001 and CNTO1959PSO3002) were 85.1% and 84.1%, respectively, and the PASI 75 rates were 91.2% and 86.3%, respectively. For the proposed pediatric study, a range of the response rates from 65% to 85% for both IGA 0/1 and PASI 75 in the guselkumab treatment group were utilized.

Power for Guselkumab and Placebo Comparisons

At baseline in Part 1, approximately 40 participants (30 in Part 1a and 10 in Part 1b) will be randomized to guselkumab, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) will be randomized to placebo.

As shown in Table 4, with the conservative assumptions of response rates of 65% in the guselkumab treatment group and 13% in the placebo group, the proposed 40 participants in the guselkumab group and 25 in the placebo group provide at least 99% power to detect a significant difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between the guselkumab and placebo treatment groups at a 2-sided significance level of 0.05. These sample sizes are also chosen to ensure sufficient power for major secondary endpoints.

Table 4: Power to Detect a Treatment Effect for Guselkumab Based on Different Assumptions of Response Rates

Endpoint IGA Score of 0 or 1/PASI 75 at Week 16		Power
Placebo (n=25)	Guselkumab (n=40)	
13%	65%	>99%
13%	70%	>99%
13%	75%	>99%
13%	85%	>99%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index

Assumptions for Etanercept Response Rates

The PGA responder (0 or 1) rate in the etanercept group of the etanercept pediatric plaque psoriasis study was 53% and the PASI 75 rate was 57%.[25] Therefore, a range of response rates from 53% to 60% for both IGA 0/1 and PASI 75 in the etanercept active comparator treatment group is utilized for the proposed pediatric study.

Power for Etanercept and Placebo Comparisons

With approximately 25 participants (15 in Part 1a and 10 in Part 1b) randomized to receive etanercept, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) in the placebo group, there will be at least 81% power to detect a significant difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between etanercept and placebo treatment groups at a 2-sided significance level of 0.05 (Table 5).

Table 5: Power to Detect a Treatment Effect for Etanercept Based on Different Assumptions of Response Rates

Endpoint IGA Score of 0 or 1/PASI 75 at Week 16		Power
Placebo (n=25)	Etanercept (n=25)	
13%	53%	81%
13%	55%	85%
13%	60%	92%

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index

In Part 2, at least 10 participants will be enrolled, and will depend on the number of participants in Part 1 who are exposed to guselkumab, to ensure a total of at least 100 participants from Part 1 and Part 2 will be exposed to guselkumab in this study.

9.3. Populations for Analyses

Descriptive statistics will be provided for participant disposition, demographics, baseline disease characteristics, and prior psoriasis medications for all participants randomized in Part 1 and all participants enrolled in Part 2. Details will be provided in the SAP.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Analysis Data Set

For the efficacy analyses, all randomized participants in Part 1 will be included. Participants will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received. In addition, efficacy summaries will also be provided for participants enrolled in Part 2.

9.4.1.2. Efficacy Definitions

Treatment Failure: Participants who discontinue study treatment due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis are considered treatment failures. The treatment failure rules will be documented in detail in the SAP.

PASI 50 Responders: Participants with ≥50% improvement in PASI from baseline.

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

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

PASI 100 Responders: Participants with 100% improvement in PASI from baseline.

Loss of PASI 90 Response: Defined as <90% improvement in PASI from baseline after Week 16 in a participant who had achieved ≥90% improvement in PASI from baseline at Week 16.

Loss of 50% of PASI Improvement: Defined as a loss of ≥50% of the improvement in PASI at Week 16 after treatment is withdrawn.

9.4.1.3. Primary Analysis

There are 2 primary estimands corresponding to the 2 co-primary endpoints in this study for participants randomized in Part 1 of this study: the proportion of participants who achieve an IGA score of cleared (0) or minimal (1) and the proportion of participants who achieve a PASI 75 response at Week 16. These 2 co-primary endpoints will be compared between the guselkumab group and the placebo group. In the primary efficacy analysis, data from all randomized participants will be analyzed according to their assigned treatment group. Participants who meet treatment failure criteria or initiate use with a low to high potency topical steroid as rescue treatment before Week 16 will be considered nonresponders for the primary endpoints at Week 16. In addition, participants who do not return for evaluation at Week 16 will be considered nonresponders at Week 16.

To address the primary objective, a 2-sided (α=0.05) Fisher's exact test, stratified by age and region, will be used for the co-primary endpoints. The exact 95% confidence interval for treatment difference between guselkumab and placebo treatment groups will be provided.

The study will be considered positive if the guselkumab group is significantly different from the placebo group for both co-primary endpoints. If one of the comparisons is not significant at the 2-sided α-level of 0.05, the co-primary endpoints will be considered not significant.

In addition, the comparison between etanercept and placebo for the co-primary endpoints will be performed and nominal p-values will be reported.

Subgroup analyses will be performed to evaluate consistency of the co-primary endpoints over demographics (including baseline weight), baseline disease characteristics and prior medications. Sensitivity analyses and per-protocol analysis will be performed for the co-primary endpoints and will be documented in the SAP.

9.4.1.4. Major Secondary Analyses

For the major secondary analyses, the Fisher's exact test, stratified by age and region, will be used to compare the proportion of participants responding to treatment. Continuous response parameters will be compared using an MMRM analysis or an ANCOVA model, adjusting for baseline value, age group, and region. All statistical testing will be performed at 2-sided (α=0.05). The major secondary analyses are based on participants randomized in Part 1 of the study and are:

- The proportion of participants who achieve a PASI 90 response at Week 16 will be compared between the guselkumab group and the placebo group.
- The proportion of participants who achieve an IGA score of cleared (0) at Week 16 will be compared between the guselkumab group and the placebo group.
- The proportion of participants who achieve a PASI 100 response at Week 16 will be compared between the guselkumab group and the placebo group.
- The change from baseline in CDLQI at Week 16 will be compared between the guselkumab group and the placebo group.

To control the overall Type 1 error rate, the primary analysis and major secondary analyses for the comparisons between the guselkumab and placebo groups will be tested in a fixed sequence as ordered above. That is, the first major secondary endpoint will be tested only if the co-primary endpoints are positive, and the subsequent endpoint will be tested only if the preceding endpoint in the sequence is positive. Details about the estimands corresponding to these major secondary endpoints will be specified in the SAP.

In addition, the comparison between etanercept and placebo for the major secondary endpoints will be performed and nominal p-values will be reported.

9.4.1.5. Other Secondary Analyses

In addition to the primary and major secondary analyses, the analyses for other efficacy endpoints will be performed and nominal p-values will be provided. The Fisher's exact test, stratified by age and region, will be used to compare the proportion of participants responding to treatment. Continuous response parameters will be compared using an MMRM analysis or an ANCOVA model, adjusting for baseline value, age, and region. Life table estimates will be provided for the time to event variables. All statistical testing will be performed at 2-sided (α=0.05). The other secondary analyses are:

Secondary Analyses for Participants Randomized in Part 1

- The proportion of retreated participants that achieve a PASI 90 response over time after retreatment will be summarized.
- The proportion of retreated participants that achieve PASI responses (PASI 50, 75, 90, and 100) or IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) over time after retreatment will be summarized.
- The time to loss of 50% of the Week 16 PASI improvement (ie, time to retreatment) after withdrawal will be summarized for participants randomized to guselkumab group.
- The time to loss of PASI 90 response after withdrawal will be summarized for participants randomized to guselkumab group.
- The proportion of participants who achieve a PASI 50 response at Week 16 will be compared between the guselkumab group and the placebo group.
- The proportion of participants who achieve an IGA score of mild or better ($\leq$2) at Week 16 will be compared between the guselkumab group and the placebo group.

- The percent improvement from baseline in PASI will be summarized over time through Week 16.
- The proportion of PASI responses (PASI 50, 75, 90, and 100) will be summarized over time through Week 16.
- The proportion of IGA responses (IGA of cleared [0], minimal [1], or mild [2], IGA of cleared [0] or minimal [1], and IGA of cleared [0]) will be summarized over time through Week 16.
- The proportion of participants with CDLQI=0 or 1 at Week 16 will be compared between the guselkumab group and the placebo group among randomized participants with a baseline CDLQI>1.
- Body surface area involved (BSA) and change from baseline in BSA at Week 16 will be compared between the guselkumab group and the placebo group.
- BSA and change from baseline in BSA will be summarized over time through Week 16.
- The proportion of participants with FDLQI=0 or 1 at Week 16 will be compared between the guselkumab group and the placebo group among randomized participants with a baseline FDLQI>1.
- The change from baseline in FDLQI at Week 16 will be compared between the guselkumab group and the placebo group.

In addition, relevant comparisons at Week 16 will also be conducted between the etanercept group and the placebo group.

Secondary Analyses for Participants Enrolled in Part 2

PASI responses, IGA responses, PASI percent improvement, the change from baseline in CDLQI and FDLQI, the proportion of participants achieving a CDLQI of 0 or 1, and the proportion of participants achieving an FDLQI of 0 or 1 will be summarized over time through Week 52 for participants enrolled in Part 2.

In additional, efficacy in the LTE period will be summarized separately for participants in Part 1 and Part 2 of the study.

9.4.2. Usability Assessments

The usability of the CCI [redacted] will be assessed in Part 2 of the study using a CCI [redacted] and responses will be presented.

9.4.3. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, changes in laboratory assessments, changes in vital signs, and suicidal ideation and behavior based on C-SSRS will be summarized. Treatment emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

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

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using MedDRA. Intervention-emergent adverse events are adverse events with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Safety will be summarized separately for Part 1 and Part 2.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an adverse event, or who experience a severe or a serious adverse event.

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

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of related AEs as assessed by the investigator.
- 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. Descriptive statistics will be calculated for each laboratory analyte and changes from baseline at each scheduled time point. In addition, National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades will be used in the summary of laboratory data. A listing of participants with post-baseline abnormal laboratory results based on NCI-CTCAE grades will also be provided.

Vital Signs

Descriptive statistics of heart rate, blood pressure (systolic and diastolic) values, and temperature, and changes from baseline will be summarized by treatment group.

Pain During Injection

Pain during injection assessed using FPS-R (Appendix 17, Section 10.17) and VAS (Appendix 18, Section 10.18) will be summarized by study intervention received.

Head Circumference

Head circumference will be summarized over time by treatment group.

Immunoglobulin (Ig) Analyses

The serum levels of IgG, IgA and IgM will be summarized by treatment group.

Suicidal Ideation and Behavior

Suicidal ideation and behavior based on the C-SSRS and AEs will be summarized descriptively.

Anticipated Events

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen. For the purposes of this study the event of psoriasis will be considered an anticipated event. Serious adverse events relating to lack of efficacy (eg, events attributed to "psoriasis") or progression of the disease under study will not be individually unblinded for expedited reporting. These anticipated events will be recorded and reported as outlined in Appendix 19, Section 10.19.

9.4.4. Other Analyses

Pharmacokinetic Analyses

Serum guselkumab concentrations over time will be summarized for treated participants. Descriptive statistics, including arithmetic mean, SD, median, interquartile range, minimum, and maximum will be calculated at each nominal sampling timepoint. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) 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. In addition, serum guselkumab concentrations will be summarized at the time of retreatment in participants who withdrawn from guselkumab at Week 16.

A population PK analysis using a nonlinear mixed-effects modeling (NONMEM) approach will be used to characterize the disposition characteristics of guselkumab 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 age) 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.

Pharmacokinetic/Pharmacodynamic Analyses

If feasible, a suitable population PK/pharmacodynamic (PD) model will be developed to describe the exposure-response relationship in this study. 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.

Immunogenicity Analyses

The incidence and titers of anti-guselkumab antibodies will be summarized for all participants who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab). A listing of participants who are positive for antibodies to guselkumab will be provided.

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

9.5. Interim Analysis

One interim analysis is planned for this study after all participants ≥12 to <18 years of age in Part 1a have completed Week 16. All available guselkumab PK data for participants ≥12 to <18 years of age through Week 16 will be evaluated via modeling and simulation, to determine if the body weight-based dose used in Part 1a provided exposure comparable to adults, or whether a revised body weight-based dose should be instituted in Part 1b. This evaluation will be conducted by sponsor personnel who are otherwise not participating in the conduct of this study. Efficacy data will not be analyzed in the interim analyses and no adjustment will be made for the significance level.

The planned interim PK analyses will be documented separately.

9.5.1. Data Monitoring Committee

Safety monitoring will be performed by a sponsor medical monitor throughout the study, as well as by an independent DMC. Any safety concerns will be communicated to the sponsor. The DMC will be an independent committee of 3 members and will include individuals with expertise in pediatric dermatology, and biostatistics. None of the members will be participating as investigators in the study. The major function of this committee will be to monitor the safety of the study intervention. The DMC will periodically review tabulated safety summaries and any additional safety data that the DMC may request during the conduct of the study. Prior to any DMC review, the DMC charter will define and document the content of the safety summaries, the DMC's role and responsibilities, and the general procedures (including communications).

Prior to enrollment of participants ≥6 to <12 years of age in Part 1b and enrollment of participants ≥12 to <18 years of age into Part 2, the DMC will review the available safety data from the participants enrolled in Part 1a of the study who have completed their Week 16 visit, and provide a recommendation as to whether the sponsor can initiate enrollment of Part 1b and Part 2. Additionally, prior to enrollment of participants ≥6 to <12 years of age into Part 2, the DMC will review all available safety data once all participants in Part 1b have completed 16 weeks of treatment and provide a recommendation as to whether enrollment of participants ≥6 to <12 years of age into Part 2 can be initiated.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Trademarks

AE	adverse event
ANOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CHF	congestive heart failure
CL/F	clearance
COVID-19	SARS-CoV-2
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	database lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
FDLQI	Family Dermatology Life Quality Index
HBc	hepatitis B virus core
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
ICF	informed consent form
Ig	immunoglobulin
IGA	Investigator Global Assessment
IgG1	Immunoglobulin G1
IgG1λ	immunoglobulin G1 lambda
IGRA	interferon gamma release assay
IL	interleukin
IWRS	interactive web response system
LTE	long-term extension
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
MTX	methotrexate
NAbs	neutralizing antibodies
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic
PFS	prefilled syringe
PFS-U	Pre-filled syringe with an UltraSafe PLUS™ Passive Needle Guard or Pre-filled syringe with an UltraSafe Passive® Needle Guard
CCI	[redacted]
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PQC	product quality complaint
PsA	psoriatic arthritis
PSSD	Psoriasis Symptom and Sign Diary
q8w	every 8 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
V/F	volume of distribution

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

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 participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

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 participants, 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) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

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

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.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 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 participant:

- 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

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 participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants 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 adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

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 if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS AND ASSENT FORM

A limited number of study sites will be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (Sponsor and the Study Site) agree, and if participation is allowed by local regulations and EC/IRB requirements, the Sponsor will provide an eTablet device (e.g., iPad®) to the study site to use for the electronic informed consent. Overall the consent process will remain the same, as described in this section; however, at the study sites utilizing electronic informed consent, participants or their legally acceptable representatives will be able to review the entire informed consent form content on the eTablet. The ability for participants or their legally acceptable representatives to review the paper informed consent form is always an option at sites utilizing electronic informed consent. Depending on local regulations and EC/IRB requirements, the participants or their legally acceptable representatives and person obtaining consent will either apply their handwritten signature electronically directly onto the eTablet, or apply their handwritten signature to a printed paper copy of the informed consent in accordance with local regulations.

Each participant (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 participant 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 participants 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. Participants 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 participant will receive for the treatment of his or her disease. Participants 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 participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant 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 participant'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 participant.

If the participant 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 participant or legally acceptable representative is obtained.

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

When prior consent of the participant is not possible and the participant's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

RECRUITMENT STRATEGY

This section is not applicable as the enrollment part of this study is closed.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

The informed consent obtained from the participant (or his or her legally designated representative) includes information about, and where required per applicable regulations, 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. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant 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 or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory research is not conducted under standards appropriate for the return of data to participants. 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 participants 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.

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 guselkumab, to understand

psoriasis, to understand differential intervention responders, and to develop tests/assays related to guselkumab and psoriasis. The research may begin at any time during the study or the post-study storage period. The post-study storage period will begin after completion of the final clinical study report.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

COMMITTEES STRUCTURE

Data Monitoring Committee

Safety monitoring will be performed by a sponsor medical monitor throughout the study, as well as by an independent DMC. Any safety concerns will be communicated to the sponsor. The DMC will be an independent committee of 3 members and will include individuals with expertise in pediatric dermatology, and biostatistics. None of the members will be participating as investigators in the study.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the study site or investigator and not previously published, and any data, or analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use. Data for all indications will be submitted according to local requirements.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright

protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

DATA QUALITY ASSURANCE

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 direct transmission of efficacy data to the vendor database and then 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 the CRF 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.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

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 participant 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 and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

The investigator or trained study personnel administered C-SSRS will be recorded and will be considered source documentation.

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

CASE REPORT FORM COMPLETION

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

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

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

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

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

MONITORING

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 into the CRF with the source documents (eg, hospital/clinic/physician’s office medical records); a sample may be reviewed. 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 documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

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

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

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. Participant 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.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, 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. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

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.

STUDY AND SITE CLOSURE

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 participants by the investigator
- Discontinuation of further study intervention development

10.3. Appendix 3: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4, Pregnancy and Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Girl of Childbearing Potential

A girl is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Girl Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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

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

Examples of Contraceptives

As noted in Inclusion Criterion 7, study participants who are girls of childbearing potential must be using a highly effective method of contraception. Examples of highly effective methods of contraception are provided below; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR FEMALE PARTICIPANTS DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]

• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY for girls of childbearing potential (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy during the study

Any participant who becomes pregnant during the study must discontinue further study treatment.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition 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 adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event 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 participant 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For etanercept, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

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

Possible

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

Probable

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

Very Likely

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

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 participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

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

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)

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

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, 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 adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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

- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant 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 a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 16 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

A 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 participants, 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.

All CCI associated with device-related PQCs will be investigated including the return of the device to the sponsor for inspection. PFS-U should be retained for further investigation if requested by the sponsor.

Procedures

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

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.1.2, Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.5. Appendix 5: 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. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant 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 participants 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.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). Tuberculosis, a comprehensive international approach. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.6. Appendix 6: Hepatitis B Virus (HBV) Screening With HBV DNA Testing

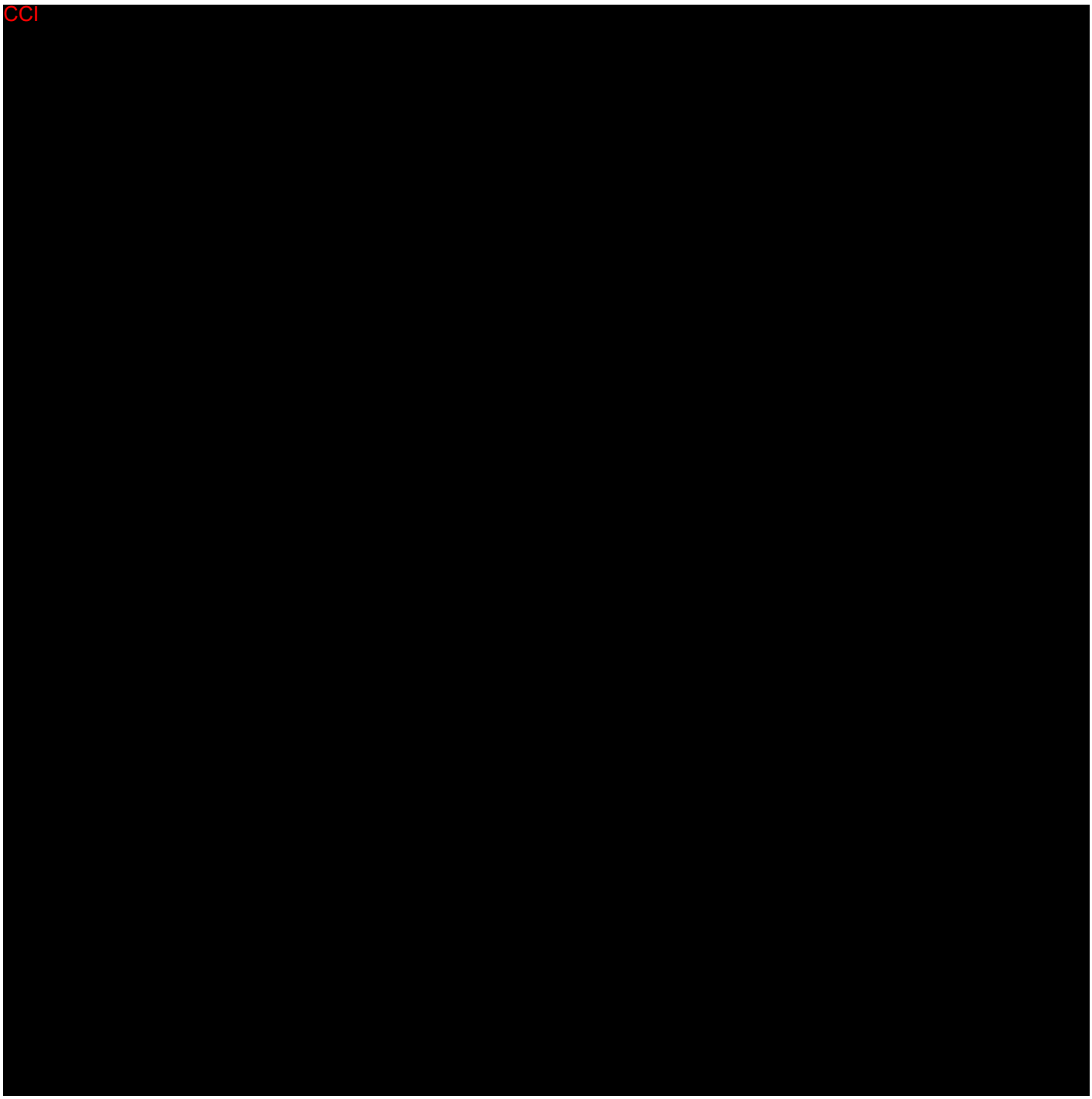
Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

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

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

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

10.7. Appendix 7: Investigator's Global Assessment (IGA)



10.8. Appendix 8: Psoriasis Area and Severity Index (PASI)

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 the disease is calculated as follows.

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

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

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

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

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

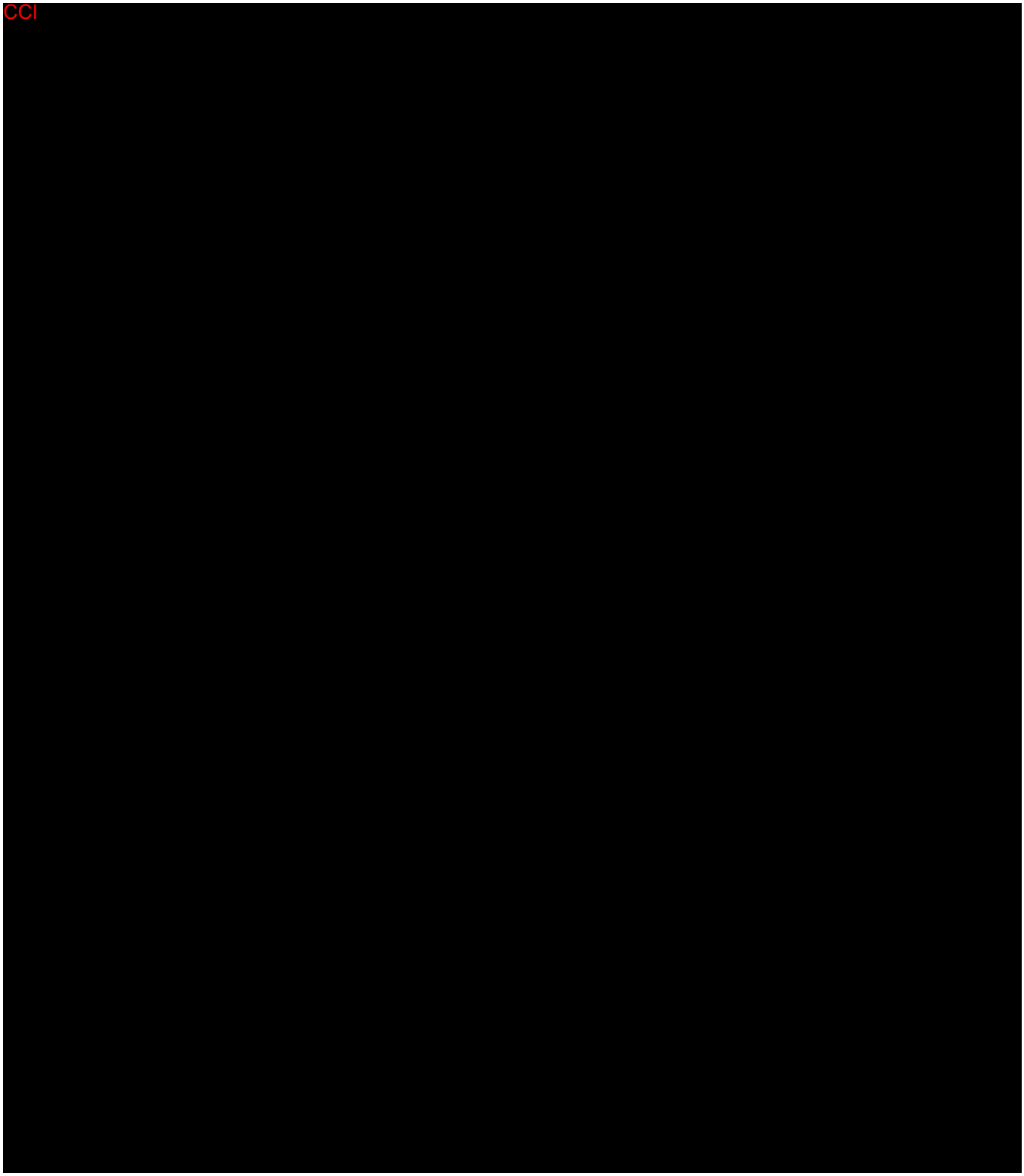
a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula is:

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

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

10.9. Appendix 9: Children's Dermatology Life Quality Index



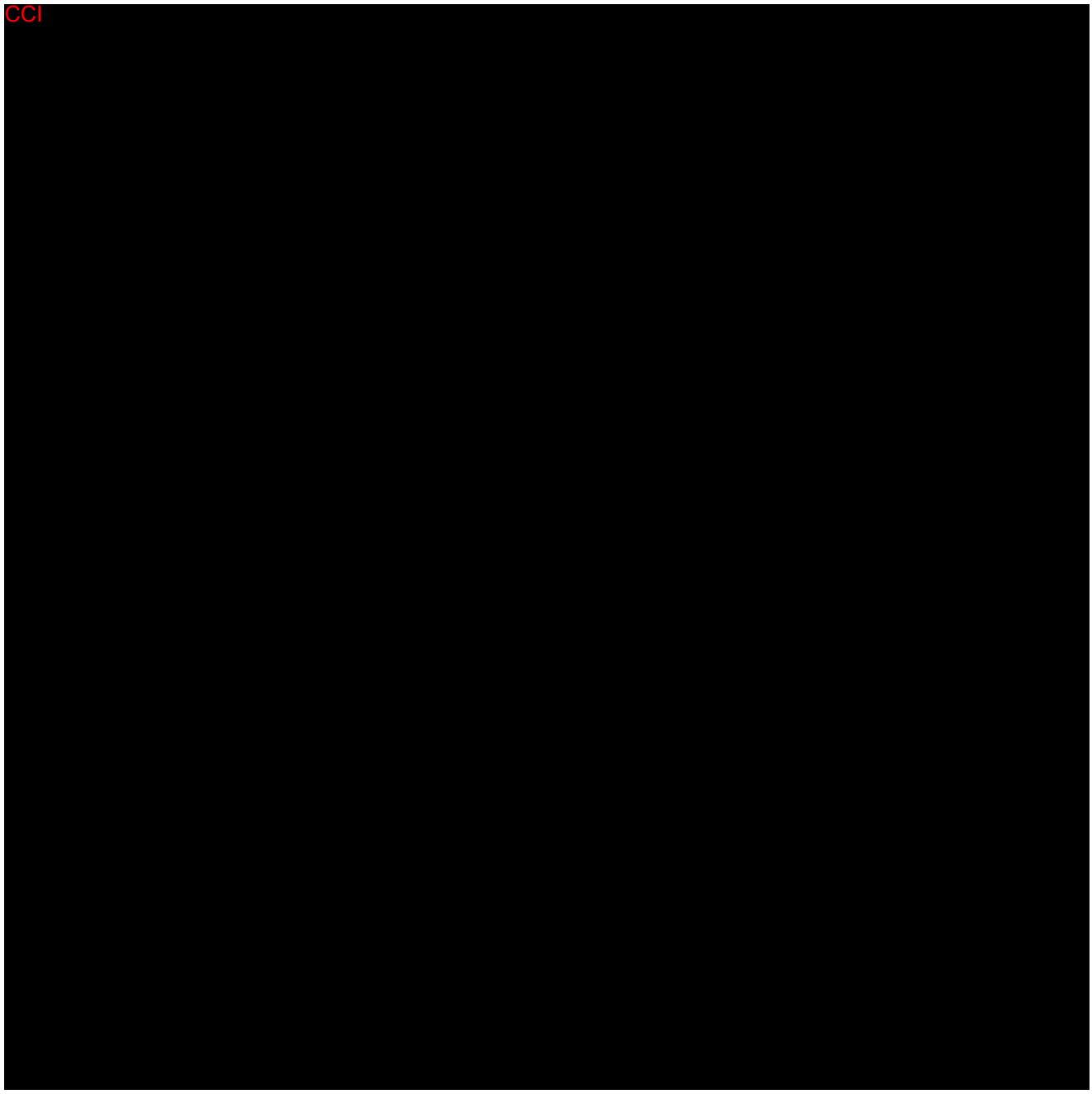
10.10. Appendix 10: Family Dermatology Life Quality Index

The Family Dermatology Life Quality Index (FDLQI)

CCI

[redacted]

CCI



10.11. Appendix 11: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities 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.

Protocol-Required Safety Laboratory Assessments

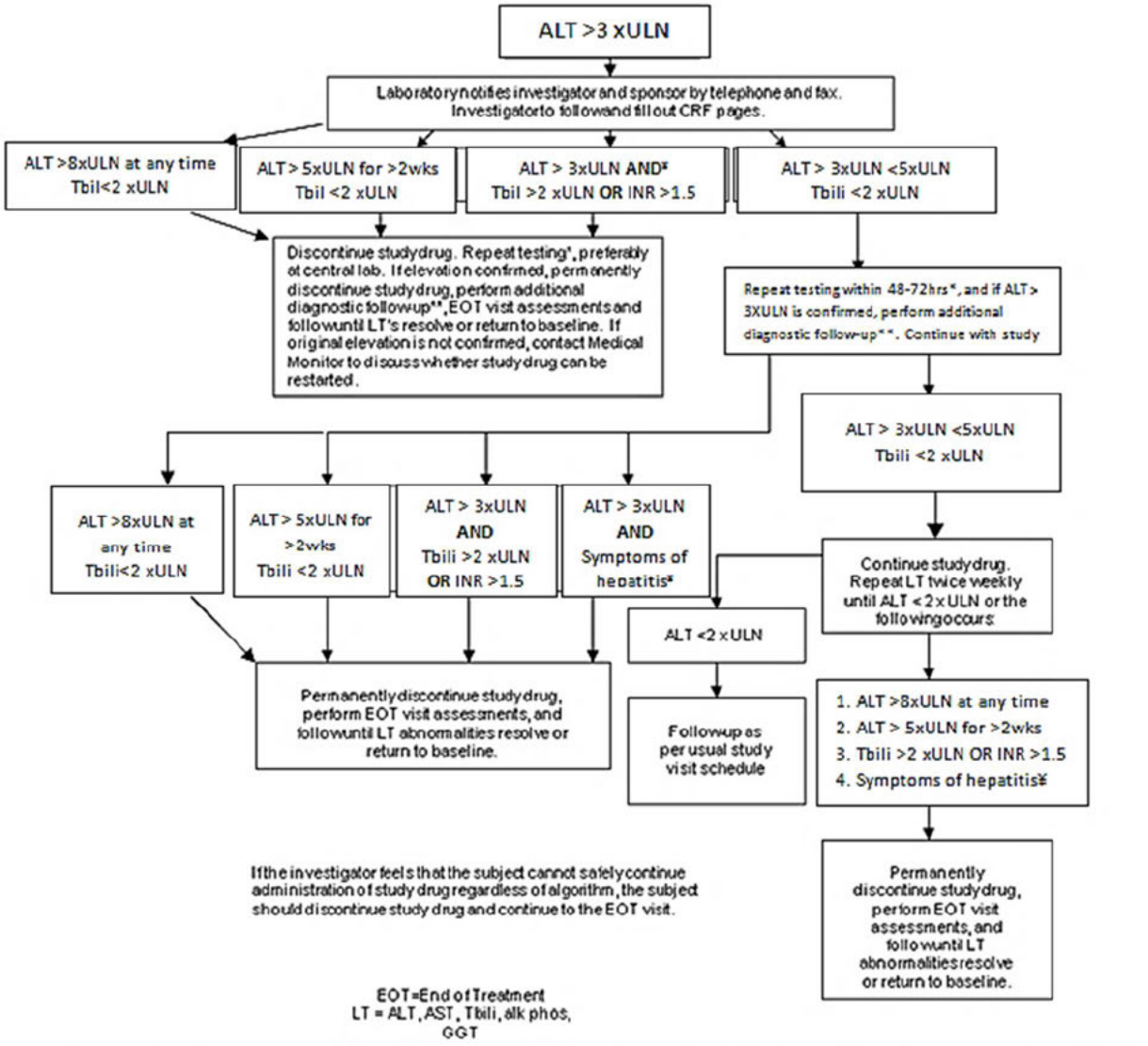
Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH	White Blood Cell (CBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Bands
Clinical Chemistry	Sodium Potassium Chloride Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic	Total bilirubin Indirect bilirubin Alkaline phosphatase Calcium Phosphate Albumin Total protein	
Other Screening Tests	• Urine pregnancy testing for girls of childbearing potential only • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], and hepatitis C virus antibody; serum antibody titers to varicella, measles, mumps, and rubella) • Serum IgG, IgM, IgA levels		

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.

10.12. Appendix 12: Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease

The ALT criteria in this algorithm are also applicable to AST.

NOTE: "Liver tests" or "LT's" is the proper name for what are often called "liver function tests" or "LFT's"



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

**SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED

THE COMPLETE WORK-UP BELOW (ITEMS 1-5) SHOULD BE PERFORMED IN EVERY SITUATION WHERE "" APPEARS ABOVE. ITEMS 6-7 ARE OPTIONAL, TO BE CONSIDERED ON CASE-BY-CASE BASIS. ALL CASES SHOULD BE REPORTED WITH APPROPRIATE SOURCE DOCUMENTATION.**
THE STUDY MEDICAL MONITOR SHOULD BE NOTIFIED WHEN THE ABNORMALITIES ARE DETECTED AND PROVIDED WITH AN UPDATE OF THE RESULTS OF THE DIAGNOSTIC WORK-UP

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	**ALT ≥ 3 × ULN**	**≥ 5**
Cholestatic	**ALT ≥ 3 × ULN**	**≤ 2**
Mixed	**ALT ≥ 3 × ULN and AP ≥ 2 × ULN**	**> 2 to < 5**

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy).
2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented.

If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.
   - If patient is immunosuppressed, test for HCV RNA and HEV RNA.
   - If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.
5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:
   - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
   - if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
   - in cases of DILI where continued use or re-exposure to the implicated agent is expected.
   - if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

7. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

Abbreviations

AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
CMV	cytomegalovirus
CRP	C-reactive protein
CT	computerized tomography
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EOI	end of intervention
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
IgM	immunoglobin M
INR	international normalized ratio
LT/LFT	liver tests/liver function tests
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
Tbili	total bilirubin
TIBC	total iron binding capacity
ULN	upper limit of normal
WBC	white blood count

10.13. Appendix 13: Columbia-Suicide Severity Rating Scale (Children's Baseline)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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C-SSRS—Children's Baseline (Version 6/23/10)
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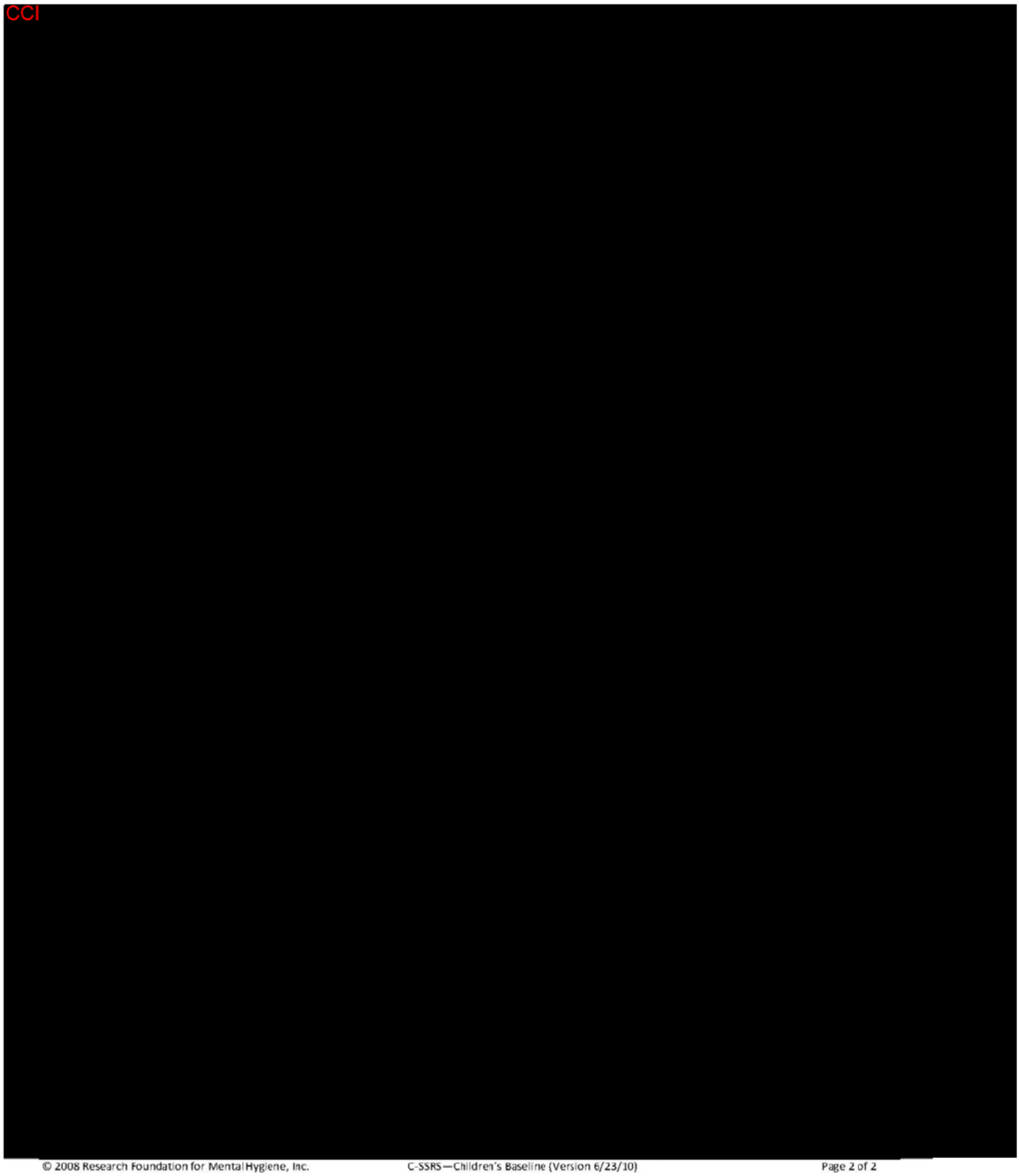

C-SSRS—Children's Baseline (Version 6/23/10) Page 2 of 2

10.14. Appendix 14: Columbia-Suicide Severity Rating Scale (Baseline/Screening)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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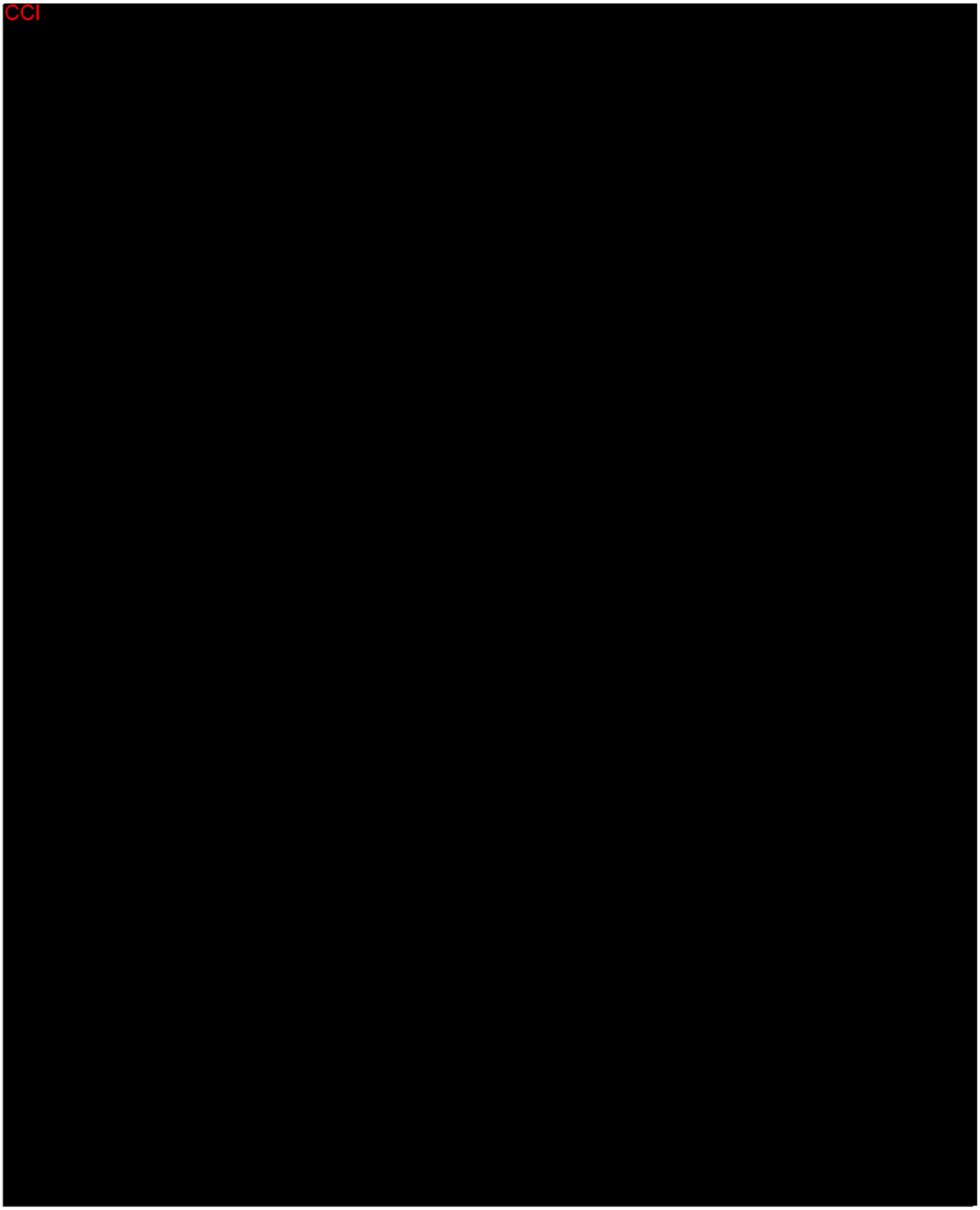

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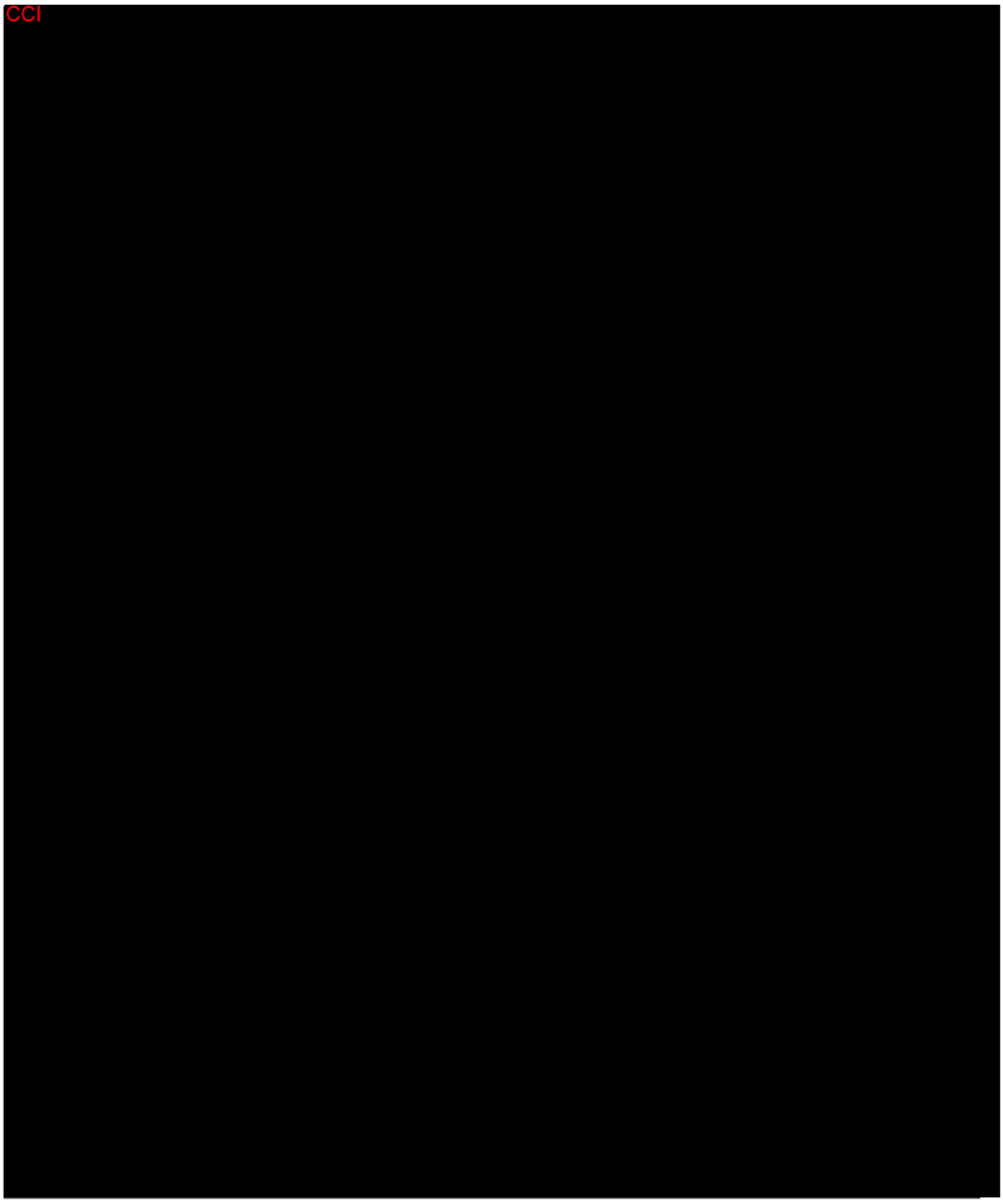

C-SSRS—Baseline/Screening(Version 1/14/09)
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10.15. Appendix 15: Columbia-Suicide Severity Rating Scale (Children's Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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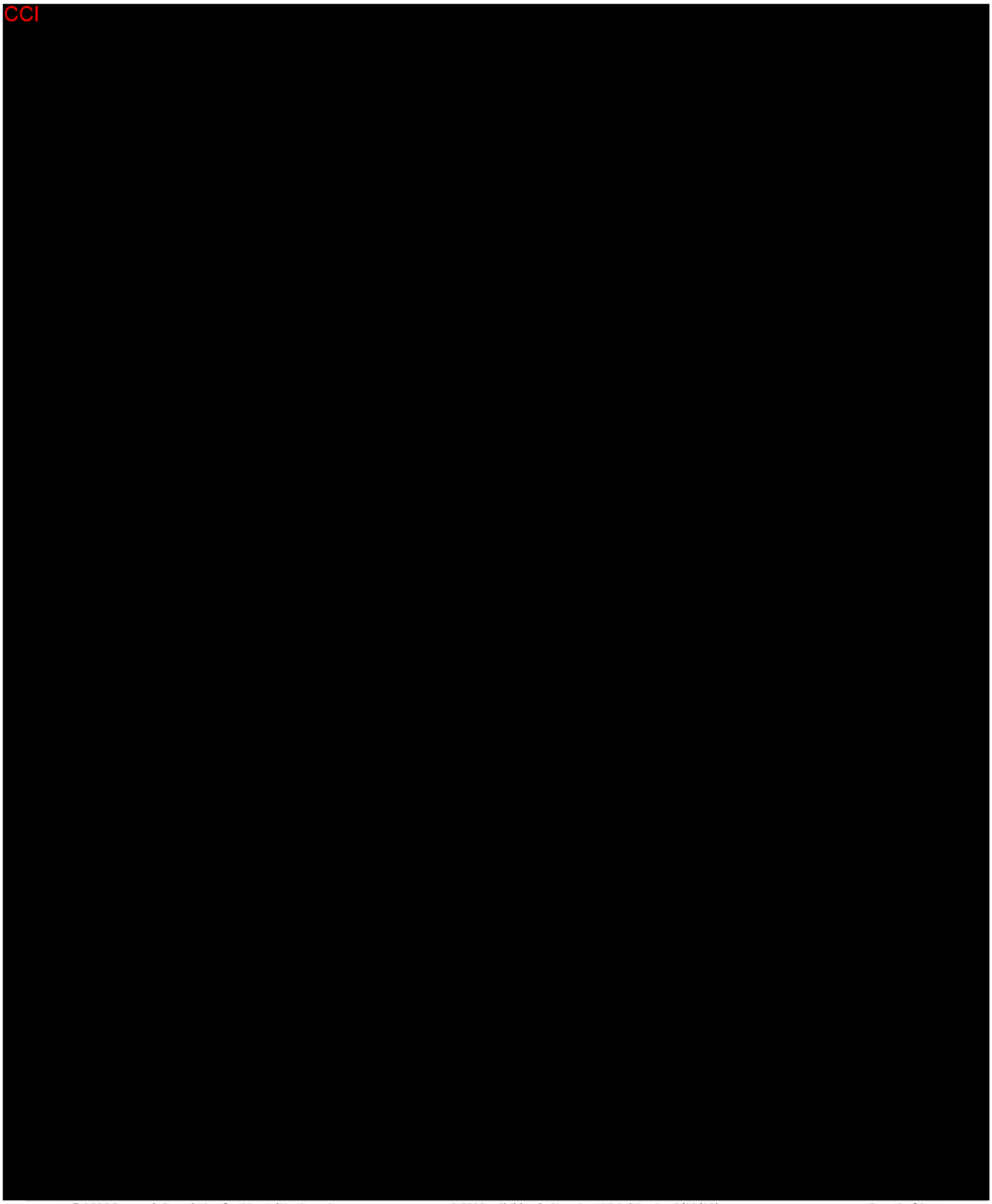

C-SSRS—Children's Since Last Visit (Version 6/23/10)
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10.16. Appendix 16: Columbia-Suicide Severity Rating Scale (Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

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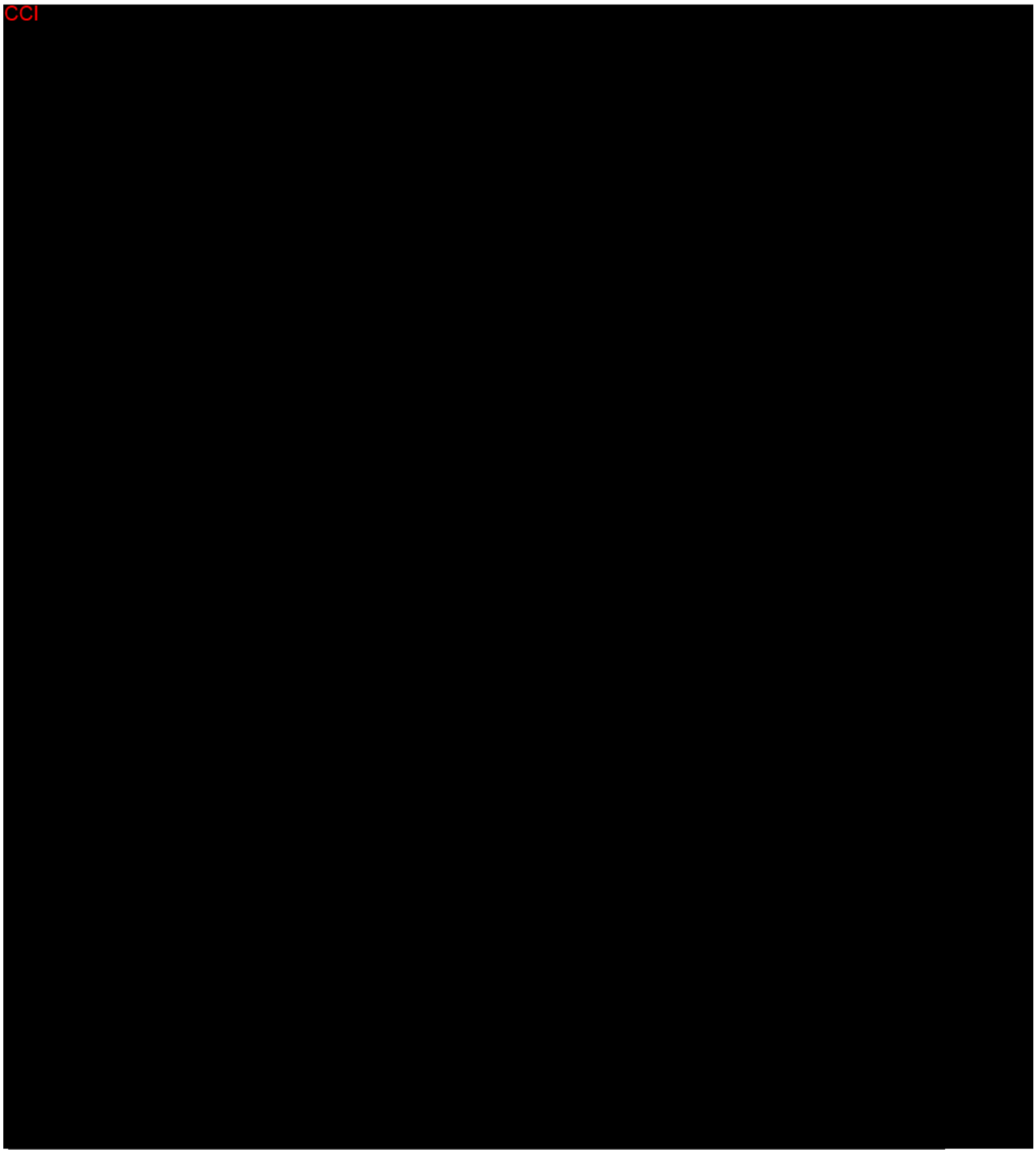

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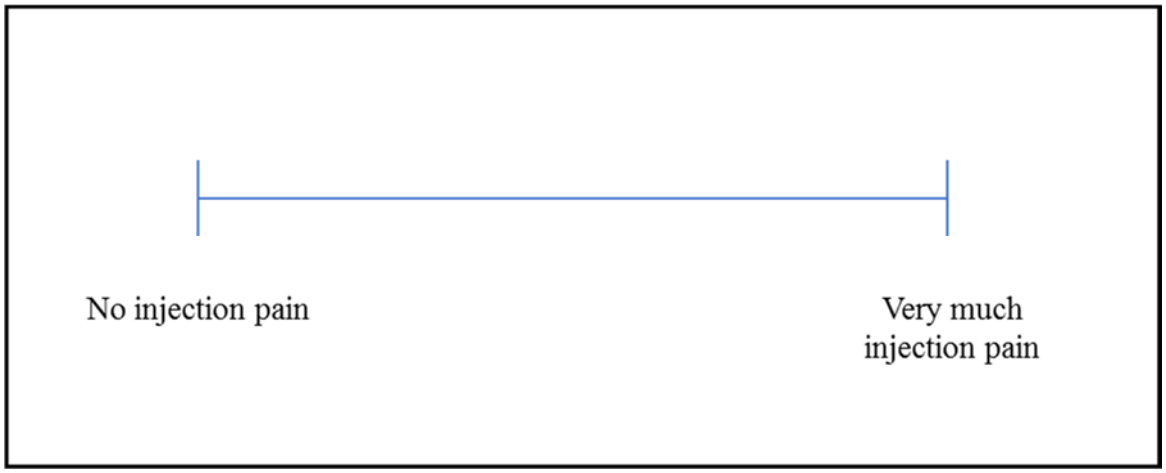
10.17. Appendix 17: Faces Pain Scale – Revised (FPS-R) for Injection Pain

CCI

10.18. Appendix 18: Injection Pain Visual Analog Scale (VAS)

The participant will evaluate injection pain intensity by answering the following question:

Please rate the pain you experienced with the injection by placing a vertical mark on the line below.



The line will be 100 mm in length. The participant will be instructed to make a mark on the line to indicate the intensity of the pain he/she experienced with the injection

Using a standard ruler, a trained observer (an individual under the supervision of the principal investigator who observes and instructs participants regarding trial procedures) will measure the distance in millimeters (0-100) from the left of the scale to the participant's mark and record this distance in the case report form.

10.19. Appendix 19: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the event of psoriasis will be considered an anticipated event.

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 8.3.1. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).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10.22. Appendix 22: Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation or quarantine of participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

If, as a result of the COVID-19 pandemic, visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted, after consultation with the participant, investigator, and the sponsor..

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the CSR.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation / study intervention storage and administration [including training where pertinent])
  - procurement of study intervention by patients (or designee) or shipment of study intervention from the study site directly to patients for at home administration

  - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
  - other procedures may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

10.23. Appendix 23: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 4 (24 February 2022)

Overall Rationale for the Amendment: Clarifications and additions to align with the latest protocol template for COVID-19 situations, tuberculosis language, handling potential Hy's law situations, and a clarification on a post-trial access and the long-term extension.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis; Section 6.1, Study Interventions Administered; Section 8, Study Assessments and Procedures	Update language for post-trial access	Clarification of minimum post-trial access for patients reaching 18 years of age prior to or during the LTE
Section 1.3.3 Long-term Extension Phase (Week 60 Through Study Completion/Termination)	Clarified that participants will be able to begin self-administration in the LTE	Further clarification that self-administration is allowed in the LTE
Section 5.1. Inclusion Criteria	Updated Inclusion Criteria 11	Clarification for suspected false-positive QuantiFERON®-TB tests
Section 5.2 Exclusion Criteria	Added Exclusion Criteria 42 for COVID-19 infections	Added language to align with the latest immunology-specific protocol template update
5.3 Lifestyle Considerations	Added recommendation to be up to date on all vaccinations including COVID-19	Added language to align with the latest immunology-specific protocol template update
6.5.6 Vaccinations (including COVID-19)	Added vaccinations section to Concomitant Therapy Section	Added language to align with the latest immunology-specific protocol template update
7.1 Discontinuation of Study Intervention	Clarified language regarding discontinuation of study intervention for TB	Updated language to align with the latest immunology-specific TB protocol template language
Section 8 Study Assessments and Procedures	Clarified language regarding false-positive TB tests	Added clarifying statement on how to handle suspected false-positive TB tests
8.3.1.2 Serious Adverse Events	Updated Hy's law language	Added clarification statement on how to handle potential Hy's law cases
Section 10.3 Appendix 3: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Minor updates to the appendix.	Incorporation of clarifying edits from the latest protocol template update.
Section 10.12 Appendix 12: Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease	Minor updates to the appendix.	Incorporation of clarifying edits from the latest protocol template update.

Section Number and Name	Description of Change	Brief Rationale
Section 10.22 Appendix 22: Guidance on Study Conduct During the COVID-19 Pandemic	Added COVID-19 appendix	COVID-19 appendix added to align with latest Sponsor COVID-19 protocol template
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 3 (19 Feb 2020)

Overall Rationale for the Amendment: To clarify information related to the management of liver function test abnormalities.

Section Number and Name	Description of Change	Brief Rationale
1.3.1 Schedule of Activities—Screening Through Week 52 — Part 1a and 1b	**Clinical Laboratory Assessment—Chemistry** Added footnote w: w. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.12).	Footnote added to clarify that testing will be performed to evaluate specific markers of liver function abnormalities.
1.3.2 Schedule of Activities—Screening Through Week 52 — Part 2	**Clinical Laboratory Assessment—Chemistry** Added footnote v: v. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.12).	Footnote added to clarify that testing will be performed to evaluate specific markers of liver function abnormalities.
1.3.3 Schedule of Activities—Long-term Extension Phase (Week 60 Through Study Completion/Termination)	**Clinical Laboratory Assessment—Chemistry** Added footnote k: k. Includes liver function testing described in Section 8.2.3. A description of the required approach for evaluation of specific LFT abnormalities is in Appendix 12 (Section 10.12).	Footnote added to clarify that testing will be performed to evaluate specific markers of liver function abnormalities.
7.1. Discontinuation of Study Intervention	Item **(bullet# 11)** was inserted: The participant has liver test abnormalities as described in Section 8.2.3 and Appendix 12 (Section 10.12). Such abnormalities would include the following: • ALT or AST >8 x ULN • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN **and** (total bilirubin >2 x ULN **or** international normalized ratio [INR] >1.5) • ALT or AST >3 x ULN **and** symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%])	This item was added to clarify the criteria for discontinuation of study intervention due to liver test abnormalities.

Section Number and Name	Description of Change	Brief Rationale
8.2.3. Clinical Safety Laboratory Assessments	Information regarding abnormal liver function tests and retesting was added as a **third paragraph**: If laboratory testing for a participant who is enrolled in the study and receiving study intervention reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN, study agent should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours, if possible, but no later than 72 hours following notification of test results. Additional clinical and laboratory studies and consultations may be performed to evaluate the underlying etiology of abnormal findings. See Appendix 12 (Section 10.12; Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease) for additional information on monitoring and assessment of abnormal liver function tests.	A paragraph was added to clarify the cutoffs for abnormal liver function tests, what action should be taken in the event of an abnormal test, that additional testing may be requested, and the appropriate appendix number for liver function tests was added.
10.12. Appendix 12	Added updated Appendix 12: Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease.	This Appendix was added with the most current updated version. The Appendix provides detailed guidance regarding additional tests and evaluations to be obtained in the setting of specific patterns of liver enzyme abnormalities.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 (08 May 2019)

Overall Rationale for the Amendment: To clarify that assessment of serum guselkumab concentrations and antibodies to guselkumab are not required at Weeks 0, 4, and 12 for participants who were randomized to etanercept.

Section number and Name	Description of Change	Brief Rationale
Section 1.3.1. Screening Through Week 52 – Part 1a and 1b.	Added footnote (y) to Week 0, 4, and 12 for rows of Serum guselkumab concentration and Antibodies to guselkumab. Footnote added: y. Participants randomized to etanercept will not require a blood draw for pharmacokinetics and/or immunogenicity assessments at these visits.	To clarify that assessment of serum guselkumab concentrations and antibodies to guselkumab are not required at Weeks 0, 4, and 12 for participants who were randomized to etanercept.
Section 8. Study Assessments and Procedures. Screening Phase.	Deletion of reference to Appendix 6: As outlined in the eligibility criteria, participants must undergo testing for TB ~~(see Appendix 6)~~ and their medical history assessment must include specific questions	Inappropriate internal referencing to Appendix 6.

Section number and Name	Description of Change	Brief Rationale
	about a history of TB or known exposure to individuals with active TB.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (09 May 2018)

Overall Rationale for the Amendment: The overall reason for the amendment is to address health authority advice.

Section number and Name	Description of Change	Brief Rationale
Sec 1.3.1. Schedule of Activities. Screening Through Week 52 – Part 1a and 1b	Physical examination: added Week 20 visit Footnote added to Vital signs[k]; and all subsequent footnotes were updated. Height: added Weeks 12, 20, and 36 visits Hematology: added Weeks 8, 36, and 52 visits Chemistry: added Weeks 8, 36, and 52 visits Antibodies to guselkumab: added Week 4 visit Footnoted added: k. Vital signs include heart rate, blood pressure, and temperature.	To address regulatory authority's request.
Sec 1.3.1. Schedule of Activities. Screening Through Week 52 – Part 1a and 1b	Assessment of injection pain: removed Week 8.	Removed to correct error.
Sec 1.3.2. Schedule of Activities. Screening Through Week 52 – Part 2	CCI [redacted]: Added Weeks 4, 20, 28, 36, and 44 visits. Physical examination: added Week 20 visit Footnote added to Vital signs[i]; and all subsequent footnotes were updated. Height Assessment: added Weeks 12, 20, and 36 visits Hematology: added Weeks 8, 36, and 52 visits Chemistry: added Weeks 8, 36, and 52 visits Antibodies to guselkumab: added Week 4 visit Footnote f: updated "HCP" references with "study staff". Footnote added: i. Vital signs include heart rate, blood pressure, and temperature.	To address regulatory authority's request.
Section 1.3.3. Long-Term Extension Phase	Footnote added to Vital signs[f]; and all subsequent footnotes were updated. Footnoted added: f. Vital signs include heart rate, blood pressure, and temperature.	To address regulatory authority's request.
Section 2.3.1. Guselkumab	Updated internal reference from "(IB, Section 6)" to "(IB, Section 5)".	To address incorrect internal reference.
Section 4.1: Overall Design	Updated "HCP" references with "study staff". Updated "very" with "ultra-" high potency topical steroids.	Consistent terminology. Consistent terminology.

Section number and Name	Description of Change	Brief Rationale
	Added "(should not initiate rescue topical steroids at or after Week 16)."	Clarification on initiating rescue topical steroids.
Section 5.1. Inclusion Criteria. #16	Added "≥" to 4.5 x 10^3 cells/µL to white blood cells.	To address the missing sign.
Section 5.1. Exclusion Criteria. #20	Updated "(…see inclusion criterion 10)" to "(…see inclusion criterion 12)".	To address incorrect internal reference.
Section 6.1 Study Interventions Administered	Removed "commercially available" to read "This will be either the CCI PFS…" . Added "Patients or caregivers may be retrained at any time during the study, including if there is a use issue reported by the patient or caregiver." Updated "HCP" references with "study staff".	Updated to remove an error. To address regulatory authority's request. Consistent terminology.
Section 6.4. Study Intervention Compliance	Added "Etanercept dosing should occur within a range of ±3 days of the scheduled date."	Additional guidance on etanercept dosing window.
Section 6.5.1. Rescue Medication	Updated "very" with "ultra-" high potency topical steroids. Added "(should not initiate rescue topical steroids at or after Week 16)."	Consistent terminology. Clarification on initiating rescue topical steroids.
Section 7.1. Discontinuation of Study Intervention	Updated "…symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm mercury (Hg)." with "…symptomatic hypotension (defined as systolic BP < [70 + 2 x age in years]).[30]" Updated "…shown no improvement…" with "…shown insufficient improvement…"	To address regulatory authority's request.
Section 8. Study Assessments and Procedures. Overview	Added "The approximate total volume of blood per type of sample to be collected through Week 52 is presented in Table 1." Updated "…approximately 66.5 mL (Table 1) with maximum volumes of 10 mL at screening and 10.5 mL at other study visits." with "approximately 79.5 mL with maximum volume of 17.5 mL at screening and 10.5 mL at other study visits (Table 2)." Added "Where possible, tests are combined to allow for fewer draw tubes and in the interest of keeping blood volumes to a minimum. Therefore, the total volume is less than that presented in Table 1." Updated volumes for Table 1: -Hematology: from 5 to 8 for per participant, and 10 to 16 for total volume -Serum chemistry: from 5 to 8 for per participant, and 12.5 to 20 for total volume	To address regulatory authority's request and updated total volumes based on additional laboratory timepoints.

Section number and Name	Description of Change	Brief Rationale
	-Serology (HIV, hepatitis): from 6 to 6.5 for volume per sample and for total volume -QuantiFERON-TB testing: from 3 to 4 for volume per sample and for total volume -Pharmacokinetics sample only: from 3 to 2 for per participant, and 7.5 to 5 for total volume -Pharmacokinetics and immunogenicity samples: from 5 to 6 for per participant, and 17.5 to 21 for total volume -Approximate total: from 66.5 mL to 82.5 mL Added new Table 2: Approximate Volume of Blood to be Collected per Visit Through Week 52.	
Section 8. Study Assessments and Procedures. Part 2.	Updated "HCP" references with "study staff".	Consistent terminology.
Section 8. Study Assessments and Procedures. Study-Specific Materials.	Added "• iPad® and site user guide, if the study site is participating in electronic informed consent"	Add information about electronic informed consent.
Section 8.2.2. Vital Signs	Updated "Heart rate and blood pressure will be measured." to "Heart rate, blood pressure, and temperature will be measured."	To address regulatory authority's request.
Section 8.2.9. Allergic Reactions	Updated "…symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure." with "…symptomatic hypotension (defined as systolic BP < [70 + 2 x age in years]).[30]"	To address regulatory authority's request.
Section 8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information	Changed subheadings "All Adverse Events" and "Serious Adverse Events" to numbered subheadings as Section 8.3.1.1. and Section 8.3.1.2, respectively. Table of contents updated accordingly.	Administrative update to link to appropriate protocol sections.
Section 8.3.1.1 All Adverse Events (new numbered heading)	Added "All SAEs and nonserious AEs that represent events of suicidal ideation or suicidal behavior, including any of the following diagnoses, must be reported to the sponsor following the procedures outlined in Section 8.3.1.2: • Suicidal ideation • Suicidal behavior, including completed suicide • Self-injurious behavior"	To address regulatory authority's request.
Section 8.3.5. Events of Special Interest	Updated internal reference from "Section 8.3.1" to "Section 8.3.1.2."	Internal consistency for reference.
Section 8.10. Usability Assessment	Updated "…the HCP will determine whether the pediatric participant of their caregiver…" to "…the study staff will determine whether the participant (≥12 years of age) or their caregiver…" Updated "Following the second independent self- or caregiver-administration with the CCI …" to	Internal consistency and to address regulatory authority's request.

Section number and Name	Description of Change	Brief Rationale
	"Following the subsequent independent self- or caregiver-administrations with the CCI …" Added internal reference "(See Section 1.3: Schedule of Activities)" Updated "If the self-injections have been performed by the pediatric participant…" to "If the injections have been performed by the participant…"	
Section 9.4.1.3. Primary Analysis	Updated "Participants who meet treatment failure criteria before Week 16…" to "Participants who meet treatment failure criteria or initiate use with a low to high potency topical steroid as rescue treatment before Week 16…"	Clarification of treatment failure criteria.
Section 9.4.3. Safety Analyses: Vital Signs	Updated vital signs to add temperature: "…blood pressure (Systolic and diastolic) values, and temperature, and…"	To address regulatory authority's request.
Section 9.5.1. Data Monitoring Committee	Updated "…committee of approximately 3 to 5 members and will include experts in pediatric dermatology, and biostatistics." to "…committee of 3 members and will include individuals with expertise in pediatric dermatology, and biostatistics."	To address regulatory authority's request.
Section 10.2. Appendix 2. Informed Consent process and Assent Form	Added "A limited number of study sites will be asked by the Sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. If both parties (Sponsor and the Study Site) agree, and if participation is allowed by local regulations and EC/IRB requirements, the Sponsor will provide an eTablet device (e.g., iPad®) to the study site to use for the electronic informed consent. Overall the consent process will remain the same, as described in this section; however, at the study sites utilizing electronic informed consent, participants or their legally acceptable representatives will be able to review the entire informed consent form content on the eTablet. The ability for participants or their legally acceptable representatives to review the paper informed consent form is always an option at sites utilizing electronic informed consent. Depending on local regulations and EC/IRB requirements, the participants or their legally acceptable representatives and person obtaining consent will either apply their handwritten signature electronically directly onto the eTablet, or apply their handwritten signature to a printed paper copy of the informed consent in accordance with local regulations."	Add information about electronic informed consent.
Section 10.2. Appendix 2. Committees Structure. Data Monitoring Committee	Updated "…committee of approximately 3 to 5 members and will include experts in pediatric dermatology, and biostatistics." to "…committee of 3 members and will include individuals with expertise in pediatric dermatology, and biostatistics."	To address regulatory authority's request.

Section number and Name	Description of Change	Brief Rationale
Section 10.4. Appendix 4	Updated internal reference from "(refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information)" to "(refer to Section 8.3.1.2, Serious Adverse Event Information)"	Internal consistency for reference.
Section 10.19. Appendix 19.	Added a new step to the checklist: Step 1: Tap air bubbles to top. Updated Step 3 text from "Was the orange band visible after removing air bubbles?" to "Was the orange priming band no longer visible after removing air bubbles?" Added "for Steps 1 through Step 3" in Step 3 Delete asterisk and its reference statement in Step 4 "*if No and the participant/caregiver injects the wrong dose, follow procedures for reporting a product quality complaint (PQC)." Added "while the orange cover sleeve was fully depressed" in Step 6. Added "quality compliant" in Step 6.	To address corrections.
Section 10.21. Appendix 21	Added "The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC)."	Update protocol amendment history.
Throughout the protocol	All references to the "QuantiFERON-TB Gold test" were updated to "QuantiFERON-TB test", and Appendix 5 was deleted.	Updated based on revised laboratory text.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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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 intervention, 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): PPD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	30-Aug-2024 22:10:48 (GMT)	Document Approval