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Secukinumab AIN457

Clinical Trial Protocol CAIN457F2304E1 / NCT03769168

An extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability up to 4 years in patients with Juvenile Idiopathic Arthritis subtypes of Juvenile Psoriatic Arthritis and Enthesitis Related Arthritis

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List of abbreviations

ACR	American College of Rheumatology
ACR	Albumin-creatinine ratio
ADA	Anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
Alb	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCOVA	analysis of covariance
AS	Ankylosing Spondylitis
ATC	Anatomical Therapeutic Classification
AST	aspartate aminotransferase
BDR	Bioanalytical Data Report
BMI	Body Mass Index
BP	Blood pressure
BSA	body surface area
BUN	blood urea nitrogen
Cavg	average concentration of drug in blood
C-SSRS	Columbia Suicide Severity Rating Scale
CD-ROM	compact disc – read only memory
CDC	Center of Disease Control
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CHAQ©	Childhood Health Assessment Questionnaire
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CO_2	carbon dioxide
COAR	Clinical Operations, Analytics & Regions
COX-2	cyclooxygenase-2
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTRD	Clinical Trial Results Database
CTT	Clinical Trial Team
CV	coefficient of variation
DMARD	Disease-modifying antirheumatic drugs

DMC	Data Monitoring Committee
eCRF	electronic case record form
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ERA	Enthesitis Related Arthritis
EMA	European Medicines Agency
eSAE	Electronic Serious Adverse Event
EOT	End of Treatment
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma - Glutamyl transferase
h	Hour
hCG	Human chorionic gonadotropin
β-hCG	Beta Human chorionic gonadotropin
HDL	High-density lipoprotein
HLA	human leukocyte antigen
i.v.	Intravenous
IA	Interim Analysis
IB	Investigator's brochure
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for use
IG	Immunogenicity
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
LDH	lactate dehydrogenase
LDL	Low Density Lipoprotein

LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
mAbs	Monoclonal antibodies
MABEL	minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
mg	milligram(s)
ml	milliliter(s)
mL	milliliter(s)
MRSD	maximum recommended starting dose
NCDS	Novartis Clinical Data Standards
NOVDD	Novartis Data Dictionary
NSAID	Nonsteroidal anti-inflammatory drugs
PA	Posteroanterior
PCR	Protein-creatinine ratio
PD	pharmacodynamic
PFS	pre-filled syringes
PIP	pediatric investigation plan
PK	pharmacokinetic(s)
PRN	pro re nata
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PSW	premature patient/ withdrawal
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
RF	Rheumatoid Factor
s.c.	Subcutaneous
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SJC	Swollen Joint Count
SOP	Standard Operating Procedures
SpA	Spondyloarthropathy
SOM	Site Operations Manual
SSZ	sulfasalazine
SUN	Standardization of uveitis nomenclature

SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TJC	Tender Joint Count
TP2	Treatment Period 2
TNF	tumor necrosis factor
UK	United Kingdom
ULN	upper limit of normal
ULQ	upper limit of quantification
US	United States
VAS	Visual Analogue Score
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 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 patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
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 consent (WoC)	Withdrawal of consent from the study is defined as when a patient 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

Protocol summary

Protocol number	CAIN457F2304E1
Full Title	An extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability up to 4 years in patients with Juvenile Idiopathic Arthritis subtypes of Juvenile Psoriatic Arthritis and Enthesitis Related Arthritis
Brief title	Secukinumab long-term safety, tolerability and efficacy in JPsA and ERA up to 4 years
Sponsor and Clinical Phase	Novartis Pharma AG
Investigation type	Drug
Study type	Interventional
Purpose and rationale	CAIN457F2304 is a 2-year Phase III study which enrolled children ≥2 to <18 years of age with active ERA or JPsA categories of JIA. The study CAIN457F2304E1 is designed as an up to 4-year extension to the core study CAIN457F2304. The aim of this 4-years extension study is to provide continuous treatment with secukinumab (AIN457) in pre-filled syringes (PFS) for patients who complete the core study CAIN457F2304 Week 104 and opt to enter the extension trial and to obtain further long-term efficacy, safety and tolerability information. Patients from core study CAIN457F2304 can participate in this optional, open label extension study for a minimum of one year or until one of the following conditions are met, whichever is earlier; the drug is locally approved, marketed, and reimbursed, OR– secukinumab can be provided free of charge to patients in compliance with local guidelines, OR– a maximum of 4 years study duration.
Primary Objective(s)	To evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.
Secondary Objectives	1. To evaluate the long-term safety, tolerability and immunogenicity of secukinumab as assessed by vital signs, clinical laboratory variables and adverse events monitoring over time up to Week 308. 2. To evaluate the long-term effect of secukinumab treatment for all patients and each JIA category with respect to:- - JIA ACR/50/70/90/100 and inactive disease status - Each JIA ACR core component - Change from baseline of core study CAIN457F2304 - Juvenile Arthritis Disease Activity Score (JADAS) - Total Enthesitis count - Total Dactylitis count 3. To evaluate Pharmacokinetics (PK) of secukinumab
Study design	This is a multicenter, optional, open-label, pediatric extension study of subcutaneous (s.c.) secukinumab in pre-filled syringes to evaluate the long-term efficacy, safety and tolerability up to 4-years in patients with JIA subtypes of JPsA and ERA.

Population	Male and female patients aged from ≥2 years to <18 years at SCREENING in the core study CAIN457F2304, who are diagnosed with either Enthesitis Related Arthritis (ERA) based on fulfilling the ILAR JIA classification criteria or Juvenile Psoriatic Arthritis (JPsA) based on fulfilling a modified ILAR JIA classification criteria who have completed the entire treatment period up to and including Week 104 of the core study.
Key Inclusion criteria	1. Patients must have participated in core study CAIN457F2304, and must have completed the entire treatment period up to and including Week 104. 2. Patients must be deemed by the investigator to benefit from continued secukinumab therapy. 3. For patients who did not reach the age of consent (as per local law): Parents or legal guardian's signed written informed consent and child's assent, if appropriate, must be obtained prior to participation in the study and before any study related procedure is performed. Of note, if the patient reaches age of consent (age as per local law) during the study, they will also need to sign the corresponding study ICF (Informed Consent Form). 4. For patients who reached the age of consent (age as per local law), signed written informed consent must be obtained prior to participation in the study and before any study related procedure are performed.
Key Exclusion criteria	1. Plans for administration of live vaccines during the extension study period. 2. Any patient taking other concomitant biologic immunomodulating agent(s) except secukinumab. 3. Any patient who is deemed not to be benefiting from the study treatment based upon lack of improvement or worsening of their symptoms. 4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 5. Females of child-bearing 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 an effective contraception.
Study treatment	All subjects will receive the same dose of secukinumab at Week 104E1 as they were receiving at Week 100 in core study. No re-randomization is planned. The two treatment groups are: • Group1: Secukinumab (AIN457) 75mg/0.5mL, liquid formulation provided in 0.5 mL PFS (Pre-filled syringe) • Group 2:Secukinumab (AIN457) 150mg/1.0mL, liquid formulation provided in 1.0 mL PFS (Pre-filled syringe) **Starting Week 108** The dose may be escalated from 75 mg to 150 mg sc for patients whose signs and symptoms are not fully controlled, as judged by the investigator, with the current 75 mg. Further the dose may also be escalated to 300 mg s.c. every 4 weeks for patients 50kg and over and currently on 150 mg dose, and whose signs and symptoms are not controlled well, as judged by investigator.

	The dose escalation from secukinumab 75 mg sc to 300 mg sc should be implemented in two steps (first 150 mg sc and then 300 mg sc based on investigator's judgement).
Efficacy assessments	• JIA ACR 30, 50, 70, 90 and 100 response criteria, • Physician's Global Assessment of disease activity (VAS) (Visual Analogue Score), • Parent's/patient's Global Assessment of patients overall well-being (VAS included within CHAQ©), • Childhood Health Assessment Questionnaire (CHAQ©), • Active joint count, • Joint count with limited range of motion, • CRP (C-Reactive Protein) (local), • Inactive disease status, • [redacted], • Swollen Joint Count (SJC), • Tender Joint Count (TJC), • JADAS score, • Total Enthesitis count • Total Dactylitis count,
Safety Assessments	• Adverse events/serious adverse events (AE/SAE) • Electrocardiogram (ECG), (local), • Laboratory evaluations, • Immunogenicity, • Injection site reactions, • Physical examination, • Vital signs, • Height and weight, • Pregnancy and assessment of fertility, • Tolerability of secukinumab
Pharmacokinetic assessments	• Secukinumab levels
Data analysis	All data will be summarized descriptively for all patients by a dose group and/or possibly by JPsA and ERA subtypes. Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patients in each category will be presented. The 95% confidence intervals will be provided as appropriate to evaluate the efficacy of the treatment regimens.
Key words	JIA, JPsA, ERA, secukinumab (AIN457)

1 Introduction

1.1 Background

Juvenile Idiopathic Arthritis (JIA) represents a heterogeneous group of chronic idiopathic arthritides of at least 6 weeks duration, which presents in children less than 16-years of age. These conditions have variable clinical presentations and prognoses, variable age of onset, and are a major cause of morbidity. The reported prevalence and incidence of JIA varies widely. The prevalence in Europe ranges from 0.2 to 2.0 per 1000 children, and in the US (United States), the prevalence has been reported to be approximately 0.45 per 1000 children.

The International League of Associations for Rheumatology (ILAR) classification criteria (Petty et al 2004) identify the following 7 JIA categories characterized by different clinical presentations:

- Polyarthritis (Rheumatoid Factor (RF) positive);
- Polyarthritis (Rheumatoid Factor (RF) negative);
- Oligoarthritis;
- Juvenile psoriatic Arthritis (JPsA);
- Enthesitis Related Arthritis (ERA);
- Systemic Arthritis and;
- Undifferentiated Arthritis

Of the 7 JIA categories, Juvenile Psoriatic Arthritis (JPsA) and Enthesitis Related Arthritis (ERA) represent a spondyloarthropathy (SpA) similar to the adult spondyloarthropathies of Psoriatic Arthritis (PsA) and Ankylosing Spondylitis (AS).

Juvenile Psoriatic Arthritis (JPsA) is an inflammatory arthritis, which can present with or without psoriasis skin involvement and accounts for approximately 5% to 10% of the total JIA population. The current ILAR classification criteria for JPsA include two distinct groups of patients; one clinically similar to JIA oligoarthritis and the other clinically similar to the adult spondyloarthritis condition of PsA (Martini 2003, Horneff 2009, Martini 2012). Those with an oligoarthritis like condition usually present at a young age (2 to 4 years old) with asymmetric oligoarthritis, are at risk for the development of iridocyclitis, and are frequently ANA (Antinuclear antibodies) positive. Those with a more adult PsA-like condition usually present at a later age (> 6 to 9 years old) with a lower extremity arthritis, enthesitis and, in a minority of patients, axial involvement, and are often Human Leukocyte Antigen HLA-B27 positive.

Enthesitis Related Arthritis (ERA) is a clinically heterogeneous group including some who have predominantly enthesitis, enthesitis and arthritis, juvenile ankylosing spondylitis, or inflammatory bowel disease-associated (IBD) arthropathy. ERA accounts for approximately 3% to 11% of JIA.

ERA has a strong genetic predisposition as evidenced by a positive family history and the high frequency of the presence of HLA-B27 in affected patients. The hallmarks of the disease are pain, stiffness, and eventual loss of mobility of the back, similar to adult ankylosing spondylitis. ERA should be suspected in any child with chronic arthritis of the axial and peripheral skeleton, enthesitis (inflammation at points where tendons insert to bone), and Rheumatoid Factor (RF) and Anti-nuclear antibody (ANA) seronegativity. Peripheral arthritis, also similar to adult AS, usually affecting few joints of the lower extremity, precedes axial involvement, and arthritis of the sacroiliac joints may take years to develop. Unlike adults with AS, the arthritis in children with ERA can be very

aggressive and lead to hip replacement more often than in adult AS patients. Radiographic changes of the sacroiliac joint include joint space narrowing, erosions, sclerosis, osteoporosis of the pelvis, and fusion (a late finding).

In 2011, the American College of Rheumatology (ACR) established JIA treatment guidelines which are applicable to all JIA categories, including the spondyloarthropathies JPsA and ERA. The guidelines aim to quickly control active inflammation and patient symptoms and to prevent/minimize disease and/or treatment related morbidities (e.g. growth disturbances, joint damage, and functional limitations). In general, the treatment goal is to target controlling the inflammation with NSAIDs (Non-steroidal anti-inflammatory drugs), corticosteroids as intra-articular injections, DMARDs (Disease modifying anti-rheumatic drugs) and biologic agents either as monotherapy or in combination with other therapies (DMARD and/or NSAID). Successful management requires careful long-term monitoring of disease activity and willingness to adjust treatments as necessary to achieve and maintain the lowest level of disease activity.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that targets (Interleukin) IL-17A and neutralizes it's activity. Secukinumab treatment has demonstrated significant and clinically meaningful efficacy in treating adults with ankylosing spondylitis (AS) and psoriatic arthritis (PsA), both are approved indications.

Patients from core trial CAIN457F2304 study can participate in this optional open label extension study for a minimum of one year or until one of the following conditions are met, whichever is earlier: the drug is locally approved, marketed, and reimbursed, OR– secukinumab can be provided free of charge to patients in compliance with local guidelines, OR– a maximum of 4 years study duration.

1.2 Purpose

Study CAIN457F2304 is a 2-year Phase III study which enrolled children ≥2 to <18 years of age with active ERA or JPsA categories of JIA. The study CAIN457F2304E1 is designed as an up to 4-year extension to the core study CAIN457F2304. The aim of this 4-year extension study is to provide continuous treatment with secukinumab in pre-filled syringes (PFS) for patients who complete the core study CAIN457F2304 Week 104 and opt to enter the extension trial and to obtain further long-term efficacy, safety and tolerability information.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

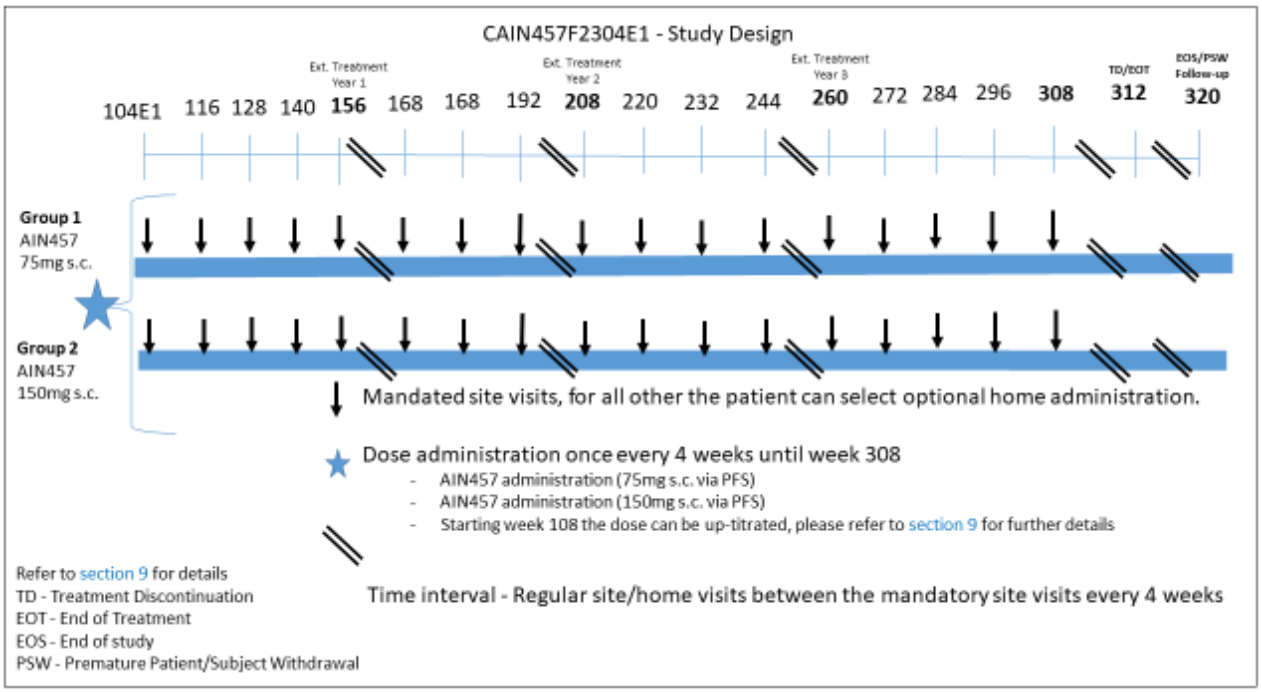
Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the long-term efficacy of secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.	• JIA ACR Response
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
• To evaluate the long-term safety, tolerability and immunogenicity of secukinumab as assessed by vital signs, clinical laboratory variables and adverse events monitoring over time up to Week 308	• AEs • Lab values • Vital signs • Anti-Drug Antibodies (ADAs)
• To evaluate the long-term effect of secukinumab treatment for all patients and each JIA category with respect to: ➢ JIA ACR/50/70/90/100 and inactive disease status; ➢ Each JIA ACR core component; ➢ Change from baseline of core study CAIN457F2304 ➢ Juvenile Arthritis Disease Activity Score (JADAS); ➢ Total Enthesitis count; ➢ Total Dactylitis count	• JIA ACR /50/70/90/100 • JIA ACR Core Components • Inactive Disease Status • JADAS Score • Total Enthesitis count • Total Dactylitis count
• To evaluate pharmacokinetics (PK) of secukinumab	• Secukinumab serum concentrations and derived PK parameters
[redacted]	

3 Study design

A multicenter, optional, open-label, pediatric extension study of subcutaneous secukinumab in pre-filled syringes to evaluate the long-term efficacy, safety and tolerability up to 4-years in patients with Juvenile Idiopathic Arthritis subtypes of Juvenile Psoriatic and Enthesitis Related Arthritis.

The aim of this 4-year extension study is to provide continuous treatment with secukinumab in pre-filled syringes (PFS) for patients who complete the core study CAIN457F2304 and opt to enter the extension trial and to obtain further long-term efficacy, safety and tolerability information.



4 Rationale

4.1 Rationale for study design

This up to 4-year open label extension study will offer continuous secukinumab therapy to patients who opt to continue in to the extension study from the core study CAIN457F2304 and will provide long-term efficacy and safety data. Patients can exit the study upon their own wish or based on the advice of the investigator at any time.

Although the cause for arthritis in children and adults is not known, children are expected to respond similarly to adults with similar conditions. Data from multiple secukinumab studies evaluating a range of doses (75 mg to 300 mg) are available for two adult spondyloarthritides (AS (Ankylosing Spondylitis) and PsA (Psoriatic Arthritis)) and RA (Rheumatoid Arthritis). A favorable benefit risk was established in adult ankylosing spondylitis and psoriatic arthritis patients. These indications are approved in multiple countries including the European Union (EU) and the US.

Based on the totality of the adult arthritis clinical data where secukinumab treatment resulted in robust efficacy in adults with a spondyloarthropathy (PsA or AS), the appropriate pediatric arthritic population to study secukinumab treatment is children aged $\geq$ 2 to $<$ 18 years diagnosed with enthesitis related arthritis or juvenile psoriatic arthritis JIA which are the two JIA categories which represent pediatric correlates of the approved adult SpA indications. The core study is adequately powered to demonstrate effectiveness of secukinumab treatment in a placebo-controlled study design following EMA (European Medicine Agency) JIA treatment guidelines evaluating a pediatric dose regimen equivalent to the 150 mg adult AS and PsA dose regimen. No additional safety risks or vulnerabilities are expected from exposure to secukinumab at this dose in the proposed pediatric population.

The patient population will be described in more detail in the Section 5.

4.2 Rationale for dose/regimen and duration of treatment

The dose selection for secukinumab in pediatric JPsA and ERA is based on the expectation that children will respond similarly to adults with similar conditions. In the pivotal adult psoriatic arthritis and ankylosing spondylitis Phase III randomized placebo-controlled studies, secukinumab 150 mg administered weekly for the first 4 weeks and monthly thereafter demonstrated significant efficacy and a favorable safety profile. In both adult AS and PsA, secukinumab treatment led to significant improvement in patient's clinical signs and symptoms as well as improved quality of life. Based on this data, secukinumab has received approval in multiple countries, including the European Union and the US, for these indications at this dose. For adults with PsA, a 300mg dose regimen was a more effective dose in treating the psoriasis of patients with moderate to severe skin involvement and in treating the arthritic component in patients who did not respond adequately to a (Tumor necrosis factor) TNF inhibitor. For both indications, the recommended dose in (Tumor necrosis factor) TNF-α naïve patients is 150 mg by subcutaneous injection at Weeks 0, 1, 2 and 3, followed by monthly dosing starting at Week 4 (Cosentyx® (Secukinumab) label 2016).

The 300 mg dose is approved as the maintenance regimen every 4 weeks for moderate to severe psoriasis, as well as for PsA patients with concomitant moderate to severe PsO and PsA patients who are inadequate responders to anti-TNF agents. There is an ongoing variation to allow PsA patients without moderate to severe psoriasis with inadequate response to the 150 mg dose to increase their dose to 300 mg. With regards to Ankylosing Spondylitis it has been shown in study CAIN457F2314 that for higher hurdle efficacy endpoints, such as a 40% improvement in Assessment of Spondyloarthritis International Society Criteria (ASAS40), ASAS partial remission (ASAS-PR) and Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease, higher efficacy response rates were achieved for 300 mg versus 150 mg. This supports that some patients benefit from access to the higher maintenance dose of 300 mg.

[redacted]

[redacted]

[redacted]

The doses and regimen selected for secukinumab Phase III study (CAIN457F2304) are projected to deliver efficacy while at the same time ensuring patient safety. The proposal to continue treatment with s.c. doses of 75 mg and 150 mg administered every four weeks, as well as the additional treatment duration of up to 208 weeks (last dose at Week 308) (leading to an overall treatment period [core plus extension] of 312 weeks) is based on the need for long-term treatment exposure in patients suffering from a chronic illness such as psoriatic arthritis.

[redacted]

[redacted]

Thus, given the results outlined above, and in order to maintain a high proportion of clinically meaningful response during the entire duration of the extension study, the dosing options available, at the investigator's discretion, are:

1. The dose of secukinumab can be escalated from 75 mg sc every 4 weeks to 150 mg sc every 4 weeks for patients whose signs and symptoms are not fully controlled with the current dose of 75 mg, and may improve with higher dose as judged by the investigator.
2. Further, the dose can also be escalated to 300 mg sc every 4 weeks for patients 50kg and over currently on 150 mg dose whose signs and symptoms are not fully controlled, and may improve further with an increase in dose as judged by investigator.
3. Dose escalation from secukinumab 75 mg to 300 mg has to be done in two steps (first 150 mg then 300 mg if patient is 50kg or over and based on investigator's judgement), also considering the gap between the 2 escalations to review the response.

To maintain a clinically meaningful response during the entire duration of the extension study, the dose of secukinumab can be escalated from 75 mg sc every 4 weeks to 150 mg sc every 4 weeks for patients whose signs and symptoms may be improved with a higher dose, as judged by the investigator. Further, the dose can also be escalated to 300 mg sc every 4 weeks for patients 50kg and over and currently on 150 mg dose, as judged by investigator.

The extension study will continue to evaluate three doses (75 mg, 150 mg and 300mg) using PFS in order to characterize the long-term safety profile for a higher and a lower secukinumab dose.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

There is no placebo control group or active comparator in this study given the purpose and main objectives.

4.4 Purpose and timing of interim analyses/design adaptations

Interim analyses may be performed for purposes of publication and/or to support health authority interactions, as necessary.

4.5 Risks and benefits

Secukinumab has shown efficacy in several inflammatory diseases, including PsA, AS, and psoriasis. The large safety dataset of secukinumab cross-indication did not show unexpected safety issues relative to the known mode of action. In general, secukinumab is safe and well-tolerated and has demonstrated a similar safety profile to other (monoclonal antibodies) mAbs (including etanercept and ustekinumab). The most frequently reported AEs are non-serious infections, especially upper respiratory tract infections. In addition, there is an increase in mucosal or cutaneous candidiasis with secukinumab compared with placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment. There is also a small increase in neutropenia cases with secukinumab compared with placebo. Common Terminology Criteria for

Adverse Event (CTCAE) Grade 3 neutropenia (<1.0-0.5 x 10^9/L) was uncommonly observed with secukinumab, most were mild to moderate, transient and reversible, and without a temporal relationship to serious infections. Hypersensitivity reactions include urticaria. Rare events of anaphylactic reaction to secukinumab have also been observed in clinical studies.

The immunogenicity potential, e.g. eliciting the production of anti-drug antibodies (ADAs) is low. In psoriasis, psoriatic arthritis and ankylosing spondylitis clinical studies, less than 1% of patients treated with secukinumab (n>9600) developed antibodies over up to 52 weeks of treatment.

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from its mechanism of action is anticipated to be similar or improved compared to the other approved inflammatory cytokine-targeting therapies. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance to the investigators provided by Novartis and in the current version of the Investigator's brochure (IB) for secukinumab. Based on overall risk-benefit assessment, the current trial with secukinumab is justified.

It should be noted that patients must be deemed by the investigator to benefit from continued secukinumab therapy.

5 Population

The study population will consist of male and female patients aged from ≥2 years to <18 years at SCREENING in the core study CAIN457F2304, who are diagnosed with either Enthesitis Related Arthritis (ERA) based on fulfilling the ILAR JIA classification criteria or Juvenile Psoriatic Arthritis (JPsA) based on fulfilling a modified ILAR JIA classification criteria who have completed the entire treatment period up to and including Week 104 of the core study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient must have participated in core study CAIN457F2304, and must have completed the entire treatment period up to and including Week 104.
2. Patients must be deemed by the investigator to benefit from continued secukinumab therapy.
3. For patients who did not reach the age of consent (as per local law): Parent's or legal guardian's signed written informed consent and child's assent, if appropriate, must be obtained prior to participation in the study and before any study related procedure is performed. Of note, if the patient reaches age of consent (as per local law) during the study, they will also need to sign the corresponding study ICF (Informed Consent Form).
4. For patients who reached the age of consent (age as per local law), signed written informed consent must be obtained prior to participation in the study and before any study related procedure are performed.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Plans for administration of live vaccines during the extension study period.

2. Any patient taking other concomitant biologic immunomodulating agent(s) except secukinumab.
3. Any patient who is deemed not to be benefiting from the study treatment based upon lack of improvement or worsening of their symptoms.
4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
5. Females of child-bearing 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 an effective contraception as defined in Section 8.4.6.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply the following study drugs:

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Packaging of Drug	Sponsor (global or local)
Secukinumab (AIN457) 75 mg/0.5mL	liquid formulation provided in 0.5 mL pre-filled syringe	Subcutaneous	Labelled Investigational Drug	Sponsor global
Secukinumab (AIN457) 150 mg/1.0mL	liquid formulation provided in 1 mL pre-filled syringe	Subcutaneous	Labelled Investigational Drug	Sponsor global

All study drugs will be labeled accordingly:

- AIN457 150 mg/1.0mL
- AIN457 75 mg/0.5mL

For detailed instructions on handling of the study drug, please refer to Section 6.7.1.2.

Before enrolment in this extension study, all patients electing to continue will sign an Informed Consent form. Detailed instructions for self-administration of the “s.c” injection using the PFS formulation will be provided to each patient or parent/guardian. Each injection will be administered into an appropriate injection site of the body. For the first visit at Week 104E1, injections will be performed at site.

Starting from Week 108 patients will have the choice of self-administration or injection by parent/guardian (once trained) at home or continuing with administration at site, based on personal preference and the investigator’s clinical judgment. Site staff or parent/guardian (once trained) will administer the injection to patients who are not able or feel insecure to self-administer the PFS injection.

6.1.2 Additional study treatments

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

6.1.3 Treatment group

All subjects (in Treatment Period (TP3) of core study) will continue to receive the same dose of secukinumab at Week 104E1 as they were receiving at the last visit Week 100 of the core study. Patients who would be blinded at Week 100 still in Treatment Period (TP2) and choose to enter the extension study, will also receive secukinumab 75mg or 150 mg at Week 104E1 according to their weight as they were receiving at the last visit Week 100 of the core study. No re-randomization is planned.

At Week 104 of core study, all eligible patients from core study can opt to be enrolled in extension study via Interactive Response Technology (IRT) and will receive secukinumab dosing. The Week 104E1 will be performed on the same day once the Week 104 is completed by patient. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the extension study inclusion/exclusion criteria. The IRT will then specify a unique medication number for the first package of investigational treatment to be dispensed to the patient for Week 104E1.

From Core Week104/Extension Week 104E1 until Week 308

Group 1: secukinumab 75mg/0.5ml once every four weeks until (and including) Week 308
Group 2: secukinumab 150mg/1.0ml once every four weeks until (and including) Week 308

At each study treatment time point starting at Week 108, one or two s.c. injections in the form of PFS will be administered. This will be open label treatment.

- The dose may be escalated from 75 mg to 150 mg sc for patients whose signs and symptoms are not fully controlled, as judged by the investigator, with the current 75 mg dose.
- Further the dose may also be escalated to 300 mg s.c. every 4 weeks for patients 50kg and over and currently on 150 mg dose, and whose signs and symptoms are not controlled well, as judged by investigator.
- The dose escalation from secukinumab 75 mg sc to 300 mg sc should be implemented in two steps (first 150 mg sc and then 300 mg sc based on investigator's judgement).

As this long-term study extends the pivotal registration study CAIN457F2304 by up to an additional 4-years it may be affected by agency review or potential product approval considerations. If the product is approved during study conduct, dose groups in this extension study may be amended (via a future protocol amendment) based on eventual agency recommendations for product usage in this indication.

6.1.4 Treatment duration

Patients who completed the core CAIN457F2304 study and who are deemed by the investigator to benefit from continuous secukinumab therapy can participate in this optional open label extension study. Patients can participate for a minimum of one year or until one of the following conditions

are met, whichever is earlier: the drug is locally approved, marketed, and reimbursed, OR– secukinumab can be provided free of charge to patients in compliance with local guidelines, OR– a maximum of 4 years study duration.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the patient/guardian to notify the study site about any new medications the patient takes after he/she was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered at least once between the start of the first dose in this extension trial and the date of the last study visit in the extension study must be recorded in the concomitant medications/significant non-drug therapies eCRF page, including those which were started before Week 104E1 and continued into the extension study where study treatment is administered.

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 enrolling a patient or allowing a new medication to be started. Medications /treatments not explicitly mentioned in the protocol can be evaluated by Novartis for suitability with the study on a case-by-case basis.

Guidelines for the use of specific medications are provided below.

Non-biologic DMARDs (limited to MTX or SSZ)

For patients on Methotrexate (MTX) (maximum of 20 mg/m^2/ Body Surface Area (BSA)/ week) and folic/folinic acid supplementation (according to standard medical practice of the center), or sulfasalazine (SSZ) (only for ERA patients, stable dose of <50 mg/kg/day and up to max 3000 mg/day), dose may be adjusted as deemed appropriate and necessary by the investigator.

Systemic corticosteroids

Treatment with oral corticosteroids ≤ 0.2 mg/kg/day (or maximum 10 mg/day whichever is lower) of oral prednisone (or equivalent) is permitted, dose may be adjusted as deemed appropriate and necessary by the investigator.

Any change in the dose of oral corticosteroids during the trial should be recorded on the corresponding eCRF page.

Intra-articular corticosteroid injections will be permitted. No more than 4 joints per 24-week period may be injected and no single injection should exceed 40 mg of triamcinolone (or equivalent) during any 52-week period. Intra-articular corticosteroid injections will be recorded appropriately and the injected joints will be considered active for the following 3 months for the purposes of analysis.

Non-steroidal anti-inflammatory drugs (NSAIDs) (including selective cyclooxygenase-2 (COX-2) inhibitors), low strength opioids and acetaminophen/paracetamol

Patients are permitted to enter the trial using regular dose of a single non-steroidal anti-inflammatory drugs (NSAID) for their arthritis. Dose may be adjusted as deemed appropriate and necessary by the investigator. Other NSAIDs, low strength opioids, and paracetamol/acetaminophen are permitted during the trial only if used on an as required (PRN) basis for non-arthritis treatment. In such cases,

the patient must refrain from intake of the PRN medication during at least 24 hours before a visit with a disease activity assessment.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 is NOT allowed after enrollment due to their confounding effect and/or safety interactions.

Note: Live vaccination is NOT allowed until the last study dose. Killed or inactivated vaccines may be permitted according to the investigator's discretion.

It is recommended not to initiate biologic treatment until 3 months after the last dose of study drug. Therefore, biologic treatment should not be used any time during study participation.

Table 6-2 Prohibited Medication

Medication	Action taken
Any biologic drugs, including but not limited to TNFα inhibitors, other biologic drug directly targeting IL-17 or IL-17 receptor, any biological DMARD (bDMARDs)	Discontinue investigational treatment, complete Week 312/EOT visit
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g. alemtuzumab (Campath), anti-CD4, anti-CD5, anti-CD3, and anti-CD19].	Discontinue investigational treatment, complete Week 312/EOT visit
Leflunomide	Discontinue investigational treatment, complete Week 312/EOT visit
Any investigational treatment or participation in any interventional trial	Discontinue investigational treatment, complete Week312/EOT visit
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN	Discontinue investigational treatment, complete Week 312/EOT visit
Intramuscular or intravenous corticosteroid treatment are not permitted	To be reviewed on a case by case basis
Live vaccinations	Discontinue investigational treatment, complete Week 312/EOT visit

6.2.3 Rescue medication

Rescue medication is defined as medication used to control symptoms that are not adequately controlled on investigational study treatment.

Use of rescue medication is prohibited. Please see Section 6.2.1 and Section 6.2.2 for details on concomitant therapy and prohibited medications, respectively. Although no patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, patients will be discontinued from the study and complete Week 312/EOT visit if treated with prohibited medications (as described in Section 6.2.2) and should complete an Early termination visit at the earliest possible time point and enter the Post-treatment follow-up period. Efficacy and safety will be assessed in detail at every study visit and, patients who are deemed by the Investigator not to be benefiting from study treatment, or for any reason on the patient's own accord, will be free to discontinue study participation at any time.

Use of rescue medication must be recorded on the corresponding eCRF page.

6.2.3.1 Recommendation

Table 6-3 Recommendation

Medication	Action taken
Conventional DMARDs (except SSZ (for ERA only) or MTX) including apremilast	To be reviewed on a case by case basis.
Leflunomide with cholestyramine	To be reviewed on a case by case basis.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

This being an extension study, the patient numbers will remain same as that of core study CAIN457F2304; new patient numbers will NOT be assigned.

Each patient is identified in the extension study by a patient number (patient No.), that is assigned when the patient is first enrolled in core study (CAIN457F2304) and is retained as the primary identifier for the patient throughout his/her entire participation in the extension trial. The patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database.

6.3.2 Treatment assignment, randomization

All patients will continue to receive secukinumab dosing based on their weight at each drug dispensing visit.

There is no re-randomization in this extension study, see Section 6.1.3 for more details.

6.4 Treatment blinding

Treatment will be open to patients, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

Starting from Week 108, the secukinumab dose can be escalated from 75 mg to 150 mg for patients whose signs and symptoms are not fully controlled with the current dose of 75 mg, and may improve with higher dose as judged by the investigator.

Further, the dose can also be escalated to 300 mg for patients currently on 150 mg, and whose signs and symptoms are not fully controlled and may improve further with an increase in dose as judged by the investigator.

The dose escalation from secukinumab 75 mg sc to 300 mg sc should be implemented in two steps (first 150 mg sc and then 300 mg sc based on investigator's judgement) .

All escalation are allowed only at mandated site visits. For patients escalated to 150 mg or 300 mg, no dose reduction can be performed at a later stage.

6.5.1 Dose escalation guidelines

6.5.1.1 Starting dose

The starting dose of study treatment during extension study, administered at Week 104E1 visit, will be 75 mg/0.5mL or 150 mg/1.0mL.

6.5.2 Dose modifications

Investigators are permitted to increase the dose from 75 mg to 150 mg or from 150 mg to 300 mg for patients, per their discretion at each drug dispensing visit starting from Week 108.

No dose adjustments or interruptions are permitted for patients, in any other case unless there is a medical/safety reason documented by the investigator that indicates the rationale for the dose adjustment or interruption.

The reason for any study treatment interruption must be recorded on the corresponding eCRF page.

6.5.3 Follow-up for toxicities

Not applicable

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Drugs administered at Week 104E1 and other drugs/procedures continuing or started during the extension roll over visit will be entered in the concomitant medications or significant non-drug therapies eCRF page.

For visits where treatment is administered at site: compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 6.5.2. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

For visits where treatment is administered at home: The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with secukinumab (AIN457) as detailed in pharmacokinetics section.

6.6.2 Emergency breaking of assigned treatment code

Not applicable

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs Section 6.1.1.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.8 Administration

Secukinumab solution for s.c. injection will be provided in PFS. One s.c. injection should be self-administered at each visit / time-point (secukinumab 75mg in 0.5mL or secukinumab 150mg in 1mL) until (and including Week 308). Starting at Week 108 only one or two s.c. injections would be dispensed for each dosing time point, depending on the secukinumab dose the patient is assigned to by the investigator.

Subjects will be instructed at Week 104E1 by site staff on how to self-inject secukinumab via PFS, in accordance with the Instructions for use (IFU). The study treatment solution should be injected subcutaneously into an appropriate injection site, and each injection should be given at a different site.

Each new injection should be given at least one inch from the previously used site. If the subject chooses the abdomen, 2 inches area around navel should be avoided. Investigational treatment should not be injected into areas where the skin is tender, bruised, red, or hard, or where the subject has scars or stretch marks. Injection sites should be rotated to reduce the risk of reaction.

Single syringes will be packed in individual boxes. The boxes containing the PFS with study treatment solution should be kept at 2 to 8°C (36°F to 46°F, do not freeze) and protected from light. Prior to administration, the unopened boxes containing the PFS should be allowed to come to room temperature in a place protected from light for approximately 20 minutes. Used syringes should be disposed immediately after use in a sharps container OR according to the regulatory requirements in the respective country.

The caregiver or site staff will administer the injection only to those subjects who are not able to self-administer the PFS injection.

6.8.1.1 Handling of study treatment and additional treatment

6.8.2 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's brochure. 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 (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

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. Patients will be asked to return all unused study treatment and packaging 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 study treatment, 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.

6.8.3 Handling of additional treatment

Not applicable

6.9 Instruction for prescribing and taking study treatment

The first study treatment administration will occur at the Week104E1 visit after inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn.

Starting at Week 108 of extension study the patients will be allowed to self-administer or parent/guardian can inject the patient with the PFS at home or continuing with administration at site, based on personal preference and the investigator's clinical judgment, only if they have exhibited correct use for self-administering the PFS at the site.

At such time points, a patient or parent/guardian would be allowed to administer study medication after having received proper training by site staff and having exhibited ability to perform the injection procedure to the patient at the site.

It should be recorded on the corresponding eCRF(s) whether the patient self-administered the PFS and whether it was administered at home or at the site.

Study treatment may be self-administered by patient or can be administered by parent/guardian subcutaneously every four weeks throughout the study at all site/optional home visits. The parent/guardian or site staff will administer the injection only to those patients who are not able or feel insecure to self-administer the PFS injection.

All study medication packages assigned to the patient during the study will be in the IRT database. It shall be recorded on the corresponding eCRF(s) whether the patient self-administered the PFS, or whether site staff or the caregiver administered the PFS and whether it was administered at home or at site.

For those who wish to self-inject, initially self-injection by patient or by parent/guardian will take place under the supervision of a site staff member. At Week 104E1 visit the patients, parent/guardian will be instructed by the site staff, using the Instructions for use (IFU), on how to self-inject or inject the patient via PFS.

The copy of the PFS will be provided by site staff to the patient, parent/guardian. Detailed instructions for self-administration of study treatment will be described in the Instructions for use (IFU). Patients, parent/guardian will be asked to raise questions (if any), and then to proceed with self-injection or injection to the patient.

At subsequent site visits, patients, parent/guardian will be asked to refer to the Instructions for use (IFU) and to proceed with self-injection or injecting the patient.

At each subsequent study visit at site, all study assessments, including the completion of Patient Reported Outcomes (PROs) and pre-dose blood sample collection (wherever required), should be completed prior to the self-administration of the study treatment.

All dosages dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number. For those patients who opt for domiciliary / home administrations (at protocol specified time points) site staff will dispense (via IRT), at the prior site visit, an appropriate number of investigational treatment packages for the applicable upcoming domiciliary administrations.

If the subject is not able / not confident to self-administer the PFS, and the caregiver is unable/unwilling to perform the injection, he/she should visit the site every 4 weeks during the treatment period and site staff will administer the PFS.

Administration of study treatment must occur only after the study assessments for the visit have been completed (when these visits occur at site), and with the timing indicated in Table 8 -1 (Assessment Schedule).

For extension study the first study treatment administration will occur at the Week 104E1. At each subsequent site visit, all study assessments (as applicable per Table 8-1) should be completed prior to the injection of study treatment. Administration of study treatment should occur after sample collection for PK assessments (at visits specified in Table 8-1).

All investigational treatment kits assigned by the IRT will be recorded in the IRT. The Investigator must promote compliance by instructing the patient/guardian to attend the study visits as scheduled and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient/guardian should be instructed to contact the Investigator if he/she is unable for any reason to attend a study visit as scheduled.

Should a visit be delayed, every attempt should be made to bring the patient back on schedule for the next visit (referring to Baseline visit of core trial).

7 Informed consent procedures

Patients from core CAIN457F2304 study can participate in this optional, open label extension study after providing personally signed and dated written informed consent form, (witnessed, where required by law or regulation and IRB/IEC approved.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any extension study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must 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 guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Females of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy was to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an “X” or “S”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled 4 weeks after last study drug administration for the Week 312/EOT visit. At this visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF. The patient should then return for the final follow up visit 12 weeks after last drug administration. Week 320/PWD (Premature Withdrawal of Subject) at which time all of the assessments listed for the final visit will be performed.

Table 8-1 Assessment Schedule

Period	Extension Treatment (Year 1)													
Visit Name	**W104E1**	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**
Weeks	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Days	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Informed consent	X[14]													
Inclusion / Exclusion criteria	X[14]													
Patients details entry in extension database	X[14]													
Relevant Medical History /Current Medical Condition	X[14]													
Ongoing / Concomitant Medications and Non-Drug Therapies	X[14]													
Physical Examination				S			S			S				S
Body Height				X			X			X				X
Body Weight	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Blood Pressure				X			X			X				X
Pulse rate				X			X			X				X

Period	Extension Treatment (Year 1)													
Visit Name	**W104E1**	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**
Weeks	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Days	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Electrocardiogram (ECG)[1](Local)														S
Hematology				X			X			X				X
Clinical Chemistry				X			X			X				X
Urinalysis local dipstick				X			X			X				X
Urinalysis (microscopic analysis)	X[12]													
Lipid profile (fasting)				X			X			X				X
C-reactive protein[2](Local)				X			X			X				X
PK blood collection[3]							X							X
Immunogenicity[4]							X							X
Urine pregnancy dipstick test (for females of childbearing potential)				S			S			S				S
Serum pregnancy test (for females of childbearing potential)	X[5]													

Period	Extension Treatment (Year 1)													
Visit Name	**W104E1**	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**
Weeks	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Days	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Adverse Events	X	Update as necessary												
Serious Adverse Events	X	Update as necessary												
Roll Over - Enrollment to Extension Study (Contact IRT)	X[14]													
Contact IRT [6]		X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Dose administration[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Site Visit (Mandatory)	X			X			X			X				X
Site/Home Visit[8]		X	X		X	X		X	X		X	X	X	
Physician global assessment of disease activity (PGA) VAS[9]				X			X			X				X
CHAQ© - Including parent's /patients Global Assessment of patients overall well-being (VAS)				X			X			X				X
Active joint count[13]				X			X			X				X

Period	Extension Treatment (Year 1)													
Visit Name	**W104E1**	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**
Weeks	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Days	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Tender and Swollen Joint Count				X			X			X				X
Joint count with limited range of motion				X			X			X				X
Assessment of morning stiffness due to ERA/JPsA				X			X			X				X
Assessment of Uveitis				X			X			X				X
Tot. Enthesitis count				X			X			X				X
Tot. Dactylitis count				X			X			X				X
Study treatment completion information														
Study completion information[10]														

Period	Extension Treatment (Year 2)												
Visit Name	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	**W208**
Weeks	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**
Physical Examination						S							S
Body Height						X							X
Body Weight	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Blood Pressure						X							X
Pulse rate						X							X
Electrocardiogram (ECG)[1](Local)													S
Hematology						X							X
Clinical Chemistry						X							X
Urinalysis						X							X
Urinalysis (microscopic analysis)	X[12]												
Lipid profile (fasting)						X							X
C-reactive protein[2](Local)						X							X
PK blood collection[3]						X							X

Period	Extension Treatment (Year 2)												
Visit Name	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	**W208**
Weeks	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**
Immunogenicity[4]						X							X
Urine pregnancy dipstick test (for females of childbearing potential)						S							S
Serum pregnancy test (for females of childbearing potential)	X[5]												
Adverse Events	Update as necessary												
Serious Adverse Events	Update as necessary												
Contact IRT [6]	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Dose administration[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Site Visit (Mandatory)			X			X			X				X
Site/Home Visit[8]	X	X		X	X		X	X		X	X	X	
Physician global assessment of disease activity (PGA) VAS[9]						X							X
CHAQ© - Including parent's /patients Global						X							X

Period	Extension Treatment (Year 2)												
Visit Name	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	**W208**
Weeks	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**
Assessment of patients overall well-being (VAS)													
Active joint count[13]						X							X
Tender and Swollen Joint Count						X							X
Joint count with limited range of motion						X							X
Assessment of morning stiffness due to ERA/JPsA						X							X
Assessment of Uveitis						X							X
Tot. Enthesitis count						X							X
Tot. Dactylitis count						X							X
Study treatment completion information													
Study completion information[10]													

Period	Extension Treatment (Year 3)												
Visit Name	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	**W256**	**W260**
Weeks	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Physical Examination						S							S
Body Height						X							X
Body Weight	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Blood Pressure						X							X
Pulse rate						X							X
Electrocardiogram (ECG)[1](Local)													S
Hematology						X							X
Clinical Chemistry						X							X
Urinalysis						X							X
Urinalysis (microscopic analysis)	X[12]												
Lipid profile (fasting)						X							X
C-reactive protein[2](Local)						X							X
PK blood collection[3]						X							X

Period	Extension Treatment (Year 3)												
Visit Name	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	**W256**	**W260**
Weeks	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Immunogenicity[4]						X							X
Urine pregnancy dipstick test (for females of childbearing potential)						S							S
Serum pregnancy test (for females of childbearing potential)	X[5]												
Adverse Events	Update as necessary												
Serious Adverse Events	Update as necessary												
Contact IRT [6]	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X[11]	X
Dose administration[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
Site Visit (Mandatory)			X			X			X				X
Site/Home Visit[8]	X	X		X	X		X	X		X	X	X	
Physician global assessment of disease activity (PGA) VAS[9]						X							X
CHAQ© - Including parent's/patients						X							X

Period	Extension Treatment (Year 3)												
Visit Name	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	**W256**	**W260**
Weeks	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**
Days	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**
Global Assessment of patients overall well-being (VAS)													
Active joint count[13]						X							X
Tender and Swollen Joint Count						X							X
Joint count with limited range of motion						X							X
Assessment of morning stiffness due to ERA/JPsA						X							X
Assessment of Uveitis						X							X
Tot. Enthesitis count						X							X
Tot. Dactylitis count						X							X
Study treatment completion information													
Study completion information[10]													

Period	Extension Treatment (Year 4)														
Visit Name	**W264**	**W268**	**W272**	**W276**	**W280**	**W284**	**W288**	**W292**	**W296**	**W300**	**W304**	**W308**	**Unscheduled Visit**	**W312 TD/EOT**	**EOS/PSW Follow-UpW320**
Weeks	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**NA**	**208**	**216**
Days	**1120**	**1148**	**1176**	**1204**	**1232**	**1260**	**1288**	**1316**	**1344**	**1372**	**1400**	**1428**	**NA**	**1456**	**1512**
Physical Examination						S						S	S	S	S
Body Height						X						X	X	X	X
Body Weight	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X	X	X
Blood Pressure						X						X	X	X	X
Pulse rate						X						X	X	X	X
Electrocardiogram (ECG)[1](Local)														S	
Hematology						X						X	X	X	X
Clinical Chemistry						X						X	X	X	X
Urinalysis						X						X	X	X	X
Urinalysis (microscopic analysis)	X[12]														
Lipid profile (fasting)						X						X	X	X	
C-reactive protein[2] (Local)						X						X	X	X	
PK blood collection[3]						X						X	X	X	

Period	Extension Treatment (Year 4)														
Visit Name	**W264**	**W268**	**W272**	**W276**	**W280**	**W284**	**W288**	**W292**	**W296**	**W300**	**W304**	**W308**	**Unscheduled Visit**	**W312 TD/EOT**	**EOS/PSW Follow-UpW320**
Weeks	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**NA**	**208**	**216**
Days	**1120**	**1148**	**1176**	**1204**	**1232**	**1260**	**1288**	**1316**	**1344**	**1372**	**1400**	**1428**	**NA**	**1456**	**1512**
Immunogenicity[4]						X						X	X	X	
Urine pregnancy dipstick test (for females of childbearing potential)						S						S	S	S	S
Serum pregnancy test (for females of childbearing potential)	X[5]														
Adverse Events	Update as necessary													X	X
Serious Adverse Events	Update as necessary													X	X
Contact IRT [6]	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X[11]	X	X	X	
Dose administration[7]	X	X	X	X	X	X	X	X	X	X	X	X			
Site Visit (Mandatory)			X			X			X			X	X	X	X
Site/Home Visit[8]	X	X		X	X		X	X		X	X				
Physician global assessment of disease activity (PGA) VAS[9]						X						X	X	X	
CHAQ© - Including parent's						X						X	X	X	

Period	Extension Treatment (Year 4)														
Visit Name	**W264**	**W268**	**W272**	**W276**	**W280**	**W284**	**W288**	**W292**	**W296**	**W300**	**W304**	**W308**	**Unscheduled Visit**	**W312 TD/EOT**	**EOS/PSW Follow-UpW320**
Weeks	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**NA**	**208**	**216**
Days	**1120**	**1148**	**1176**	**1204**	**1232**	**1260**	**1288**	**1316**	**1344**	**1372**	**1400**	**1428**	**NA**	**1456**	**1512**
/patients Global Assessment of patients overall well-being (VAS)															
Active joint count[13]						X						X	X	X	
Tender and Swollen Joint Count						X						X	X	X	
Joint count with limited range of motion						X						X	X	X	
Assessment of morning stiffness due to ERA/JPsA						X						X	X	X	
Assessment of Uveitis						X						X	X	X	
Tot. Enthesitis count						X						X	X	X	
Tot. Dactylitis count						X						X	X	X	
Study treatment completion information														X	
Study completion information[10]															X

X = Assessment to be recorded in the clinical database or received electronically from a vendor
S = Assessment to be recorded in the source documentation only
1 = ECG to be collected locally at the end of every year
2 = CRP will be measured at the local lab, including during unscheduled visit, and the actual sample collection date, time and result will be collected.
3 = PK – Pharmacokinetic samples should be obtained prior to study drug administration. 2 aliquots to be collected at each scheduled visit
4 = IG - Immunogenicity samples should be obtained prior to study drug administration. 2 aliquots to be collected at each scheduled visit
5 = Only if positive pregnancy urine dipstick test, samples to be collected and shipped to central lab
6 = IRT to be contacted based on type of visit

a. For Site administration:- Contact IRT every week
b. For Home administration:- Contact IRT at the previous site visit and collect drug for subsequent home visits.

7 = Study drug administration is to be done after all assessments are completed. All dose escalations are allowed only at mandated site visits. For patients escalated to 150 mg or 300 mg, no dose reduction can be performed at a later stage.
8 = Starting Week 108 patients will have the choice of self-administration or injection by parent /guardian (once trained) at home visits in which there are no scheduled site assessments or they can come to the site if they are not able or feel insecure to self-administer.
9= In order to prevent bias, the physician's global assessment of disease activity (VAS) should be completed prior to the investigator reviewing the parent's /patients Global Assessment of disease activity (which is completed as part of the CHAQ©).
10 = If patients decides to discontinue study at any point of time, the patients would need to complete the follow-up visit 12 weeks after the last dose.
11 = Weight to be taken and IRT to be contacted if the patient comes for site administration
12 = If the dipstick result is positive for protein, glucose and/or blood, a urine sample will be sent to central laboratory for microscopic analysis.
13 = The site will need to submit the joint count assessment worksheet to central vendor for ACR pediatric response at each scheduled visit, the results will be communicated to the investigator.
14= Assessment required only at first visit, not listed for the subsequent year.

8.1 Screening

There is no screening and re-randomization in this extension study. At Week 104, all eligible patients from the core study can opt to be enrolled in the extension study via Interactive Response Technology (IRT). They will continue to receive secukinumab dosing, which is assigned based on their weight.

The Week 104E1 will be performed on the same day once the Week 104 is completed by patient. Patients must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any extension study assessments are performed.

The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will then specify a unique medication number for the first package of investigational treatment to be dispensed to the patient for Week 104E1.

8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristics will NOT be separately captured in the extension database, patient No. from core CAIN457F2304 study will be the only information captured.

Investigators will have the discretion to record ongoing medical history in the extension database whenever in their judgment.

Investigator does have to capture all ongoing AE and concomitant medication at Week 104 of core trial to the extension study database.

8.3 Efficacy

The efficacy outcome measures used in this study are standard measures used across JIA trials.

- JIA ACR 30, 50, 70, 90 and 100 response criteria
- Physician's Global Assessment of disease activity (VAS)
- Parent's/patient's Global Assessment of patient's overall well-being (VAS included within CHAQ©)
- Childhood Health Assessment Questionnaire (CHAQ©)
- Active joint count
- Swollen Joint Count (SJC)
- Tender Joint Count (TJC)
- Joint count with limited range of motion
- CRP (local)
- Inactive disease status
- JADAS score
- Total dactylitis count
- Total enthesitis count
- [redacted]

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

Table 8-2 Efficacy outcome measures and related assessments

Outcome measure	Relevant section	Efficacy assessment										[redacted]	
		CHAQ© * including parent's/patient's Global Assessment (VAS)	Physician global assessment (VAS)	Active Joint count	Tender and Swollen Joint Count	Joint count with limited range of motion	C-reactive protein	Assessment of morning stiffness due to ERA/JPsA	Uveitis	Tol. Enthesitis count	Tol. Dactylitis count		PK blood collection
		Section 16.6 Section 8.3.1.2 & 3	Section 16.5 Section 8.3.1.1	Section 8.3.1.4	Section 8.3.1.7	Section 8.3.1.5	Section 8.3.1.6	Section 8.3.4	Section 8.3.5	Section 8.3.6	Section 8.3.7		Section 8.5.2
JIA ACR Response	Section 16.8 Section 8.3.1	X	X	X	X	X	X						
JIA ACR 50/70/90/100 JIA ACR Core Components	Section 16.8 Section 8.3.1	X	X	X	X	X	X						
Inactive Disease Status	Section 8.3.2							X	X				
JADAS Score	Section 8.3.3	X	X	X	X	X	X						
Total Enthesitis count	Section 8.3.6									X			
Total Dactylitis count	Section 8.3.7										X		
Secukinumab serum concentrations and derived PK parameters	Section 8.5.2												X

8.3.1 JIA ACR response criteria

Standard ACR pediatric Criteria (JIA ACR criteria) consists of 6 core components which will be assessed as scheduled in Table 8-1. JIA ACR 30/50/70/90/100 are defined as 30%, 50%, 70%, 90% and 100% improvement from baseline of core study CAIN457F2304 respectively in a minimum of three variables in the core set with no more than one variable worsening more than 30% as defined in the ACR criteria.

The 6 core set variables are summarized below:

- Physician global assessment of disease activity on a 0 - 100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity
- Parent or patient's (if appropriate in age) Global Assessment of patient's overall well-being on a 0-100 mm VAS from 0 mm = very well to 100 mm = very poor.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ©)
- Number of active joints using the ACR definition (any joint with swelling or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity)
- Number of joints with limited range of motion
- Laboratory measure of inflammation: CRP (local) (mg/L)

The respective response variables listed above will be used by a central vendor to determine ACR Pediatric response. These results will be communicated to the investigator. Additionally, these components will be used to determine JADAS and inactive disease status (Wallace et al 2011) as part of secondary [redacted] analyses.

8.3.1.1 Physician's Global Assessment of disease activity (VAS)

The physician will rate the patient's current condition on a 0-100 mm VAS Section 16.5, ranging from no disease activity (0 mm) to very severe disease activity (100 mm), at each scheduled visit for all patients throughout the study.

Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left. To enhance objectivity, the physician must not be aware of the specific parent's or patient's global assessment of patient's overall well-being, when performing his own assessment on that patient.

8.3.1.2 Parent's/patients Global Assessment of patients overall well-being (VAS)

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

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

8.3.1.3 Childhood Health Assessment Questionnaire (CHAQ©)

The Childhood Health Assessment Questionnaire (CHAQ©), Section 16.6, will be used to assess physical ability and functional status of patients as well as quality of life. The disability dimension consists of multiple choice and VAS items concerning difficulty in performing eight

common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from four response categories, ranging from 'without any difficulty' to 'unable to do'.

This questionnaire should be completed by the parent (or, for patients 18 years and older, the questionnaire will be completed together by both the patient and parent) according to schedule in Table 8-1.The (CHAQ©) will be completed only in a validated version of the instrument in the language understandable to the parent and/or patient.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 10.1.1 and Section 10.1.2 of the protocol. Investigators should not encourage the patients and/or parents to change the responses reported in the PRO questionnaires.

8.3.1.4 Active joint count

The number of joints with active arthritis at each visit will be determined by applying the ACR definition to the number of joints with swelling, tenderness and limited range of motion at each scheduled visit for all patients throughout the study (see Section 8.3.1.5 and Section 8.3.1.7 for more details).

Joint counts will be performed by an assessor who must be well trained and part of the site personnel. For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

The ACR definition of active arthritis is any joint with swelling or, in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity. The active joint count will therefore range from 0 to 73.

The site will need to submit the joint count assessment worksheet to central vendor for ACR Pediatric response at each scheduled visit per Table 8-1, the results will be communicated to the investigator.

8.3.1.5 Joint counts with limitation of motion

A total of 69 joints will be assessed for limitation of motion at each scheduled visit for all patients throughout the study. The same 75 joints assessed for tenderness (Section 8.3.1.7) will also be assessed for limitation of motion excluding the 2 sternoclavicular, 2 acromioclavicular joints as well as the 2 sacroiliac joints.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

8.3.1.6 C-reactive Protein (CRP)

C-reactive Protein CRP (local) is used as an inflammation marker, to determine its severity, and to monitor response to treatment.

CRP (local) will be measured at the local lab, at each scheduled visit for all patients throughout the study including during unscheduled visit, and the actual sample collection date, time and result will be collected.

8.3.1.7 Tender and Swollen Joint Count

Tender 75 joint counts (TJC)

The following 75 joints will be scored as either tender or not tender:

- Temporomandibular joints: 2
- Sternoclavicular joints: 2
- Acromioclavicular joints: 2
- Shoulders: 2
- Elbows: 2
- Wrists: 2
- Hands:
  - 8 Distal interphalangeal
  - 10 proximal interphalangeal
  - 10 metacarpophalangeal
- Hips: 2
- Knees: 2
- Ankles: 2
- Subtalar joints: 2
- Intertarsal joints: 2
- Feet:
  - 10 metatarsophalangeal joints
  - 10 toes
- Cervical spine is assessed as a single joint
- Thoracic spine is assessed as a single joint
- Lumbar spine is assessed as a single joint
- Sacroiliac joints: 2

Joint tenderness is to be scored as present or absent. For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

Swollen joint count (SJC)

A total of 68 joints are to be scored as either swollen or not swollen. The same 75 joints assessed for tenderness will also be assessed for swelling excluding the cervical spine, thoracic spine, lumbar spine, 2 hips and 2 sacroiliac joints.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

8.3.2 Inactive Disease Status

Clinical inactive disease definition is adapted from the ACR criteria of (Wallace et al 2011). All must be met:

- No joints with active arthritis
- No uveitis
- CRP (local) value within normal limits for the laboratory where tested or, if elevated, not attributable to ERS/JPsA Physician's global assessment of disease activity score of best possible on the scale used (i.e. best possible score is defined as ≤ 10mm)
- The absence of patient-reported morning stiffness attributable to JPsA or ERA lasting ≥15 minutes.

8.3.3 Juvenile Arthritis Disease Activity Score (JADAS)

Juvenile Arthritis Disease Activity Score (JADAS) (Consolaro et al 2009) will be derived from the following assessments performed at all scheduled visits:

- physician global assessment of disease activity;
- parent/patient global assessment of overall well-being;
- active joint count;
- Tender and Swollen Joint Count;
- CRP (local)

8.3.4 Assessment of duration of morning stiffness

The presence or absence of patient/parent-reported morning stiffness that day attributable to JPsA or ERA lasting at least 15 minutes will be assessed as part of evaluation of inactive disease status.

8.3.5 Assessment of Uveitis due to JIA

The presence or absence of uveitis that day will be assessed as part of evaluation of inactive disease status. Clinically suspected uveitis should be confirmed as per the Standardization of Uveitis Nomenclature (SUN) Working Group definition. No uveitis is defined as "grade zero cells," indicating < 1 cell in field sizes of 1 mm by a 1 mm slit beam (Zierhut 2007).

8.3.6 Total enthesitis count

The following 16 entheseal sites will be assessed for the presence or absence of tenderness (enthesitis) on each side of the body:

- Anterior Entheses: Greater trochanter of the Femur; Medial condyle of the femur; Lateral condyle of the femur
- Posterior Entheses: Greater tuberosity of humerus; medial epicondyle of humerus; lateral epicondyle of humerus, Achilles tendon; and calcaneal insertion of the plantar fascia.

8.3.7 Total dactylitis count

The dactylitis count is the number of fingers and toes presenting with dactylitis, with a range of 0-20.

[redacted]

8.3.9 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are standard measures recognized by the scientific community and used across many JIA trials.

8.4 Safety

Evaluation of all AEs and SAEs including injection site reactions, abnormal findings in ECGs, physical examination, vital signs, and laboratory assessments will occur. Anti-secukinumab antibody development (immunogenicity) will also be evaluated.

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

- Evaluation of AE/ SAEs
- Physical examination
- Vital signs
- Height and weight
- Electrocardiogram (local)
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- Immunogenicity

8.4.1 Physical examination

The physical examination will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site system. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF page. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event section of the eCRF.

8.4.2 Vital signs

This will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

Clinically notable vital signs are defined in Section 16.1.

8.4.3 Height and weight

Height in centimeters (cm) will be assessed with the patient wearing indoor clothing, but without shoes, socks, hats or hair accessories interfering with assessment, 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.

Body weight (to the nearest 0.1 kilogram (kg) will be assessed with the patient wearing similar clothing (indoor clothing but without shoes) at each visit and where possible, by the same study site staff member using the same scale throughout the study.

8.4.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except dipstick urinalysis and CRP which are done locally). Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Section 16.1. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

8.4.4.1 Hematology

Hematology will include hemoglobin, hematocrit, platelets, red blood cell (RBC), white blood cell (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophil, at scheduled visits as per assessment schedule in Table 8-1.

8.4.4.2 Clinical chemistry

Serum chemistries will include sodium, potassium, bicarbonate, BUN/urea, creatinine, glucose, calcium, phosphorus, total protein, albumin, total bilirubin (TBL), ALT (SGPT), AST (SGOT), GGT (Gamma-glutamyl transferase), alkaline phosphatase (ALP) and uric acid will be measured at scheduled visits as per assessment schedule in Table 8-1.

8.4.4.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments at scheduled visits as per Table 8-1. The urinalysis results for standard parameters such as glucose, protein, blood and WBC will be recorded in the appropriate eCRF page.

If the dipstick result is positive for protein, glucose and/or blood a urine sample will be sent to central laboratory for microscopic analysis as indicated in the renal safety Section 10.2.2.

8.4.4.4 Lipid panel

A lipid profile including total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), and triglycerides will be measured from a fasting blood sample that will be collected at scheduled visits as per assessment schedule in Table 8-1.

8.4.5 Electrocardiogram (ECG)

A standard 12-lead ECG (local) will be performed as indicated in Table 8-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection followed by vital signs and blood sampling. The Frederica's QT correction formula (QTcF) should be used for clinical decisions.

All ECGs will be collected locally at site .The investigator must maintain source ECG documents for each patient in the study. Information for all ECGs examinations must be included in the source documentation at the study site system. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event section of the eCRF.

8.4.6 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female adolescents who are menarchal or who become menarchal during the study.

A serum β-hCG test will be performed only if there is positive urine dipstick test.

Urine pregnancy tests are performed at visits indicated in Table 8-1 in all female patients of child-bearing potential. Additional pregnancy tests may be performed at the investigator's discretion during the study. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from study drug.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

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

Female patients of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study and for 20 weeks after study completion. At a minimum, the acceptable effective contraception is:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)

- Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK (United Kingdom): with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception Female should have been stable on the same pill for a minimum of 3 months before taking study treatment
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, the sterile reproductive status of the woman must have been tested by follow up hormone level assessment

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 and the need for additional pregnancy testing.

8.4.7 Tolerability of secukinumab

Tolerability will be assessed by adverse events, laboratory values, injection site reactions and immunogenicity.

8.4.8 Immunogenicity

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 8-1.

In addition, if a patient discontinues from the study at any time, he/she will need to provide a sample at the last visit. The actual sample collection date and exact time will be entered on the Immunogenicity Blood collection eCRF page. Sampling problems will be noted in the Comment section of the eCRF page.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

A laboratory manual will be provided to investigators with detailed information on sample collection, handling and shipment.

Tubes and preprinted labels will be provided by the central lab to the sites.

Analytical Method

An electrochemiluminescence method will be used for the detection of potential anti-secukinumab 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.

Table 8-3 IG sample log

Week	IG Sample number
W128	306
W156	307
W180	308
W208	309
W232	310
W260	311
W284	312
W308	313
W312	314
Unscheduled[1]	4001....

1= If an IG sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 4001, 4002, etc.

8.4.9 Other safety evaluations

Not applicable.

8.4.10 Appropriateness of safety measurements

The safety measures used in this study are standard for a use of a biologic in patients with JPsA / ERA and are standard and adequate for this indication/patient population. The frequency of the visits and the close medical monitoring will ensure possible safety concerns are properly addressed.

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be obtained for all patients and the secukinumab concentrations will be assessed in serum. The PK samples will be collected pre-dose at scheduled visits/time points as indicated in Table 8-1.

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

The actual sample collection date and exact time will be entered on the PK blood collection summary eCRF page. Sampling problems will be noted in the Comments section of the eCRF page.

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The bioanalyst will provide the samples' concentration data to the team under blinded conditions. Bioanalyst will keep this information confidential until clinical database lock.

PK sample handling, labeling and shipment instructions

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 information pre-printed on the label**.**

Analytical methods

An ELISA (enzyme-linked immunosorbent assay) method will be used for bioanalytical analysis of secukinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. The detailed method description to assess secukinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

Table 8-4 PK sample log

Week	Time	Sample number	Dose reference ID
W128 [1]	pre-dose	91	1
W156 [1]	pre-dose	92	1
W180 [1]	pre-dose	93	1
W208 [1]	pre-dose	94	1
W232 [1]	pre-dose	95	1
W260 [1]	pre-dose	96	1
W284 [1]	pre-dose	97	1
W308 [1]	pre-dose	98	1
W312 [1]	(Any time at visit)	99	1
Unscheduled	Pre-dose	2001...	

1=Required samples in every patient.

If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern: 2001, 2002, etc.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration i.e. Week 308, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Patient/parent/guardian decision
- Physician decision
- Adverse Event
- Lack of efficacy

- Loss to follow up
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the patient

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent Section 9.1.2). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up Section 9.1.3 This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Patients in consultation with the guardian or the guardian may voluntarily withdraw patient's consent to participate in the study for any reasons at any time, without being obliged to give any explanation. Withdrawal of consent from the study is defined as when a patient/guardian:

- Does not want to participate in the study anymore, and
- Discontinues all elements outlined in the protocol, 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 (e.g. telephone, e-mail, letter) to determine the primary reason for the patient/guardian'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. All biological material that has not been analyzed at the time of withdrawal must not be used.

Further attempts to contact the patient 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 patient's study withdrawal should be made as detailed in Table 8-1.

This up to 4 year extension study will offer continuous secukinumab therapy to eligible patients from the core study CAIN457F2304. Patients from core study CAIN457F2304 can participate in this optional, open label extension study for a minimum of one year or until one of the following conditions are met, whichever is earlier: the drug is locally approved, marketed, and reimbursed, OR– secukinumab can be provided free of charge to patients in compliance with local guidelines, OR– a maximum of 4 years study duration.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient/guardian, e.g. dates of telephone calls, registered letters, etc. A patient can not be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

9.1.4 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. In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, the patient must be seen as soon as possible and treated as a premature patient/subject withdrawal (PSW) provide instruction to the patient, when the patient should stop taking drug, when the patient should come for a final visit (see Table 8-1). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator/Novartis depending on local regulation will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

9.2 Study completion and post-study treatment

A patient will be considered "Treatment Completed" ONLY when the patient has received all doses at each visit as per Table 8-1.

If patient discontinues the study treatment due to any of the criteria as described in Section 9.1.1, the patient would be captured at premature discontinuation of the treatment and still needs to come for the follow up visit at Week 320.

A patient will considered "Study Completed" ONLY when the patient has completed all of the scheduled study assessment and procedures at Week 320 visit.

Information on the patient's completion or premature discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate eCRF page. Additionally, the investigator or site staff must contact the IRT as soon as possible to record the patient's study completion and/or discontinuation.

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's brochure (IB).

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 of core study CAIN457F2304 or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Section 16. 1.

Adverse events must be recorded in the Adverse Events CRF page 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 (no/yes), or other treatment (no/yes), or both, or indistinguishable
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (see Section 10.1.2 for definition of SAE)
- action taken regarding investigational treatment

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

- no action taken (e.g. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted
- investigational treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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.

Information about common side effects already known about the investigational drug can be found in the Investigator's brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient/guardian 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 Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient/guardian.

The Investigator must also instruct each patient/guardian to report any new adverse event (beyond the protocol observation period) that the patient/guardian, or the patient'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.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". 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.

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks after last administered dose of study treatment or 30 days after the patient has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this period should only be reported to Novartis if the Investigator suspects a causal relationship to study treatment.

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 the 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 resolved or continues, if and how it was treated, whether the blind was broken or not, 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 Novartis Chief Medical Office & Patient Safety (CMO&PS) 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 (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

To ensure patient 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 and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment, any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

10.1.5 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, patient 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 DAR (dose administration record) eCRF 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 within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

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

Please refer to Table 16-3 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-3 in Section 16.2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-4.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If

a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

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

For the liver events:

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

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy; based on investigator's discretion.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF pages.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24hours) increase in serum creatinine of ≥25% compared to baseline of core study CAIN457F2304 which exceeds the normal limits for the patient's gender and age during normal hydration status and continues for ≥3 consecutive months.
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 16-5 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.3.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed

or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Adapted ACR Pediatric response will be determined centrally from data (ACR components) provided by the investigator. These will be derived and communicated to the investigator the same day.

The investigator/designee is responsible for assuring that the data recorded on CRFs (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

11.2 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 are required to respond promptly to queries and confirm or make any necessary changes to the data.

Concomitant treatments and medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of 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/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data

and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 patients will be disclosed.

12 Data analysis and statistical methods

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

All data will be summarized descriptively for all patients, by dose groups and/or possibly by JPsA and ERA subtypes.

Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patient in each category will be presented. The 95% confidence intervals will be provided as appropriate to evaluate the efficacy of the treatment regimens.

12.1 Analysis sets

The following analysis sets will be used in this trial:

The Full Analysis Set (FAS) will consist of all patients who came from core trial and received at least one dose of study drug in the extension trial.

The Safety Set will consist of all patients that received at least one dose of study drug in the extension trial.

12.2 Patient demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for all patients, dose groups and/or possibly by JPsA and ERA subtypes and for all patients in the FAS population of the study. The number and percentage of patients in each category will be presented for categorical variables similarly.

12.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of active injections received will be presented for all patients by dose groups and/or possibly by JPsA and ERA subtypes. In addition, the number and percentage of patients with cumulative exposure levels will be presented.

Concomitant medication

Concomitant medications will be summarized for all patients and by dose groups and/or possibly by JPsA and ERA subtypes. Any medication given at least once between the start of the first dose in this extension trial and the date of the last study visit in the extension study will be a concomitant medication, including those which were started before Week 104E1 and continued into the extension study where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of patients receiving concomitant psoriatic arthritis therapy will be presented for all patients by dose groups , as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to psoriatic arthritis therapies previously.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

Primary objective evaluates the long-term efficacy of secukinumab with respect to JIA ACR30.

12.4.2 Variable(s)

The primary efficacy variable(s) is the clinical response to treatment according to ACR30 improvement in disease activity over time up to Week 312 in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304. ACR response criteria denote the response (i.e. improvement) in signs and symptoms of the disease of a patient compared to baseline of the core study CAIN457F2304 . The analysis of the primary variables will be based on the FAS.

12.4.3 Statistical model, hypothesis, and method of analysis

No formal hypotheses are planned for this study.

The proportion of patients meeting the ACR30 criteria will be descriptively summarized for all patients by dose groups and/or possibly by JPsA and ERA subtypes.. Treatment efficacy will be evaluated by the 95% confidence interval of the proportion of patients responding to treatment according to the ACR criteria.

Results will be presented for the FAS.

12.4.4 Handling of missing values/censoring/discontinuations

Efficacy data will be presented using all available data at the given time point of analysis.

12.4.5 Sensitivity and Supportive analyses

Sensitivity analyses may be performed to assess the robustness of missing data handling. This may include multiple imputations for all baseline and post-baseline efficacy variables of interest during the trial.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy variables

For binary variables, the proportion of responders will be summarized over analysis visits. For continuous variables, the change from baseline of core study CAIN457F2304, when available, will be presented. The 95% confidence intervals will be provided to evaluate the long-term efficacy of the treatments for the secondary variables of interest.

No statistical comparisons between treatments will be provided for the analysis of secondary [redacted].

Secondary variables include:

- JIA ACR 50/70/90/100 and inactive disease status
- Each JIA ACR core component
- Change from baseline of core study CAIN457F2304 of Juvenile Arthritis Disease Activity Score (JADAS)
- Total enthesitis count
- Total dactylitis count

[redacted]

- [redacted]
- [redacted]
- [redacted].

[redacted]

12.5.2 Safety endpoints

Adverse events

Treatment emergent adverse events (i.e. events started after the first dose of secukinumab in core study or events present prior to the first dose of secukinumab but increased in severity based on preferred term and within 84 days after last dose of secukinumab) will be summarized.

AEs will be summarized for all patients by dose groups and/or possibly by JPsA and ERA subtypes, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

[redacted]

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

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

When adjudication is required of major cardiovascular events, a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

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 and laboratory test. Change from baseline will only be summarized for patients with both baseline (of core study) and post-baseline values.

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

In addition, shift tables will be provided for all parameters to compare a patient'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 for all patients by dose groups and/or possibly by JPsA and ERA subtypes. Shifts will be presented by visit as well as for most extreme values post-baseline.

Immunogenicity

A listing of patient's positive for anti-secukinumab antibodies, both binding and neutralizing, will be provided.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented for all patients by dose group and/or possibly by JPsA and ERA subtypes.. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

ECG

Summary statistics will be presented for ECG variables by visit for all patients' dose groups and/or possibly by JPsA and ERA subtypes. Qualitative changes will be summarized.

12.5.3 Pharmacokinetics

All patients with concentration data will be included in the pharmacokinetic data analysis.

Pharmacokinetic variables

The following pharmacokinetic parameter will be determined: Cmin,ss. Cmin,ss will be determined using Phoenix software. Individual serum concentrations in g/mL will be listed. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

During modeling of the pharmacokinetics of secukinumab, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

Statistical methods for pharmacokinetic analyses

Summary statistics by visit/time will be provided for the above mentioned parameter and will include arithmetic and geometric means, standard deviation (SD), median, minimum and maximum. Individual concentrations will be listed by patient.

12.6 Interim analyses

Interim analyses may be performed for purposes of publication and/or to support heath authority interactions, as necessary.

12.7 Sample size calculation

This is an extension study, all patients complete the core study CAIN457F2304 Week 104 and opt to enter the extension trial will be included in final analysis, so no sample size justification is needed.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the Declaration of Helsinki.

13.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board (IRB)/ Independent Ethics Committee (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 must be informed about the study to the extent

possible given his/her understanding. If the patient is capable of doing so, he/she must 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 (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must 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/approval.

Female of child-bearing potential/guardian must 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 must not be entered in the study.

13.3 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, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of 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.

13.4 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.

13.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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 standard operating procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances 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 prohibition, 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.

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.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 10 Safety Monitoring must be followed. Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following defined notable laboratory or vital sign abnormalities, except creatinine clearance, will be communicated at the same time as they are sent to investigators to Novartis. Novartis will determine if further consultations with Investigator(s) are appropriate.

Laboratory Criteria

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

Biochemistry

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

  - ≥5 x ULN,
- Creatinine (serum): ≥1.5 x ULN
- Creatinine clearance (Schwartz formula): ≥ 25% decrease from baseline, ≥3 months in duration
- Protein urine dipstick:
  - New protein ≥1+, ≥3 months in duration
- Creatinine clearance (Schwartz formula): ≥ 25% decrease from baseline, ≥3 months in duration in combination with protein urine dipstick resulting in new protein ≥1+, ≥3 months in duration
- Total Cholesterol: ≥1.5xULN
- Triglycerides: ≥5.7 mmol/L.

Schwartz formula- Creatinine clearance (mL/min/1.73m2) was derived using the following formula 0.413 x length (cm) /(serum creatinine (mg/dL)

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

Vital Signs

The following criteria will be used.

Note: The age is the age at the time of the visit.

Systolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline

Diastolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline

Pulse (bpm):

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline

Note: Only post-baseline values will be flagged as notable abnormalities

Table 16-1 Reference ranges for systolic and diastolic blood pressures and pulse

Age	Systolic Blood Pressure lower and upper limits (mmHg)	Diastolic Blood pressure lower and upper limits (mmHg)	Pulse lower and upper limits (Beats per minute)
2 yrs	84-117	39-72	90-150
3 yrs	86-120	44-76	90-150
4 yrs	88-122	47-79	90-150
5 yrs	89-123	50-82	65-135
6 yrs	91-125	53-84	65-135
7 yrs	92-126	55-86	60-130
8 yrs	94-127	56-88	60-130
9 yrs	95-129	57-89	60-130
10 yrs	97-130	58-90	60-110
11 yrs	99-132	59-90	60-110
12 yrs	101-135	59-91	60-110
13 yrs	104-137	60-91	60-110
14 yrs	106-140	60-92	60-110
15 yrs	107-142	61-93	60-110
16 yrs	108-145	63-94	60-110
17 yrs	108-147	64-97	60-110
18 yrs	108-147	64-97	60-100

Table 16-2 Recommended dimensions for blood pressure cuff bladders

	Width [cm]	Length [cm]	Maximum Arm Circumference [cm]*
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44

* calculated so that the bladder can encircle even the largest arm by at least 80%

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

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

Table 16-3 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*
* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-4 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		

Criteria	Actions required	Follow-up monitoring
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks

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

Criteria	Actions required	Follow-up monitoring
	conmeds, med hx, lab) in the appropriate CRF	

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

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

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

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

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-5 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25% to 49% compared to baseline	Confirm 25% increase after 24h to 48h Follow up within 2 to 5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24h to 48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24h to 48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16.4 Appendix 4: Weight ranges: recommended maximum sample blood volume per blood draw

Recommended maximum blood collections are in accordance with the 2008 EU Commission Guideline on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population. As per the guideline, collections specified in the protocol do not exceed 3% of patients total blood volume during a 4-week period and/or 1% at any single visit. Patients total blood volume is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight, 1% is 0.8 mL blood per kg body weight. The table below outlines the maximum allowable blood volume by weight category. In order to stay within these limits, detailed instructions are provided by the Central Laboratory for all weight categories less than 38 kg. Weight range: Recommended maximum blood volume drawn per visit, and per 4 week period

Weight Range Category (kg)	Maximum Allowable Blood Volume Drawn / visit (mL)	Maximum Allowable Blood Volume Drawn / 4 week period (mL)
7-10	5.6	16.8
>10-12	8.0	24.0
>12-14	9.6	28.8
>14-26	11.2	33.6
>26-38	20.8	62.4
>38	30.4	91.2

16.5 Appendix 5: Physician's global assessment of disease activity (VAS)

The question text below will be shown to and will be answered by the physician. The physician's assessment should be made and recorded without viewing ANY of the patient's assessments. The result of the physician's assessment of the patient's disease activity should be withheld from the patient / parents/guardian so as not to influence his/her own assessment.

The following is the text of the question, but does not represent the final formatting used in the study.

"Considering all the ways ERA/JPsA affects your patient, how would you rate his or her condition today?"

No disease activity	Very severe disease activity
0	100

16.6 Appendix 6: Childhood Health Assessment Questionnaire (CHAQ©)

The following does not represent the final formatting of the CHAQ© used in the study.

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE

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

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

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

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

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

- Dressing and Grooming	☐	- Eating	☐
- Arising	☐	- Walking	☐

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

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

- Raised toilet seat	☐	- Bathtub bar	☐
- Bathtub seat	☐	- Long-handled appliances for reach	☐
- Jar opener (for jars previously opened)	☐	- Long-handled appliances in bathroom	☐

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

- Hygiene	☐	- Gripping and opening things	☐
- Reach	☐	- Errands and chores	☐

PAIN: We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had because of his/her illness IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain

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

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

Very well 0 ——————————— 100 Very poor

16.7 Appendix 7: ILAR classification criteria

	Criteria	Exclusions
JPsA (MODIFIED)	Arthritis and psoriasis, *or* arthritis with two or more of: a. Dactylitis b. Nail pitting or onycholysis c. Psoriasis in a first degree relative	• Presence of IgM RF on at least 2 occasions at least 3 months apart • Presence of systemic JIA
ERA	Arthritis and enthesitis, *or* Arthritis or enthesitis with two or more of: a. Presence of or history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain b. HLA-B27 positivity c. Acute (symptomatic) anterior uveitis d. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative e. Onset of arthritis in a boy over the age of 6 years	• Psoriasis or in first-degree relative • Presence of IgM RF on at least 2 occasions more than 3 months apart • Presence of systemic JIA
JPsA criteria (Petty et al 2004) have been modified by removal of the following 2 exclusions: 1) Arthritis in a HLA-B27 positive male beginning after the sixth birthday and 2) Diagnosis of ankylosing spondylitis, ERA, sacroiliitis with Inflammatory Bowel Disease (IBD), reactive arthritis (Reiter's syndrome), or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.		

16.8 Appendix 8: ACR response criteria

The adapted ACR Pediatric 30/50/70/90/100 criteria will be used to determine efficacy defined as improvement from baseline of at least 30/50/70/90/100% respectively in at least 3 of 6 variables with no more than one variable worsening more than 30% as defined in the ACR criteria.

The components are:

- Physician's Global Assessment of disease activity on a 0-100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity.
- Parent's or patient's (if appropriate in age) Global Assessment of patient's overall well-being on a 0-100 mm VAS from 0 mm= very well to 100 mm= very poor.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ©)

- Number of joints with active arthritis using the ACR definition (The ACR definition of active arthritis is any joint with swelling, or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity)
- Number of joints with limitation of motion
- Laboratory measure of inflammation: CRP (local) (mg/L)

16.9 Appendix 9: Criteria for defining clinical inactive disease

All must be met: Inactive disease:

- No joints with active arthritis
- No Uveitis
- CRP (local) level within normal limits in the laboratory where tested or, if elevated, not attributable to ERA/JPsA
- Physician's global assessment of disease activity score of best possible on the scale used **(**i.e. best possible score is defined as ≤10 mm**)**
- The absence of patient-reported morning stiffness attributable to JPsA or ERA lasting ≥15 minutes

Adapted from (Wallace et al 2011).