NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2311 / NCT03668613

A randomized, open-label, multicenter trial to assess the efficacy of subcutaneous secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BDR	Bioanalytical Data Report
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CDLQI	Children's Dermatology Life Quality Index
COVID-19	Coronavirus disease of 2019
CFR	Code of Federal Regulations
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CS	Corticosteroid
CTC	Common Toxicity Criteria
DMC	Data Monitoring Committee
DS & E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report/Record Form
eg	Example
eGFR	estimated Glomerular Filtration Rate
EMA	European Medical Association
EOT	End of Treatment
EOF	End of Follow-up
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma –glutamyl transferase
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HrQoL	Health-related Quality of Life
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IGA	Investigator Global Assessment

[redacted]

IgG	Immunoglobulin G
IL	Interleukin
IQS	Integrated Quantitative Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
IN	Investigator Notification
IUD	Intrauterine Device
IUS	Intrauterine System
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MAP	Meta-analytical-prediction
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial Infarction
PASI	Psoriasis Area and Severity Index
PDCO	Pediatric Committee of the European Medicines Agency
PPD	Purified Protein derivative
PFS	Pre-filled syringe
PK	pharmacokinetic
PRO	Patient reported outcome
PS	Patient Safety
PUVA	Photochemotherapy (eg psoralen + UVA treatment)
QFT	QuantiFERON TB-Gold test
QM	Quality Management
R	Randomization
rpm	Rate per minute
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sc	subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SST	Serum Separator Tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TBL	Total Bilirubin
TCS	Topical corticosteroids
Th17	T helper 17 cells
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet A, long wave 400 nm–315 nm
UVB	Ultraviolet B, medium wave 315 nm–280 nm
Vs	Versus
WBC	White blood cells / leukocytes

[redacted]

WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of subjects/subjects fulfilling certain criteria
Historical control drug	Drugs(s) used from historical data to act as a comparator to evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (eg 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (eg prior to starting any of the procedures described in the protocol)
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.”
Medication pack number	A unique identifier on the label of each investigational drug package
Subject/subject ID	A unique number assigned to each subject upon signing the informed consent
Period	The subdivisions of the trial design (eg Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
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 (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 1 (25-Sep-2020)

Amendment rationale

The rationale for the amendment is to introduce a level of flexibility in drug dispensation, protocol assessment and visit schedule if a major health care event requires it (i.e. COVID-19 pandemic) 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.

Further to the above, minor corrections, clarifications and editorial changes were undertaken in the protocol.

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.

The Amendment includes changes:

- Due to COVID-19 pandemic or any other pandemic
  - Allowing shipment of study medication to patient's home (Section 5.5.2)
  - Alternative options visits (Sections 6, 6.5, 7.1)
  - 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 Form (Section 10.2)
  - Home Nursing Informed Consent Form (Section 10.2)
- Significant Update to Original Protocol:
  - Added Inflammatory Bowel Disease as an example for discontinuation ofstudy treatment (Section 5.6.2).
  - ICF (Section 10.2)
- To manage inconsistencies and provide clarifications in the original protocol
  - clarify prior medication (Section 5.5.7)
  - correct data collection to source only (weight in IRT, Table 6-1; Table 6-2)
  - Imputation method (Section 9.4.3)
  - Remove sensitivity analysis (Section 9.4.4)
  - Add growth/weight [redacted] to Safety Section 9.5.2
  - As well as other miscellaneous minor corrections, modifications and text adjustments
    - Modification in Protocol summary secondary objectives.

[redacted]

- Modification in footnote 13 of Table 6-1.
- Modification in Urine pregnanacy test, [redacted] weight in IRT and footnote 10 in Table 6-2.
- Modification in Section 9.5.4.
- Modification in Section 9.6.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

This protocol amendment is considered substantial. However many countries participating in this study have released Urgent Safety Measure guidance stating that certain changes to a protocol due to the COVID-19 pandemic are permissible by notification or by non-substantial amendment. Therefore the final determination of the protocol classification will be done on a country by country basis based on the latest local HA guidance.

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 for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CAIN457A2311
Full Title	A randomized, open-label, multicenter trial to assess the efficacy of SC Secukinumab after twelve weeks of treatment, and to assess the long-term safety, tolerability and efficacy in subjects from 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis
Brief title	Study to assess the efficacy, safety, tolerability and PK of secukinumab in subjects 6 to less than 18 years of age with moderate to severe chronic plaque psoriasis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the efficacy of secukinumab at Week 12, based on both Psoriasis Area and Severity Index (PASI) 75 and Investigator's Global Assessment (IGA) mod 2011 0 or 1 response rates in children and adolescents aged 6 to less than 18 years at randomization with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy. This study will provide efficacy, safety and pharmacokinetic data to support the extension of label of secukinumab to include children and adolescents (6 years to < 18 years) with moderate to severe chronic plaque psoriasis. The study will assess the long-term efficacy, safety and tolerability of secukinumab over a period of up to 4 years to support the long-term use of secukinumab in pediatric patients.
Primary Objective(s)	To evaluate the efficacy of secukinumab in pediatric subjects aged 6 years to less than 18 years old with moderate to severe chronic plaque psoriasis with respect to PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo (historical control).
Secondary Objectives	Objective 1: To evaluate the efficacy of secukinumab in pediatric subjects aged 6 years to less than 18 years old with moderate to severe chronic plaque psoriasis with respect to PASI 90 at Week 12, compared to placebo (historical control). Objective 2: To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, Electrocardiogram and AE monitoring Objective 3: To evaluate the pharmacokinetics of secukinumab doses in subjects
Study design	Multi-center, open label, parallel group, two arm study. Three periods, screening (up to 4 weeks), treatment (of 208 weeks) and follow-up (of 16 weeks)
Population	Approximately 80 pediatric subjects aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis will be enrolled.
Key Inclusion criteria	Written informed assent and parental permission obtained at screening. Subjects reaching the age of consent during the study, will need to also sign the corresponding study Informed Consent. Must be 6 to less than 18 years of age at the time of randomization.

[redacted]

	Moderate to Severe plaque psoriasis, defined as a PASI score ≥ 12, and IGA mod 2011 score of ≥ 3, and Body Surface Area (BSA) involvement of ≥ 10%, at randomization History of plaque psoriasis for at least 3 months before randomization Subject being regarded by the investigator to be a candidate for systemic therapy because of: inadequate control of symptoms with topical treatment, and/or failure to respond to or tolerate previous systemic treatment and/or ultraviolet therapy
Key Exclusion criteria	Forms of psoriasis other than chronic plaque-type (eg pustular, erythrodermic and guttate psoriasis), active at randomization Female subjects 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. 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. 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. Active systemic infections during the last two weeks prior to randomization and any infections that reoccur on a regular basis.
Study treatment	Secukinumab prefilled syringes available as 75 mg /0.5 mL and 150 mg/1 ml will be provided by Novartis in an open-label fashion.
Efficacy assessments	Investigator's Global Assessment (IGA mod 2011) Psoriasis Area and Severity Index (PASI)
Key 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	Pharmacokinetics Immunogenicity IG

[redacted]

	Children's Dermatology Life Quality Index (CDLQI)
Data analysis	PASI 75 response at Week 12 and IGA 0 or 1 response at Week 12 will be evaluated and compared to historical placebo control. The secondary variable of PASI 90 response at Week 12 will be analyzed in the same way as the primary variable. Efficacy analysis will report the Bayesian posterior of the log-odds ratio between the secukinumab treatment groups and the historical placebo control. The median, 95% CI and the probability of a positive treatment difference of the posterior logs odds ratio will be presented. The co-primary efficacy variables and secondary efficacy variables will be analyzed using the Full Analysis Set (FAS).
Key words	Pediatric, psoriasis, children, adolescents, 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 United States of America.

- 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 et al 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 et al 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 et al 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 et al 2011).

The incidence of psoriasis in childhood in the US has been shown to increase with increasing age but also in recent years the 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 et al 2010).

Plaque psoriasis affects 80% to 90% of all psoriasis subjects of all age-groups (Griffiths and Barker 2007, Pariser et al 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, and hypertension, and 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 et al 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

[redacted]

significant problem affecting their Health-related Quality of Life (HrQoL) (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 et al 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-Ultraviolet B (UVB) is considered the first-line phototherapy because it is similarly effective as Psoralen + Ultraviolet A (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 European Union (EU) countries and Switzerland. However cyclosporine and methotrexate are not currently approved for the treatment of children/adolescents suffering from psoriasis.

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).

Amongst biologics, etanercept and ustekinumab have been approved not so long ago in US for moderate to severe psoriasis in pediatric patients (ustekinumab only for adolescents that is children 12 years or older). In Europe, apart from etanercept and ustekinumab (ustekinumab only for adolescents), adalimumab has also been approved recently but only for severe psoriasis

[redacted]

in children from 4 years of age. The details are available in respective prescribing information / summary of product characteristics.

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 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 et al 2008).

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the Immunoglobulin 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 T helper 17 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.

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 when compared to adults. It is also expected that the exposure-response to secukinumab in pediatric psoriasis patients would be similar to the exposure-response relationship observed in 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.

Currently, another clinical trial (CAIN457A2310) with secukinumab is already ongoing in pediatric patients with severe psoriasis. This planned trial (CAIN457A2311) will assess efficacy, safety and pharmacokinetics of secukinumab in moderate psoriasis (pediatric) patients as well as a few severe psoriasis patients.

1.2 Purpose

The purpose of this study is to assess the efficacy of secukinumab 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 at randomization with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy.

This study will provide efficacy, safety and pharmacokinetic data to support the extension of label of secukinumab to include children and adolescents (6 years to <18 years) with moderate to severe chronic plaque psoriasis.

Moreover, this study will assess the long-term efficacy, safety and tolerability of secukinumab over a period of up to 4 years to support the long-term use of secukinumab in pediatric patients.

[redacted]

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To evaluate the efficacy of secukinumab in pediatric subjects aged 6 years to less than 18 years old with moderate to severe chronic plaque psoriasis with respect to PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo (historical control).	Proportion of subjects who achieved PASI 75 and IGA mod 2011 0 or 1 response at Week 12 in each secukinumab treatment group (low dose and high dose). Placebo data are obtained from adult secukinumab placebo-controlled trials and pediatric placebo-controlled trials with secukinumab or other biologics
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To evaluate the efficacy of secukinumab in pediatric subjects with respect to PASI 90 at Week 12, compared to placebo (historical control).	Proportion of subjects who achieved PASI 90 response at Week 12 in each secukinumab treatment group (low dose and high dose). Placebo data are obtained from adult placebo-controlled trials and pediatric placebo-controlled trials
To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, ECGs, and adverse event monitoring	Height and weight, vital signs, laboratory evaluations, ECG and adverse events
To evaluate the pharmacokinetics of secukinumab in pediatric subjects	Secukinumab concentration in serum at various time points
Exploratory Objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	
To investigate the effects of treatment with secukinumab with respect to changes in CDLQI over time up to End of Treatment	Absolute and percentage change from baseline of CDLQI score over time up to End of Treatment
To investigate the effects of treatment with secukinumab with respect to CDLQI 0 or 1 score over time, up to End of Treatment	Proportion of subjects achieving CDLQI 0 or 1 over time up to End of Treatment
[redacted]	

[redacted]

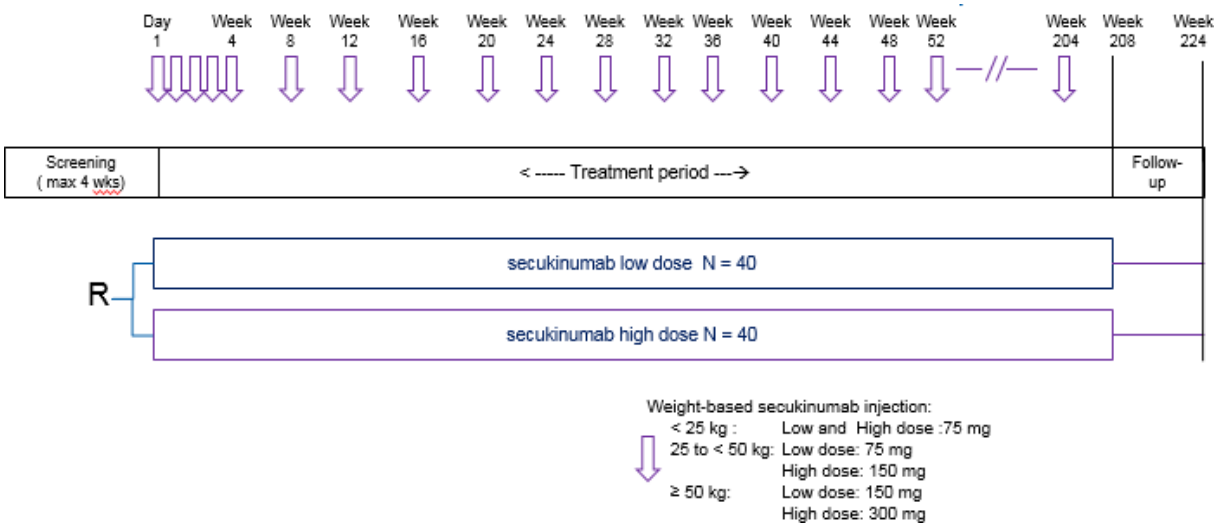
Exploratory Objective(s)	Endpoint(s) for exploratory objective(s)
[redacted]	
To investigate the development of immunogenicity against secukinumab	Development of anti-Drug Antibodies (ADA) to secukinumab

3 Investigational plan

3.1 Study design

This is an open-label, parallel-group, two-arm, multi-center, trial in pediatric subjects aged 6 years to less than 18 years, at randomization, with moderate to severe chronic, plaque psoriasis. Approximately 80 subjects (at least 60 subjects with moderate severity) will be enrolled. It is expected that subjects will be enrolled in about 40 centers worldwide. It will be targeted to have at least 5 subjects in the < 25kg weight, and at least 10 subjects in each of the other two weight groups.

Figure 3-1 Study design



The study consists of 3 periods: screening (up to 4 weeks), treatment (of 208 weeks) and post-treatment follow-up (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.

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Screening Period

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

Treatment Period

The treatment period is defined as randomization to Week 208. In this period the endpoints are assessed and subjects are followed for long-term safety and efficacy. Subjects will be randomized using 1:1 ratio into either secukinumab low dose or secukinumab high dose. Randomization will be stratified by body weight (< 25kg, 25-< 50 kg, ≥ 50kg) and disease severity (either moderate (PASI score 12-<20 and IGA 3 or 4 or PASI score ≥ 20 and IGA 3) or severe (PASI score ≥ 20 and IGA of 4), collected at Randomization Visit. The study aims to recruit at least 60 subjects with moderate disease severity and approximately 20 subjects with severe disease severity. It will be targeted to have at least 5 subjects in the < 25kg weight, and at least 10 subjects in each of the other two weight groups. Subjects will receive the appropriate dose based on their body weight category. 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 4 weekly visits 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. The dose will be adapted starting from the visit of the second consecutive weight change.

Adolescents (12-< 18 years) and children (6-< 12 years) can be included from the beginning of this study, since the DMC has approved already the enrollment of children (6-< 12 years) in study CAIN457A2310.

All subjects will visit the study site at Randomization (Day 1) and at Weeks 1, 2, 3, 4, 8, 12, 16 during which they will receive either high-dose or low-dose secukinumab treatment sub-cutaneously. Additionally, subjects will visit the site at Weeks 13, 14, 15 to provide blood samples for pharmacokinetics.

During the Treatment period subjects will receive treatment of the assigned secukinumab dose every 4 weeks. However during Weeks 16-52 site visits will be scheduled every 8 weeks and from Weeks 64-208 site visits will be scheduled every 12 or 16 weeks, to minimize the burden on the subject. Subjects will have the option to receive treatment between scheduled visits at home, following instructions provided to the subject (if ≥12 years old), parent or caregiver.

Subjects who discontinue study treatment for any reason before the end of the Treatment Period (Week 208) should have the Week 208 visit assessments performed approximately 4 weeks after their last dose of secukinumab. The subject will then enter the treatment–free Follow-up Period.

Follow-up Period

The treatment-free follow-up visits will be at Week 212, Week 216 and Week 224 (End Of Follow-up/EOF). Subjects who complete or discontinue the treatment early 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

[redacted]

visits but will be expected to return to the site after the start of the systemic treatment and perform the EOF visit.

3.2 Rationale for study design

The rationale behind this design is based on a full extrapolation approach. Novartis' proposal for a pediatric extrapolation approach is based on the Food and Drug Administration draft guidance, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, which is also reflected in ICH E11 (R1) guidance and an European Medical Association reflection Paper on extrapolation of efficacy and safety in pediatric medicine development (ICH 2000; FDA 2014; EMA 2016; ICH 2016).

Its intent is to minimize exposure of children to placebo and to overall clinical trial burden while leveraging the broad clinical information available from secukinumab trials in adult subjects as well as ongoing pediatric trial CAIN457A2310. This approach is considered appropriate due to the substantial similarity of the disease between the adults and pediatric population (Augustin 2010, Feldman and Krueger 2005, Griffiths 2007, Kimball 2012, Langley et al 2005, Leman and Burden 2001, Paller et al 2008, Pariser 2007, Tollefson 2014) as well the similarity of exposure-response, which will be validated in the small population of children and adolescents of this study. The similarity of disease characteristics of psoriasis between adult and pediatric subjects has been described extensively.

Following consultation with Health Authorities (FDA and EMA (PDCO) for overall pediatric program, the open label, design with no control arm was chosen for this particular study. Collection of pharmacokinetic information for pediatric subjects based on age and/or weight strata was recommended. In principle, if pediatric doses matching adult exposures are reasonably identified, then an uncontrolled open-label trial in pediatric subjects to collect safety and efficacy data can be acceptable. An interim PK analysis of data from the ongoing CAIN457A2310 trial (a double-blind placebo controlled and single blind active-controlled study in pediatric subjects with severe psoriasis) showed that pediatric trough concentrations for the weight and dose groups studied are consistent with the predictions from a population PK model in psoriasis patients (data on file; see Section 3.3 for more details).

The present study is being conducted to collect long term safety data and evaluate efficacy and pharmacokinetics in children. The efficacy data collected in this uncontrolled study will be compared with historical placebo data obtained from the adult program with secukinumab and pediatric placebo-controlled trials with other biologics. If data from CAIN457A2310 (pediatric subjects with severe psoriasis) are available when this study report is created, the placebo efficacy data may also be used in the efficacy analysis of study CAIN457A2311.

Finally, 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.

[redacted]

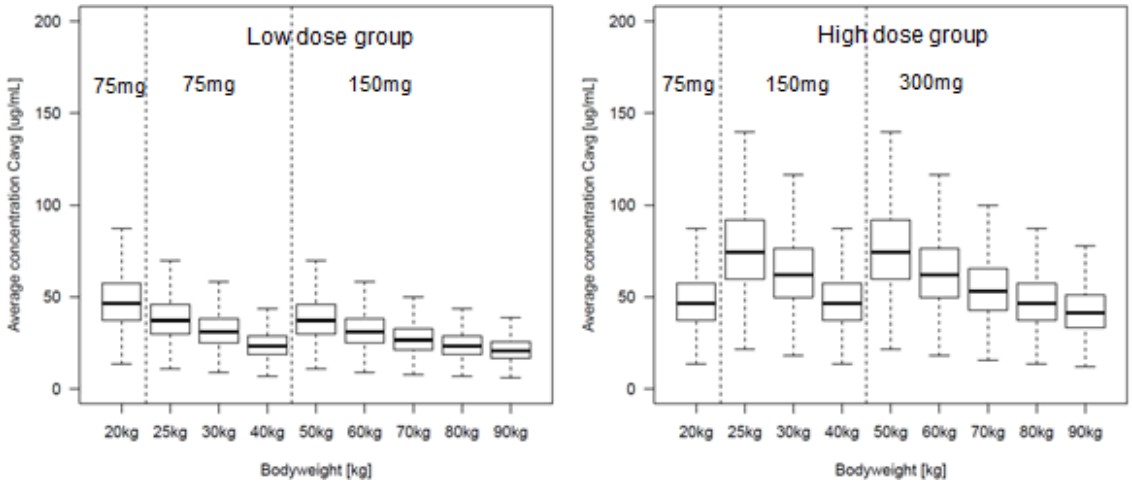
3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose selection for secukinumab in pediatric psoriasis subjects is based on the completed phase III program in adults as well as on modeling and simulation based on the results from adult phase II/III studies. Secukinumab 300 mg and 150 mg are selected based on evidence from adult phase III studies that demonstrated both doses to be safe and effective in treating moderate to severe plaque psoriasis.

The same doses were also selected for the first and ongoing pediatric study CAIN457A2310 which is a double-blind placebo controlled and single blind active-controlled study in pediatric subjects with severe 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 adult trials to predict exposure of secukinumab according to various body weights. 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).

[redacted]

Interim PK data from 23 secukinumab-treated subjects in the age range of 12 to 17 years old from study CAIN457A2310 have been evaluated (data on file). The observed pediatric trough concentrations are consistent with model predictions for the weight and dose groups studied. These data, therefore, support the selected dosing regimen from a safety and efficacy point of view for study CAIN457A2310 and for the present study CAINA457A2311.

3.4 Rational for choice of comparator

No comparator drug is included in this study. Historical placebo data from qualifying trials will be used as the control for primary and key secondary endpoint analysis as discussed in Section 9.4. This is in line with guidance from and discussions with Health Authorities including FDA and EMA (PDCO) which suggested reducing placebo exposure as well as overall clinical trial burden for pediatric population and suggest/accept use of extrapolation approach.

3.5 Purpose and timing of interim analyses/design adaptations

There are two planned interim analysis. An interim analysis, including the primary endpoint (Week 12) analysis will be conducted when all subjects have completed the Week 16 visit or the premature treatment discontinuation visit. Another interim analysis will be performed when all subjects have completed the Week 52 visit or the premature treatment discontinuation visit.

Additional analyses may be performed to support health authority interactions, as necessary.

Thereafter, efficacy and safety data collected after Week 52 until the end of study may be reported yearly in separate reports.

Trial modifications are not planned based on any interim analysis.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures and by close clinical monitoring.

Biologics are being considered a safe and effective option for treating psoriasis in the pediatric population as they are convenient to use, requiring less frequent dosing than traditional systemic 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.

Results from non-clinical studies and phase II and III clinical studies in adults did not reveal a safety concern that would preclude the use of secukinumab in children. 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 Adverse Event and Serious Adverse Event data, laboratory parameters and immunogenicity data, demonstrate a good safety profile.

Known risks of secukinumab administration includes an increased risk of infections, in particular candida infections, neutropenia and hypersensitivity reactions that can be seen with administration of any foreign proteins. Most of the infections were non-serious upper respiratory tract infections and candidiasis, mild to moderate in severity, clinically 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 may 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 et al 1997), no adverse effects of secukinumab on development of this system are expected in this trial's pediatric population (age 6 to < 18 years). 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 et al 2008) and in toxicology studies with secukinumab. Height, to measure linear growth, will be monitored throughout the study.

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 (refer to Table 5-3).

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 moderate to 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.

Approximately 80 subjects (at least 60 with moderate psoriasis) will be randomized in approximately 40 centers worldwide. Since a 15% screening failure rate is expected, approximately 95 subjects will be screened.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must 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, if subjects reach age of consent (age as per local law) during the study, at that time they will need to also sign the corresponding study Informed Consent.
2. Must be 6 to less than 18 years of age at the time of randomization.

[redacted]

3. Moderate to Severe plaque psoriasis, defined as a PASI score ≥ 12, and IGA mod 2011 score of ≥ 3, and BSA involvement of ≥ 10%, at randomization
4. History of plaque psoriasis for at least 3 months before randomization
5. Subject being regarded by the investigator to be a candidate for systemic therapy because of:
   - inadequate control of symptoms with topical treatment, and/or
   - 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/subjects.

1. Forms of psoriasis other than chronic plaque-type (eg, pustular, erythrodermic and guttate psoriasis), active at randomization.
2. Drug-induced psoriasis (ie new onset or current exacerbation from beta-blockers, calcium channel blockers or lithium)
3. Ongoing use of prohibited treatments as mentioned in Table 5-3 (Washout periods as detailed in Table 5-3 have to be adhered to).
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor,
5. Use of any other investigational treatment within 30 days for small molecules or within a period of 5 half-lives of the investigational treatment from randomization, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
6. History of severe hypersensitivity reaction or anaphylaxis to any biological agent (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 human Chorionic Gonadotropin (hCG)laboratory test
8. Female subjects of childbearing potential and/or who are at least 12 years of age; defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing and for 16 weeks after stopping study treatment (or longer if local label requires it (eg in EU 20 weeks), (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. Effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, 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) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. 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

[redacted]

- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For United Kingdom: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

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

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form

9. Active ongoing inflammatory diseases other than psoriasis that might confound the evaluation of the benefit of secukinumab therapy
10. 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. In addition, current severe progressive or uncontrolled diseases which render the subject unsuitable for the trial or puts the subject at increased risk, including 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.
11. Investigator discretion should be used for subjects with preexisting or recent-onset central or peripheral nervous system demyelinating disorders
12. Subjects with an estimated 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 days later, and if eGFR value ≥ 60, subject may be included at the discretion of the investigator.
13. Subjects with total White Blood Cell count < 2,500/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL at screening
14. Active systemic infections during the last two weeks (exception: common cold) prior to randomization and any infections that reoccur on a regular basis. 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
15. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive central laboratory test result at screening. Subjects with a positive test result 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.

[redacted]

16. Past medical history record of, or known current infection with Human Immunodeficiency Virus, hepatitis B or hepatitis C at screening
17. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years prior to screening, except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed.
18. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomization.
19. 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.
20. Hypersensitivity or allergy to any of the ingredients of study treatment
21. History or evidence of ongoing alcohol or drug abuse, within the last 24 weeks before randomization.
22. Subjects not willing to limit UV light exposure (eg, sunbathing and/or the use of tanning devices) during the course of the study.
23. Unwillingness to undergo repeated venipuncture or subcutaneous injections.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Secukinumab prefilled syringes available as 75mg/0.5ml and 150mg/1ml will be provided by Novartis in an open-label fashion.

Syringes will be labeled as:

- AIN457 75mg/0.5 mL or
- AIN457 150mg/1mL

5.1.2 Additional treatment

No additional treatment beyond investigational drug is included in this trial.

5.2 Treatment arms

Subjects will be randomized using a 1:1 ratio at the Randomization visit to two treatment arms, secukinumab low dose or secukinumab high dose. Subjects will receive sc 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 as summarized in the Table 5-1 below. Subjects will be receiving one sc injection at each drug administration of either secukinumab 75 mg or 150 mg Pre-filled Syringe (PFS) according to their treatment group.

[redacted]

Only the subjects in the ≥ 50 kg high dose treatment groups will be receiving two sc injections of 150 mg secukinumab at each administration.

Secukinumab low dose group:

According to the weight category, sc secukinumab 75 mg (in < 25 kg and 25 to < 50 kg) or 150 mg (≥ 50 kg) injections will be administered at Randomization, Weeks 1, 2, 3, 4 and thereafter every 4 weeks during the entire treatment period of the study until Week 204. After Week 16, treatment which occurs outside of the site visits, may be administered at home every 4 weeks, either by subject (self-injection is allowed for subjects ≥ 12 years) or parent/caregiver. If subject/parent does 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, sc secukinumab 75 mg (in < 25 kg), 150 mg (in 25 to < 50 kg) or 2 x 150 mg (≥ 50 kg) injections will be administered at Randomization, Weeks 1, 2, 3, 4 and thereafter every 4 weeks during the entire treatment period of the study until Week 204. After Week 16, treatment which occurs outside of the site visits, may be administered at home every 4 weeks, either by subject (self-injection is allowed for subjects ≥ 12 years) or parent/caregiver. If subject/parent does not feel confident in performing treatment administration at home they are still allowed to receive study treatment administration at site.

Table 5-1 Number of injections per visit per treatment arm

Weight	Dose (PFS)	Number of injections at each dosing
<25 kg - low dose	75 mg	1
-high dose	75mg	1
25 to <50 kg - low dose	75 mg	1
-high dose	150 mg	1
≥50 kg - low dose	150 mg	1
-high dose	300mg	2

5.3 Treatment assignment and randomization

At Randomization (Day 1) all eligible subjects/subjects will be randomized via Interactive Response Technology (IRT) to one of the two treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The subject number, the weight of the subject, the age and any relevant information related to severity, as described in the user manual, will be entered. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment

arms, which in turn are linked to medication numbers. 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 disease severity and body weight collected at Randomization Visit. This stratification ensures balanced allocation of subjects to treatment groups within the disease severity and weight strata.

The weight strata will be "body weight < 25 kg", "25 kg ≤ body weight < 50 kg" or "body weight ≥ 50 kg" and disease severity strata (refer to Table 5-2). Stratification by disease severity and body weight will occur at Randomization Visit.

Table 5-2 Disease severity classification

IGA	PASI score	Psoriasis severity
3	12-< 20	Moderate
3	≥ 20	Moderate
4	12-< 20	Moderate
4	≥ 20	Severe

It will be targeted to have at least about 5 subjects in the < 25kg weight, and at least about 10 subjects in each of the other two weight groups.

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

5.4 Treatment blinding

Medication will be labeled in an open-label fashion. Blinding requirements are not applicable for any of the parties involved.

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 Subject numbering

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

Upon signing the informed consent form, the subject is assigned the next sequential number available in the electronic data capture (EDC) system. 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 must select the eCRF book with a matching Subject Number in the EDC system to enter data.

[redacted]

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the appropriate Screening period eCRF.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study treatment.

At all visits where secukinumab is dispensed, the IRT system will allocate a unique 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). The study drug packaging has a 2-part label. The unique medication number is printed on each part of this label. 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 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 participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of study drug from the site to the participant'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

After Week 16, subjects/custodians will be expected to perform home administrations of secukinumab at the time points specified in the protocol, when they are not visiting the site for other trial related procedures. Subjects/custodians must be previously trained by site staff regarding the administration of secukinumab PFS.

It must be noted that subjects 12- < 18 years of age can self-inject only under caregiver or health care professional supervision. Subjects < 12 years of age are not allowed to self –inject at any time.

If the subject or custodian is not confident to administer medication at home, subjects 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.

For home administrations the pharmacist/ qualified site personnel will dispense, via IRT, an appropriate number of investigational treatment packages and detach outer part of the label from the packaging as indicated above. The custodians/subjects will record the date(s) of

[redacted]

administration at home and will return the used PFS and packaging at their next visit to the site. 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 PFS the latest at the completion of the study or at the time of discontinuation of the investigational treatment. Detailed instructions will be provided separately.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must 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 Country Pharma Organization Quality Assurance.

Medication labels for secukinumab 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 subject except for the medication number. They must be stored in a secured refrigerator at 2°C-8°C (36°F-46°F), and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations. Study treatments should not be frozen and must be protected from light.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all used PFS and packaging at frequent intervals (i.e. at next scheduled study visit) and unused PFS and packaging latest at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused PFS, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

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 at Section 5.5.2 must be followed.

[redacted]

The first study treatment administration will occur at the Randomization Visit (Day 1), after all study scheduled assessments have been performed (and inclusion/exclusion criteria confirmed) and 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.

Subjects will be administered study medication weekly for the first 4 weeks of the treatment period and then every 4 weeks until Week 204.

During the Follow-up period, no study medication will be administered.

Administration of secukinumab

Secukinumab Solution for Subcutaneous Injection will be provided in Prefilled syringes (75 mg/0.5 mL and 150 mg/1mL).

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 to 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.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance 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 must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational or other treatment dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

Rescue medication for psoriasis is not permitted in this study

5.5.7 Prior and Concomitant medication

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

[redacted]

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.

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started.

5.5.7.1 Permitted concomitant medications (not for psoriasis)

Concomitant medications are allowed if not listed in Table 5-3. 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 Concomitant medications eCRF or the Procedures and Significant non-drug therapies eCRF.

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

Topical corticosteroids (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 AND medication was used for 14 consecutive calendar days or less AND 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.

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 5-3). Use of bland emollients must be recorded on the 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.

The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

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

[redacted]

5.5.8 Prohibited medication

Use of any treatments displayed in Table 5-3 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 appropriate eCRF.

If a prohibited treatment listed in Table 5-3 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 5-3 presents undue safety risk for the subject, the subject should be discontinued from study treatment as per Section 5.6.2. If the subject received a live 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, and genitoanal area. The active topical treatments are limited to: mild or moderate potency corticosteroid. The subject must stop use of these topical corticosteroids (TCS) 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 as indicated in Table 5-3 below

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

Table 5-3 Prohibited medication

Prohibited Treatment	Wash-out period up to Randomization	Treatment Period[1,2]
Secukinumab	No prior use allowed	Used as study treatment
Any biologic drug directly targeting IL-17 or the IL-17 receptor (other than secukinumab [eg brodalumab, ixekizumab])	No prior use allowed	Not allowed
Any biologic directly targeting IL-12/23 or IL-23, eg briakinumab, stekinumab, guselkumab, tildrakizumab	26 weeks	Not allowed
Alefacept, efalizumab	26 weeks	Not allowed
Etanercept	4 weeks	Not allowed
Biological immunomodulating agents other than above (eg, adalimumab, infliximab)	12 weeks	Not allowed
Other systemic immunomodulating treatments (eg, methotrexate (MTX), cyclosporine A [CSA], corticosteroid, cyclophosphamide)	4 weeks	Not allowed
Photochemotherapy (eg, PUVA)	4 weeks	Not allowed

[redacted]

Prohibited Treatment	Wash-out period up to Randomization	Treatment Period[1,2]
Other systemic therapy for psoriasis (eg, retinoids, fumarates, apremilast)	4 weeks	Not allowed
Any other investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Not allowed
Phototherapy (eg, UVA, UVB)	2 weeks	Not allowed
Topical treatment[3] for psoriasis or any other skin condition (eg, corticosteroids, vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids), except on the face, scalp, hands and feet and genitoanal area during screening	2 weeks[4]	Not allowed [5]
Live vaccinations	6 weeks	Not allowed [6]

[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 at least 12hrs preceding the randomization visit

[5] Topical corticosteroids and other topical treatments will be allowed after Week 12 Visit 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 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 Emergency breaking of assigned treatment code

Not Applicable as treatment is open label.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the Week 224 visit as per the protocol. For subjects who discontinue prior to this, the study completion corresponds to the last study visit of the subject or contact of the site with custodian/subject. Study completion for the study will occur when all randomized subjects have completed the study as stated above.

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

[redacted]

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject/custodian or the investigator.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Subject/custodian's wish
- Withdrawal of consent
- Pregnancy (see Section 6.5.8 and Section 7.6)
- Ongoing use of prohibited treatment as per recommendations in Table 5-3
- 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 occuring 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.
- Live vaccination
- Any situation where study participation results in a significant risk to subject's safety

If discontinuation of study treatment occurs, the subject should NOT be considered withdrawn from the study. If the subject discontinued study treatment within the treatment period, the subject should return to the clinic after discontinuation of study drug, for Week 208 and Follow-up visits (Week 212, Week 216 and Week 224).

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 at Week 208 visit in Table 6-2 should be completed and recorded in the eCRF.

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 Week 208 visit.

The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this along with the date treatment was stopped on the eCRF page. The investigator must also contact the IRT to register the subject's discontinuation from study treatment. As mentioned above if subjects discontinues treatment early, subject is expected to perform the visits of the treatment –free follow up period.

If the subject cannot or is unwilling to attend any further visit(s), the site staff should maintain regular telephone contact with the custodian/subject to obtain at least information on adverse events or concomitant medication. This telephone contact should preferably be done according to the study visit schedule.

[redacted]

Discontinuation from the treatment-free follow-up period

Subsequently to the Week 208 visit the subject will be expected to return to the site and perform all visits of the treatment-free follow-up period as indicated in Table 6-2.

If premature withdrawal occurs for any reason in the treatment-free period (follow-up period, Week 208-Week 224), the subject is expected to return to the site and perform all assessment of visit EOF /Week 224 (see Table 6-2). 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 relevant eCRF).

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 Week 224 visit.

5.6.3 Withdrawal of informed consent

Custodians/subjects may voluntarily withdraw consent for participation in the study for any reason at any time. Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (eg telephone, e-mail, letter) to determine 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.

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 below.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg dates of telephone calls, registered letters, etc.

[redacted]

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely discontinued subject. 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 subject'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.

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 that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff or home nursing service to the participant´s home depending on local regulations and capabilities, can partially replace on-site study visits, for the duration of the pandemic/ health care disruption until it is safe for the participant to visit the site again. These contacts should occur on or around the scheduled visit dates (or more frequently if needed). Events qualifying for being reported in CRF should be entered as appropriate. 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 visit on site. If it is not feasible to conduct the EOT and EOF visit on-site, at least phone contact or if possible visits to the patient´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 custodian(s) and subject will sign first the informed consent and assent form respectively, subject will then be evaluated for eligibility and will have all screening visit assessments done as indicated in Table 6-1.

Table 6-1 and Table 6-2 list all study assessments and indicate 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 custodian/subject must sign a new ICF/assent form 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 eCRF 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 eCRF to correspond to the new screening subject number. Informed Consent for a rescreened subject must be obtained

[redacted]

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 tuberculosis test performed by the central laboratory.

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

During the treatment period, subjects may be seen at an unscheduled visit, eg 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 (as applicable) are below:

- Subject to complete CDLQI at the study site prior to any study assessments.
- Investigator to complete investigator assessments:
  - IGA mod 2011
  - PASI
  - Review of CDLQI data
  - Physical exam
- All remaining study visit procedures (eg, AE and concomitant medication collection, laboratory sample collection, vital signs measurements, etc) must be completed and results reviewed by the investigator or qualified designee prior to study treatment dosing.
- Enter PASI data into the source data worksheets and perform calculations as needed BEFORE contacting IRT at randomization Visit.
- Contact IRT to register the subject visit, as applicable
- Administration of study treatment, as applicable

[redacted]

Table 6-1 Assessment schedule (Year 1)

Period	**Scr**	**Treatment Year 1**															
Week	**-4-R[a]**	**Day 1 (R)**	**1**	**2**	**3**	**4**	**8**	**12**	**13**	**14**	**15**	**16**	**24**	**32**	**40**	**48**	**52**
Day	**-28-R[a]**	**1 (R)**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**169**	**225**	**281**	**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]	update as necessary																
Surgeries and non-drug procedures	update as necessary																
Physical Exam	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
Weight	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
[redacted]																	
Labs: Hematology[6]	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
Tuberculosis test[7]	x																
Serum pregnancy test(in females of childbearing potential) [6]	x																
Urine Pregnancy test[8](local; in females of childbearing potential)		x						x					x				x
ECG (standard 12-lead)	x							x					x				x
Blood sample for immunogenicity(pre-dose)[9]		x										x	x				x
Blood sample for PK (pre-dose)[9]		x				x		x	x	x	x	x	x				x
PASI	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

[redacted]

Period	**Scr**	**Treatment Year 1**															
Week	**-4-R[a]**	**Day 1 (R)**	**1**	**2**	**3**	**4**	**8**	**12**	**13**	**14**	**15**	**16**	**24**	**32**	**40**	**48**	**52**
Day	**-28-R[a]**	**1 (R)**	**8**	**15**	**22**	**29**	**57**	**85**	**92**	**99**	**106**	**113**	**169**	**225**	**281**	**337**	**365**
CDLQI[10]		x				x	x	x					x				x
(Serious) Adverse event assessment	update as necessary																
Randomization via IRT		x[11]															
Data entry of weight into IRT[12]		x						x				x	x	x	x	x	x
Administration of study drug[13]		x	x	x	x	x	x	x				x	x	x	x	x	x
Contact IRT	x	x	x	x	x	x	x	x				x	x	x	x	x	x

Scr= screening, R=randomization, PK=pharmacokinetics, ECG=Electrocardiogram, CDLQI= children's dermatology life quality index, IRT=Interactive response technology,

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

[a] 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.

[1] Apart from the Informed consent for this study signed by parent(s) /legal representatives, assent form will be completed as appropriate by the pediatric subjects.

[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 appropriate eCRF

[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 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 Day 1-Randomization (R) visit if screening labs were performed within 7 days from randomization.

[7] If the first tuberculosis central lab test is indeterminate, the investigator may choose to perform a second test (as part of an unscheduled visit) or refer the subject for tuberculosis workup per local guidelines. If the result of any tuberculosis central lab test is "positive" or the results of two sequential 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.

[8] Urine pregnancy test will be performed locally. 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.

[redacted]

[9] Samples shipped by the sites will be stored at the central laboratory and then shipped to reference laboratories for analysis. Each PK and IG blood sample should be collected pre-dose between Day 1 (Randomization) and Wk 52.

[10] CDLQI will no longer be completed once subjects reach 18 years of age

[11] At Day 1- Randomization the PASI Score and BSA must be calculated by appropriate site staff prior to contacting IRT. The investigator must ensure subject meets all eligibility criteria before contacting IRT to randomize the subject.

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

[13] Secukinumab will be dispensed at site visits. After Week 16 and until Week 52 monthly treatment which occurs outside the site visits, may be administered at home every 4 weeks, either by subject (self-injection is allowed for subjects ≥ 12 years) or parent/caregiver. In case subject or parent does not feel confident in performing home administrations subjects will be allowed to continue to perform drug administrations at site. These home administrations in the first year occur at Wk 20, Wk 28, Wk 36, Wk 44. During the COVID-19 pandemic, or any other pandemic, study medication may be shipped to the patient's home and administration should be completed at the scheduled timepoints.

[redacted]

Table 6-2 Assessment schedule - Years 2-4 (continued)

Period	**Treatment Period (years 2-4)**												**Follow-up Period[b]**			**Unscheduled[d]**
Week	**64**	**76**	**88**	**104**	**116**	**128**	**140**	**156**	**168**	**180**	**192**	**208 EOT**	**212**	**216**	**224 EOF**	
Day	**449**	**533**	**617**	**729**	**813**	**897**	**981**	**1093**	**1177**	**1261**	**1345**	**1457**	**1681**	**1709**	**1765**	
Concomitant medications[1]	Update as necessary															x
Surgeries and non-drug procedures	Update as necessary															x
Physical Exam	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
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
[redacted]																
Hematology[4]	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
Urine Pregnancy test (local; in females of childbearing potential)[5]	S	S	S	S	S	S	S	S	S	S	S	S			S	S
ECG (standard 12-lead)				x		x		x		x		x			x	x
Blood sample for IG[6]				x				x				x			x	x[7]
Blood sample for PK[6]				x				x				x			x	x[7]
PASI	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
CDLQI[8]	x	x	x	x	x	x	x	x	x	x	x	x				x
[redacted]																

[redacted]

Period	**Treatment Period (years 2-4)**												**Follow-up Period[b]**			**Unscheduled [d]**
Week	**64**	**76**	**88**	**104**	**116**	**128**	**140**	**156**	**168**	**180**	**192**	**208 EOT**	**212**	**216**	**224 EOF**	
Day	**449**	**533**	**617**	**729**	**813**	**897**	**981**	**1093**	**1177**	**1261**	**1345**	**1457**	**1681**	**1709**	**1765**	
(Serious) Adverse event assessment	Update as necessary															x
Data entry of weight into IRT[9]	x	x	x	x	x	x	x	x	x	x	x					
Contact IRT	x	x	x	x	x	x	x	x	x	x	x	x				
Administration of Study Drug[10]	x	x	x	x	x	x	x	x	x	x	x					
End of Treatment												x				
Study completion															x	

R=randomization, PK=pharmacokinetics, ECG=Electrocardiogram, CDLQI= children's dermatology life quality index, IRT=Interactive response technology,

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

[a] During EOT visit, subjects will have their last assessments performed for treatment period. This visit will also be performed for all subjects who will discontinue early the treatment period.

[b] Follow-up assessments are to be conducted for subjects who complete treatment period and for subjects who discontinue study treatment early

[c] EOF assessments are to be conducted for subjects who complete treatment free follow up period and for subjects who discontinue this period 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]If there is a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test must be done at the same visit and sent to central lab. 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.

[6] Samples shipped by the sites will be stored at the central laboratory and then shipped to reference laboratories for analysis. Each PK and IG sample should be collected pre-dose for Week 52 to Week 208.

[7] An unscheduled IG and/or PK sample is collected only to replace an IG or PK sample not taken at a regular scheduled visit. In case unscheduled IG sample is taken, there should always be a matching unscheduled PK sample taken at the same time point.

[8] CDLQI will no longer be completed once subjects reach 18 years of age

[redacted]

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

[10] Secukinumab will be dispensed at site visits. Between site visits, study medication will be administered every 4-weeks at home either by the subject (self-injection is allowed for subjects ≥ 12 years) or parent/caregiver until Week 204. In case subject or parent/caregiver does not feel confident in performing home administrations subjects will be allowed to continue to perform drug administrations at site. Home administrations in the years 2-4 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. During the COVID-19 pandemic, or any other pandemic, study medication may be shipped to the patient's home and administration should be completed at the scheduled timepoints.

[redacted]

6.1 Information to be collected on screening failures

All subjects who sign the informed consent but discontinue prior to randomization at Day 1 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 in the respective 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.

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 (eg demographics) or at the Randomization Visit eg patient reported outcomes (PROs), depending on the assessment.

6.2.1 Demographics

Data to be collected on all subjects include: age, sex, race, and ethnicity).

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.

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.

[redacted]

6.2.4 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 central lab testing. Any significant findings will be recorded in the relevant TB assessment eCRF and the Medical History eCRF, as necessary.

A central lab testing 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 et al 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 tuberculosis 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.
- 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.
  - Subject 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 or indeterminate, the investigator should perform workup as per local guidelines. Subject 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. The subject will not be

[redacted]

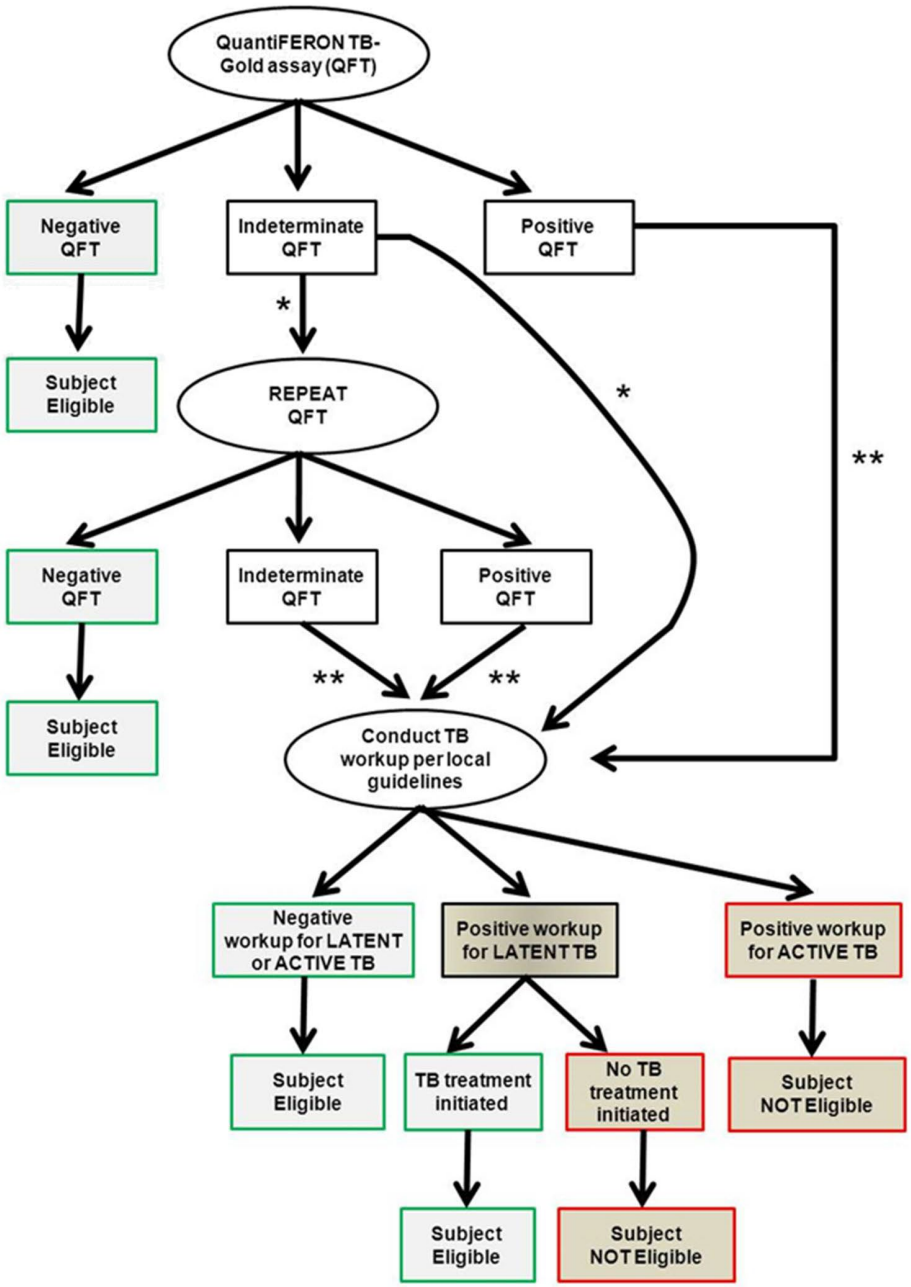
eligible for randomization if "active tuberculosis is present" or "latent tuberculosis is present" and is untreated per local guidelines.

- 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.

[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).

6.2.5 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; immunogenicity; PK; 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 at screening.

6.3 Treatment exposure and compliance

All doses of study treatment administered will be recorded on the appropriate Dosage Administration Record eCRF page. 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,

Subject compliance to the study treatment should be assessed by qualified site personnel at each study visit using the study kits and documentation regarding study treatment dispensation and administration.

Site compliance will also be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and the corresponding documentation.

6.4 Efficacy

All efficacy assessments should be performed prior to administration of study treatment. 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)

The IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-1 and Table 6-2. It is recommended that the same evaluator 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. The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

[redacted]

The IGA mod 2011 used in this study is static, ie, 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 3 or 4.

Based on this scale, a subject will be considered an IGA mod 2011 0 or 1 responder if the subject achieves a score of 0 or 1 and improved by at least 2 points on the IGA mod 2011 scale compared to baseline.

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

The investigator or trained qualified designee will complete the PASI assessment as indicated in Table 6-1, Table 6-2. Whenever possible, the same evaluator 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 and Petterson 1978, Weisman et al 2003, Gottlieb et al 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.
- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.

[redacted]

- 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 investigator or qualified designee is responsible for evaluating the subject and collecting the PASI components, scoring signs and total regional area. The PASI data will be entered into the PASI eCRF.

Based on PASI, to be eligible, a subject must have a score of 12 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.

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 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]

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).

[redacted]

6.5 Safety

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (eg, 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 must be included in the Medical History screen on the subject's eCRF. Significant findings made after the start of study (Day 1) that meet the definition of an adverse event must be recorded on the Adverse Event screen of the subject's eCRF.

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.

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

Table 6-5 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

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.

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 (Day 1) will be used to categorize the subject population at randomization to receive the corresponding doses in the high dose and low dose secukinumab groups.

6.5.5 Laboratory evaluations

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

[redacted]

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 subjects and will be stated in the laboratory manual.

During the COVID-19 pandemic or a major healthcare 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.

6.5.5.3 Estimated GFR

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

The calculation is based on the following formula:

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 0.413 \times \text{height (cm)} / \text{serum creatinine (mg/dl)}$$

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]

6.5.5.4 Urinalysis

Urine Dipstick (local)

A midstream urine sample (approximately 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.

6.5.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1, Table 6-2. When the 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 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 should be recorded as AEs.

6.5.7 Immunogenicity

Blood samples for immunogenicity (anti-secukinumab antibodies) will be taken pre-dose by direct venipuncture at the scheduled time points as indicated in Table 6-1, Table 6-2 and Appendix 2, Table 14-2. Blood samples (approximately 2 mL) will be collected into serum separator tube (SST) tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 revolutions per minute (rpm) for 10 minutes, or within sufficient time and speed to allow formation of a clear supernatant layer.

Serum samples will be split into 2 aliquots (labeled plain barrier polypropylene tubes) and then stored (within 30 minutes of serum collection by centrifugation) at approximately -70˚C to -20˚C prior to shipment on dry ice to the central laboratory. Shipment of stored aliquots from the site to the central lab should be on a pre-specified basis. To the extent possible, the site should send each aliquot of the sample to the central laboratory separately. The central lab will ship aliquots of the samples on dry ice to the analytical laboratory as per agreement with Novartis. Immunogenicity samples will only be disposed of after approval by the Sponsor.

[redacted]

The actual sample collection date and time will be entered on the relevant Blood collection for IG eCRF. In case unscheduled IG samples are taken, matching PK samples must be taken as well.

A laboratory manual will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type and sample number preprinted on the label.

Further details on labeling of the immunogenicity samples can be found in Appendix 2, Table 14-2 .

Sample stability

Due to the nature of the immunogenicity response, no real stability data can be given for immunogenicity samples.

The serum samples will be transferred on dry ice (enough dry ice to avoid thawing) from the central laboratory to the analytical laboratory at Novartis or a designated Clinical Research Organization (CRO).

Immunogenicity analytical method

An electrochemiluminescence based method will be used for the detection of potential anti-AIN457 antibody formation. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

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 subjects who are menarchal or who become 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 for on-site study visits, urine pregnancy test kits may be shipped or provided directly to the subject. After appropriate instruction, patients 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 patients perform the pregnancy test first and only if the test result is negative, they then should 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.

[redacted]

All menarchal girls and their parents/custodians 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 subject and her parents/custodians 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 subject and her parents/custodians. The privacy of the subject 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. Subjects becoming pregnant must be discontinued from study drug. However, a subject may choose to remain in the study should she become pregnant, and be followed in the treatment-free follow-up period as described in Table 6-1, Table 6-2.

Female subjects 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 (eg in EU 20 weeks).

Details on contraception methods can be found in the Exclusion criteria, Section 4.2.

It is recommended that 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.

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 Clinical Outcome Assessments (COAs)

6.6.1.1 Subject/Patient Reported Outcomes (PRO)

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 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.

[redacted]

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 indicates 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.

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

All subjects will complete the PRO questions via an electronic tablet. 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. If subject experiences any difficulties with submission after they complete the PROs, the study staff should assist with submitting the PRO responses. Attempts should be made to collect responses to all PROs for all subjects, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if subjects/subjects refuse to complete PROs, this should be documented in study source records. Subject's refusal to complete study PROs are not protocol deviations.

The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses before the clinical examination. Missing data will not be imputed.

The CDLQI questionnaire will be completed by the subject as indicated in Table 6-1, Table 6-2. CDLQI will no longer be completed, once the subjects reach 18 years of age.

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.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the subject. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.1.2 Performance Outcomes (PerfO)

Not applicable

6.6.1.4 Proxy Reported Outcomes

Not applicable

6.6.2 Resource utilization

Not applicable

[redacted]

6.6.3 Pharmacokinetics

At all study sites, blood samples will be collected for pharmacokinetics (PK) at the scheduled visits as indicated in Table 6-1, Table 6-2.

Pharmacokinetic samples will be obtained for all subjects. For a detailed description of the blood sampling schema, including time points, refer to the Blood Log in Appendix 2.

All blood samples will be taken by direct venipuncture in a forearm vein.

PK sample handling, labeling and shipment instructions

Blood samples (1 mL,) will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 rpm for 10 minutes, or within sufficient time and speed to allow formation of a clear supernatant layer. Serum samples will be split into 2 aliquots (polypropylene tubes) and then stored (within 30 min of serum collection by centrifugation) at -20°C or -70°C (approximately) prior to shipment to the central laboratory. Shipment of stored aliquots from the site to the central lab should be on a pre-specified basis. To the extent possible, the site should send each aliquot of a sample to the central laboratory separately. The central lab will ship aliquots of the samples on dry ice to the analytical laboratory as per agreement with Novartis. PK samples will only be disposed of after approval by the Sponsor.

The actual date and time of sample collection will be entered on the appropriate CRF page.

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type and sample number preprinted on the label.

Further details on labeling of the pharmacokinetic samples can be found in Appendix 2 of the protocol.

PK sample stability

Secukinumab is stable in serum samples for at least 12 months at -20°C or 32 months at -80°C.

6.6.4 Other biomarkers

Not applicable

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg, 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

[redacted]

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit or scheduled phone/virtual contact during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, 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 must 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 subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the appropriate CRF capturing AEs 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
- severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding secukinumab treatment

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

- no action taken (eg further observation only)
- secukinumab treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

[redacted]

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must 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 eg 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 Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an IN or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

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

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 in-subject 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
    - 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 out-subject 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 subject's general condition
- is medically significant, eg defined as an event that jeopardizes the subject or may require medical or surgical intervention.

[redacted]

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 subject 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 it were more severe (please refer to 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 subject 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 (please refer to Annex IV, ICH-E2D Guideline).

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

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 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 DS&E database.

Any SAEs experienced after 30 days from end of study visit or 20 weeks after 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. All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has

[redacted]

resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

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

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

Not Applicable.

7.4 Renal safety monitoring

Not Applicable.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

[redacted]

7.6 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent 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 data capture requirements (eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, 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 analyze 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 subject 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 subject's file. (Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs). The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 subjects/subjects will be disclosed.

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. 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 subject data for archiving at the investigational site.

Designated sites and investigator staff will enter the data required by the protocol into the EDC 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 subject data for archiving at the investigational site.

8.3 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the Word Health Organization (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.

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data about all study drug dispensed to the subject 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 data will be sent electronically to 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

[redacted]

locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

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

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 be presented as shown in Table 9-1.

Table 9-1 Treatment groups for analyses

Weight Category	Low dose secukinumab	High dose secukinumab
<25kg	75mg	75mg
25-<50kg	75mg	150mg
≥50kg	150mg	300mg

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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 at baseline visit. Unless otherwise specified, subjects with missing informed consent form as well as misrandomized subjects will be excluded from the randomized set.

Misrandomized subjects are subjects who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed, however have not been treated. If subjects were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned in the last randomization.

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 randomization stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses. The subjects with severe GCP violation will not be included in the FAS.

Of note, subjects excluded from the randomized set will be excluded from the FAS.

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

[redacted]

9.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

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

Medical history

All conditions entered as medical history or current medical condition at baseline will be coded using the MedDRA dictionary. These will be summarized by system organ class and preferred term of the MedDRA dictionary. In addition, summaries for psoriasis specific medical history will be provided.

9.3 Treatments

Study treatment

Exposure to study treatment will be summarized by treatment group on the safety population. The total number of injections per subject will be summarized in contingency tables and summary statistics will be performed on the duration of exposure. In addition, exposure will be categorized to certain time thresholds (eg any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) and the number of subjects within each category will be presented.

Prior and concomitant medication(s)

Prior and concomitant medications will be summarized by treatment group in separate tables.

Prior medications are defined as medications taken and stopped prior to date of first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the last day of study visit will be regarded as concomitant medication, including those which started pre-baseline and continued into the treatment period.

Medications 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 medication of a particular ATC code and at least one medication in a particular anatomical main group.

Psoriasis specific prior medication will be presented, and summary will include number of prior systemic and biologic psoriasis therapies as well as reason for discontinuation.

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized.

9.4 Analysis of the primary variable(s)

This section will detail the statistical analysis of the primary endpoint. A Bayesian analysis has been chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data.

[redacted]

Data from four secukinumab adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo-controlled trials from other biologics (Paller 2008, Landells et al 2015) will be used to obtain a historical placebo control through the Bayesian meta-analytic-predictive (MAP) framework (Spiegelhalter et al 2004, Neuenschwander et al. 2010). CAIN457A2310 data will be used if they are reported prior to the present study.

9.4.1 Primary Variable(s)

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. A PASI 75 responder is defined as a subject achieving ≥ 75% improvement (reduction) in PASI score compared to baseline. A subject is considered as IGA mod 2011 0 or 1 responder if the subject achieves a score of 0 or 1 and improved from baseline by at least 3 points on the IGA mod 2011 scale if the subject enrolled into the study with a score of 4 and by at least 2 points on the IGA mod 2011 scale if the subject enrolled into the study with a score of 3.

9.4.2 Statistical model, hypothesis, and method of analysis

In order to evaluate the efficacy of secukinumab after 12 weeks, a Bayesian model will be fitted to the co-primary endpoint on secukinumab and placebo treatments. A Bayesian method has been chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data. These data will be used to calculate the Bayesian posterior of the log odds ratio between secukinumab and placebo treatment. For the log odds of the secukinumab treatment group a non-informative prior will be used, whilst the placebo treatment group log odds response rate will be represented though the MAP prior. The MAP prior will be derived from the historical placebo data using a logistic Bayesian mixed-effects model and will represent the predicted placebo log odds response rate for this trial. The analysis will report the median of the means, the 95% credible interval and the probability of a positive treatment effect of the posterior log odds ratio. Comparisons with placebo will be performed for the low and high dose group of secukinumab separately. Analysis of the co-primary variables will be based on the Full Analysis Set (FAS).

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.

- Pure non-responder imputation (includes Bayesian Primary endpoint analysis at Week 12): Missing values with respect to response variables based on PASI score and IGA mod 2011 categories were to be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Patients with missing baseline or those with all post-baseline missing were to be imputed with non-response (in the secukinumab treatment groups).
- Descriptive summaries on response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputations (MI) method as sensitivity imputation method. Multiple imputation (MI) is a simulation based approach where

[redacted]

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 (absolute change from baseline) 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.

The following imputation methods will apply to the missing data for analysis of the long term data beyond Week 52:

- Response variables based on PASI score and IGA mod 2011 categories will be generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.
- Summaries on multiple imputation will be provided as sensitivity analysis where appropriate.

9.4.4 Sensitivity analyses

No sensitivity analysis is planned for the Bayesian primary endpoint analysis.

9.5 Analysis of secondary variables

The secondary efficacy variable is PASI 90 response at Week 12

9.5.1 Efficacy variables

The key secondary efficacy endpoint of this study is the proportion of subjects with a PASI 90 response at Week 12. These data will be analyzed in the same way as the primary endpoint though a Bayesian framework, using a Bayesian mixed-effects model. Efficacy of secukinumab low and high dose compared to historical placebo control will be performed separately. Analyses will be based on the FAS population, and historical placebo data will be incorporation into the analysis as before through the MAP framework.

Missing data will be handled with the same methods as primary endpoint analysis.

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set.

Adverse events

Treatment emergent adverse events will be summarized, and all AEs will be presented in the listings.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having at least one 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.

[redacted]

If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. 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.

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 separate AE listing will be produced for subjects who reported a treatment deviation, where AEs occurring after treatment deviation will be flagged.

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.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented for most extreme values post-baseline.

Immunogenicity

Immunogenicity data will be listed.

Vital signs

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

Only "on-treatment" vital signs will be summarized (i.e. assessments within last dose plus 84 days). All information collected will be listed by subject where on treatment and abnormal values will be flagged.

The number and percentage of subjects with newly occurring notable vital sign abnormalities will be presented. Further details on the criteria for notable abnormalities will be presented in the Statistical Analysis Plan.

ECG

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

[redacted]

Physical development

Growth and weight changes will be summarised descriptively.

[redacted].

9.5.3 Resource utilization

Not applicable

9.5.4 Health-Related Quality of Life

Children's Dermatology Quality of Life Index (CDLQI)

Seven scores will be derived from the CDLQI: the total score of each of the six dimensions (symptoms and feeling, leisure, school or holidays, personal relationships, sleep, treatment) 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 .(LOCF).

9.5.5 Pharmacokinetics

All completed subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and treatment group. In addition to mean, standard deviation, coefficient of variation, median and quartiles, the geometric mean and geometric coefficient of variation and n(log) will be presented.

9.5.6 DNA

Not Applicable.

9.5.7 Biomarkers

Not applicable

9.5.8 PK/PD

Not applicable

9.6 Analysis of exploratory variables

The following exploratory efficacy endpoints will be assessed:

[redacted]

PASI 75, PASI 90, PASI 100 and IGA 2011 0 or 1 response over time

Number of subjects with PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by treatment and visit will be presented in frequency contingency tables and will include absolute and relative frequencies.

Figures will be provided displaying responder rates by treatment including confidence intervals.

PASI score over time

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

[redacted]

9.7 Interim analyses

There are two planned interim analysis. An interim analysis of the data collected up until Week 16, including the co-primary endpoint (at Week 12) will be performed after all subjects have completed either their Week 16 visit or the premature treatment discontinuation visit. Another interim analysis will be performed when all subjects have completed the Week 52 visit, (or premature treatment discontinuation visit).

Additional analyses may be performed to support health authority interactions, as necessary.

Thereafter, efficacy and safety data collected after Week 52 until the end of study may be reported yearly in separate reports.

Trial modifications are not planned based on any interim analysis.

9.8 Sample size calculation

The sample size for this study is calculated to ensure an adequate number of subjects for PK analyses and powered efficacy analyses. Approximately 80 pediatric subjects from 6 to less than 18 years of age at randomization will be recruited. Since a 15% screening failure rate is

[redacted]

expected, approximately 95 patients will be screened. The study will aim to recruit at least 60 subjects with moderate severity and approximately 20 subjects with severe severity.

Power calculations were performed to support the co-primary endpoints PASI 75 and IGA 0 or 1 response at week 12, and secondary endpoint PASI 90 at week 12, versus placebo (historical control) for the low and high secukinumab dose regimens. Data from four adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo controlled trials (Paller et al 2008, Landells et al 2015) were used to estimate the historical placebo response rate. For study CAIN457A2310, a 10% response rate was assumed for PASI 75, IGA 0 or 1 and PASI 90 response for the placebo group. The power calculation was performed assigning pediatric data moderate heterogeneity and adult trial data substantial heterogeneity (Neuenschwander et al.2010), thus allowing pediatric trial data to be given twice the weight compared to adult trial data. All the calculations were performed in the R package RBesT (version 1.1) through the meta-analytical-predictive framework (Spiegelhalter et al. 2004, Neuenschwander et al. 2010), and the predicted response rate of the placebo group for this study are presented in Table 9-2 below by endpoint.

Table 9-2 Predictive placebo response rates for this study from model of historical data

Endpoint	Mean	Standard Deviation	Median	95% CI
IGA 0 or 1	9%	6%	8%	1-23%
PASI 75	10%	6%	9%	2-25%
PASI 90	6%	4%	5%	1-18%

Requiring that the posterior probability of the log odds ratio difference between placebo and secukinumab exceeds with at least 97.5% zero leads to a power of approximately 99% for each co-primary endpoint when assuming a sample size of 40 pediatric patients per treatment group and true response rates of 10% and 65% for PASI 75 and 9% and 45% for IGA mod 2011 0 or 1 response for placebo and secukinumab respectively.

For the secondary endpoint of PASI 90 response, assuming a response rate of 6% and 39% for placebo and secukinumab respectively, the power to provide a posterior probability of at least 97.5% that the PASI 90 response rate on secukinumab is greater than placebo at week 12 is approximately 99%.

The assumed response rates for secukinumab are based on confirmatory efficacy in the adult phase III program (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed 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. Subjects who turn 18 years of age during the trial must sign the general informed consent form.

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.

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 study ICF.

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form, consent form updates, subject recruitment procedures (eg, advertisements) and any other written information to be provided to subjects/subjects. 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 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

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.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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 subjects/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

[redacted]

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.

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 intended to eliminate an apparent immediate hazard to subjects 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 subject 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 must be followed.

12 References

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13 Appendix 1: Clinically notable laboratory parameters

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

Unless otherwise indicated, 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

- Alamine Aminotranferase (ALT)(SGPT):
  >Upper Limit of Normal ()
  ≥3 x ULN
  ≥5 x ULN
  ≥8 x ULN
  ≥10 x ULN
- Aspartate Aminotranferase (AST) (SGOT):
  >ULN
  ≥3 x ULN
  ≥5 x ULN
  ≥8 x ULN
  ≥10 x ULN
- Total Bilirubin (TBL)
  >ULN,
  ≥1.5xULN,
  ≥ 2xULN
- Alkaline Phosphatase (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

[redacted]

≥3 x ULN
≥5 x ULN

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:
  - Grade 1:<LLN – 3.0 x10E9/L
  - Grade 2:<3.0 – 2.0 x10E9/L
  - Grade 3:<2.0 – 1.0 x10E9/L
  - Grade 4: <1.0 x10E9/L
- Absolute Lymphocytes: < LLN
- Absolute Eosinophils: ≥ 1.1 x ULN
- Absolute Eosinophils: ≥0.45 x 109/L

[redacted]

14 Appendix 2: Blood collection log for pharmacokinetics and immunogenicity

Table 14-1 Blood collection log for pharmacokinetics

Visit	Timepoint	Volume	Analyte	Sample number[1]	PK collection number /Dose Reference ID[1]
Randomization/Day 1	Pre-dose	1 mL	AIN457 for PK	1	1
Week 4	Pre-dose	1 mL	AIN457 for PK	2	2
Week 12	Pre-dose	1 mL	AIN457 for PK	3	3
Week 13	168 hours[2]	1 mL	AIN457 for PK	4	3
Week 14	336 hours[2]	1 mL	AIN457 for PK	5	3
Week 15	504 hours[2]	1 mL	AIN457 for PK	6	3
Week 16	672 hours[2]	1 mL	AIN457 for PK	7	3
Week 24	Pre-dose	1 mL	AIN457 for PK	8	4
Week 52	Pre-dose	1 mL	AIN457 for PK	9	5
Week 104	Pre-dose	1 mL	AIN457 for PK	10	6
Week 156	Pre-dose	1 mL	AIN457 for PK	11	7
Week 208	672 hours[3]	1 mL	AIN457 for PK	12	8
Week 224	3360 hours[3]	1 mL	AIN457 for PK	13	8

[1] If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 1001, 1002, etc.

[2] Scheduled time points for sample numbers 4, 5, 6, 7 (168, 336, 504 and 672 hours post-dose, respectively) refer to the last previous dose given at Week 12 (Dose Reference ID = 3)

[3] Scheduled time points for sample numbers 12 and 13 (672 and 3360 hours post-dose, respectively) refer to the last dose given at Week 204 (Dose Reference ID = 8)

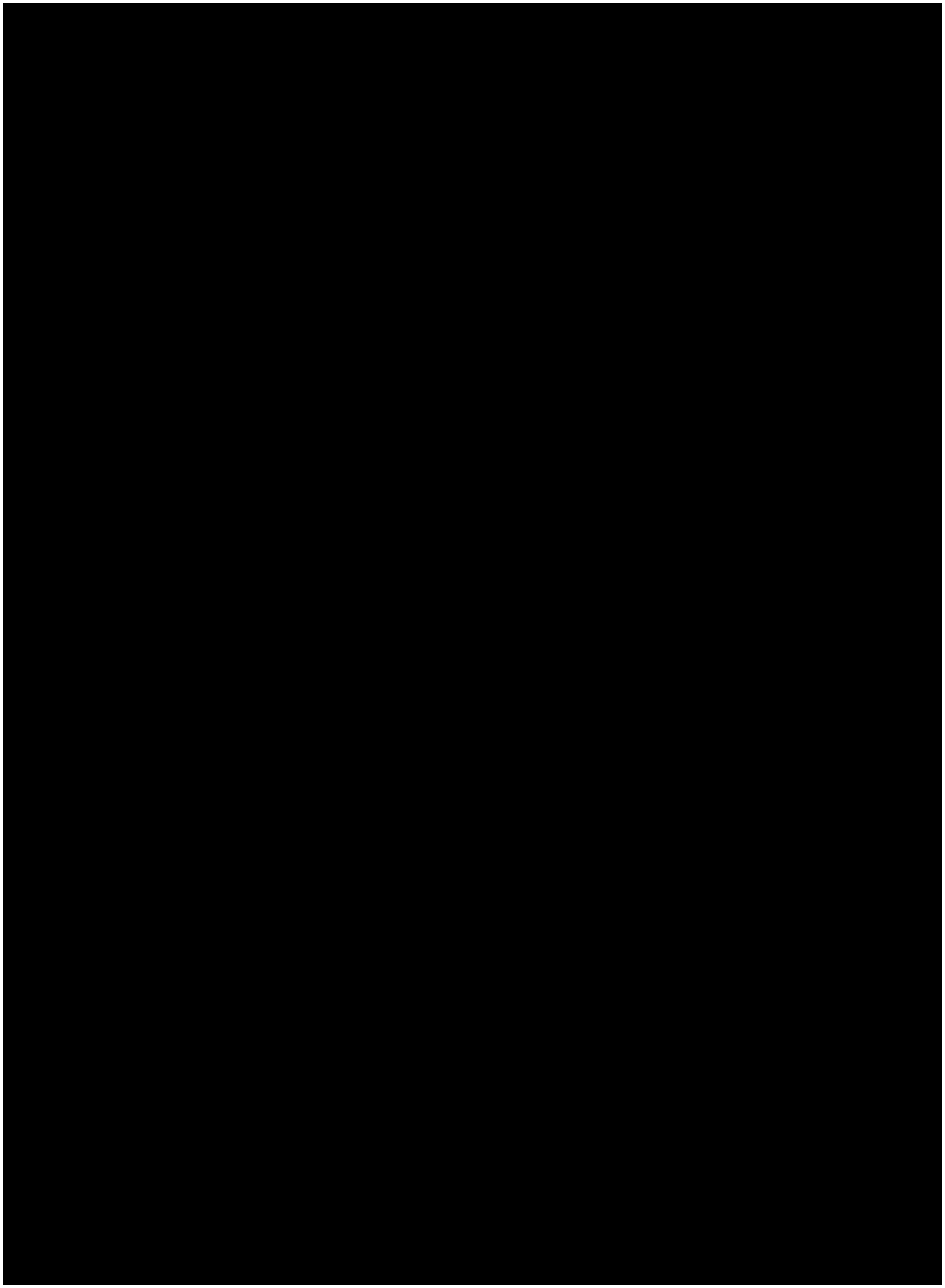
Table 14-2 Blood Collection for Immunogenicity

Visit	Timepoint	Volume	Analyte	Immunogenicity Sample number[1]
Randomization/Day 1	Pre-dose	2 mL	anti-AIN457 for IG	501
Week 16	Pre-dose	2 mL	anti-AIN457 for IG	502
Week 24	Pre-dose	2 mL	anti-AIN457 for IG	503
Week 52	Pre-dose	2 mL	anti-AIN457 for IG	504
Week 104	Pre-dose	2 mL	Anti-AIN457 for IG	505
Week 156	Pre-dose	2 mL	Anti-AIN457 for IG	506
Week 208	672 hours[2]	2 mL	Anti-AIN457 for IG	507
Week 224	3360 hours[2]	2 mL	anti-AIN457 for IG	508

[1] If an IG sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 3001, 3002, etc.

[2] Scheduled time points for sample numbers 12 and 13 (672 and 3360 hours post-dose, respectively) refer to the last dose given at Week 204

[redacted]



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

[redacted]