NOVARTIS

Clinical Development - General Medicine

Secukinumab/AIN457

Clinical Trial Protocol CAIN457A2310 / NCT02471144

A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis

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[redacted]

List of abbreviations

AE	adverse event
ACR	American college of Rheumatology
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
BDR	Bioanalytical Data Report
b.i.d.	twice a day
BUN	Blood Urea Nitrogen
CFR	US Code of Federal Regulations
CDLQI	Children's Dermatology Life Quality Index
CHAQ©	Childhood Health Assessment Questionnaire
COVID-19	Coronavirus disease of 2019
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CS	Corticosteroids
CT	Computerized Tomography
CTC	Common Toxicity Criteria
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Board
DNA	Deoxyribonucleic acid
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
e.g.	Example
EOI	End of Induction
EOM	End of Maintenance
EOT	End of Treatment
EOF	End of Follow up
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunosorbent Assay
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
FAS	Full Analysis Set

[redacted]

FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma –glutamyl transferase
GTD	Global Trial Director
GWA	genome-wide association
HA	Health Authorities
hCG	Human chorionic gonadotropin
HCP	Health Care Professional
HRQoL	health-related quality of life
HIV	Human Immunodeficiency virus
IA	Interim Analysis
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
[redacted]	[redacted]
IGA	Investigator's Global Assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IgG	Immunoglobulin G
IL	interleukin
i.v.	intravenous
IN	Investigator Notification
IQS	Integrated Quantitative Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IUD	Intrauterine device
IUS	Intrauterine System
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LLOQ	lower limit of quantification
MACE	Major Adverse Cardiovascular events
MAP	Meta-Analytic-Prediction
MedDRA	Medical dictionary for regulatory activities

[redacted]

MRI	Magnetic Resonance Imaging
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
[redacted]	[redacted]
p.o.	oral(ly)
PASI	Psoriasis Area and Severity Index
PCR	Protein over Creatinine Ratio
PFS	Pre-filled Syringe
PRO	Patient Reported Outcome
PT/INR	Prothrombin Time/International Normalized Ratio
PUVA	Photo chemotherapy (e.g. psoralen + UVA treatment)
QFT	QuantiFERON TB-Gold test
R	Randomization
RDC	Remote Data Capture
SAE	serious adverse event
s.c.	Subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standardized MedDRA queries
SST	Serum Separator Tube
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TBL	Total Bilirubin
TCS	Topical Corticosteroid
Th17	T helper 17 cells
TNF	Tumor necrosis factor
UV	Ultraviolet
UVA	Ultraviolet A, long wave 400 nm–315 nm
UVB	Ultraviolet B, medium wave 315 nm–280 nm
VAS	Visual Analog Scale
vs	Versus
WBC	White blood cells / leukocytes
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication.
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment 4 (18-Sep-2020)

The rationale for this amendment is to introduce a level of flexibility in drug dispensation, protocol assessments and visit schedule if a major health care event like COVID-19 (Coronavirus disease of 2019) pandemic requires it, thus allowing patients to remain in the trial and continue treatment while being monitored for safety.

The purpose of these changes, is to reduce the risk of exposure for patients and site staff and potentially the risk of transmission of infectious diseases (e.g. COVID-19).

These changes are limited to the duration of COVID-19 pandemic or of any other major health care event and must be done in accordance with the local rules and regulations relevant to pandemic containment measures.

In addition, renal and liver monitoring procedures will no longer be followed for subjects who reach adulthood (≥ 18 years). These procedures were introduced for the pediatric population in this study but are no longer relevant once subjects reach adult age, considering that secukinumab has been approved for adults in all major markets since 2014 without any requirement for renal and liver safety monitoring. Review of the trial data by the independent DMC has not revealed any concern about renal or liver safety in pediatric subjects treated with secukinumab. Novartis will continue renal and liver safety monitoring in pediatric subjects (<18 years) in this study.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to the protocol

The amendment includes changes:

- Due to COVID-19 pandemic or any other pandemic
  - Allowing shipment of study medication to the patient's home (Section 5.5.2)
  - Alternative options to visits (Sections 6, 6.5)
  - Local laboratory testing for safety purposes (Section 6.5.5)
  - Home Pregnancy testing (Section 6.5.8)
  - Remote PRO collection (Section 6.6.1.1)
  - Informed consent procedures (Section 10.2)
- To update safety monitoring
  - Discontinuation of liver monitoring in adults (Section 7.3)
  - Discontinuation of renal monitoring in adults (Section 7.4)
  - Small modifications and clarifications on Specific Renal Alert Criteria and Actions in Table 7-1 of Section 7.4.
  - Added Inflammatory Bowel Disease as an example for discontinuation of study treatment in Section 5.5.9.
- To manage inconsistencies in the original protocol
  - Added age stratum (Section 9.4.2, 9.5.2)

[redacted]

- For handling of missing values/censoring/discontinuations, modified non-responder imputation was replaced with pure non-responder imputation. This change was in line with HA recommendation and the pivotal adult studies (Section 9.4.3)
- Added age stratum and replaced modified non responder imputations with pure non-responder imputations (Section 9.4.4)
- For Health-related Quality of Life, CDLQI 0 or 1 related text was added. The Van-Elteren testing and Hodges-Lehmann estimates for CDLQI total score were removed as relevant CDLQI 0 or 1 analysis was already included to compare with controls (Section 9.5.5)
- As well as other miscellaneous minor corrections and clarifications.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. This protocol amendment is considered substantial. The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

COVID-19 related measures may/will be implemented immediately and prior to IRB/IEC and HA approvals. Submission for review and approval to IRB/IEC and Health Authorities should occur as early as possible.

The changes herein affect the Informed Consent. Sites are required to update and submit a revised Informed Consent for approval that takes into account the changes described in this protocol amendment.

[redacted]

Summary of previous amendments

Amendment 3 (April 2018)

Amendment 2 (February 2016)

Amendment 1 (April 2015)

[redacted]

Amendment 3

Amendment rationale

The main purpose of this amendment is to include an additional Interim Analysis prior to the Week 24 analysis once sufficient safety [redacted] have been collected. This analysis aligned with the efficacy extrapolation principle, is expected to provide the basis for a submission package to health authorities (HA), with the intent to allow earlier availability of secukinumab to pediatric patients in countries which accept a submission of clinical data with use of extrapolation methodology. This analysis may be performed before all subjects have reached the primary endpoint.

In addition to that, some clarifications, as well as editorial changes were undertaken in the protocol.

At the time of the protocol amendment finalization, a total of 120 subjects have been enrolled. The changes resulting from this amendment will not impact the study population or the study design.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to the protocol include the following:

- Section 3.5, Purpose and Timing of Interim Analyses and Section 9.6 Interim Analyses were revised with the additional interim analysis information
- Information for blinding relevant to the additional interim analysis was provided in Section 5.4
- The changes were made in data analysis Section 9.6 to reflect the additional interim analysis. Moreover, following changes have been made in Section 9:
  - Clarification regarding one-sided p-values for hypothesis testing but two-sided for the others in Section 9.
  - In Section 9.4.3, clarification regarding the definition of non-responder imputation and emphasizing a modified approach to be used.
  - In Section 9.4.4, one of the sensitivity analyses was changed to analysis using modified non-responder imputation for missing data.
  - [redacted]
- Section 5.5.10, language related to Withdrawal of Consent was updated as per European Economic Area's General Data Protection Regulation (GDPR) requirement
- In Section 5.5.7.2 and Section 5.5.8 it is clarified that corticosteroid topical treatment during screening period is also allowed for hands and feet, which is aligned with what is stated in Table 5-2.
- Clarification regarding the timing of screening visit was provided, in form of footnote in Table 6-1

[redacted]

- Following clarification related to drug self-administration has been added to Section 5.2, Section 5.5.2, Table 6-1 and Table 6-2:
  - Subjects <12 years of age must not self-administer. However, adolescents (aged 12 to <18 years) can self-administer while under supervision by Health Care Professional (HCP) or caregiver/guardian
- In Table 7-1, clarification added regarding Protein Creatinine Ratio (PCR) analysis following estimated Glomerular Filtration Rate (eGFR) decrease from baseline
- In Section 5.5.7, a clarification was added regarding prior medications
- Clarification that Children's Dermatology Life Quality Index (CDLQI) will no longer be completed once the subject reaches 18 years of age was provided in , Section 6.6.1.1 and Table 6-1
- In Section 6 in the order of assessment paragraph it is mentioned that the CHAQ questionnaire must be reviewed by the investigator
- Assessment schedule Table 6-1 was corrected to indicate that the optional X-ray is part of the screening procedure
- In Section 7.2.2 SAE reporting, a sentence was added to explain that SAEs after 20 wks since last dose should be reported to Novartis only if the investigator suspects a causal relationship to study treatment
- [redacted]
- A footnote was added in Table 13-1 for vital signs, to indicate that values outside the provided ranges are considered notable

Amendment 2

Amendment rationale

One key purpose for Amendment 2 is to modify inclusion criterion 5 to align with the text agreed with the Pediatric Committee (PDCO) of the European Medicines Agency (EMA).The inclusion criterion will now read:

Patient being regarded by the investigator to be a candidate for systemic therapy because of:

(1) inadequate control of symptoms with topical treatment, or

(2) failure to respond to or tolerate previous systemic treatment and/or UV therapy

As of today only 4 patients have been randomized, thus the impact of this update to the subject population is very limited.

Another key purpose of this Amendment, is to include the Childhood Health Assessment Questionnaire (CHAQ©) for those subjects with History of Psoriatic Arthritis. This addition is made following a request by the Japanese Health Authority. Further to that, some protocol text changes were undertaken following requests from IRBs.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

[redacted]

As mentioned in the rationale of Amendment 2 the inclusion criterion 5 was revised in the protocol Section 4.1 and in the Protocol Summary. Subsequently the purpose of the study Section 1.2 was also updated to reflect this revision.

Regarding addition of the CHAQ© the following protocol sections were revised or newly created:

Secondary objectives in Section 2.2 were revised. Section 6, order of assessments and Table 6-1 were revised. Section 6.6.1.2 was created. Section 9.5.5 was revised. Appendix 7 was created to describe the CHAQ© questionnaire.

Additionally other changes to the protocol include the following:

- [redacted]
- In Section 4.1 Inclusion Criteria and Synopsis text was corrected to state IGA of 4
- In Section 4.2 Exclusion Criteria, previous exclusion criteria 18 and 19 were merged into one. They were previously separate due to a typing error
- In Section 5.2 Treatment Arms, clarifications were provided
- In Section 5.2 , high dose group paragraph a correction was made stating that last dose in the extension treatment period occurs at Week 232 and not at EOT
- In Section 5.4 Treatment Blinding, clarifications were provided
- A phrase was added in the beginning of Section 5.5 to indicate availability of sponsor medical personnel to advise on trial related medical questions or problems
- In Section 5.5.4, the number of overall injections was corrected to 92 from 86 and text was added explaining that the removable caps of the secukinumab pre-filled syringes and the needle covers of the etanercept pre-filled syringes contain latex
- In Section 5.5.9 Treatment Discontinuation, subject's wish, withdrawal of consent, renal events and live virus vaccinations were added to the list
- In Section 5.5.12, a clarification was provided concerning emergency unblinding
- In Table 6-2 Assessment schedule: Added height, weight and physical examination at the 8 Weeks follow up visit
- In Table 6-4 PASI scoring system, some typographical errors were corrected
- A sentence was added in Section 6.5.8 to reiterate the responsibility of the sites to start performing urine pregnancy testing during the study once female subjects reach menarche or 12 years of age
- In Section 7.4 Renal Safety Monitoring, for better clarity <49% of eGFR was replaced by <50%; also "abnormal serum glucose" was replaced by "normal serum glucose".
- In Section 8.3 Data Base Management and Quality Control, clarifications were provided
- Clarifications were provided and text improvements were done in Section 9.4, analysis of the primary variables and in Section 9.5, analysis of secondary variables.
- Section 9.4.3 Handling of missing values, was updated
- Section 12 References, was updated with two references for CHAQ©

[redacted]

- [redacted]
- Other minor changes like text revisions or improvements were done throughout the protocol, as needed

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, certain changes herein affect the Informed Consent, which will be updated take into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

This amendment has been generated in order to provide more details and clarification on the duration of contraception requested during the study and to give option to align the duration on local label requirements.

The protocol has not been submitted to any Health Authorities or any Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs). This study has not yet started and no patients have been enrolled. Therefore, this amendment will not influence the study population or results.

Changes to the protocol

Section 4.2 (Exclusion criteria 9) has been updated with regard to the duration of use of effective contraception and to reflect that females of child-bearing potential can only enter the study if they are willing to prevent pregnancy **during the indicated duration**.

Section 6.5.8 was updated with regard to the duration of use of effective contraception and to reflect that if females of child-bearing potential do not agree to abstinence and who are or might become sexually active they must be informed of the need to use effective contraception **during the indicated duration**.

All changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. This amended protocol serves as the initial protocol, therefore a copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities. In addition, the changes herein affect the Informed Consent, which take into account the changes described in this amended protocol.

[redacted]

Protocol summary

Protocol number	CAIN457A2310
Title	A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis.
Brief title	Study of efficacy and safety of secukinumab in pediatric patients with severe plaque psoriasis.
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The efficacy and safety of secukinumab has been demonstrated in adults in a comprehensive phase II/III program. It is now appropriate that a similar assessment is made in the pediatric population with a dosing regimen that can be extrapolated from the adult efficacious dose. The purpose of this trial is to demonstrate the efficacy and safety of secukinumab compared to placebo and etanercept in children and adolescents aged 6 to less than 18 years with severe plaque psoriasis.
Primary Objective(s)	To demonstrate the superiority of secukinumab in pediatric subjects with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.
Secondary Objectives	To demonstrate superiority of secukinumab (low and high dose) in subjects with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo. To assess efficacy of secukinumab in subjects with severe chronic plaques psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo. To assess efficacy of secukinumab in subjects with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90 , PASI 100 and IGA mod 2011 0 or 1 at Week 16 and over time up to Week 52. To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared to placebo, and over time up to Week 52. To investigate the effects of treatment with secukinumab with respect to changes in CDLQI at Week 12, compared to placebo, and over time up to Week 52. To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared to placebo, and over time up to Week 52. To evaluate the effects of treatment of secukinumab on disability at Week 12 and over time up to Week 52 by use of the Childhood Health Assessment Questionnaire (CHAQ©), for subjects with history of psoriatic arthritis To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of s.c. injections, vital

	signs, clinical laboratory variables, ECGs, and adverse events monitoring, compared to placebo.
Study design	Multicenter, randomized, double-blind, parallel group, placebo- and active (etanercept)-controlled study. 12 week induction treatment period followed by a 40 week maintenance treatment period, a 184 week open-label extension treatment period and a 16 week follow-up off treatment period.
Population	Pediatric subjects aged 6 years to less than 18 years with severe chronic plaque psoriasis. Approximately 160 subjects aged 6 years to <18 years will be enrolled, of which at least 30 will be 6 years to <12 years old.
Inclusion criteria	• Patient must be 6 to less than 18 years of age at the time of randomization (Subjects 12 to less than 18 years enrolled from beginning of trial; Subjects 6 to less than 12 years enrolled after positive external DMC recommendation following review of data from the first 80 adolescents) • Severe plaque psoriasis, defined as a PASI score ≥ 20, and IGA mod 2011 score of 4, and BSA involvement of ≥10%, at randomization • History of plaque psoriasis for at least 3 months • Patient being regarded by the investigator to be a candidate for systemic therapy because of: • (1) inadequate control of symptoms with topical treatment, or • (2) failure to respond to or tolerate previous systemic treatment and/or UV therapy
Exclusion criteria	• Forms of psoriasis other than chronic plaque-type or drug-induced psoriasis, active at randomization • Female patients of childbearing potential (menarchal or become menarchal during the study) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception • Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy • Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy • Ongoing infections as evidenced by chest X-ray, CT scan or MRI , obtained within 12 weeks prior to randomization, and evaluated by a qualified physician • History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection • History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening
Investigational and reference therapy	Secukinumab tested at low dose and high dose will be available in prefilled syringes as a 150 mg in 1.0 mL syringe and a 75 mg in a 0.5 mL syringe

[redacted]

	Secukinumab placebo will be available in prefilled syringes in a form to match secukinumab syringes Etanercept active comparator will be provided centrally or as available in local markets
Efficacy assessments	• Psoriasis Area and Severity Index (PASI) score • PASI 50 response: subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline • PASI 75 response: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline • PASI 90 response: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline • PASI 100 response / remission: complete clearing of psoriasis (PASI=0) [redacted] • Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4) • Children's Dermatology Life Quality Index • Childhood Health Assessment Questionnaire (CHAQ©)
Safety assessments	• Adverse Events • Physical exam • Vital signs • Height and weight • Laboratory evaluations (hematology, clinical chemistry, urinalysis) • ECG • Pregnancy and assessments of fertility
Other assessments	[redacted]
Data analysis	The statistical hypotheses for PASI 75 response at Week 12 and IGA 0 or 1 response at Week 12 being tested is that there is no difference in the proportion of subjects with PASI 75 response and IGA 0 or 1 response at Week 12 in any of the secukinumab groups versus placebo. The secondary variable of PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 will be analyzed for superiority comparison of secukinumab doses versus placebo. The PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 will be analyzed in the same way as the primary variables. The co-primary efficacy variables and secondary efficacy variable will be analyzed using the FAS
Key words	Severe plaque psoriasis, pediatric, secukinumab

[redacted]

1 Introduction

1.1 Background

Psoriasis is a chronic relapsing inflammatory skin disease with an estimated prevalence of 0.32% in children under the age of 18 in 1996 (National Center for Health Statistics of the Centers for Disease Control and Prevention 1996). Since then, more epidemiologic studies have provided estimates on the prevalence of psoriasis in children in Europe and the USA.

- In the United Kingdom, prevalence of psoriasis was 0.55% in children aged 0 to 9 years and 1.37% in children and adolescents aged 10 to 19 years, with a higher prevalence in girls than in boys (Gelfand 2005).
- In Germany, 0.71% of children were affected by psoriasis and the prevalence increased from 0.12% at the age of 1 year to 1.2% at the age of 18 years (Augustin 2010).
- Results from a survey among dermatologists and general practitioners in the Netherlands suggested a prevalence of 0.37% in children aged 0 to 10 years, and 1.09% in children aged 11 to 19 years (de Jager 2009).
- In the USA, a Southern California study in children enrolled in an integrated health plan reported a 0.30% prevalence of psoriasis in children aged 2 to 19 years. The prevalence increased consistently after 5 years of age and was higher in females than in males. Stratification by gender (males vs. females) and age group yielded an overall prevalence of 0.17 % vs 0.21%; ages 2-5 years, 0.03% vs. 0.04%; ages 6-11 years, 0.16% vs. 0.15%; ages 12-19 years, 0.25% vs. 0.33% (Wu 2011).

The incidence of psoriasis in childhood in the US has been shown to increase with increasing age but also in recent years. Incidence of psoriasis in children increased significantly from 29.6 per 100,000 in 1970-1974 to 62.7 per 100,000 in 1995-1999 (Tollefson 2010).

Plaque psoriasis affects 80 to 90% of all psoriasis subjects of all age-groups (Griffiths 2007; Pariser 2007) and hence is the most common variant in pediatric subjects. Most children manifest with plaque psoriasis in patterns similar to adult subjects, with lesions localized to the scalp, post auricular region, elbows, and knees; however, lesions in children are often smaller, thinner, and less scaly than those seen in adults. Involvement of the face and flexural regions is more common in children than adults, and psoriatic lesions in the diaper area are prevalent during infancy.

As in adults, pediatric psoriasis is frequently associated with significant co-morbidities like diabetes mellitus, Crohn's disease, obesity, hypertension, high cholesterol, psychological and psychiatric impact. The overall rate of comorbid conditions in psoriasis subjects under 20 years of age is double that of their peers who do not have psoriasis (Augustin 2010). A pediatric study using an international cohort of psoriasis subjects found that a significantly higher percentage of children with psoriasis showed excess adiposity (37.9% vs. 20.5%) or obesity (20.2% vs 7.3%), significantly higher than the general pediatric population (Paller 2013).

The psychological impact of psoriasis can be particularly traumatic to children and adolescents. In children with at least one of 12 different skin diseases, children with psoriasis reported the greatest impairment to quality of life. Itch or pain was reported in the same study as the most significant problem affecting their health-related quality of life (Beattie 2006). Psoriasis, a

debilitating and disfiguring skin condition, is an independent risk factor for psychiatric comorbidities in children and adolescents. Compared with a matched psoriasis-free control cohort in a study based on health services claims data in the USA, pediatric subjects had approximately 25% to 30% greater risks of being given a diagnosis of any psychiatric disorder, depression, or anxiety subsequent to the psoriasis diagnosis (Kimball 2012).

Due to the higher prevalence of plaque psoriasis in children compared to other types and the significant physical and psychological burden it carries in the pediatric population, Novartis plans to study secukinumab in the treatment of plaque psoriasis in patients from 6 to less than 18 years of age.

The treatments for psoriasis have expanded over the past decade though in children treatment is frequently off-label. The use of topical therapy in childhood is the first line of treatment for skin-limited disease. With chronicity of illness and in more severe cases, phototherapy and systemic therapy are added to help induce remission (Silverberg 2009).

Topical therapies represent the vast majority of prescriptions (57 to 91%), while systemic agents are rarely used (4%), and biologics being even more rarely used (0.4%) (Wu 2011, Kimball 2012). Commonly used topical treatments for psoriasis include corticosteroids, coal tar, anthralin, calcipotriol either alone or in combination with topical steroids, tazarotene and calcineurin inhibitors (Burden 1999, Farber 1999, Benoit 2007). None of these treatments have been approved for the treatment of psoriasis in children below 12 years of age. Phototherapy is extensively used in adults and is a treatment option for some children with widespread plaques. Narrow-Band-UVB is considered the first-line phototherapy because it is similarly effective as Psoralen + UVA (PUVA), more convenient, and less carcinogenic (Van Weelden 1990). PUVA therapy is not generally recommended in children, but may be used with caution in adolescents (Burden 1999).

Systemic therapy is usually considered if the disease is moderate to severe in intensity, and not adequately controlled by topical therapies. Systemic treatments approved for use in adult psoriasis include acitretin, methotrexate, cyclosporine, and biologics. Acitretin is approved for subsets of psoriatic pediatric patients in some EU countries and Switzerland. However cyclosporine and methotrexate are not currently approved for the treatment of children/adolescents suffering from psoriasis. While there is no biologic approved for the treatment of psoriasis in subjects below the age of 18 years in the USA, etanercept, adalimumab and infliximab are tumor necrosis factor-alpha inhibitors that are used for the treatment of pediatric autoimmune diseases and have been used off-label to treat pediatric subjects with psoriasis (de Jager 2010, Luu 2013). In Europe, Enbrel (etanercept) was approved in 2011 for "*Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies".* Approval was based on a double-blind, placebo controlled study in moderate to severe pediatric subjects (Paller 2008); a retrospective analysis of results in severe subjects aged from 8 to 17 years showed that PASI 75 at Week 12 was achieved in 54.7% of subjects receiving etanercept vs. 11.3% of subjects receiving placebo, $p<0.001$ (Landells 2010).

Use of methotrexate, cyclosporine, retinoids (particularly acitretin), and, with a much lower frequency, dapsone and hydroxyurea has been reported in the literature (Zappel 2004; Benoit 2007). Most experience has been reported with retinoids, but the potential effect on bone growth

and teratogenicity limit their use in children and adolescents. Use of cyclosporine and methotrexate is limited by their adverse event (AE) profile (kidney dysfunction, hypertension and liver dysfunction, respectively). Reports on the use of biologics in pediatric patients are scarce (Benoit 2007).

In summary, a very limited number of systemic drugs for the treatment of psoriasis are approved for children, and the few approved drugs all have severe limitations. There is a high medical need to evaluate the treatment of psoriasis in patients less than 18 years of age where controlled studies are mostly missing (Burden 1999; Farber 1999; Benoit 2007; Paller 2008).

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralizes the bioactivity of this cytokine. IL-17A is the central lymphokine of a newly defined subset of inflammatory T cells, the Th17 cells which, in several animal models, are pivotal in several autoimmune and inflammatory processes. IL-17A is mainly produced by memory effector CD4+ and CD8+ T lymphocytes. IL-17A is being recognized as one of the principal pro-inflammatory cytokines in immune mediated inflammatory diseases. Its neutralization is expected to treat the underlying pathophysiology of immune mediated disease, and as a consequence provide relief of symptoms.

In adult phase II/III studies, secukinumab 300 mg and 150 mg has been shown to be efficacious with an acceptable safety profile, with secukinumab 300 mg comparable to 150 mg and both doses comparable to placebo over 12 weeks and etanercept over 52 weeks of treatment (Langley 2014).

Based on the natural history of psoriasis and the similar clinical features and histology in adults and pediatric population (Burden 1999; Farber 1999; Benoit 2007), it is expected that a human monoclonal antibody such as secukinumab will have an identical mode of action in children and would be metabolized similarly when compared to adults. Now that efficacy and safety have been demonstrated in adults in a comprehensive phase II/III program, it seems appropriate that the pediatric population can be exposed to secukinumab in long term studies with a dosing regimen that is extrapolated from the adult efficacious dose.

1.2 Purpose

The purpose of this study is to demonstrate superior efficacy of secukinumab versus placebo at Week 12, based on both PASI 75 and IGA mod 2011 0 or 1 response rates in children and adolescents aged 6 to less than 18 years with severe chronic plaque psoriasis who are candidates for systemic therapy because of: (1) inadequate control of symptoms with topical treatment, or (2) failure to respond to or tolerate previous systemic treatment and/or UV therapy. Moreover, this study will assess the long term safety and tolerability of secukinumab in this pediatric age group [redacted]

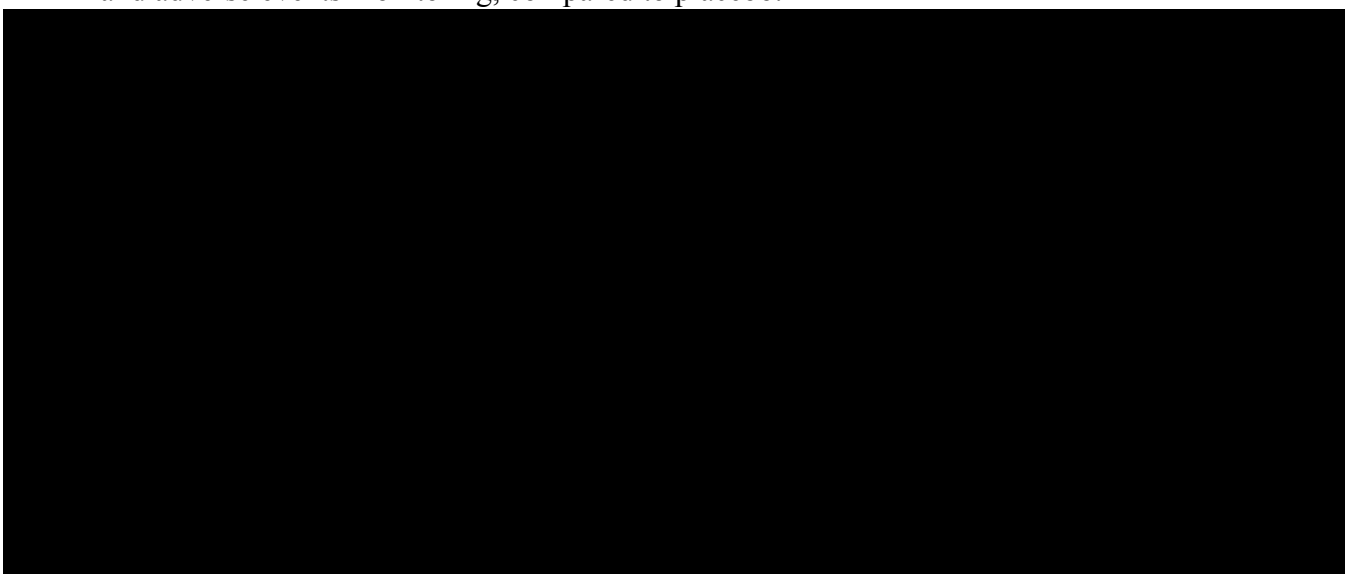
2 Study objectives

2.1 Primary objective(s)

To demonstrate the superiority of secukinumab (low and high dose) in pediatric subjects with severe chronic plaque psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.

2.2 Secondary objectives

- To demonstrate superiority of secukinumab (low and high dose) in subjects with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaques psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90 , PASI 100 and IGA mod 2011 0 or 1 at Week 16 and over time up to Week 52.
- To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment with secukinumab with respect to changes in CDLQI at Week 12, compared to placebo, and over time up to Week 52.
- To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared to placebo, and over time up to Week 52.
- To evaluate the effects of treatment of secukinumab on disability at Week 12 and over time up to Week 52 by use of the Childhood Health Assessment Questionnaire (CHAQ©), for subjects with history of psoriatic arthritis.
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of s.c. injections, vital signs, clinical laboratory variables, ECGs, and adverse events monitoring, compared to placebo.



3 Investigational plan

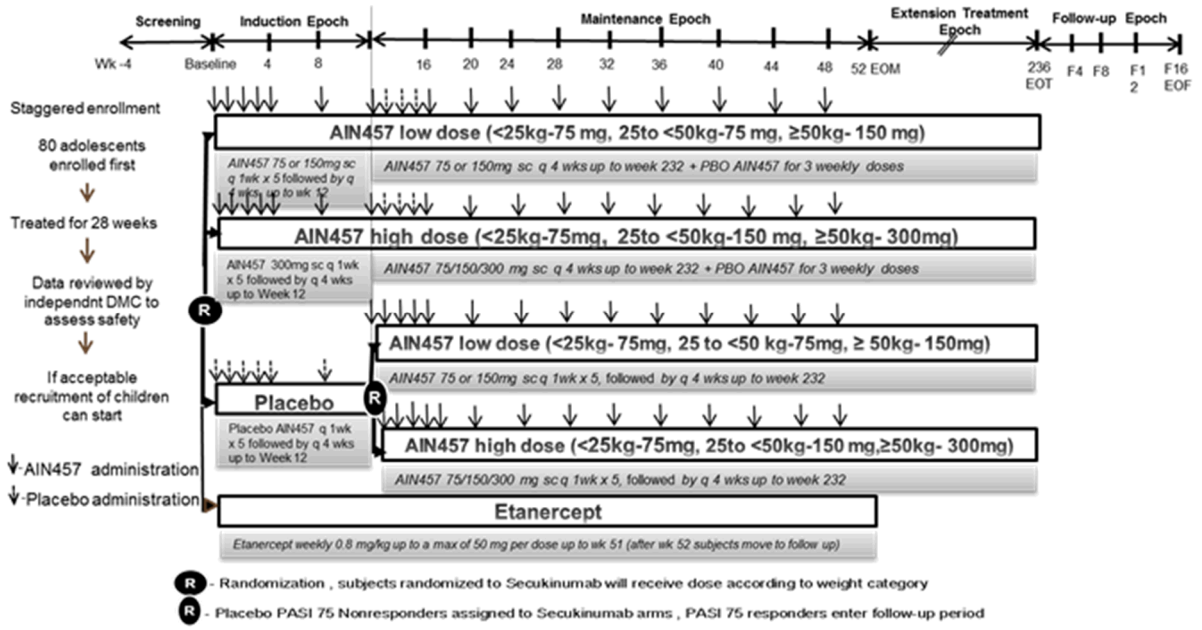
3.1 Study design

This is a multicenter, randomized, double-blind, placebo- and active-controlled (etanercept in single blinded arm) study in pediatric subjects aged 6 years to less than 18 years with severe chronic plaque psoriasis. Approximately 160 subjects aged 6 years to <18 years will be enrolled, of which at least 30 will be 6 years to <12 years old. It is expected that subjects will be enrolled at approximately 70 study sites worldwide.

Two age subgroups will be studied in a staggered approach within this clinical study: 12 to less than 18 years of age, and 6 to less than 12 years of age (age for the subgroups determined at the time of randomization). Enrolment of children aged 6 to less than 12 years will begin after a favorable recommendation by an independent external Data Monitoring Committee (DMC) who will review data of approximately 80 (approximately 40 treated with secukinumab) enrolled adolescents (aged 12 to less than 18 years) treated for 28 weeks. Adolescents will continue to be recruited while the data from the first 80 subjects are being collected and analyzed.

Subjects will be randomized using a 1:1:1:1 ratio into one of the treatment arms: secukinumab low dose, secukinumab high dose, etanercept or placebo. Subjects randomized to secukinumab treatment arms (high dose and low dose) will receive dose based on the weight category (<25 kg, 25 to <50kg, ≥50 kg). If a subject moves into a higher or lower weight group at two consecutive visits with weight measurements during the maintenance (from Week 12 onwards as assessed at monthly visits, i.e. Week 13, 14, 15 will not be taken into account) or during extension treatment period (as assessed at scheduled site visits), the subject will receive dosing according to the new (higher or lower) weight group respectively.

Figure 3-1 Study design



The study consists of 5 Epochs: screening (up to 4 weeks), induction (of 12 weeks), maintenance (of 40 weeks), extension treatment epoch (open-label of 184 weeks) and post-treatment follow-up epoch (of 16 weeks). An outline of the visits is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 6-1, Table 6-2.

Screening Epoch

The screening epoch of up to 4 weeks will be used to assess eligibility of the subjects and to taper subjects off prohibited medications.

Induction Epoch

The induction epoch is defined as randomization through Week 12 (prior to dose). In this epoch the study is both active and placebo-controlled and at its completion the primary endpoint is assessed (Week 12).

At the start of the induction epoch, eligible subjects will be randomized in a 1:1:1:1 ratio into one of four treatment groups (etanercept, secukinumab low dose group, secukinumab high dose group, or placebo group). The randomization will be stratified by age (<12 years or ≥12 years) and weight (<25, 25-<50, ≥50) at randomization; Subjects randomized to the secukinumab treatment group will receive respective high and low doses according to their weight category. Subjects randomized to the placebo group will be pre-assigned to either the low- or high-dose group of secukinumab, at the Randomization visit, in case they are not achieving a PASI 75 response as assessed at Week 12. During the induction epoch, all subjects will be visiting the study site at Randomization and Weeks 1, 2, 3, 4, 8, and 12. The secukinumab and placebo treatment groups will receive s.c. study treatment and/or s.c. placebo weekly for four weeks (randomization and Weeks 1, 2, and 3) and then one dose of study treatment and/or placebo at

Weeks 4 and 8 (last dose during the induction epoch). Secukinumab will be administered at site. Subjects in the etanercept arm will receive weekly s.c. dose of 0.8 mg/kg (up to a maximum of 50 mg) of open-label etanercept. Etanercept will be administered at site during site visits and at home or at the site for the remaining weekly visits based on the visit schedule (Table 6-1 and Table 6-2).

Assessments for the primary endpoint will be done at Week 12 for all treatment arms prior to the dose at Week 12.

For subjects who discontinue study treatment for any reason before the end of the induction epoch, an EOI Visit (Week 12 Visit) should be performed approximately four weeks after their last dose of study drug and then the subject will enter the post-treatment follow-up period and perform F4, F8, F12 and F16 visits. If subjects start another systemic anti psoriatic treatment during follow up, they do not need to continue with the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

Placebo PASI 75 responders at Week 12, at the completion of the Induction epoch, cannot continue into the Maintenance epoch but must enter the post treatment follow-up epoch instead, perform first visit F4 and four weeks later perform visit EOF and complete the study. If subjects start another systemic anti psoriatic treatment during follow up, they do not need to perform the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

Maintenance Epoch

The maintenance epoch is defined as Weeks 12 (from dosing) through Week 52. In this epoch the study is active-controlled and the objectives focus on the maintenance of the response observed at Week 12.

Subjects who were receiving secukinumab or etanercept during induction will continue in maintenance with the same treatment.

Subjects who were on placebo during induction and at Week 12 were PASI 75 responders cannot continue into maintenance epoch but will need to move into the follow-up epoch and terminate the study.

Subjects who were on placebo during induction and at Week 12 were PASI 75 non-responders will be switched to either secukinumab low dose or secukinumab high dose treatment group in maintenance epoch according to their baseline randomization.

The dose given at Week 12 for the placebo and the secukinumab arms is the first dose of the maintenance epoch and is followed by doses of secukinumab study treatment and / or placebo weekly up to Week 15, and every four weeks starting at Week 16 and up to Week 48.

Assessments for all the treatment arms will be done at Week 52 prior to dose at Week 52.

The Week 52 visit is the planned End of Maintenance epoch (EOM) visit. The EOM visit is considered complete when week 52 assessments are finished.

[redacted]

At the end of the maintenance epoch, subjects on secukinumab will enter the open-label extension treatment epoch of the study whereas subjects on etanercept will enter the post-treatment follow-up epoch and thereafter will complete the study.

For subjects who discontinue study treatment for any reason before the end of the maintenance epoch, the Week 52 Visit (planned End of Maintenance Period (EOM) visit) should be performed approximately 4 weeks after their last dose of study drug in the maintenance epoch and then the subject will enter the post-treatment follow-up epoch and perform F4, F8, F12 and F16 (EOF) visits. If subjects start another systemic anti psoriatic treatment during follow up, they do not need to continue with the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

Extension Treatment Epoch

The extension treatment epoch is defined as Week 52 (from dosing) until Week 236. At this epoch the subjects are all treated with secukinumab and the purpose is the collection of long term safety and efficacy data.

At the end of the maintenance epoch, all subjects on secukinumab will enter the extension treatment epoch of the study and will continue to receive the same dose of secukinumab they had received at completion of maintenance epoch.

Subjects who participated in the maintenance epoch but prematurely discontinued the study will not be able to enter the extension treatment epoch of the study. Patients receiving etanercept will not be eligible to enter the extension treatment epoch. Instead, at Week 52, they will complete an EOM visit and then enter the post-treatment follow-up epoch. The first secukinumab dose of the Extension Treatment epoch is administered at Week 52. Subsequent doses of secukinumab will be administered every four weeks until the End of Treatment (EOT). For subjects who discontinue study treatment for any reason before the end of the extension treatment epoch, the End of Extension Treatment (EOT) visit should be performed approximately 4 weeks after their last dose of secukinumab. The subject will then enter the post-treatment follow-up epoch (perform F4, F8, F12 and F16 visits). If subjects start another systemic anti psoriatic treatment during follow up, they do not need to continue with the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

Follow-up Epoch

The treatment-free follow-up visits will be at Week 240 (Post-treatment Follow-up visit F4, which is 4 weeks post EOT and 8 weeks post last dose of secukinumab), Week 244 (Post-treatment Follow-up visit F8, which is 8 weeks post EOT and 12 weeks post last dose of secukinumab), Week 248 (Post-treatment follow-up visit F12) and Week 252 (Post-treatment follow-up visit F16 (i.e. EOF, End of follow -up)). Subjects who complete or discontinue the treatment are expected to perform the complete treatment-free follow up period unless they start another systemic anti psoriatic treatment. In this case they do not need to continue with the remaining follow up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

[redacted]

Subjects who completed the extension treatment epoch will enter the treatment-free follow up epoch. In addition, the following subjects will enter the treatment-free follow up epoch:

- Subjects randomized to placebo that were PASI 75 responders at the End of Induction (EOI) epoch and completed the End of Induction (EOI) visit. These subjects are not eligible to continue to maintenance. These subjects are expected to do F4 (Post-treatment Follow-up visit F4, which is 4 weeks post EOI and 8 weeks post last study treatment) and four weeks later perform the End of Follow-up (EOF) visit and complete the study.
- Subjects who discontinued prematurely from the induction epoch. (Subjects should be scheduled for the EOI visit approximately 4 weeks after their last treatment dose and then enter the treatment-free follow up epoch.)
- Subjects on secukinumab who completed the maintenance epoch and the EOM visit and do not want to continue into the extension treatment l epoch.
- Subjects on etanercept arm who completed the maintenance epoch and the EOM visit. These subjects are not eligible to continue into extension treatment epoch.
- Subjects who discontinued prematurely from the maintenance epoch. (Subjects should be scheduled for the EOM visit approximately 4 weeks after their last treatment dose and then enter the treatment-free follow up epoch).
- Subjects who discontinued prematurely from the extension treatment epoch. (Subjects should be scheduled for the EOT visit approximately 4 weeks after their last treatment dose and then enter the treatment-free follow up epoch).

3.2 Rationale of study design

The double-blind, randomized, parallel-group, placebo controlled design used in this study is aligned with adult phase III trials with secukinumab. The primary endpoint of the trial at Week 12 will allow for assessment of efficacy at a point in time for which efficacy data from all currently approved systemic therapies for pediatric psoriasis as well as phase III adult data for secukinumab are available. The blinding in the secukinumab arms is maintained beyond the primary endpoint so as to ensure reliable efficacy measures beyond the induction epoch of 12 weeks.

This is the first pediatric study in psoriasis for secukinumab. The sequential planning of the study recruitment allows to first assess an initial benefit-risk evaluation in adolescents before enrolling children 6 to less than 12 years of age while also capturing a subject population representative of those with highest unmet medical need. The lower age of enrollment has been limited to 6 years since the prevalence of psoriasis in the 0 to less than 6 age group is very low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

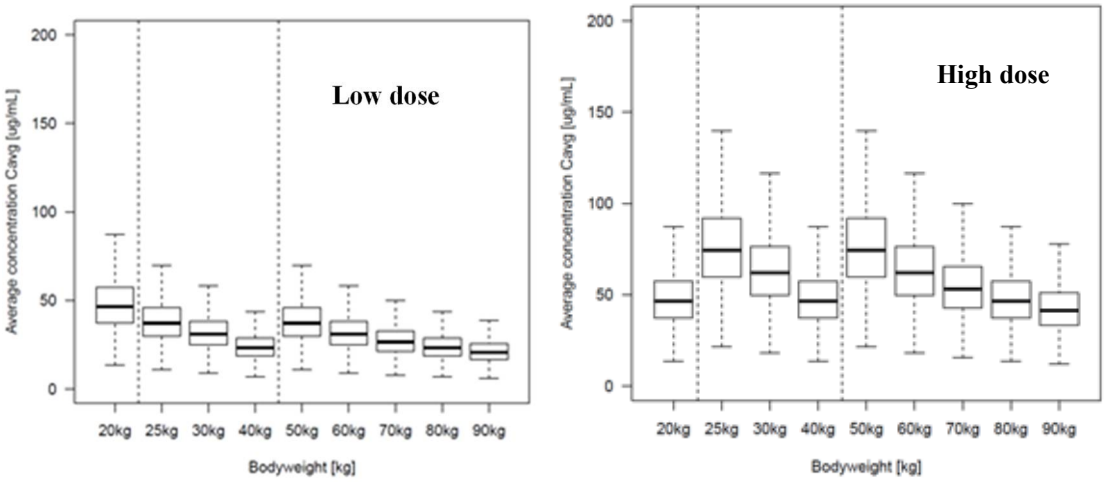
The dose selection for secukinumab in pediatric psoriasis subjects is based on the recently completed phase III program in adults as well as modeling and simulation based on the results from adult phase II/III studies. Secukinumab 300 mg and 150 mg are selected based on evidence

[redacted]

from adult phase III studies that demonstrated both doses to be safe and effective in treating moderate to severe plaque psoriasis.

The proposed doses for the high dose and low dose secukinumab arms are based on a population-PK model that has been built based on the pool of key phase II/III trials to predict exposure of secukinumab according to various body weights (Figure 3-2). This dosing rationale assumes that the concentration-response relationship and disease characteristics (onset, severity, progression) in children are similar to adults with no major differences in target expression of IL-17A. Therefore, similar PK concentration profiles across the adult and pediatric populations will achieve comparable response.

Figure 3-2 Average concentration for the proposed low dose and high dose secukinumab arms



Extrapolation of the exposure in children / adolescents in a bodyweight range down to 20 kg to allow maintaining exposure levels similar to those observed in adults with 50 kg body weight led to selection of 75mg, 150 mg and 300 mg within weight categories as follows:

Subjects ≥50 kg: 150 mg (low dose group) or 300 mg (high dose group)

Subjects 25 kg to < 50 kg: 75 mg (low dose group) or 150 mg (high dose group)

Subjects < 25 kg: 75 mg (for both dose groups in order to ensure no overly high exposures in this sub-population).

The dosing regimen used is consistent with that of adults and the total study duration including one year of blinded treatment plus the open-label extension treatment epoch and follow-up epoch (>5 drug half-lives) will allow for assessment of long term safety and efficacy.

3.4 Rationale for choice of comparator

The use of placebo is in accordance with health authority guidelines (FDA Guidance E10, and EMEA/CPMP Position Statement (EMEA/17424/01) and the Declaration of Helsinki Item 32. Etanercept was chosen as an active comparator, since it is the first biologic medication approved for use in children and adolescents with severe psoriasis in the European Union and elsewhere

and is in accordance with Health Authority feedback. However there will be no formal comparison between secukinumab and etanercept treatment groups.

The placebo arm is double blinded and the etanercept arm is single (efficacy assessor) blinded to prevent observer bias, and not subject-blinded because the dosing regimens of the two products are so different that double blinding is considered inappropriate in children due to the number of additional placebo injections needed in order to achieve a true double-blind administration. Site personnel performing the efficacy assessments, will be blinded to all treatment allocation, whilst site personnel performing the remaining assessments will be blinded to the secukinumab/secukinumab placebo allocation only (see also Section 5.4).

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis for the sole purpose of evaluating safety and efficacy in the adolescent population will be conducted once at least 80 adolescents complete 28 weeks of treatment (dosed up to Week 24). Enrollment of the pediatric population aged 6 to less than 12 years will begin only if there are no serious efficacy and/or safety concerns based on DMC's recommendation. No conclusions regarding demonstration of efficacy affecting the conduct of the study will be made.

A full analysis, including the primary endpoint (at week 12) analysis will be conducted when all subjects have completed the Week 24 visit. Another full analysis will be performed when all subjects have completed the Week 52 visit.

An additional interim analysis will be performed prior to the Week 24 analysis. Under the provision that sufficient safety [redacted] data have been collected, this analysis, aligned with efficacy extrapolation principle, is expected to provide the basis for a submission package to health authorities (HA). The intention of this interim analysis is to potentially make secukinumab available to pediatric patients sooner, by way of an earlier HA approval based on this analysis, in countries which accept a submission of clinical data with use of extrapolation methodology. This analysis may be performed before all subjects have reached the primary endpoint. It is expected that data from at least approximately 100 patient years of secukinumab treatment will be included in this analysis.

Efficacy and safety data collected during the extension treatment epoch (until the end of study) may be reported yearly in separate reports.

If requested by Health Authorities, additional interim analyses may be performed for instance on [redacted] data to confirm modeling assumptions. For these occasions [redacted] will share data with [redacted] in a blinded fashion. Overall, should such requests occur during the blinded portion of the study, they will be performed without unblinding of Novartis personnel. Unblinded data will only be made available to independent Novartis/CRO individuals involved in the preparation of the interim analyses and who are not directly involved in the study conduct.

3.6 Risks and benefits

Biologics like secukinumab are an attractive option for treating psoriasis in the pediatric population as they are convenient to use, requiring less frequent dosing than traditional systemic

[redacted]

agents such as methotrexate, cyclosporine, and acitretin. In addition, they lack many of the potential end-organ toxicities of traditional agents because of their targeted action.

Non-clinical studies and phase II and III clinical studies in adults have not shown any impediment to using secukinumab subcutaneously in man. In adult studies, secukinumab has shown a very good efficacy profile in the treatment of moderate to severe chronic plaque psoriasis. The safety data from the completed and ongoing studies including AE and SAE data, laboratory parameters and immunogenicity data demonstrate a good safety profile which included an observed risk of infections in particular candida infections and neutropenia or hypersensitivity reactions that can be seen with administration of foreign proteins. Most of the infections were non-serious, mild to moderate in severity, clinically easily manageable and did not lead to treatment discontinuation. Cases of neutropenia were uncommon, generally mild to moderate and transient and did not lead to treatment discontinuation, and only a few cases were timely associated with non-serious infections.

Potential risks for subjects on secukinumab include malignancies, major adverse cardiovascular events (MACE), Crohn's disease, immunogenicity, and interactions with live vaccines.

Since the immune system was shown to reach adult levels of maturation by 6 years of age (Comans-Bitter 1997), no adverse effects of secukinumab on development of this system are expected in this trial's pediatric population (age 6 to <18years). Consequently, no additional risks of infections, malignancies, or impact on peripheral competent immune cells over those described for adults are anticipated for this pediatric group.

A potential for increased exposure of secukinumab at lower body weights has been suggested by the analysis of population pharmacokinetic data. Consequently, weight category based dosing has been instituted to ensure that exposure levels of secukinumab are comparable across all weight groups in the study population.

No adverse effects are anticipated with respect to linear bone growth and development given the absence of bone findings in knock-out mice (Kokubu 2008) and in toxicology studies with secukinumab. Height to measure linear growth will be monitored all through the study.

Potential risks for subjects on etanercept could include common side effects of etanercept namely injection site reactions, upper respiratory infections, and headache. Injection site reactions such as redness, rash, swelling, itching, or bruising usually subside within 3 to 5 days. The subjects may also be at increased risk for infections and possibly cancer, as etanercept is a medication that has the potential to suppress the immune system.

Prior to participating in a clinical trial with secukinumab, participants should consider completion of all age appropriate immunizations according to immunization guidelines. Subjects treated with secukinumab should not receive live vaccines. Non-live vaccinations received during secukinumab treatment may not elicit an immune response sufficient to prevent disease.

[redacted]

4 Population

The study population will consist of male and female subjects age 6 to less than 18 years of age (at the start of study treatment) with severe plaque psoriasis who are candidates for systemic treatment.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional exclusions should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed assent and parental permission (age as per local law) obtained at screening before any assessment is performed. Of note, that if subjects reach age of consent (age as per local law) during the study, they will need to also sign the corresponding study Informed Consent(s).
2. Must be 6 to less than 18 years of age at the time of randomization
   a. Subjects 12 to less than 18 years enrolled from beginning of trial
   b. Subjects 6 to less than 12 years enrolled after positive DMC recommendation following review of data from the first 80 adolescents
3. Severe plaque psoriasis, defined as a PASI score ≥ 20, and IGA mod 2011 score of 4, and BSA involvement of ≥10%, at randomization
4. History of plaque psoriasis for at least 3 months
5. Patient being regarded by the investigator to be a candidate for systemic therapy because of:
   (1) inadequate control of symptoms with topical treatment, or
   (2) failure to respond to or tolerate previous systemic treatment and/or UV therapy

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis), active at randomization
2. Drug-induced psoriasis (i.e., new onset or current exacerbation from beta-blockers, calcium channel blockers or lithium)
3. Ongoing use of prohibited treatments as mentioned in Table 5-2 (Washout periods as detailed in Table 5-2 have to be adhered to).
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor, or to etanercept
5. Use of any other investigational treatment within 4 weeks before randomization, or within a period of 5 half-lives of the investigational treatment, whichever is longer.

[redacted]

6. History of severe hypersensitivity reaction or anaphylaxis to any biological agents (human monoclonal antibody or soluble receptor)
7. Pregnant or nursing (lactating) females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
8. Female patients (< 18 years of age) of childbearing potential (menarchal or becoming menarchal during the study) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 6.5.8
9. Female patients (who become ≥18 years of age during the study) of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for a minimum of 16 weeks after stopping study treatment or longer if local label requires it (e.g. in EU 20 weeks). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception:
    a. Male or female condom with or without spermicide
    b. Cap, diaphragm or sponge with spermicide
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment

10. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab and/or etanercept therapy
11. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
12. Investigator discretion should be used for subjects with preexisting or recent-onset central or peripheral nervous system demyelinating disorders
13. Subjects with a Glomerular Filtration Rate (eGFR), estimated by the Schwartz equation, of < 60 mL/min/1.73 m^2 at screening. Assessment may be repeated once, two or more

[redacted]

days later, and if eGFR value ≥ 60, subject may be included at the discretion of the investigator.

14. Subjects with total WBC count <2,500/μL, or platelets <100,000/μL or neutrophils <1,500/μL or hemoglobin <8.5 g/dL at screening
15. Ongoing infections and in particular tuberculosis. If warranted for a subject and based on the investigator's judgment, an X-ray or MRI (at pre specified sites) may be performed as part of the screening procedure.
16. Active systemic infections during the last two weeks (exception: common cold) prior to randomization and any infections that reoccur on a regular basis.
17. Investigator/qualified site staff discretion should be used regarding subjects who have traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for subjects with underlying conditions that may predispose them to infection, such as advanced or poorly controlled diabetes
18. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) at screening. Subjects with a positive QFT test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to local country guidelines prior to randomization.
19. Known infection with HIV, hepatitis B or hepatitis C at screening
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening
21. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomization.
22. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
23. Hypersensitivity or allergy to any of the ingredients of study treatments, including etanercept.
24. History or evidence of ongoing alcohol or drug abuse, within the last 24 weeks before randomization.
25. Subjects not willing to limit UV light exposure (e.g., sunbathing and/or the use of tanning devices) during the course of the study.
26. Unwillingness to undergo repeated venipuncture or subcutaneous injections.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The following study treatments will be used:

Investigational drug

[redacted]

- Secukinumab prefilled syringes, available as a 150 mg in 1.0 mL and as a 75 mg in 0.5 mL syringes. Provided by Novartis.

Reference therapies

- Secukinumab placebo: secukinumab placebo available as 1 mL and 0.5 mL prefilled syringes, provided by Novartis in a form to match secukinumab prefilled syringes.
- Etanercept active comparator (not a biosimilar):
  a. as provided centrally by a CRO or
  b. as available and purchased locally

All study treatments will be labelled appropriately.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

Subjects will be randomized using a 1:1:1:1 ratio into one of the treatment arms mentioned below. Subjects randomized to secukinumab treatment arms (high dose and low dose) will receive dose according to the weight category (<25 kg, 25- <50kg, ≥50 kg). Subjects in the two secukinumab arms weighing ≥50kg will receive 150 mg (low dose group) and 300 mg (high dose group), 25 to <50 kg will receive 75mg (low dose group) and 150 mg (high dose group) and <25kg will receive 75mg for both dose groups. In order to maintain the treatment blind, all subjects in secukinumab or placebo arms will receive 2 s.c. injections at each dose, except for subjects <25kg weight category who will receive only 1 injection of either 75 mg secukinumab or matching placebo (Table 5-1).

Table 5-1 Secukinumab/Placebo treatment arms and injections at each visit during Induction and maintenance epoch

Weight category at randomization	Treatment arms	Blinded Dose (PFS)	Number of injections at each visit during Induction Epoch	Number of injections at each visit during Maintenance Epoch
<25 kg	AIN high dose	75mg/0.5mL AIN	1	1
	AIN low dose	75mg/ 0.5mL AIN	1	1
	Placebo high dose(pre assigned at randomization)	75mg/0.5mL AIN PBO	1	1*
	Placebo low dose (pre-assigned at randomization)	75mg/0.5mL AIN PBO	1	1*
25 to <50kg	AIN high dose	2x75mg/0.5mL AIN	2	2
	AIN low dose	75mg/0.5mL AIN +75mg/0.5mL AIN PBO	2	2
	Placebo high dose(pre assigned at randomization)	2x75mg/0.5mL AIN PBO	2	2*
	Placebo low dose (pre-assigned at randomization)	2x75mg/0.5mL AIN PBO	2	2*
≥50kg	AIN high dose	2x150mg/1.0ml AIN	2	2
	AIN low dose	150mg/1.0mL AIN+150mg/1.0mL AIN PBO	2	2
	Placebo high dose(pre assigned at randomization)	2x150mg/1.0mL AIN PBO	2	2*
	Placebo low dose (pre-assigned at randomization)	2x150mg/1.0 mL AIN PBO	2	2*

*Placebo PASI 75 non responders will start receiving at Week 12 active treatment (secukinumab) high or low, as preassigned at randomization

- **Etanercept active comparator group**: S.C. etanercept 0.8 mg/kg (up to a maximum dose of 50 mg) once per week, for 51 weeks administered at home (self-injected or by caregiver) or at the study site. No subject blinding will be introduced for this arm, but the efficacy assessor will be blinded as regards to treatment assignment.
- **Secukinumab low dose group**: According to the weight category, s.c. secukinumab 75 mg (in <25 kg and 25 to <50 kg) or 150 mg (≥50 kg) injections at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and Placebo secukinumab at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the extension treatment epoch until Week 232. Subjects and all site staff will be blinded as regards to treatment assignment and secukinumab dose levels during the induction and maintenance epochs. After data base lock for Week 52

analysis has been performed, the placebo injection will no longer be administered and the study will become open label. In the extension treatment epoch, between the site visits, subjects will be expected to perform the study treatment administrations at home. This can be self-administered by subject or by caregiver. Subjects <12 years of age must not self-administer. However, adolescents (aged 12 to ≤18 years) can self-administer while under supervision of HCPs or caregiver/guardian. If subject/parent do not feel confident in performing treatment administration at home they are still allowed to receive study treatment administration at site.

- **Secukinumab high dose group**: According to the weight category , s.c. secukinumab 75mg (in <25 kg), 150mg (25 to <50 kg), 300 mg (≥50 kg) injections at Randomization, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and Placebo secukinumab at Weeks 13, 14 and 15 during the blinded phase of the study; thereafter at Week 52 and every 4 weeks during the extension treatment epoch until Week 232. Subjects and all site staff will be blinded as regards to treatment assignment and secukinumab dose levels during the induction and maintenance epochs. After data base lock for Week 52 analysis has been performed, the placebo injection will no longer be administered and the study will become open label. In the extension treatment epoch, between the site visits, subjects will be expected to perform the study treatment administrations at home. This can be self-administered by subject or by caregiver. Subjects <12 years of age must not self-administer. However, adolescents (aged 12 to ≤18 years) can self-administer while under supervision of HCPs or caregiver/guardian. If subject/parent do not feel confident in performing treatment administration at home they are still allowed to receive study treatment administration at site.
- **Placebo group**: Placebo secukinumab (one/two s.c. injections per dose) once per week for four weeks (at Randomization, Weeks 1, 2 and 3), followed by dosing every four weeks (Weeks 4 and 8). Subjects and the efficacy assessor will be blinded as regards to treatment assignment. At Week 12, subjects in the placebo group based on their PASI 75 response status at Week 12 will proceed as follows:
  - **PASI 75 responders on placebo** will discontinue study treatment at Week 12 and enter the treatment-free follow-up epoch for 8 weeks or until systemic therapy begins
  - **PASI 75 non-responders on placebo** will receive high dose or low dose secukinumab, according to the pre-assignment at the Randomization visit, and receive their treatment according to the weight category based on the weight measured at Week 12 visit (<25 kg, 25- <50kg, ≥50 kg), on Weeks 12, 13, 14, 15, and then every four weeks starting at Week 16 until Week 48 during the maintenance epoch; thereafter Week 52 and every 4 weeks during the extension treatment epoch until week 232. After data base lock for Week 52 analysis has been performed, the placebo injection will no longer be administered and the study will become open label. In the extension treatment epoch, between the site visits, subjects will be expected to perform the study treatment administrations at home. This can be self-administered by subject or by caregiver. Subjects <12years of age must not self-administer. However, adolescents (aged 12 to ≤18 years) can self-administer while under supervision of HCPs or caregiver/guardian. If

subject/parent do not feel confident in performing treatment administration at home they are still allowed to receive study treatment administration at site.

5.3 Treatment assignment, randomization

At Randomization (Visit 2), all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The qualified site personnel will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The subject number, the weight of the subject and the age will be entered. The IRT will assign a randomization number to the patient. For the subjects who will receive secukinumab or secukinumab placebo, this number will be used to link the patient to a treatment arm and will specify a unique medication number for the package or packages of investigational treatment to be dispensed to the patient. Each subject will receive one or two packages per dispensing visit, depending on the treatment group and treatment epoch. For those subjects who will be randomized to etanercept, medication will be provided centrally (by a CRO) or purchased from the local market. The randomization number will not be communicated to the caller or other site members.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication number (for the secukinumab and the secukinumab placebo treatment arms). A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Stratification

Randomization will be stratified by age and body weight collected at Randomization Visit. This stratification ensures balanced allocation of subjects to treatment groups within the age and weight strata.

The age strata is “age < 12” or “age ≥ 12”. The weight strata will be “body weight < 25 kg”, “25 kg ≤ body weight < 50 kg” or “body weight ≥ 50 kg”. Stratification by age and body weight will occur at Randomization Visit. For the randomization at Randomization Visit, it will be targeted to have at least approximately 30% of the subjects in each weight stratum.

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

Within each weight stratum, subjects will be assigned to the high dose or the low dose treatment group for secukinumab or placebo (see Table 5-1).

5.4 Treatment blinding

The secukinumab and the placebo arms are double blind (patient, investigator and assessor) until the data base lock for Week 52 analysis. However, for placebo PASI 75 responders

unblinding will occur at Week 12, since these subjects cannot continue into the Maintenance period but need to enter the post treatment follow-up period.

The etanercept arm is single (assessor) blind until the moment subjects complete the Week 52 visit and enter the follow-up period. Site staff (with the exception of the efficacy assessor), subject and sponsor are not blinded to the Etanercept arm for the entire treatment duration with Etanercept.

Any interim data analyses for the DMC or any other interim analyses which may be requested by health authorities during the blinded portion of the study will be performed without unblinding of Novartis personnel. Unblinded data will only be made available to independent Novartis/CRO individuals involved in the preparation of the interim analyses and who are not directly involved in the study conduct.

Secukinumab and placebo treatment arms

Subjects, investigator staff, and data analysts will remain blinded to the identity of the treatment from the time of randomization, using the following methods: (1) Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study, (2) the identity of the placebo and secukinumab in prefilled syringes will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Subjects on secukinumab arms, or those who were on placebo arm in induction and PASI 75 non-responders at Week 12, will remain blinded until Week 52 database lock.

Subjects who were on placebo arm in induction and PASI 75 responders at Week 12 will be unblinded to their treatment at Week 12, since they cannot continue into the maintenance epoch of the protocol and must enter the treatment-free follow-up. However the unblinding occurs after the primary endpoint assessments at Week 12 will have been completed.

An interim analysis will be performed before the planned IA at Week 24 and possibly before all subjects have reached the primary endpoint. In order to maintain the blind, the sponsor study team which will be directly involved in this analysis will no longer be part of the study conduct. The sponsor team members who will be involved in the study conduct after the interim data base lock, will not have access to any patient-level unblinded interim data until at least the data base lock for the next interim analysis at Week 24. The detailed procedures will be described in a separate charter.

After the interim database lock for the analysis at Week 24, designated Sponsor team members will be unblinded, whereas as mentioned earlier the subjects, investigator staff and persons performing the assessments will remain blinded until the database lock at Week 52.

Etanercept arm

Person(s) performing efficacy assessments will remain blind to the identity of the treatment from the time of randomization until Week 52 visit of a patient, using the following methods: (1) Randomization data will be strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study, (2) etanercept treatment will be dispensed and administered by qualified site personnel other than the efficacy assessor (3) the efficacy assessor

[redacted]

will not speak to the subject or parent or other site personnel for study matters other than those associated directly with the performed efficacy assessments.

All treatment arms

For all treatment groups, unblinding of site personnel during the induction and the maintenance epochs other than described above will only occur in the case of subject emergencies.

At the time of the interim evaluation of the data from the first 80 adolescent subjects by the external Data Monitoring Committee (DMC), designated Sponsor personnel (other than the study team) involved with the interim analyses will be unblinded.

After the Week 52 database lock (start of open label extension treatment), all subjects, sponsor team members, site personnel and persons performing the assessments will be unblinded for all treatment arms.

[redacted]

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason. Study treatment **must** be discontinued after emergency unblinding.

5.5 Treating the subject

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems

5.5.1 Patient numbering

Each subject is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next available sequential number by the investigator. At each study site, the first subject is assigned subject number 1, and subsequent subjects are assigned consecutive numbers (e.g. the second subject is assigned subject number 2; the third subject is assigned subject number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site should select the CRF book with a matching Subject Number from the OC/RDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

[redacted]

5.5.2 Dispensing the investigational treatment

Secukinumab and Secukinumab placebo

Each study site will be supplied by Novartis with secukinumab active and placebo treatment in packaging of identical appearance. The secukinumab active and placebo treatment packaging has a 2-part label. A unique medication number is printed on each part of this label.

At all visits where secukinumab active and/or placebo is dispensed, the IRT system will allocate a medication number which will be transmitted to the pharmacist (or other qualified site personnel) responsible for dispensation of study treatments. The pharmacist (or other qualified site personnel) will then identify the study treatment package(s) to administer to the subject corresponding to the medication number(s). Immediately before preparation of the study treatment, the pharmacist (or other qualified site personnel) will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number. These documents will be kept in a secured location as appropriate. The study treatment will be administered by study nurse/ qualified site personnel individual.

During the COVID-19 pandemic or similar major health care disruption that limits or prevents on-site study visits, delivery of study drug directly to a subjects's home is generally permitted in the event the Investigator has decided that an on-site visit by the subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. The dispatch of study drug from the site to the subject's home remains under the accountability of the Investigator.

At the site level, the agreement with approval of the Principal Investigator, Independent Ethics Committee/ Institutional Review Board (IEC/IRB) and any other Board as appropriate should be in place to implement home delivery.

Home administration of secukinumab and secukinumab placebo

After Week 52, subjects will be expected to perform home administrations of secukinumab or secukinumab placebo Pre-filled Syringe (PFS) at the protocol specified time points, when they are not visiting the site for other trial related procedures. Subjects/custodians will be previously trained by site staff regarding the administration of secukinumab, secukinumab/placebo. Only adolescent subjects ≥ 12 years and <18 of age are allowed to self-inject under HCPs or caregiver/guardian supervision.

If the subject or custodian is not confident to administer medication at home he/she should visit the site every 4 weeks and according to the visit schedule, to have the administrations performed there by the site staff. Alternatively, if possible, local arrangements can be done for a trained nurse to administer medication to the subject at home. This person must be sufficiently trained before.

For these cases the pharmacist/ qualified site personnel will dispense, via IRT, an appropriate number of investigational treatment packages for home administrations and detach outer part of the label from the packaging as indicated above. The subjects will record the date(s) of administration at home and will return the used PFS and packaging at their next visit to the site.

[redacted]

Site staff are to transcribe this information into the appropriate Dosage Administration Record eCRF.

The used PFS should be disposed immediately after use in a sharps container OR according to the requirements of the respective countries and brought back to site. Subjects will be asked to return all unused medication the latest at the completion of the study or at the time of discontinuation of the investigational treatment. Detailed instructions will be provided separately.

Etanercept (Enbrel®)

Etanercept (Enbrel®) will be either provided centrally via a CRO or by purchase from local markets. Etanercept will be provided locally with support as needed by Novartis Country Pharma Organization (CPO).

Etanercept should be dispensed as described in the Instructions for use/package leaflet. As per label, the quantity of the etanercept to be administered to pediatric subjects is dependent on their weight. Subjects will receive weekly s.c. dose of 0.8 mg/kg (up to a maximum of 50 mg) The pharmacist will receive from the study coordinator / study nurse the weight of etanercept subjects in all study visits where the weight assessment is performed. Based on the weight of the patient, the pharmacist will prepare a dispensation sheet containing at a minimum, study identification, subject number, the weight of the subject, the etanercept form to be administered, date and the amount of drug (volume) the patient will need to receive. It will be dated and signed by the Pharmacist. This sheet will be filed in a secure place with other drug related documentation. A copy of it will be provided together with the etanercept medication to the site staff, who is going to administer the medication to the subject. Alternatively if etanercept administration will occur at home a copy of it will be handed to the subject/custodian or trained nurse/caregiver. Detailed instructions will be provided separately.

Home administration of Etanercept (Enbrel®)

Alternatively, outside of the scheduled site visits, weekly etanercept medication can be administered at home by subject, trained custodian or trained nurse /caregiver. The first dose of etanercept should be administered at the site under the instruction/supervision of the qualified site staff. Qualified site staff will provide the subjects/custodians trained nurse/caregiver with appropriate training and necessary instructions as applicable to their local regulations.

Etanercept administration must follow the instructions for use as described in the package leaflet and the volume administered will be stated in the etanercept dispensation sheet, as prepared by the pharmacist. Each dose, taken home will be documented appropriately by the subject/custodian or trained nurse/caregiver. Site staff will transcribe this information into the appropriate Dosage Administration Record eCRF. Detailed instructions will be provided separately.

Subjects should be instructed on proper storage, transport of the treatment, as well as about the disposal of used syringes. Sharps containers will be provided for subjects to transport the used syringes back to the site at frequent intervals for proper disposal. Detailed instructions will be provided separately.

[redacted]

5.5.3 Handling the study treatment

The pharmacist or site personnel must maintain an accurate record of the shipment and dispensing of all study treatments in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all used study treatment and packaging at frequent intervals and all unused study treatment and packaging the latest at the end of the study or at the time of discontinuation of study treatment.

5.5.3.1 Handling of investigational treatment

Investigational treatment (secukinumab and secukinumab placebo prefilled syringes) must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels for secukinumab and secukinumab placebo prefilled syringes will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number. They must be stored in a secured refrigerator at 2-8°C (36-46°F), and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. Study treatments should not be frozen.

5.5.3.2 Handling of other study treatment

Etanercept will be provided either centrally or obtained from local market and will be stored and handled according to the conditions mentioned in the package leaflet by the manufacturer. It must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

Any labelling of etanercept for use by study subjects will be done according to local requirements.

5.5.4 Instructions for prescribing and taking study treatment

All study treatments will be administered subcutaneously throughout the study. All doses of study treatments at scheduled site visits will be administered at the study site after the study assessments for the visit have been completed. Prior to administration to the subject, the study treatment will be dispensed by the qualified site personnel appointed at the study site.

For home administrations the processes described earlier must be followed.

It needs to be noted that site staff other than efficacy assessor(s) will be unblinded regarding which subject receives investigational drug (secukinumab or secukinumab placebo) which receives active comparator (etanercept). They will not be aware regarding who is receiving active secukinumab and who is receiving placebo.

The first study treatment administration will occur at the Randomization Visit, after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and

[redacted]

only after the scheduled blood samples have been drawn. Similarly, at each other visit, all study assessments should be completed prior to the administration of study treatment.

During the induction epoch for the secukinumab or secukinumab placebo treatment groups the number of injections in total will be:

- For the weight group <25 kg: 6 injections
- For the weight groups 25 to <50kg and ≥50kg : 12 injections

During the maintenance epoch for the secukinumab treatment group the number of injections in total will be:

- For the weight group <25 kg: 13 injections
- For the weight groups 25 to <50kg and ≥50kg : 26 injections

During the extension epoch for the secukinumab treatment group the number of approximate injections in total will be:

- For the weight group <25 kg: 46 injections
- For the high dose weight groups 25 to <50kg and ≥50kg: 92 injections
- For the low dose weight groups 25 to <50kg and ≥50kg: between 46-92 injections*

* 92 injections is only the theoretical maximum. After the week 52 interim data base lock the study will become open label and the placebo injection that the low dose group was taking to maintain the double blind will no longer be administered. Thus a subject in this treatment group will be receiving only one injection instead of previously two.

During the induction, for the etanercept treatment group the total number of injections will depend on the etanercept forms available centrally or in the local markets and on the weight of the subject and will be between 12 and 24. Always, every effort should be done for a subject to receive the minimal amount of injections aligned with the required etanercept dose to be administered.

During the maintenance, for the etanercept treatment group the amount of injections will depend on the etanercept forms available centrally or in the local markets and on the weight of the subject and will be between 40 and 80. Always, every effort should be done for a subject to receive the minimal amount of injections aligned with the required etanercept dose to be administered

All kits of investigational treatment assigned by the IRT (for secukinumab and secukinumab placebo) will be recorded/data-based in the IRT.

The investigator should promote compliance by instructing the subject to attend visits as planned so that the study treatment can be administered as foreseen in the study protocol. Similarly, for home administration of study drugs (etanercept; secukinumab or secukinumab placebo in extension treatment epoch) compliance can be promoted by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

[redacted]

Administration of secukinumab/secukinumab placebo

Secukinumab Solution for Subcutaneous Injection (active or placebo, respectively) will be provided in Prefilled syringes (75 mg/0.5 mL and 150 mg/mL).

The study treatment solution **must** be injected into **non-affected** areas of the skin.

If possible, throughout the trial, the study treatment should be administered to body regions, changing the injection site from visit to visit, for example: right thigh, left thigh, right abdominal area, left abdominal area.

Single prefilled syringes will be packed in individual boxes. The boxes containing the syringes with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) and protected from light. They should not be frozen or shaken. Prior to administration the boxes containing the syringes with study treatment solution should be allowed to come to room temperature unopened for about 15-30 minutes before administration. Used syringes should be disposed immediately after use in a sharps container or according to the requirements of the respective countries. For home administration please refer to Section 5.5.2.

Note: The removable cap of the secukinumab pre-filled syringe 1 mL and 0.5mL form contains a derivative of natural rubber latex. Although no natural rubber latex is detected in the cap, the safe use of the secukinumab 1 mL or 0.5 mL pre-filled syringe in latex-sensitive individuals has not been studied.

Administration of Etanercept

Etanercept medication will be administered as described in the local instructions for use/package leaflet (see also Section 5.5.2)

Etanercept medication can be administered either at site or at home. The preferred option would be the home administration and should be encouraged and facilitated by the site. The decision nevertheless remains with subject/custodian. Depending on local capabilities, study personnel or trained nurse /caregiver should also be considered to administer the Etanercept medication at the subject's home. Qualified site staff will discuss all options with the subject/custodian and support their decision.

For subjects who opt for home administration, at each site visit commercially available etanercept medication will be handed. The amount of medication should be sufficient to cover the time period until the next scheduled site visit with surplus medication to cover for eventual misuse or malfunctioning of etanercept syringe or for delay in presenting to the next visit.

For more information about home administration refer to Section 5.5.2.

Note: The needle cover of the pre-filled Etanercept syringe and pens contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled by, or when Etanercept is administered to, persons with known or possible latex sensitivity. The majority of Etanercept patients in this study are expected to use the 25 mg powder for solution for injection rather than the prefilled syringe or pen.

5.5.5 Permitted dose adjustments and interruptions of study treatment

No dose adjustments or interruptions are permitted.

[redacted]

5.5.6 Rescue medication

Rescue medication for psoriasis is not permitted in this study.

5.5.7 Prior and Concomitant treatment

Relevant treatments (excluding those for psoriasis) taken within 6 months from screening date must be entered in the Prior and Concomitant Medications eCRF.

All treatments ongoing or starting at screening or at any point in the study and for any reason NOT including psoriasis will be entered in the Prior and Concomitant Medications eCRF or the Procedures and Significant Non-drug Therapies eCRF.

Any psoriasis treatments used from the time subject started to treat psoriasis will be reported on the Prior psoriasis therapy eCRF and not in the Prior and Concomitant Medications eCRF. This includes all topical treatments, systemic treatments and phototherapies for psoriasis administered prior to Randomization Visit (Section 6.2.2). Any treatment used to treat a symptom of psoriasis but not the condition itself should not be entered on the Prior Psoriasis Therapies CRF (e.g., enter antihistamine or bland emollient in the concomitant medications eCRF and enter any non-medicated intervention in the Procedures and Non-drug therapies eCRF).

Topical corticosteroids (TCS) must be recorded in the concomitant medications TCS eCRF. Start date, end date, dose, unit, frequency, route and reason for administration or change are to be recorded (see Section 5.5.7.1.).

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded

5.5.7.1 Permitted concomitant medications (not for psoriasis or psoriatic arthritis)

Concomitant medications are allowed if not listed in Table 5-2. Dose adjustments of these medications should be avoided during the study. If a dose adjustment of these medications does occur, they must be recorded on the Prior and Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF.

Subjects who are receiving treatments known to worsen psoriasis (e.g. beta-blockers) must be on stable dose for at least 4 weeks before Randomization Visit.

TCS and other topical treatments will be allowed from Week 12 visit and until the end of study only if:

- medication was started after the week 12 visit was completed;
- medication was used for 14 consecutive calendar days or less;
- medication was used for an indication other than psoriasis and not on the area affected with psoriasis.

Use of these TCS must be recorded on the Concomitant medications TCS eCRF.

[redacted]

There is no restriction on the use of anti-histamines or of corticosteroid drops used in the eye or ear during the study

5.5.7.2 Permitted concomitant medication for psoriasis

After the screening period, the use of concomitant medication for psoriasis in all body regions is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions (not listed in Table 5-2). Use of bland emollients must be recorded on the Prior and Concomitant medications eCRF. Use of any other non-medicated interventions must be recorded on the Procedures and Significant non-drug therapies eCRF.

The definition of "bland" excludes all topical medications that contain pharmacologically active ingredients such as (but not limited to) lactic acid, salicylic acid, urea, α-hydroxy acids or fruit acids.

Once the subject is screened and if the subject has intolerable scaling and/or itching, the use of bland emollients is permitted. The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

A topical corticosteroid (CS) treatment of mild or moderate activity is allowed for the face, scalp, hands, feetand genitoanal area during the screening period, but not after the subject has been randomized. These topical CS must not be used during the 12 hours preceding the Randomization study visit. Use of these topical CS must be recorded on the Prior psoriasis therapy eCRF if used to treat psoriasis. If not used to treat psoriasis it should be entered in the TCS eCRF (Section 5.5.7.1).

5.5.8 Prohibited Treatment

Use of any treatments displayed in Table 5-2 that could confound the efficacy are NOT allowed during the study for any indication and wash-out periods for these treatments prior to randomization are indicated in the table. If the use of these treatments is required, then the subject should **NOT** be randomized into the study

The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All prohibited medications and significant non-drug therapies administered after the subject starts treatment with study treatment must be listed on the Prior and Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF or Concomitant medications TCS eCRF for any TCS used by subjects after randomization.

If a prohibited treatment listed in Table 5-2 was used during the study, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the investigator, if the subject's use during the study of a prohibited treatment listed in Table 5-2 presents undue safety risk for the subject, the subject should be discontinued from study treatment as per Section 5.5.9. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

During the screening period, subjects will be allowed to use some active topical treatments for any indication in the following body regions: face, scalp, hands, feet and genitoanal area. The

active topical treatments are limited to: mild or moderate potency CS. The subject must stop use of these topical CS at least 12 hours preceding the Randomization visit.

For all other body regions, a washout period of 2 weeks applies for all active topical treatments for any indication (Table 5-2).

The Sponsor will be notified if a prohibited treatment is taken while the subject is on study.

Table 5-2 Prohibited treatment

Prohibited Treatment	Wash-out period up to Randomization	Induction Epoch[1,2]	Maintenance Epoch[1,2]	Open label Epoch[1,2]
Alefacept, briakinumab, efalizumab, ustekinumab	26 weeks	Not allowed	Not allowed	Not allowed
Biological immunomodulating agents other than above (e.g., adalimumab, infliximab)	12 weeks	Not allowed	Not allowed	Not allowed
Etanercept	No prior use allowed			
Other systemic immunomodulating treatments (e.g., MTX, cyclosporine A [CSA], corticosteroid, cyclophosphamide)	4 weeks	Not allowed	Not allowed	Not allowed
Photochemotherapy (e.g., PUVA)	4 weeks	Not allowed	Not allowed	Not allowed
Other systemic therapy for psoriasis (e.g., retinoids, fumarate)	4 weeks	Not allowed	Not allowed	Not allowed
Any other investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Not allowed	Not allowed	Not allowed
Phototherapy (e.g., UVA, UVB)	2 weeks	Not allowed	Not allowed	Not allowed
Topical treatment[3] for psoriasis or any other skin condition (e.g., corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids), except on the face, scalp, hand and feet and genitoanal area during screening	2 weeks[4]	Not allowed	Not allowed[5]	Not allowed[5]
Live virus vaccinations	6 weeks	Not allowed [6]	Not allowed [6]	Not allowed [6]
Killed virus vaccinations	None	Allowed	Allowed	Allowed

1. If a prohibited treatment of psoriasis is used during the study, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study.
2. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
3. Including intra-articular or peri-articular injections. Note that inhaled corticosteroids as well as corticosteroid drops in the eye or ear or nasal sprays are permitted.
4. Mild to moderate topical corticosteroids are allowed only during the screening period if used only on the face, scalp, hands and feet and/or genitoanal area and if not used during the 12 h preceding the randomization visit

5. Topical corticosteroids and other topical treatments will be allowed during maintenance and extension treatment epoch only if (all must apply):
   - medication was started after the Week 12 visit was completed;
   - medication was used for 14 consecutive calendar days or less;
   - medication was used for an indication other than psoriasis and not on the area affected with psoriasis
6. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

Exposure to light

Subjects need to be advised to limit exposure to ultraviolet (UV) light (including sunbathing and/or use of UV tanning devices) during the study to avoid possible effect on psoriasis

5.5.9 Discontinuation of study treatment and of treatment-free period

Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

Study treatment *must* be discontinued under the following circumstances:

- Subject's wish
- Withdrawal of consent
- If the investigator/qualified site staff believe that for a given subject continuation of the study treatment would be detrimental to the subject's well-being.
- Emergence of the following AEs: AEs that in the judgment of the investigator/qualified site staff, taking into account the subject's overall status, prevent the subject from continuing study treatment for example sepsis or newly occurring or worsening Inflammatory Bowel Disease, including Crohn's disease and ulcerative colitis.
- Any laboratory abnormalities that in the judgment of the investigator/qualified site staff, and taking into consideration the subject's overall status, prevents the subject from continuing study treatment.
- Any requirements met for liver events or liver laboratory value triggers as described in Appendix 2, Table 14-2
- Any requirement met for renal events as described in Section 7.4
- Live virus vaccination
- Pregnancy (see Section 6.5.8 and Section 7.5)
- Ongoing use of prohibited treatment as per recommendations in Section 5.5.8.
- Emergency unblinding.
- Any protocol deviation that results in a significant risk to patient's safety

If discontinuation occurs for any reason in a treatment epoch, the investigator/qualified site staff must make every effort to determine the primary reason for a subject's discontinuation from the study. This information will then be recorded by investigator/qualified site staff on the applicable end of study epoch eCRF.

Subjects discontinued from study treatment will NOT be considered discontinued from the study. On the applicable end of treatment epoch eCRF (EOI, EOM, and EOT completion

[redacted]

eCRFs), the investigator/qualified site staff must record the date and primary reason for stopping study treatment.

At the time of the study treatment discontinuation visit, if it has been approximately 4 weeks post last dose of study treatment then the assessments described EOI Visit Week 12 (for early discontinuation during induction epoch) or EOM Visit Week 52 (for early discontinuation during maintenance epoch) or EOT Visit Week 236 (for early discontinuation during extension epoch) should be completed at this visit.

If it has not been approximately 4 weeks post last dose of study treatment at the time of the study treatment discontinuation visit, then the subject should be scheduled to return 4 weeks post last dose for their EOI, EOM or EOT visit as appropriate.

The investigator/qualified site staff must contact the IRT when the subject performs the EOI, EOM, EOT Visits as appropriate, to register the subject's early completion of the study due to study treatment discontinuation.

See Section 6 for the required assessments of these subjects after study treatment discontinuation.

Discontinuation from a treatment-free period

If premature withdrawal occurs for any reason in the treatment-free period (follow up epoch, Week 240-Week 252), the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the applicable end of study period eCRF (Follow up epoch completion eCRF EOF, Visit Week 252 (F16)). Of note, if subjects start another systemic anti psoriatic treatment during follow up, they do not need to continue with the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

See Section 6 for the required assessments of these subjects who discontinue from the Follow up period.

5.5.10 Withdrawal of consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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

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

[redacted]

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

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

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

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

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Director (GTD) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will inform the patient orally and in written how to contact his/her backup in cases of emergency or when he/she is unavailable, to ensure that un-blinding can be performed at any time. The investigator will provide protocol number, study treatment name if available and patient number.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Study treatment must be discontinued after emergency unblinding.

Subjects, who are prematurely unblinded and are discontinued from study treatment, will be requested to return for the applicable end of period visit (EOI Visit Week 12 or the EOM Visit Week 52 or Week 236 EOT) and the four follow-up visits (Visits Week 240, Week 244, Week

[redacted]

248 and Week 252). If subjects start another systemic anti psoriatic treatment during follow up, they do not need to continue with the remaining follow-up visits but they will be expected to return to site after the start of the systemic treatment and perform End of Follow-up (EOF) visit.

5.5.13 Study completion and post-study treatment

Study completion for each individual subject occurs when the End of Follow-up visit (EOF) has been performed as per protocol. For a discontinued subject study completion corresponds to the last study visit of the patient or contact of the site with him/her. Study completion for the study will occur when all subjects who have been randomized will have completed the study as stated above.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and be treated as a prematurely discontinued patient (see Section 5.5.9). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

Subjects who prematurely discontinue study treatment for any reason should be scheduled for an End of Induction (EOI) or End of Maintenance (EOM) or End of treatment (EOT) visit as in Table 6-1 and Table 6-2. If the subject is unable to return for the EOI or EOM or EOT visits, every effort should be made to contact the patient by telephone to obtain safety related information (primarily AEs) during the 20 weeks following the last dose of study drug. Documentation of attempts to contact the patient should be recorded in the source documents.

6 Visit schedule and assessments

Subjects should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule.

During the COVID-19 pandemic or similar major health care disruption which limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented such as phone calls, virtual contacts (e.g. teleconsult) or visits by site staff or a home nursing service to the subject´s home depending on local regulations and capabilities, that can partially replace on-site study visits, for the duration of the pandemic until it is safe for the subject to visit the site again. These contacts should occur on or around the scheduled visit dates (or more frequently if needed). Every effort should be made to complete all study visit assessments feasible per protocol. Special effort should be made to conduct the scheduled EOT and EOF visits on site. If it is not feasible to conduct these visits on-site, at least phone contact or if possible, visits to the subject´s home by site staff as mentioned previously should be attempted.

Screening will be flexible in duration and will last up to a maximum of 4 weeks. During this time, the subject will sign the informed consent form, be evaluated for eligibility and will have all screening visit assessments done as indicated in Table 6-1.

Table 6-1, Table 6-2 lists all of the assessments and indicates with an "x" at which visits the assessments are performed.

If for any reason the subject is a screen failure, the subject may be rescreened. There is no restriction on the number of times a potential subject may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening.

If a subject rescreens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. For all subjects, the investigator/qualified site staff will record if the subject was rescreened on the rescreening CRF and any applicable screening numbers the subject was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the Informed consent CRF to correspond to the new screening subject number. Informed Consent for a rescreened subject must be obtained prior to performing any study related assessment or collecting any data for the Screening Visit. For rescreening, all screening assessments must be performed as per protocol, except for the tuberculosis (TB) work up, if applicable, if performed not more than 12 weeks before randomization.

If the date of a TB work up is less than 12 weeks from the projected randomization date, then it is not required that the TB work up be repeated. However, the subject must repeat the QuantiFERON test performed by the central laboratory.

At the discretion of the investigator, laboratory assessments at randomization visit need not to be performed if screening laboratory assessments were performed within 7 days from randomization.

During the treatment epochs, subjects may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis, or AEs that in the opinion of the investigator need intervention or repeated laboratory testing. During these unscheduled visits, study treatment will **NOT** be administered. The assessment(s) performed at an unscheduled visit are at the investigator's discretion.

Suggested order of assessments:

Suggested guidelines for conduct of the visit assessments are below:

- Subject to complete CDLQI at the study site prior to any study assessments
- Parent/custodian (or together with subject if subject is of 18 years of age or older) to complete childhood health assessment questionnaire, CHAQ©
- Efficacy assessor to complete efficacy assessments.
  1. IGA mod 2011 (all visits)
  2. PASI (all visits)
- Investigator to complete investigator assessments
  1. Review CDLQI and CHAQ data (at applicable visits)

[redacted]

2. Physical exam (at applicable visits)

- All remaining study visit procedures (e.g., laboratory sample collection, vital signs measurements) must be completed prior to study treatment dosing.
- Enter PASI data into the source data worksheets and perform calculations as needed BEFORE contacting IRT at randomization and Week 12 Visit.
- Contact IRT to register the subject visit, as applicable
- Administration of study treatment, as applicable

[redacted]

Table 6-1 Visit and assessment schedule for the Blinded Epoch

Epoch	Scr	Induction Epoch							Maintenance Epoch												
Visit	1	2	3	4	5	6	7	8[a] EOI	9	10	11	12	13	14	15	16	17	18	19	20	21[b] EOM
Week	-4-R*	R	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52
Day	-28-R*	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365
Obtain informed consent [1]	x																				
Subject demographics	x																				
Inclusion/exclusion[2]	S	S																			
Psoriasis history/prior therapies	x																				
Medical history and prior medications	x																				
Concomitant medications[3]	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Surgeries and non-drug procedures	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Physical Exam	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height[4]	x	x				x	x	x				X	x	x	x	x	x	x	x	x	x
Weight	x	x				x	x	x				X	x	x	x	x	x	x	x	x	x
Vital signs (BP & pulse)	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
[redacted]																					
Labs: Hematology[6]	x	x		x		x	x	x		x		X	x	x	x	x	x	x	x	x	x
Blood chemistry[6], Urinalysis (local)	x	x				x	x	x				X	x	x			x				x

[redacted]

Epoch	Scr	Induction Epoch							Maintenance Epoch												
Visit	1	2	3	4	5	6	7	8[a] EOI	9	10	11	12	13	14	15	16	17	18	19	20	21[b] EOM
Week	-4-R*	R	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52
Day	-28-R*	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365
Renal monitoring (conditional) Urinalysis, Urine Microscopy, Fasting Glucose. [6, 7]						x	x	x				X	x	x	x	x	x	x	x	x	x
Tuberculosis test[8]	x																				
Pregnancy test (in females of childbearing potential) [6,9]	x	x						x						x			x				x
Chest X ray (optional) [10]	x																				
ECG (standard 12-lead)	x							x						x							x
[redacted]																					
PASI	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
IGA mod 2011	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
CDLQI [12]		x				x	x	x						x			x				x
CHAQ© (for subjects with History of Psoriatic Arthritis only)		x				x	x	x						x			x				x
Adverse event assessment	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
SAE assessment	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
[redacted]																					
Randomization via IRT [13]		x																			
Data entry of weight into IRT[14]		x	x			x	x	x				X	x	x	x	x	x	x	x	x	x

[redacted]

Epoch	Scr	Induction Epoch							Maintenance Epoch												
Visit	1	2	3	4	5	6	7	8[a] EOI	9	10	11	12	13	14	15	16	17	18	19	20	21[b] EOM
Week	-4-R*	R	1	2	3	4	8	12	13	14	15	16	20	24	28	32	36	40	44	48	52
Day	-28-R*	1	8	15	22	29	57	85	92	99	106	113	141	169	197	225	253	281	309	337	365
Administration of study drug (double blind: secuk/placebo)		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Dispense etanercept [15]		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
End of induction eCRF completion								x													
End of maintenance eCRF completion																					x
Contact IVRS/IWRS	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	

R=Randomization, [redacted] ECG=Electrocardiograms, CDLQI= children's dermatology life quality index, SAE=serious adverse events, IRT=Interactive response technology, EOI- End of induction, EOM- End of Maintenance.

X=assessment entered or transferred into the clinical database. S= assessment only recorded in source.

*Before randomizing the subject, the site must ensure that all assessments of the screening visit have been performed, all lab results are available and subject is eligible. Special attention must be given to tuberculosis testing as results take longer to be available.

[a] During Week 12 visit subjects will have their last assessment performed for the induction epoch prior to the dose at this visit. [redacted]

[b] During Week 52 visit subjects will have their last assessments performed for the maintenance epoch (EOM) and will enter the open-label extension treatment epoch. [redacted]

[1] There are two types of informed consent for this study, the general informed consent/assent [redacted]

[2] These assessments are supported by and are stored with the source documentation. However, data regarding to which inclusion/exclusion criteria are met are captured on the Inclusion/Exclusion screen eCRF.

[redacted]

[3] Information on Topical Corticosteroid medication, that a subject may use, is entered in the Concomitant medications-topical corticosteroids eCRF

[4] Measured standing and barefoot, using the same calibrated stadiometer.

[redacted]

[6] Samples will be shipped to and analyzed by the central lab. At the discretion of the investigator, laboratory assessments need not to be performed again at Randomization (R) visit if screening labs were performed within 7 days from randomization.

[7]As part of the renal safety monitoring (details in Section 7.4) certain alert conditions may be fulfilled based on biochemistry and urine dipstick results. As a follow up action urine samples (first morning void) must be shipped to central lab for quantitative urinalysis and/or urine microscopy. Similarly, fasting glucose analysis may be also be required based on glucose urine dipstick result.

[8] If the first QuantiFERON® TB-Gold In-Tube test is indeterminate, the investigator may choose to perform a second QuantiFERON® TB-Gold In-Tube test (as part of an unscheduled visit) or refer the subject for tuberculosis workup per local guidelines. If the result of any QuantiFERON® TB-Gold In-Tube test is “positive” or the results of 2 sequential QuantiFERON® TB-Gold In-Tube tests are ”indeterminate”, the subject must be referred to have a tuberculosis workup per local guidelines (if no workup within 12 weeks prior to randomization is available). The subject will not be eligible for randomization if “active tuberculosis is present “or if “latent tuberculosis is present and is untreated as per local guidelines.” No QuantiFERON® TB-Gold In-Tube test is to be done at the central laboratory after the subject has been randomized.

[9] Serum pregnancy tests will be performed at screening and urine pregnancy test at all other scheduled visits. If there is a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test done at the same visit. Pregnancy tests will be performed in female subjects of child bearing potential, i.e. those who have started menstruation and/or are of age 12 or older.

[10] Optional assessment. Chest X-ray or chest MRI (at prespecified sites) may be performed based on the investigator’s judgment, to assess presence of infections or malignancies.

[redacted]

[12] Text only version will be used in all subjects. Assessment will no longer be performed once subjects reach 18 years of age.

[13] At visit 2 the PASI Score and BSA must be calculated by efficacy assessor/appropriate site staff prior to contacting IRT. The investigator must ensure subject meets all eligibility criteria before contacting IRT to randomize the subject. At Visit 8 (week12), the site should have the PASI 75 responder status calculated prior to contacting IRT to communicate it.

[14] For every visit (including unscheduled), weight measured at that visit will be entered into IRT.

[15] Etanercept will be administered weekly up to and including Week 51. Outside of site visits, administration should preferable occur at home by subject, or caregiver. Alternatively if subject/parent does not feel confident in performing study treatment administration at home, they are allowed to receive study treatment administration at site.

[redacted]

Table 6-2 Visit and Assessment schedule for the Extended treatment epoch

Epoch	Extension Treatment Epoch																Follow-up Epoch				Unscheduled [d]
Visit	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	End of ext. treat. (EOT)[b]	F4[c]	F8[c]	F12[c]	F16[c] EOF	
Week	52[a]	64	76	88	104	116	128	140	156	168	180	192	208	220	232	236	240	244	248	252	
Day	365	449	533	617	729	813	897	981	1093	1177	1261	1345	1457	1541	1625	1653	1681	1709	1737	1765	
Concomitant medications[1]		x	x	x	x	x	x	x	x	X	x	X	x	x	x	x	x	x	x	x	x
Surgeries and non-drug procedures		x	x	x	x	x	x	x	x	X	x	X	x	x	x	x	x	x	x	x	x
Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		S		S	S
Height[2]		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		x		x	x
Weight		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		x		x	x
Vital signs (BP & pulse)		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
[redacted]																					
Hematology[4]		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		x		x	x
Blood Chemistry[4] , Urinalysis (local)		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		x		x	x
Renal monitoring [5] (conditional) Urinalysis[4] , Urine Microscopy[4], Fasting Glucose[4]		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x		x		x	x

[redacted]

Epoch	Extension Treatment Epoch																Follow-up Epoch				Unscheduled [d]
Visit	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	End of ext. treat. (EOT)[b]	F4[c]	F8[c]	F12[c]	F16[c] EOF	
Week	52[a]	64	76	88	104	116	128	140	156	168	180	192	208	220	232	236	240	244	248	252	
Day	365	449	533	617	729	813	897	981	1093	1177	1261	1345	1457	1541	1625	1653	1681	1709	1737	1765	
Pregnancy test (in females of childbearing potential) [4,7]		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x				x	x
ECG (standard 12-lead)					x		x		x		x		x			x				x	x
[redacted]																					
PASI		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
IGA mod 2011		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
CDLQI		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x					x
Adverse event assessment		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
SAE assessment		x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
[redacted]																					
Data entry of weight into IRT[9]	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x						
Contact IVRS/IWRS	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x						
Dispensing[10] secukinumab	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x						

[redacted]

Epoch	Extension Treatment Epoch																Follow-up Epoch				Unscheduled [d]
Visit	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	End of ext. treat. (EOT)[b]	F4[c]	F8[c]	F12[c]	F16[c] EOF	
Week	52[a]	64	76	88	104	116	128	140	156	168	180	192	208	220	232	236	240	244	248	252	
Day	365	449	533	617	729	813	897	981	1093	1177	1261	1345	1457	1541	1625	1653	1681	1709	1737	1765	
End of Extension Treatment eCRF completion																x					
End of Follow-up eCRF completion																				x	

[redacted], ECG=Electrocardiogram, CDLQI= children's dermatology life quality index, SAE=serious adverse events , IRT=Interactive response technology, EOI- End of induction, EOM- End of Maintenance, EOT- End of Extension Treatment , EOF- End of Follow-up

X=assessment entered or transferred into the clinical database. S= assessment only recorded in source

[a] Week 52 is the final visit in maintenance epoch and the first visit in the extension epoch. Assessments done for the EOM will be used for the extension treatment epoch.

[b] During EOT visit subjects will have their last assessments performed for extension treatment epoch [redacted]

[c] Follow-up assessments are to be conducted for subjects who complete extension treatment epoch and for subjects who discontinue study treatment early

[d] The assessments performed at an unscheduled visit are at the investigator's discretion

[1] Information on Topical Corticosteroid medication, that a subject may use, is entered in the Concomitant medications-topical corticosteroids eCRF

[2] Measured standing and barefoot, using the same calibrated stadiometer,

[redacted]

[4] Samples will be shipped to and analyzed by the central lab.

[5] As part of the renal safety monitoring (details in Section 7.4) certain alert conditions may be fulfilled based on biochemistry and urine dipstick results. As a follow up action urine samples (first morning void) must be shipped to central lab for quantitative urinalysis and/or urine microscopy. Similarly, fasting

[redacted]

glucose analysis by the central lab may also be required based on the glucose urine dipstick result. Once a subject reaches adulthood (≥18 years of age) this procedure no longer needs to be followed.

[redacted]

[7] Serum pregnancy tests will be performed at screening and urine pregnancy test at all other scheduled visits. If there is a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test done at the same visit. Pregnancy tests will be performed in female subjects of child bearing potential, that is those who have started menstruation and/or are of age 12 or older.

[redacted]

[9] For every visit weight measured at that visit will be entered into IRT

[10] Secukinumab will be dispensed at site visits. In the extension treatment epoch, between site visits, it will be administered every 4 weeks at home, either by subject (self-injection only for adolescents of at least 12 years of age and under supervision) or by caregiver. In case subject or parent does not feel confident in performing home administrations they will be allowed to continue to perform administration at site. These administrations should occur at Wk 56, Wk 60, Wk 68, Wk 72, Wk 80, Wk 84, Wk 92, Wk 96, Wk 100, Wk 108, Wk 112, Wk 120, Wk 124, Wk 132, Wk 136, Wk 144, Wk 148, Wk 152, Wk 160, Wk 164, Wk 172, Wk 176, wk 184, Wk 188, Wk 196, Wk 200, Wk 204, Wk 212, Wk 216, Wk 224 and Wk 228.

[redacted]

6.1 Information to be collected on screening failures

All subjects who sign the informed consent but discontinue prior to randomization at Visit 2 are considered to be screen failures.

If a subject discontinues prior to randomization, the IRT provider must be notified within 5 days, and the reason for the subject not being randomized will be entered on the Screening Phase Disposition eCRF. The Screening visit date, the Demography eCRF, the Informed Consent eCRF, the Inclusion/Exclusion eCRF, and the subject rescreening eCRF must be completed. The AE eCRF should be completed for any SAEs that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. The Death eCRF should be completed in the case of a death during the screening period. The withdrawal of consent eCRF must be completed if consent was withdrawn during the screening period before the subject was randomized.

For all subjects who sign the informed consent and entered into the next period of the study, all AEs **occurring after the informed consent is signed** will be recorded on the AE eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Subject demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study treatment administration. These may be in the screening period (e.g. demographics) or at the Randomization Visit (e.g. PROs), depending on the assessment.

6.2.1 Demographics

Data to be collected on all patients include: year of birth, age, sex, race, ethnicity, and child-bearing potential (for females).

6.2.2 Psoriasis medical history / Previous psoriasis therapy

Disease history will be collected at the screening visit. The information to be collected and entered in the Psoriasis History eCRF and Prior Psoriasis Therapies eCRF includes the following:

- The date of first diagnosis of plaque psoriasis (by a physician)
- The previous treatments of psoriasis (including previous use systemic therapies, biologic therapies, as well as phototherapy and/or photo chemotherapy or topical use) and the reason for discontinuation of each therapy
- The presence of psoriatic arthritis and the date of first diagnosis (by a physician)

6.2.3 Relevant medical history / current medical conditions

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

[redacted]

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

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2.4 Chest X-ray (optional)

Chest X-ray is an optional assessment which can be performed in screening at the discretion of the investigator, if warranted for the subject. This is aimed to detect ongoing infection and particularly tuberculosis or malignancy.

A chest X-ray (or chest MRI at pre specified sites) must only be done after it is fairly certain that the subject meets the other inclusion/exclusion criteria, in order to minimize unnecessary exposure to X-ray radiation for subjects.

If the chest X-ray or MRI evaluated by a qualified physician shows evidence of ongoing infections or malignancy and the subject was not treated subsequent to the X-ray (or MRI), the subject will not be eligible to enter the study.

6.2.5 Determination of Tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. TB status must be determined by medical history, signs, symptoms and TB testing (QuantiFERON-TB Gold assay). Any significant findings will be recorded in the TB assessment eCRF and the Medical History eCRF, as necessary.

QuantiFERON TB-Gold In-Tube assay

A QuantiFERON® TB-Gold In-Tube assay (QFT) will be performed to assess the TB status at screening for all subjects. This test will only be used to determine subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection (Doherty 2008).

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

The QuantiFERON®-TB Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Refer to Figure 6-1 for guidance on subject eligibility with respect to TB testing. The results of a workup for a subject with a positive or indeterminate test must be recorded on the Tuberculosis assessment eCRF.

- If the test result is **negative**, the subject may be randomized.

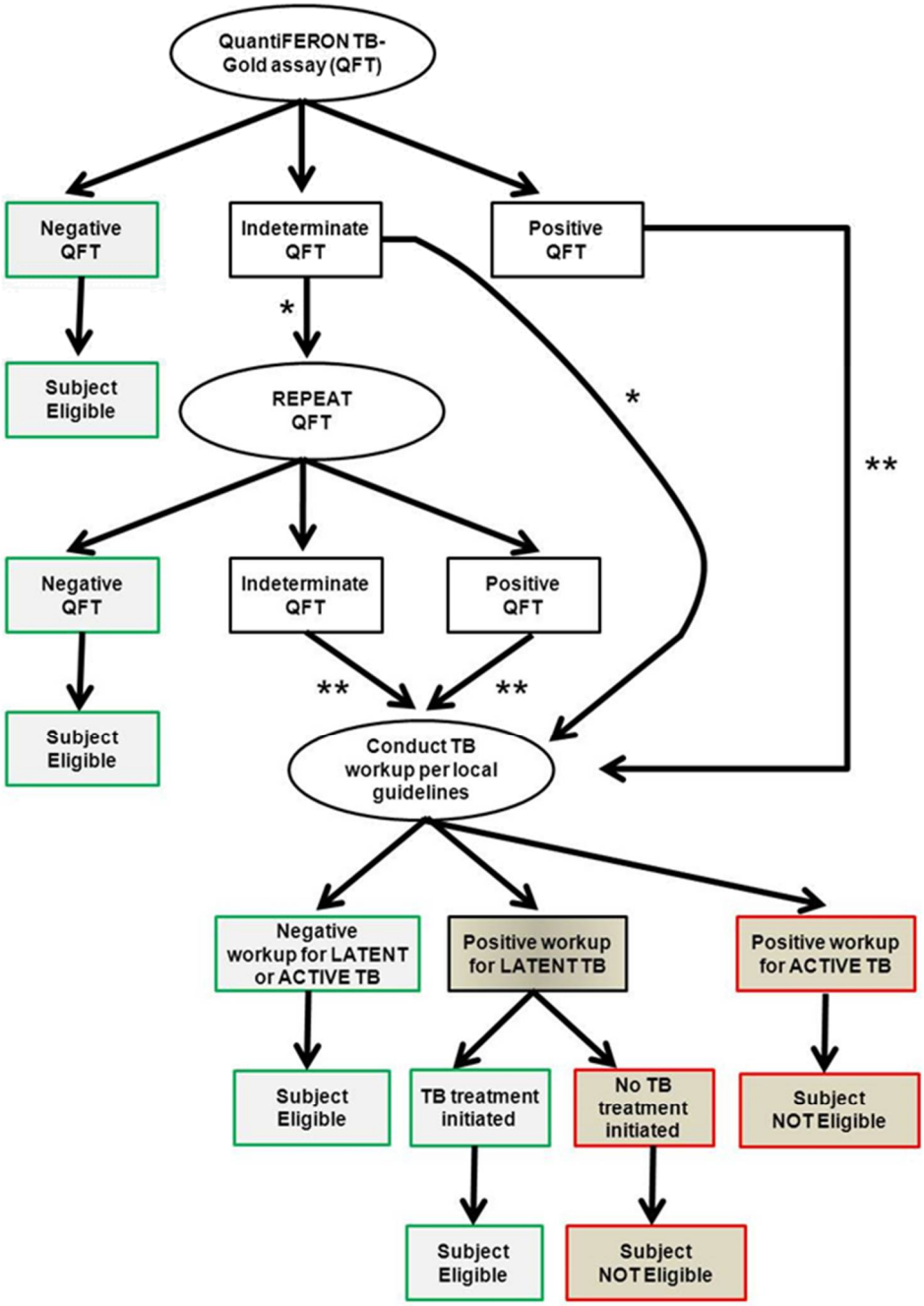
[redacted]

- If the test result is **positive**, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
- Subjects' positive for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects positive for active TB per workup are not eligible for the study. Subjects negative for TB (no signs of latent or active TB) per workup may be randomized to the trial.
- If the test result is **indeterminate**, the investigator **may repeat the test once or may proceed directly to perform workup** for the test result as per local procedures. This action is at the discretion of the investigator. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
- If the second test is negative, the subject may be randomized.
- If the second test is positive, the investigator should perform workup as per local guidelines. Subjects' positive for **latent** TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects **positive** for **active** TB per workup **are not eligible** for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial.
- If the second test is again indeterminate, the investigator should perform follow-up for the test result as per local procedures. Subjects tested positive for **latent** TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice. Subjects positive for **active** TB per workup are not eligible for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial if the workup was conducted 12 within weeks prior to randomization.

If eligibility is being assessed with only 1 test result and a TB workup (i.e., no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the screening period (within 4 weeks prior to randomization) and TB workup will only be considered if it was completed **within 12 weeks** prior to randomization. Subjects' positive for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice and will be maintained for the prescribed duration. Subjects positive for active TB per workup are not eligible for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial.

[redacted]

Figure 6-1 Tuberculosis screening flowchart



The subject will not be eligible for randomization if "active tuberculosis is present "or if "latent tuberculosis is present and is untreated as per local guidelines."

* If the first QuantiFERON® TB-Gold In-Tube test (QFT) is indeterminate, the investigator may choose to perform a second QFT or refer the subject for tuberculosis workup per local guidelines.

** If the result of any QFT is "positive" or the results of 2 sequential QFTs are "indeterminate", the subject must be referred to have a tuberculosis workup per local guidelines (if no workup within 12 weeks prior to randomization is available).

6.2.6 Other baseline characteristics

Baseline characteristic data to be collected on all subjects include (all labs are central except where indicated):

ECG, vital signs; hematology; clinical chemistry; local urinalysis; past medical history record of HIV, hepatitis B or hepatitis C status; [redacted] PASI; IGA mod 2011; cDLQI. A serum pregnancy test will be performed for females of child bearing potential or of at least 12 years of age.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page (visit specific and summary pages).

Information on drug dispensing, administration, accountability will be collected in drug accountability logs and other documents as appropriate. For drug administrations at home subject will record relevant information at home which will then be transcribed at the corresponding documents at site including Dosage Administration Record eCRF page (see also Section 5.5).

Compliance will also be assessed and confirmed by field monitor via drug accountability logs and via info documentation and information provided by IRT and by the qualified site personnel responsible for treatment dispensation, preparation, administration and accountability.

6.4 Efficacy

All efficacy assessments should be performed prior to administration of study treatment. Qualified site personnel (efficacy assessors) other than those treating the subjects, blinded to the allocation, will perform the efficacy assessments.

There are two co-primary efficacy variables in this study: PASI 75 response and IGA mod 2011 0 or 1 response.

The following order should be applied when performing the efficacy assessments during study visits:

- Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4)
- Psoriasis Area and Severity Index (PASI; score from 0 – 72)
- [redacted]

6.4.1 Investigator Global assessment (IGA mod 2011)

An efficacy assessor other than the investigator treating the subject will perform IGA mod 2011 assessment as indicated in Table 6-3. It is recommended that the same assessor conducts the efficacy assessment throughout the study whenever possible.

The IGA mod 2011 rating scale for overall psoriatic disease is shown in Table 6-3 below.

The IGA mod 2011 scale has been developed based on a previous version of the scale used in secukinumab phase II studies in collaboration with health authorities, in particular the FDA.

[redacted]

The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

The IGA mod 2011 used in this study is static, i.e., it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

The IGA mod 2011 score will be recorded in the eCRF.

Table 6-3 IGA mod 2011 scale

0	Clear, No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	Almost clear- Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild- Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate -Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe- Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions

Based on this scale, a subject will be eligible to participate in the study if the subject has an IGA mod 2011 score at baseline of 4.

Based on this scale, a subject will be considered as IGA mod 2011 0 or 1 responder if the subject achieves a score of 0 or 1 and improved by at least 3 points on the IGA mod 2011 scale compared to baseline. The IGA score will be recorded in the study-specific paper source form then will be entered into the eCRF at all visits with exception of Randomization visit when it will be also entered into the IRT to assess eligibility based on IGA mod 2011 score.

6.4.2 Assessment of total body surface area (BSA) and psoriasis area safety index (PASI)

The efficacy assessor (other than the investigator treating the subject) will complete the PASI assessment as indicated in Table 6-1, Table 6-2. Whenever possible, the same assessor should perform this efficacy assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations will be done: Each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting four percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

A PASI score (Fredriksson 1978, Weisman 2003, Gottlieb 2005) will be derived as indicated in Table 6-4. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

- The neck is assessed as part of the head.

[redacted]

- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.
- When scoring the severity of erythema, scales should not be removed.

Table 6-4 PASI scoring system

Body region	Erythema (E)	Thickening (I) (plaque elevation, induration)	Scaling (D) (desquamation)	Area score (A) (based on true area %)*
Head (H)†	0=none	0=none	0=none	0 = no involvement
	1= slight	1= slight	1= slight	1 = >0-<10%
	2= moderate	2= moderate	2= moderate	2 = 10-<30%
	3= severe	3= severe	3= severe	3 = 30-<50%
	4=very severe	4=very severe	4=very severe	4 = 50- <70%
				5 = 70-<90%
				6= 90 -100%
Trunk (T)‡	0=none	0=none	0=none	0 = no involvement
	1= slight	1= slight	1= slight	1 = >0-<10%
	2= moderate	2= moderate	2= moderate	2 = 10-<30%
	3= severe	3= severe	3= severe	3 = 30-<50%
	4=very severe	4=very severe	4=very severe	4 = 50- <70%
				5 = 70-<90%
				6= 90-100%
Upper limbs (U)	0=none	0=none	0=none	0 = no involvement
	1=slight	1=slight	1=slight	1 = >0-<10%
	2=moderate	2=moderate	2=moderate	2 = 10-<30%
	3=severe	3=severe	3=severe	3 = 30-<50%
	4=very severe	4=very severe	4=very severe	4 = 50- <70%
				5 = 70-<90%
				6 = 90-100%
Lower limb (L)§	0=none	0=none	0=none	0 = no involvement
	1=slight	1=slight	1=slight	1 = >0-<10%
	2=moderate	2=moderate	2=moderate	2 = 10-<30%
	3=severe	3=severe	3=severe	3 = 30-<50%
	4=very severe	4=very severe	4=very severe	4 = 50- <70%
				5 = 70-<90%
				6 = 90-100%

* Percentage (not score) of body region (not whole body) affected will be entered in the eCRF

† Neck is assessed as part of the Head (H) body region.

‡ Axillae and groin are assessed as part of the Trunk (T) body region.

§ Buttocks are assessed as part of the Lower limbs (L) body region.

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the formula:

PASI=0.1 (EH+IH+DH)AH+0.2(EU+IU+DU)AU+0.3(ET+IT+DT)AT +0.4(EL+IL+DL)AL

[redacted]

The keys for the letters are provided in Table 6-4.

PASI scores can range from a lowest value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.

The efficacy assessor is responsible for evaluating the subject and collecting the components, scoring signs and total regional area. The efficacy assessor/qualified site staff will record PASI data in the study-specific paper source worksheet at study visits and subsequently, investigator/qualified site staff will enter the data into PASI eCRF.

Calculations based on collected PASI components (e.g. total PASI score, BSA, PASI 75 responder status- as applicable) will be done by efficacy assessor/qualified site staff. These will also be entered in the PASI source worksheet and PASI eCRF as required.

At Visit 1 and Visit 2, the efficacy assessor/qualified site staff, after collecting the components of the PASI calculation, must calculate and verify (as indicated previously) the total PASI score and the total BSA.

Based on PASI, to be eligible, a subject must have a score of 20 or more at the Randomization Visit.

Based on total BSA, to be eligible, a subject must have 10% or more total BSA involved at the Randomization Visit.

Only if the above eligibility criteria and all other eligibility criteria are fulfilled should site contact IRT at the Randomization Visit to randomize the subject.

At Visit 8 (Week 12), the efficacy assessor/qualified site staff, after collecting the components of the PASI calculation, must calculate (as indicated previously) the total PASI score. In addition the PASI 75 responder status of the subject must be calculated. Subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline (Randomization Visit) are defined as **PASI 75 responders**. Those achieving < 75% improvement are considered as PASI 75 non-responders. These will also be entered in the PASI source worksheet and PASI eCRF.

Once this is calculated and verified the site can contact IRT and indicate whether the subject is PASI 75 responder on PASI 75 non responder.

Definitions of efficacy variables based on PASI

The following definitions are used in this study (see CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004)):

PASI 50 response (partial response): subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders

PASI 75 response: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders

PASI 90 response: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders

PASI 100 response / remission: complete clearing of psoriasis (PASI=0)

[redacted]

[redacted]

6.4.4 Appropriateness of efficacy assessments

The PASI score, the assessment of the severity of the psoriasis symptoms and the extent to which the subject's body area is affected by the disease, is considered acceptable by health authorities (CHMP guideline on the treatment of psoriasis-CHMP/EWP/2454/02 2004) to assess efficacy in conjunction with Investigator's Global Assessment (IGA).

6.5 Safety

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

During the COVID-19 pandemic or similar major health care disruption that limits or prevents on-site study visits, phone calls, virtual contacts (e.g. teleconsult), or visits by site staff or home nursing service depending on local regulations and capabilities may occur on or around scheduled protocol visit dates (or more frequently if needed). This will be done for safety monitoring and discussion of the subject´s health status until the subject can again visit the site. Case report forms (e.g. AEs, concomitant medications, procedures and non-drug therapies) should be updated as appropriate.

6.5.1 Physical examination

A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, and vascular and neurological systems will be performed as indicated in Table 6-1, Table 6-2. Investigator should pay special attention to any signs or symptoms of potential skin or mucosal candida infections.

If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator.

If possible, assessments for an individual subject should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the screening visit (Visit 1) must be included in the Medical History screen on the subject's eCRF. Significant findings made after

[redacted]

the start of study (Visit 1) that meet the definition of an adverse event must be recorded on the Adverse Event screen of the subject's eCRF.

[redacted]

6.5.3 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 6-1, Table 6-2. If possible, assessments should be performed by the same study site staff member throughout the study.

After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic **blood pressure will be measured twice** (measurements separated by 1 to 2 minutes) using a validated device, with a cuff that is appropriately sized for the subject's arm circumference. The average of the two measurements will be entered on the Vital Signs eCRF.

Whether action needs to be taken to address notable vital signs will be decided by the investigator/qualified site staff, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol. Notable values for vital signs are indicated in Appendix 1, Table 13-1.

6.5.4 Height and weight

Height and body weight will be measured at visits as in Table 6-1, Table 6-2. Height measurements (in indoor clothing, but without shoes, socks, hats or hair accessories interfering with assessment) will be made using a stadiometer that is calibrated on a regular basis. Height measurements will be performed twice and the reported height will be the mean of the 2 measurements.

If possible, body weight assessments (in indoor clothing, but without shoes) should be performed by the same study site staff member and using the same scale throughout the study. The body weight recorded at Randomization (Visit 2) will be used to categorize the subject population at randomization and placebo PASI 75 non-responders at Week 12 respectively, to receive the corresponding doses in the high dose and low dose secukinumab groups.

[redacted]

6.5.5 Laboratory evaluations

Subjects should avoid smoking within the hour preceding the blood draws.

A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. The blood volume drawn will be adjusted for pediatric patients and will be stated in the laboratory manual.

During the COVID-19 pandemic or a major health care disruption that limits or prevents on-site study visits and central lab sampling, performing the safety lab tests locally, will be allowed in case it is needed to check safety parameters. Depending on local regulations, technical capabilities and following any applicable training in the required process, qualified staff may visit the subject at home to draw blood/ urine samples if needed to check safety parameters.

Clinically notable values for key laboratory tests are defined in Section 13, Appendix 1. For identification of pediatric abnormal values for all parameters, the laboratory manual must also be consulted.

Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at scheduled study visits, as specified in Table 6-1, Table 6-2.

6.5.5.2 Clinical chemistry

Serum chemistry will include urea or BUN, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

Serum chemistry will be measured at scheduled study visits as specified in Table 6-1, Table 6-2.

Estimated GFR

In addition estimated Glomerular Filtration Rate (eGFR) as per Schwartz et al (Schwartz 2009) will be calculated and reported by the Central Laboratory, whenever a serum creatinine is performed.

The calculation is based on the following formula:

eGFR (ml/min/1.73m2) = 0.413 x height (cm) / serum creatinine (mg/dl)

Height will be provided by the site to the central lab.

For eGFR, baseline value for the decrease from baseline criterion will be calculated as the average of values prior to the first dose (i.e. screening and baseline values).

[redacted]

Fasting glucose (conditional)

In case urine dipstick evaluation shows new glucosuria ≥ 1+, a fasting blood sample must be collected and sent to central lab for glucose analysis. More details can be found in Section 7.4.

6.5.5.3 Urinalysis

Urine Dipstick (local)

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative 'dipstick' evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood, micro albumin.

Urinalysis will be measured locally at scheduled study visits as specified in Table 6-1, Table 6-2.

Quantitative Urinalysis (conditional) and Urine Microscopy (conditional)

If the dipstick result is positive for protein, glucosuria and/or blood, a urine sample will be sent to central laboratory for microscopic analysis which will include WBC, RBC, crystals, casts as indicated in the renal safety section (Section 7.4).

Furthermore, whenever eGFR decrease meets alert values as indicated in renal safety section (Section 7.4) a urine sample must be sent to the central laboratory for quantitative urinalysis. This analysis will include protein and creatinine to calculate the protein over creatinine ratio (PCR) and other parameters like bilirubin, blood, color, glucose, ketones, leukocytes, esterase, nitrite, pH, protein, specific gravity, urobilinogen.

6.5.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1, Table 6-2. When ECG is performed at scheduled visits, the investigator will review and initial tracing, and store with the subject's source documentation. All ECGs must be performed on the ECG machines provided to the study site.

All ECGs will be independently reviewed by a central reader. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Even though there is no exclusion criterion specifically based on the ECG, the ECG performed at screening (Visit 1) must be reviewed for major abnormalities before dosing at the randomization visit. If the ECG findings are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status including medical history and concomitant medications), the subject should not receive treatment and should exit the study. If a clinically relevant abnormality is noted on the screening ECG it should be reported in the Medical History eCRF. Clinically relevant abnormalities noted after the screening ECG (Visit 1) should be recorded as AEs.

[redacted]

[redacted]

6.5.8 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become

[redacted]

menarchal during the study. In this study pregnancy tests will be performed in female subjects who are menarchal or become menarchal during the study and/or are 12 years of age or older at the beginning or at any point during the study. Sites must ensure that pregnancy testing commences once any of these conditions are fulfilled.

Serum pregnancy test will be performed for all females of child-bearing potential according to the schedule in Table 6-1, Table 6-2.

During the COVID-19 pandemic or similar major health care disruption, that limits or prevents female subjects of childbearing potential or at least of 12 years of age to visit the site, urine pregnancy test kits may be shipped or provided directly to the subject. After appropriate instruction, subjects can perform the urine pregnancy test at home at the time points specified in the protocol and report the result to the site. It is important that subjects perform the pregnancy test first and only if the test result is negative should they then proceed with the administration of the study drug. A communication process should be established with the subject so that the site is informed of the pregnancy test results. In these communications the privacy of the subject should be considered in accordance with the local law and ethics.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio-educational economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric subject and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must be discontinued from study drug. However, a patient may choose to remain in the study should she become pregnant, and be followed in the treatment-free follow-up epoch as described in Table 6-1, Table 6-2.

Female patients of child-bearing potential who do not agree to abstinence and who are or might become sexually active must be informed of the need to prevent pregnancy, by using effective methods of contraception during dosing of study treatment and for a minimum of 16 weeks after stopping study treatment or longer if local label requires it (e.g. in EU 20 weeks). At a minimum, the acceptable effective contraception is:

- Barrier methods of contraception:

a. Male or female condom with or without spermicide

b. Cap, diaphragm or sponge with spermicide

- Use of established oral, injected or implanted hormonal methods of contraception**,** intrauterine device (IUD) or intrauterine system (IUS)

The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen.

[redacted]

6.5.9 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic immunomodulating agent in psoriasis.

6.6 Other assessments

6.6.1 Health related Quality of Life

The impact of psoriasis on various aspects of subject's health-related quality of life (HRQoL) will be assessed by Children's Dermatology Life Quality Index (CDLQI).

The impact of Psoriatic Arthritis, on those subjects who have reported History of Psoriatic Arthritis will be assessed by their parent/custodian via the use of the childhood health assessment questionnaire, CHAQ© .

Sufficient time must be allowed for completion of both questionnaires. Questionnaires must be completed in a quiet environment.

Completed questionnaires will be reviewed and examined by the site staff (not the investigator or evaluator of the subject for the physician assessments), before the clinical examination, for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed then the events must be recorded as per instructions given in Section 7 of the protocol. Study site staff should not encourage the subjects to change the responses reported in the completed questionnaire.

6.6.1.1 Children's Quality of Life Index (CDLQI)

The Children's Dermatology Life Quality Index (Lewis Jones and Finlay, 1995) is a 10-item general dermatology disability index designed to assess health-related quality of life in pediatric subjects aged 4 to 16 years. It is self-explanatory and may be completed by the child with assistance from parents or caregivers as necessary. The 10 questions cover six areas of daily activities including symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. The questions are based on the preceding week to permit accurate recall.

Each question is answered on a 4-point Likert scale scored from 0 to 3. These are added to give a minimum score of 0 and maximum score of 30. A higher CDLQI score indicated greater degree of QoL impairment.

CDLQI is available in two versions, text only and text with cartoons. The text only version will be used in this study. The mean completion time of the text version is 120 seconds.

The purpose of the CDLQI in this study is to investigate the effects of treatment of secukinumab with respect to CDLQI at Week 12, compared to placebo, and over time up to Week 52.

This questionnaire should be completed in the language the subject is most familiar with before any other clinical assessments,

The questionnaire should be completed by the subject with the help of parent/custodian if and as needed. The site staff may help understand the questions, as necessary. The subject should be given sufficient space and time to complete the questionnaire. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing

[redacted]

responses before the clinical examination. Once subjects reach 18 years of age CDLQI must no longer be completed.

The CDLQI questionnaire will be completed by the subject as indicated in Table 6-1, Table 6-2.

During the COVID-19 pandemic or similar major health care disruption that limits or prevents on-site study visits, CDLQI questionnaire data may be collected remotely (e.g. via telephone interview of the subject) by qualified site personnel. This will depend on local regulations, technical capabilities and following any applicable training in the required process. Documentation of the procedure should follow the vendor emergency manual directives.

6.6.1.2 Childhood Health Assessment Questionnaire (CHAQ) for subjects with Psoriatic Arthritis

The childhood health assessment questionnaire CHAQ© (Singh et al 1994;Ruperto et al 2001), will be used to assess physical ability and functional status of patients as well as quality of life, for those children only who have reported History of Psoriatic Arthritis. A representative example of the questionnaire is provided in Appendix 7.

The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and other "activities". The person completing the questionnaire chooses from four response categories, ranging from 'without any difficulty' to 'unable to do'.

The CHAQ© will be completed by a parent/custodian only if a validated version of the instrument is available in the language understandable to the parent at the visits indicated in Table 6-1. The same parent/custodian should preferably complete the questionnaire at all visits required per protocol. If patients turn 18 years of age during the study, the questionnaire will be completed together by the patient and the parent/custodian for the remaining visits.

6.6.1.2.1 Parent's or patient's global assessment of patient's overall well-being (VAS)

The parent's or patient's global assessment of patient's overall well-being will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from very well (0 mm) to very poor (100 mm).

Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

6.6.1.2.2 Parent's or patient's assessment of pain (VAS)

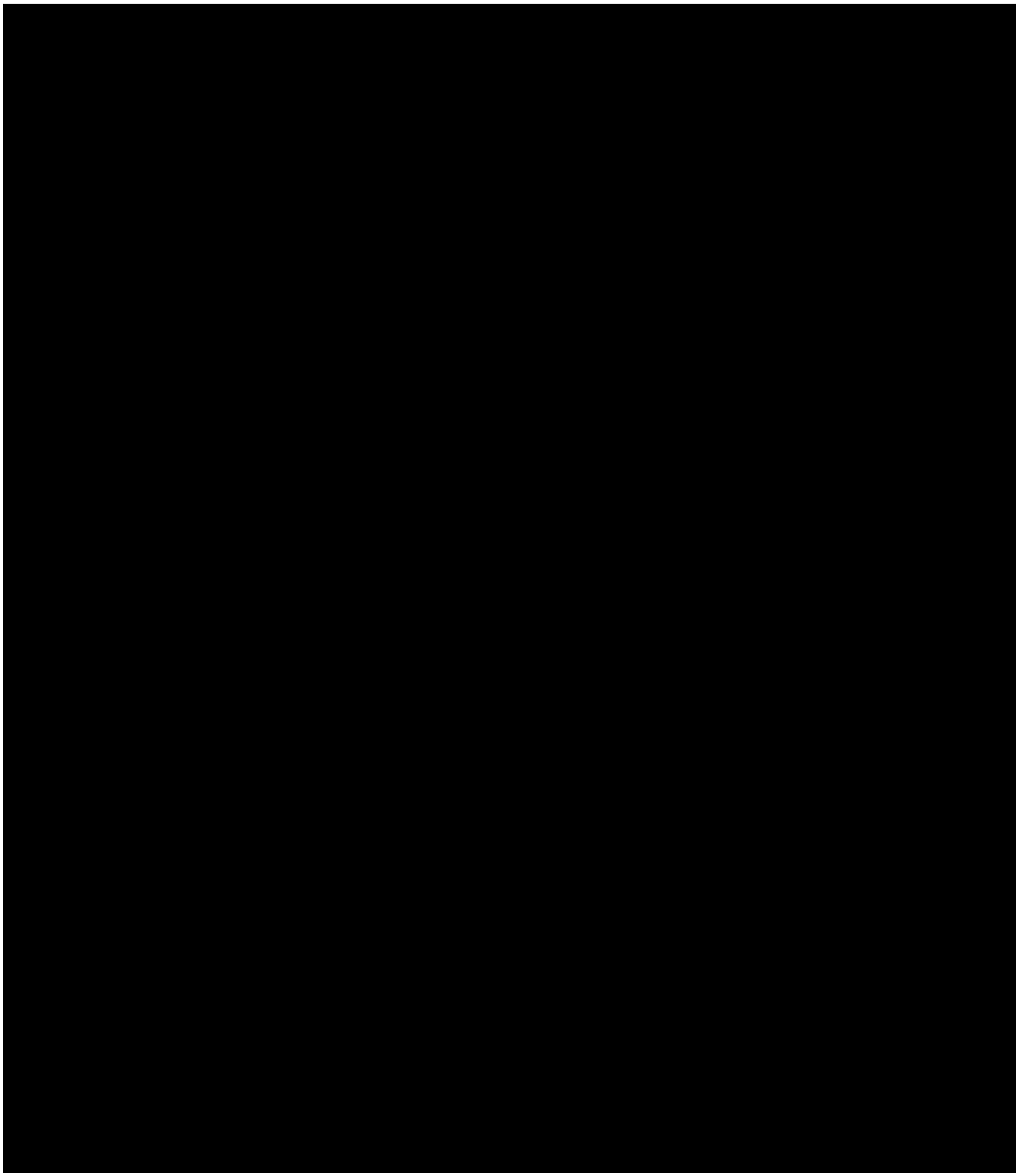
The parent's or patient's assessment of pain will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from no pain (0 mm) to very severe pain (100 mm).

Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

6.6.2 Resource utilization

Not applicable

[redacted]



[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

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

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit or scheduled phone contact during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Notable ranges for labs values are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities

[redacted]

  - severe: prevents normal activities.
- its relationship to the
  - study treatment (no/yes), or
  - investigational treatment (no/yes), or
  - the other study treatment (non-investigational) (no/yes), or
  - both or indistinguishable
- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding [study/investigational] treatment *(select as appropriate)*

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Worsening of psoriasis in this study is evaluated via the use of PASI, IGA mod 2011 and cDLQI assessments and is not expected to be captured as an AE in the eCRF. Exceptions include cases when a) a new type of psoriasis is diagnosed e.g. guttate psoriasis) or b) the worsening of psoriasis is so severe that a qualitatively different status is reached.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Drug Safety and Epidemiology (DS&E) as per section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 20 weeks after last dose was taken or until 30 days after

[redacted]

the last study visit (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAE reported until 20 weeks after last dose was taken or until End of study visit (whichever is later) must be recorded in the AE eCRF. SAEs beyond that date will only be recorded in the Novartis Drug Safety and Epidemiology database.

Any SAEs experienced after the 30 days from end of study visit or after the 20 weeks since last dose was taken (whichever is later), should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics

[redacted]

committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events will be followed for pediatric subjects. The liver safety monitoring procedure is applicable until the subject reaches adulthood. Once a subject reaches adulthood (≥18 years of age) this procedure no longer needs to be followed. However, if a subject is followed up for a specific event with liver monitoring procedures while turning 18, follow-up should continue until the event stabilizes or resolves.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 of Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and

[redacted]

the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

To ensure patient safety and enhance reliability in determining the nephrotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events will be followed for pediatric subjects. The renal safety monitoring procedure is applicable until the subject reaches adulthood. Once a subject reaches adulthood (≥18 years of age) this procedure no longer needs to be followed. However, if a subject is followed up for a specific event with renal monitoring procedures while turning 18, follow-up should continue until the event stabilizes or resolves.

The following two categories of renal adverse events have to be considered during the course of the study:

1. Serum event:

- confirmed decrease in estimated glomerular filtration rate (eGFR) of ≥ 25% compared to baseline during normal hydration status as estimated by Schwartz equation :
  eGFR (ml/min/1.73m2) = 0.413 x height (cm) / serum creatinine (mg/dl)

2. Urine event: New onset (≥1+) proteinuria, hematuria or glucosuria

- new onset of proteinuria should be confirmed by urinary protein creatinine ratio

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

[redacted]

Table 7-1 Specific Renal Alert Criteria and Actions

Serum Event	
Estimated GFR decrease 25 – <50% compared to baseline and eGFR <90mL/min/1.73m^2	Confirm[1] 25%-<50% decrease and eGFR <90mL/min/1.73m^2 after 24-48h, if possible. If it persists[1] follow up with repeat, if possible, within 2-5 days and perform urinary PCR on a first morning urine collection. Then do some frequent monitoring (preferably weekly) until event resolves[2] or stabilizes[3]. If event does not resolve or stabilize consider consulting nephrologist and/or drug interruption.
Acute Kidney Injury: Serum Estimated GFR decrease ≥ 50 % compared to baseline	Follow up within 24-48h if possible. If value persists, consider consulting nephrologist and/or drug interruption.
Urine Event	
New dipstick proteinuria ≥ 1+	Confirm[1] value after 24-48h, if possible. If dipstick value confirmed: a) perform[1] urinary protein creatinine ratio (PCR) within 2-5 days, if possible, on a first morning urine collection. b) perform urine microscopy and evaluate. If PCR > 0.2 g/g and/or urine microscopy has findings (e.g. crystals, casts, dysmorphic RBC, leukocytes) consider consulting nephrologist or drug interruption or discontinuation.
New dipstick glucosuria ≥ 1+ not due to diabetes	Confirm value after 24-48h, if possible. If it persists: a) perform, blood glucose (fasting). b) perform urinary protein/creatinine ratio. If PCR ratio > 0.2 g/g and blood glucose normal consider consulting nephrologist and /or drug interruption or discontinuation.
New dipstick hematuria ≥ 1+ not due to trauma or menses	Confirm[1] value after 24-48h, if possible. If it persists: a) perform[1] urinary protein creatinine ratio (PCR) within 2-5 days if possible, on a first morning urine collection. b) perform urine microscopy and evaluate. If PCR > 0.2 g/g and /or urine microscopy has findings (e.g. crystals, casts , dysmorphic RBC, leukocytes) consider consulting nephrologist or drug interruption or discontinuation.

For all renal events:

Urine samples for testing for renal monitoring, and particularly those for the PCR ratio determination, must be collected at the first morning void.

Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed

[1]Investigator and subject may decide to perform urinary PCR already with the first repeat

Monitor patient regularly (frequency at investigator's discretion) until either:

[2]Event resolution: estimated GFR within 20% of baseline and >90mL/min/1.73m^2 or PCR < 0.2 g/g (<22.6 mg/mmol).

[3]Event stabilization: estimated GFR within 20% of baseline OR >90mL/min/1.73m^2 or PCR < 0.3 g/g (<34 mg/mmol).

[redacted]

7.5 Pregnancy reporting

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

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization, Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or designee review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

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

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

Subjects/custodians will use an electronic tablet device to enter PRO data (CDLQI) as indicated in Section 6.6.1. The data will be transmitted by the site, processed centrally by the vendor and the results will be sent electronically to Novartis (or designee). A tablet device Site Manual will be provided for instructions related to tablet data entry. There are no other source data for this questionnaire, the data are entered directly in the tablet. In case of a technical issue related to the tablet use during a study visit with a CDLQI assessment and which cannot be resolved

during the visit, a paper CDLQI questionnaire can be used as an emergency back-up solution. Data captured via the paper questionnaire will be retrieved and managed by the PRO vendor and transferred to Novartis according to the vendor's standard procedure.

For CHAQ© the parents/custodians will complete the questionnaire. Questionnaire will be completed together with patient if the patient is 18 years of age or older. The completed questionnaire will be transmitted to the vendor. The data will then be processed centrally by the vendor and the results will be sent electronically to Novartis (or designee).

[redacted]

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) will be appointed to monitor the safety and efficacy of the study subjects.

The safety and efficacy data from the first 80 adolescent subjects will be evaluated before children ages 6 to < 12 years can be enrolled. Further to that, safety and efficacy data will be reviewed by the DMC during the study, as described in the Secukinumab DMC Charter.

Details regarding the DMC process, responsibilities and membership will be available, as needed, in the relevant Secukinumab DMC charter.

8.5 Adjudication Committee

Not required.

9 Data analysis

Treatment groups for analyses will include as shown in Table 9-1.

Table 9-1 Treatment groups for analyses

Weight category	Up to Week 12			
	Low dose secukinumab	High dose secukinumab	Placebo	Etanercept (max 50mg per dose)
<25kg	75mg	75mg	X	0.8mg/kg
25-<50kg	75mg	150mg	X	0.8mg/kg
≥50kg	150mg	300mg	X	0.8mg/kg

Weight category	Week 12-52

[redacted]

	Low dose secukinumab	High dose secukinumab	Placebo to Low dose secukinumab	Placebo to High dose secukinumab	Etanercept (max 50mg per dose)
<25kg	75mg	75mg	75mg	75mg	0.8mg/kg
25-<50kg	75mg	150mg	75mg	150mg	0.8mg/kg
≥50kg	150mg	300mg	150mg	300mg	0.8mg/kg

Weight category	**Entire Study**					
	Low dose secukinumab	High dose secukinumab	Placebo	Etanercept (max 50mg per dose)	Any Low dose secukinumab	Any High dose secukinumab
<25kg	75mg	75mg	x	0.8mg/kg	75mg	75mg
25-<50kg	75mg	150mg	x	0.8mg/kg	75mg	150mg
≥50kg	150mg	300mg	x	0.8mg/kg	150mg	300mg

Summary statistics for continuous variables will include n, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, p-values will be presented as one-sided for hypothesis testings and as two-sided for other analysis. Two-sided 95% confidence intervals will be displayed.

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. (Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind treatment was not administered to the subject).

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment epoch. Subjects will be analyzed according to treatment received.

9.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics variables for each treatment group and for all subjects in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

[redacted]

Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary. Summaries for psoriasis specific medical history will be provided as well.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set.

The number of active and placebo injections will be summarized by treatment group by means of contingency tables. The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be displayed.

Prior and concomitant treatment

Prior and concomitant treatments will be summarized by treatment group in separate tables. Prior treatments are defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant treatment, including those which were started pre-baseline and continued into the treatment epoch.

Treatments will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will also show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group. Psoriasis specific prior treatments will be presented as well.

In addition, non-drug therapies will be summarized.

9.4 Analysis of the primary variable(s)

This section will detail the statistical analysis of the primary endpoints. Details of the hypothesis testing strategy including primary and secondary endpoints to handle multiplicity are provided in Section 9.5.1.

9.4.1 Variable(s)

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA 0 or 1 response at Week 12. The analysis of the co-primary variables will be based on the FAS.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypotheses for PASI 75 response at Week 12 and IGA 0 or 1 response at Week 12 being tested is that secukinumab (low or high dose) is not superior to placebo in the proportion of subjects with PASI 75 and IGA 0 or 1 response at Week 12.

[redacted]

Let p_j denote the proportion of PASI 75 responders at Week 12 for treatment group *j* and r_j denote the proportion of IGA 0 or 1 responders at Week 12 for treatment group *j*, *j*=0, 1, 2, where

- 0 corresponds to placebo,
- 1 corresponds to secukinumab low dose,
- 2 corresponds to secukinumab high dose.

The following hypotheses will be tested

H_1: $p_1 - p_0 \leq 0$ versusH_{A1}: $p_1 - p_0 > 0$,

H_2: $p_2 - p_0 \leq 0$ versus H_{A2}: $p_2 - p_0 > 0$,

H_3: $r_1 - r_0 \leq 0$ versus H_{A3}: $r_1 - r_0 > 0$,

H_4: $r_2 - r_0 \leq 0$ versus H_{A4}: $r_2 - r_0 > 0$.

In other words:

H_1: Secukinumab low dose is not superior to placebo with respect to PASI 75 response at

Week 12

H_2: secukinumab high dose is not superior to placebo with respect to PASI 75 response at

Week 12

H_3: secukinumab low dose is not superior to placebo with respect to IGA 0 or 1 response at Week 12

H_4: secukinumab high dose is not superior to placebo with respect to IGA 0 or 1 response at Week 12

The primary analysis method will be the exact logistic regression with all 4 treatment groups (including etanercept); baseline bodyweight, age stratum and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fitted. Confidence intervals for risk difference will be derived based on the exact method.

9.4.3 Handling of missing values/censoring/discontinuations

The following imputation methods will apply to the missing data for analysis up to Week 52 including primary W12 analysis:

- Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputations (MI) method as primary imputation method. Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

[redacted]

- (Pure) Non-responder imputation will be used as a sensitivity method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories will be imputed with non-response regardless to the reason for missing data. Subjects with missing baseline or those with all post-baseline missing will be imputed with non-response.

The following imputation methods will apply to the missing data for analysis of the long term

[redacted]

9.4.4 Supportive analyses

Sensitivity analyses will be performed as follows:

- PASI 75 and IGA 0 or 1 response at Week 12 will be evaluated using an exact logistic regression model with treatment group, baseline bodyweight stratum, age stratum and baseline PASI as effects with pure non-responder imputations for missing values.
- Primary analysis will also be evaluated on the subset of adolescents

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary variable in testing strategy is the PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 (for superiority comparison of secukinumab doses versus placebo). The PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 will be analyzed in the same way as the primary variables.

The secondary efficacy variable PASI 90 at Week 12, will be analyzed using the FAS unless otherwise specified.

Testing strategy

The family-wise type I error will be set to α=2.5% (one-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy. The procedure allows the type I error rate associated with a rejected hypothesis to be reallocated according to a set of pre-specified rules. The hypotheses associated to the primary and secondary variables are as below.

Co-primary variables:

H_1 to H_4 (see Section 9.4.2)

Secondary variable:

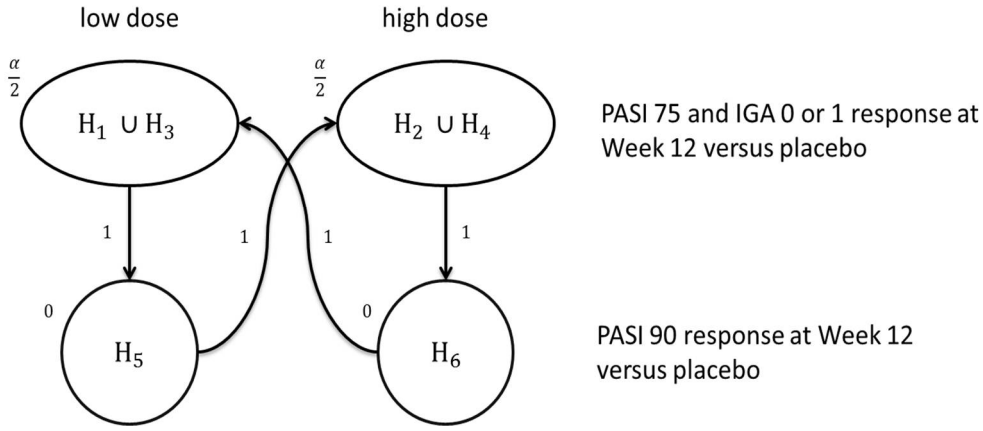
H_5: secukinumab low dose is not superior to placebo with respect to PASI 90 response at Week 12

[redacted]

H_6: secukinumab high dose is not superior to placebo with respect to PASI 90 response at Week 12

The graphical approach of (Bretz 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy in Figure 9-1.

Figure 9-1 Testing strategy



One-sided p-values will be derived. The family-wise error will be set to α=2.5% (one-sided). The hypotheses are mapped into two sets (H_1, H_3 and H_5) or (H_2, H_4 and H_6) such that hypotheses within a set correspond to the same secukinumab (AIN457) dose regimen. In essence, the type-I-error probability will be equally split for both sets of hypotheses and within each set the hypothesis are tested sequentially as follows:

Within each pair, of hypotheses (H_1 or H_3) and (H_2 or H_4), each hypothesis is tested at α/2 (one-sided). Only if both hypotheses of a pair are rejected, the testing sequence will continue.

In the next step of the sequence, the null hypotheses corresponding to the PASI 90 comparison of secukinumab (AIN457) versus placebo is tested. H_5 and H_6 will be tested at α/2 (one-sided).

If all hypotheses within a set referring to a secukinumab dose regimen have been rejected, i.e., either (H_1, H_3 and H_5) or (H_2, H_4 and H_6), the corresponding type I error probability can be passed on to the other set of hypotheses, and if needed, hypotheses can be retested at a higher significance level.

9.5.2 Other Efficacy variables

PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time

Summary statistics for PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the exact method.

For PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response at each visit, each secukinumab dose regimen will be compared to placebo (up to Week 12 only) [redacted] by exact logistic

regression with treatment group, baseline bodyweight stratum, age stratum and baseline PASI score as explanatory variables.

For PASI 75, PASI 90 and IGA 0 or 1 response the placebo-adjusted response rates including 95% confidence interval (exact method) will be derived by visit up to Week 12. Similarly, estimates for the difference in response rates for secukinumab minus [redacted] will be derived over time.

Figures will also be provided.

PASI score over time

Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group. Figures will also be provided.

IGA mod 2011 score over time

Summary statistics for the IGA mod 2011 score over time will be presented by visit and treatment group in contingency tables.

[redacted]

9.5.3 Safety variables

All safety evaluations will be performed on the Safety set.

Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment and within 84 days after the last study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 84 days after the last study

[redacted]

treatment) will be summarized. Only primary paths within MedDRA will be considered for adverse event reporting.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

These summaries will be presented separately for induction period and entire treatment period.

Confidence intervals for relative frequencies will be derived as well according to the exact method.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes will be presented.

In supplementary analyses, for selected adverse events exposure (or observation) time adjusted analyses in terms of incidence rate will be provided for the entire treatment period.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline.

For each parameter, the maximum change from baseline within each study period will be analyzed analogously.

In addition, shift tables will be provided for all lab parameters to compare a subject's baseline laboratory evaluation relative to the most extreme post-baseline laboratory test value. Shift tables with respect to Common Toxicity grade Criteria (CTC) and normal ranges will be provided by laboratory test and treatment group.

Incidence rates of notable abnormalities (see Appendix 1) will be presented.

[redacted]

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented

[redacted]

by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

All information collected will be listed by patient and abnormal values (see Appendix 1) will be flagged.

ECG

Summary statistics will be presented for ECG variables by visit and treatment group.

[redacted]

Growth and weight gain

Growth and weight gain will be summarized descriptively.

9.5.4 Resource utilization

Not Applicable.

9.5.5 Health-related Quality of Life

Children's Dermatology Quality of Life Index (CDLQI)

The CDLQI measures functional disability of subjects with dermatological disorders that are less than 18 years of age and had been utilized as a relevant clinical measure in atopic dermatitis, as well as other dermatitis clinical trials. The CDLQI is a simple, validated, self-administered 10-item questionnaire. The instrument contains six functional scales (i.e., symptoms and feeling, leisure, school or holidays, personal relationships, sleep and treatment). The questions are based on the preceding week to permit accurate recall. For the CDLQI, each question will be answered on a 4-point Likert scale scored from 0 to 3. Seven scores will be derived from the CDLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

For each of the seven scores the percentage change from baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group in contingency tables. The CDLQI 0 or 1 achievement will be analyzed by visit and treatment group.

Childhood Health Assessment Questionnaire (CHAQ©)

Changes in health-related quality of life for subjects with history of psoriatic arthritis will be measured using CHAQ©.

Descriptive statistics will be used to summarize patient responses on the CHAQ© Questionnaire by treatment, total score and by domain.

For parent's or patients global assessment of patient's overall well-being and of pain (VAS score) summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

[redacted]

[redacted]

9.5.8 Biomarkers

Not applicable

9.5.9 PK/PD

Not applicable

9.6 Interim analyses

An interim analysis will be conducted once at least 80 adolescents complete 24 weeks of treatment. The key efficacy and safety data will be reviewed by the DMC to ensure that no serious efficacy or safety concerns are observed with the study treatments. Enrollment of the pediatric population aged 6 to less than 12 years will begin only when the safety and efficacy evaluation is satisfactory based on the DMC's recommendation.

An additional interim analysis, will be conducted once sufficient safety [redacted] data have been collected. This analysis, aligned with the efficacy extrapolation principle, is expected to provide the basis for a submission package to health authorities (HA), with the intent to allow earlier availability of secukinumab to pediatric patients, in countries which

[redacted]

accept a submission of clinical data with use of extrapolation methodology. This analysis may be performed before all subjects have reached the primary endpoint. It is expected that data from at least approximately 100 patient years of secukinumab treatment will be included in this analysis.

This interim analysis will consist of a Bayesian full extrapolation approach using adult efficacy data along with available pediatric [redacted], safety, and efficacy data to support a submission to Health Authorities for plaque type psoriasis in a pediatric population of ages 6 to 18 years. This analysis will use a Bayesian meta-analytic-prediction (MAP) approach (Neuenschwander 2010) to demonstrate the consistency of efficacy responses between adults and pediatric population. The MAP approach is based on a Bayesian random-effects meta-analysis and provides a prediction of adult efficacy response rates in a new trial. The prediction will take into account uncertainty due to sample size and due to between-trial heterogeneity.

The observed pediatric response rates at Week 12 for PASI 75, PASI 90 and IGA 0/1 in this study will be checked for consistency with predicted response rates based on Novartis adult studies (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) using a predictive check method.

Since the planned hypothesis will not be tested at this interim, the type-I error probability will not be adjusted for this interim and full alpha will be kept for the hypothesis test in the final analysis.

A full analysis of all data collected up to Week 24, including primary endpoint at Week 12 will be performed after all subjects have completed either the Week 24 visit or the premature treatment discontinuation visit (i.e., EOI (Week 12 visit) for subjects discontinuing during induction epoch or EOM (Week 52 visit) for subjects discontinuing during the maintenance epoch visit. Data from subjects who have completed the treatment-free follow-up visits up to this time point (after premature discontinuation from the induction or the maintenance epoch) will also be included in this analysis.

Another full analysis of all data collected up to Week 52, including primary endpoint at Week 12 will be performed after all subjects have completed either the Week 52 visit or the premature treatment discontinuation visit (i.e., EOI (Week 12 visit) for subjects discontinuing during induction epoch or EOM (Week 52 visit) for subjects discontinuing during the maintenance epoch visit. Data from subjects who have completed the treatment-free follow-up visits up to this time point (after premature discontinuation from the induction or the maintenance epoch) will also be included in this analysis.

Efficacy and safety data collected during the extension treatment epoch (until the end of study) may be reported yearly in separate reports.

9.7 Sample size calculation

Approximately 160 pediatric subjects from 6 to less than 18 years of age, with 2 subgroups: 6 to less than 12 years of age, and 12 to less than 18 years of age.

Stratification is planned for age (<12 years, >=12 years) and weight (<25kg, 25-<50kg and ≥50kg). It will be targeted to have at least 30 subjects in the <12 years subgroup at a minimum. Enrollment of children aged 6 to less than 12 years will proceed after efficacy and

[redacted]

safety data for approximately 80 (approximately 40 treated with AIN) enrolled adolescents (aged 12 to less than 18 years) treated for 28 weeks have been reviewed and deemed satisfactory by a Data Monitoring Committee.

Since two secukinumab dose regimens will be tested versus placebo with respect to the co-primary endpoints (PASI 75 response and IGA 0 or 1 response at Week 12), the type-I-error will be split to 1.25% one-sided for each comparison. With 40 subjects per group and assuming a response rate of 10% for PASI 75 response and IGA 0 or 1 response in the placebo group, the power to show a response rate of 65% for PASI 75 response and 45% for IGA 0 response in the secukinumab groups based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions) is approximately 99% for PASI 75 response and approximately 88% for IGA mod 2011 0 or 1 response. For the secondary endpoint of PASI 90 response at week 12, assuming a response rate of 8% in the placebo group, the power to show a significant difference between a secukinumab dose and placebo, assuming a response rate of 39% in the secukinumab groups based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions) is approximately 82% for PASI 90 response. The assumed response rates for secukinumab are based on the confirmatory efficacy in severe patients in the adult phase III program. At Week 12, PASI 75 response rates of 11% and PASI 90 response rates of 7% have been reported in the placebo group in Paller et al (2008) for children and adolescents aged 4-17 years.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the

investigator must be agreed to by Novartis before submission to the IRB/ IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

In pediatric patients (< 18 years of age) parental permission and, whenever possible, child assent is needed instead of the procedure for informed consent used for research involving adults. In general, one or both parents or a guardian must be provided with the information ordinarily required for informed consent, so that they may decide whether to allow the child to participate, and children capable of assent must also express their willingness to participate. These forms will be submitted for IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

During the COVID-19 pandemic or similar major health care disruption that may challenge the ability to obtain a standard written informed consent due to limitations that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevails and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs or assent forms by trial subject/ guardian and person obtaining informed consent, etc).

In case Home Nursing (other than study treatment administration) is implemented during the COVID-19 pandemic or similar major health care disruption, a separate Home Nursing informed consent document must be used in addition to the main ICF.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of

[redacted]

Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

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

Unless otherwise indicated (e.g. liver and renal safety monitoring procedure, Section 7.3 and Section 7.4 respectively) no specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the investigator whether & which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

Laboratory values

Newly occurring selected notable laboratory abnormalities in pediatric patients at the time of the assessment:

Biochemistry and Urinalysis

- Alanine transaminase (ALT)(SGPT):
  Upper Limit of Normal (ULN)
  ≥3 x ULN
  ≥5 x ULN
  ≥8 x ULN
  ≥10 x ULN
- Aspartate transaminase (AST) (SGOT):
- >ULN
- ≥3 x ULN
  ≥5 x ULN
  ≥8 x ULN
  ≥10 x ULN
- Total Bilirubin (TBL)
  >ULN,
  ≥1.5xULN,
  ≥ 2xULN
- ALP
  >ULN
  ≥1.5xULN,
  ≥2xULN,
  ≥3x ULN
  ≥5xULN
- ALT and/or AST >3x-, 5x-, 10x ULN accompanied by TBL >2xULN
- ALT or AST >3x ULN and TBL >2x-, and ALP >2 x ULN.
- ALP >3x ULN and TBL >2x ULN

- Gamma-Glutamyltransferase (GGT):
  >ULN
  ≥3 x ULN
  ≥5 x ULN

Renal function

For the parameters related to renal function (e.g. eGFR according to Schwartz, urine protein, urine blood, glucosuria) the instructions provided in the renal safety monitoring section must be followed (Section 7.4).

Hematology

- Hemoglobin: ≥ 20 g/L decrease from baseline,

or < 85 g/L for < 16 years of age

< 100 g/L for ≥ 16 years of age

- Absolute neutrophils:

Grade 1: <LLN – 1.5 x 10E9/L

Grade 2: <1.5 – 1.0 x 10E9/L

Grade 3: <1.0 – 0.5 x 10E9/L

Grade 4: <0.5 x 10E9/L

- Criteria based on CTC grades for platelet count:

Grade 1: <LLN – 75.0 x 10E9/L

Grade 2: <75.0 – 50.0 x 10E9/L

Grade 3: <50.0 – 25.0 x 10E9/L

Grade 4: <25.0 x 10E9/L

- Criteria based on CTC grades for WBC:

G1:<LLN – 3.0 x10E9/L

G2:<3.0 – 2.0 x10E9/L

G3:<2.0 – 1.0 x10E9/L

G4: <1.0 x10E9/L

- Absolute Lymphocytes: < LLN
- Absolute Eosinophils: ≥ 1.1 x ULN
- Absolute Eosinophils: ≥0.45 x 109/L

Vital Signs

The following notable criteria will be used for systolic and diastolic BP and pulse. The age indicated is the age at the time of the visit.

[redacted]

Table 13-1 Notable Pediatric ranges for vital signs*

Age	Systolic BP	Diastolic BP	Pulse (BPM)
6 yrs	91-125	53-84	60-130
7 yrs	92-126	55-86	60-130
8 yrs	94-127	56-88	60-130
9 yrs	95-129	57-89	60-110
10 yrs	97-130	58-90	60-110
11 yrs	99-132	59-90	60-110
12 yrs	101-135	59-91	60-110
13 yrs	104-137	60-91	60-110
14 yrs	106-140	60-92	60-110
15 yrs	107-142	61-93	60-110
16 yrs	108-145	63-94	60-110
17 yrs	108-147	64-97	60-100
18 yrs	-	-	60-100

Source: http://www.who.int/childgrowth/standards
*values outside the provided ranges are considered notable

The Recommendations for the dimensions of Blood Pressure Cuff Bladders are noted in the following table.

Table 13-2 Recommended Dimensions for Blood Pressure Cuff Bladders

`	Width [cm]	Length [cm]	Maximum Arm Circumference [cm]*
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
*calculated so that the bladder can encircle even the largest arm by at least 80%			

Source: Feld and Corey H (2007): Hypertension in childhood, Pediatric in Review 28: 283-98

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity *

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

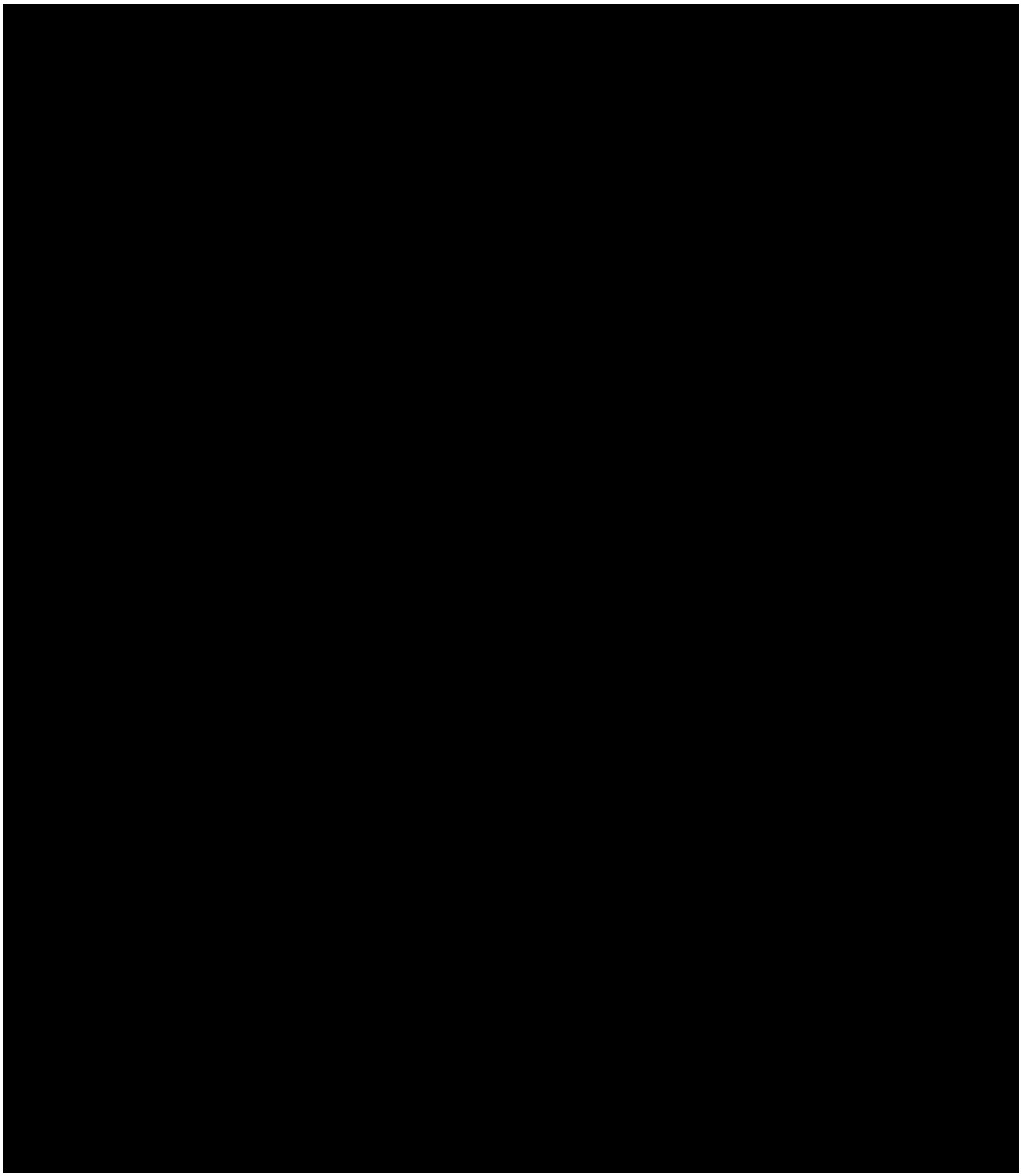
Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the subject • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.



16 Appendix 4: Weight and recommended blood volumes

European Medicines Agency (EMA) recommendations for trial related blood loss (including any losses in the maneuver) in pediatric populations are that no more than 3% of total blood volume should be taken during a four week period and not more than 1% of total blood volume at a single time-point. At a total blood volume estimated at 80 to 90ml per kilogram (kg) body weight, this equates to 2.4mL to 2.7mL blood per kg body weight during a four week period, or 0.8mL to 0.9mL blood per kg at any one time.

These recommended volumes must not be exceeded for any patient. Please use the information below to ensure that the recommended volumes are adhered to.

Table 16-1 Total blood volume, 1% and 3% of total blood volume by weight assuming 85mL per kg total blood volume

Weight (Kg)	Total Blood Volume* (mL)	1% Blood Volume (mL)**	3% Blood Volume (mL)**
5	425	4	12
10	850	8	24
15	1275	12	36
20	1700	17	51
25	2125	21	63
30	2550	25	75
35	2975	29	87
40	3400	34	102
45	3825	38	114
50	4250	42	126
55	4675	46	138
60	5100	51	103
65	5525	55	165
70	5950	59	177
75	6375	63	186
80	6800	68	204

*all blood volumes are rounded down

18 Appendix 6: CDLQI questionnaire

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	□ □ □ □
2.	Over the last week, how **embarrassed** or **self-conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	□ □ □ □
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	□ □ □ □
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	□ □ □ □
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	□ □ □ □
6.	Over the last week, how much have you	Very much	□

[redacted]

	avoided **swimming** or **other sports** because of your skin trouble?		Quite a lot □ Only a little □ Not at all □
7.	Last week, Was it **school time?** **OR** was it **holiday time**?	**If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school □ Very much □ Quite a lot □ Only a little □ Not at all □
		If holiday time: How much over the last week, has your skin problem interfered with enjoyment of the **holiday**?	Very much □ Quite a lot □ Only a little □ Not at all □
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much □ Quite a lot □ Only a little □ Not at all □
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much □ Quite a lot □ Only a little □ Not at all □
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much □ Quite a lot □ Only a little □ Not at all □

Please check that you have answered EVERY question. Thank you

[redacted]

19 Appendix 7: CHAQ Questionnaire

1990 Original version by Singh G et al. 1998 Cross-cultural adapted version by Woo P, Murray KJ, Nugent J for PRINTO

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please tick the one response which best describes your child's usual activities **OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS**. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
DRESSING & PERSONAL CARE					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?					
- Shampoo his/her hair?					
- Remove socks?					
- Cut fingernails?					
GETTING UP					
Is your child able to:					
- Stand up from a low chair or floor?					
- Get in and out of bed or stand up in a cot?					
EATING					
Is your child able to:					
- Cut his/her own meat?					
- Lift up a cup or glass to mouth?					
- Open a new cereal box?					
WALKING					
Is your child able to:					
- Walk outside on flat ground?					
- Climb up five steps?					

*** Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Walking stick
- Walking frame
- Crutches
- Wheelchair
- Devices used for dressing (button hook, zip pull, long-handled shoe horn, etc.)
- Built up pencil or special utensils
- Special or built up chair
- Other (Specify:_____)

*** Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- Dressing and personal care
- Getting up
- Eating
- Walking

		Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
32	**HYGIENE**					
33	Is your child able to:					
34	- Wash and dry entire body?					
35	- Take a bath (get in and out of bath)?					
36	- Get on and off the toilet or potty?					
37	- Brush teeth?					
38	- Comb/brush hair?					
39	**REACH**					
40	Is your child able to:					
41	- Reach and get down a heavy object such as a large game or books from just above his/her head?					
42	- Bend down to pick up clothing or a piece of paper from the floor?					
43	- Pull on a jumper over his/her head?					
44	- Turn neck to look back over shoulder?					
45	**GRIP**					
46	Is your child able to:					
47	- Write or scribble with pen or pencil?					
48	- Open car doors?					
49	- Open jars which have been previously opened?					
50	- Turn taps on and off?					
51	- Push open a door when he/she has to turn a door knob?					
52	**ACTIVITIES**					
53	Is your child able to:					
54	- Run errands and shop?					
55	- Get in and out of a car or toy car or school bus?					
56	- Ride bike or tricycle?					
57	- Do household chores (e.g. wash dishes, take out rubbish, hoovering, gardening, make bed, clean room)?					
58	- Run and play?					

59 *** Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

60	- Raised toilet seat	- Bathrail
61	- Bath seat	- Long-handled appliances for reach
62	- Jar opener (for jars previously opened)	- Long-handled appliances in bathroom

63 *** Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

64	- Hygiene	- Gripping and opening things
65	- Reach	- Errands and chores

PAIN: We are also interested in learning whether or not your child has been affected by pain because of his or her illness.

66 How much pain do you think your child has had because of his/her illness IN THE PAST WEEK?

Place a mark on the line below, to indicate the severity of the pain

67 No pain 0 ——————————— 100 Very severe pain

68 **GENERAL EVALUATION:** Considering all the ways that arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

69 Very well 0 ——————————— 100 Very poor