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Secukinumab (AIN457)

Clinical Trial Protocol CAIN457F2304 / NCT03031782

A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
AG	Aktien Gesellschaft
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
BDR	Bioanalytical data report
BP	Blood pressure
[redacted]	[redacted]
Cavg	Average concentration
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CFR	US Code of Federal Regulations
CHAQ	Childhood Health Assessment Questionnaire
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP	C-reactive Protein
CS	Corticosteroid
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DDE	Direct data entry
DMARD	Disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency
ERA	Enthesitis-Related Arthritis
[redacted]	[redacted]
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hCG	Human Chorionic Gonadotropin

[redacted]

HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
IA	Interim Analysis
IB	Investigators Brochure
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
[redacted]	[redacted]
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IN	Investigator Notification
INH	isonicotinylhydrazide
INR	International normalized ratio
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
[redacted]	[redacted]
LDL	Low-density lipoprotein
LFT	Liver function test
LLOQ	Lower level of quantification
MedDRA	Medical dictionary for regulatory activities
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OC/RDC	Oracle Clinical/Remote Data Capture
PCR	Polymerase chain reaction
PFS	Prefilled Syringe
PK	Pharmacokinetics
[redacted]	[redacted]
PPD	Purified protein derivative
PsA	Psoriatic Arthritis
PRO	Patient Reported Outcome
PRN	As required
PSW	Premature subject withdrawal
PUVA	Photochemotherapy
QTcF	QTc Interval by Fridericia's equation

[redacted]

RA	Rheumatoid Arthritis
RBC	Red blood cell
REB	Research Ethics Board
RF	Rheumatoid Factor
RU	Healthcare Resource Utilization
SAE	Serious Adverse Event
s.c.	Subcutaneous
sCr	Serum creatinine
SGOT	Serum glutaminc oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SI	Sacroiliac (joint)
SJC	Swollen Joint Count
SNP	Single Nucleotide Polymorphism
SpA	Spondyloarthropathy (or spondyloarthritis)
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	Serum total bilirubin
TD	Study Treatment Discontinuation
tid	Twice daily
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
Tx	Treatment
ULN	Upper limit of normal
UK	United Kingdom
US	United States
UV	Ultraviolet
VAS	Visual Analogue Score
WBC	White blood cell
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
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 (e.g. prior to starting any of the procedures described in the protocol)
Study Period	A portion of the study which serves a specific purpose. Typical periods are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of 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

[redacted]

Amendment 2 (04 Jun 2020)

Amendment rationale

The reason for this amendment is to adapt the protocol to COVID 19 pandemic/epidemic related challenges and the potential impact on the conduct of clinical trials

Changes to the protocol

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

Section 5.5.2 is updated to include text allowing for shipment of IMP to the patient's home during a major health care disruption (e.g., COVID 19 pandemic/epidemic). Section 5.5.4 also includes this language with the addition of guidance on collecting pregnancy test for patients where IMP is shipped to the patient's home and how to report the home administration.

Additional clarifications for instances where the IMP is shipped to the patient's home are added to Section 6 and Section 6.3.

Other minor points have been updated or corrected as well to further optimize the clinical trial protocol.

IRBs/IECs

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

This amended protocol is considered non-substantial as it includes measures in response/relation to the pandemic/epidemic COVID 19 situation and will not be submitted to IRB/IEC approval prior to implementation in line with the guidance from multiple health authorities worldwide.

The changes herein does not affect the main Global Model Informed Consent. Sites are required to submit for approval an additional Informed Consent that takes into account delivery of IMP directly to a participant's home and home administration.

Summary of previous amendments

Amendment 1 (April 2017)

Amendment rationale

At the time of this amendment no subjects have been randomized in the study. No change to the study population is proposed by this amendment

This protocol amendment is issued for the following reason:

1. To clarify and correct errors in the ILAR diagnostic criteria detailed in Appendix 7.

[redacted]

Changes to the protocol

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

The ILAR classification criteria in Section 19, Appendix 7 has been corrected and the supportive reference added.

The wording of the two ILAR classification criteria exclusions for JPsA listed in Section 1.1, Background, have been revised to be consistent with Section 19 Appendix 7. ILAR Classification criteria.

Section 3.1 Study Design and Section 3.5 Purpose and timing of interim analyses/design adaptations it has been clarified that patients that discontinue prior to the Week 12 visit may be replaced.

The definition of study completion and eligibility to enter into an extension study in Section 5.6.1 Study completion and post-study treatment, has been clarified.

Section 6 Visit schedule and assessments the suggested order of assessments has been amended in order for the local laboratory samples, specifically CRP, to be taken first to minimize any delays.

[redacted]

Section 6.4.10 Assessment of Uveitis due to JIA has been clarified that only clinically suspected Uveitis needs to be confirmed using the SUN working group definition.

[redacted]

An omitted criteria has been added to Section 21, Appendix 9: ACR response criteria for correctness and consistency with Section 6.4.1 JIA ACR response criteria.

Typographical errors have been corrected to increase clarity and consistency of the text.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do NOT affect any informed consent form (ICF).

[redacted]

Protocol summary

Protocol number	CAIN457F2304
Title	A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in Juvenile Idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis
Brief title	Secukinumab safety and efficacy in JPsA and ERA
Sponsor and Clinical Phase	Novartis Pharma AG
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate the efficacy and safety of secukinumab treatment in children ≥ 2 to < 18 years of age with active ERA (Enthesitis-Related Arthritis) and JPsA (Juvenile Psoriatic Arthritis) categories of JIA (Juvenile Idiopathic Arthritis) and to demonstrate the sustained efficacy of secukinumab by using a flare prevention design in a double-blind placebo control treatment withdrawal part of the trial. Additionally, this study will evaluate predicted pediatric doses to achieve secukinumab level equivalency of adult 150 mg dosing
Primary Objective(s)	To demonstrate that the time to flare in Treatment Period 2 is longer with secukinumab for combined ERA and JPsA groups than with placebo
Secondary Objectives	1. To evaluate the effect of secukinumab treatment for all patients and each JIA category in Treatment Period 1 up to Week 12 (end of Treatment period 1) with respect to: • JIA ACR (American College of Rheumatology) 30/50/70/90/100 and inactive disease status • Each JIA ACR core component • Change from baseline Juvenile Arthritis Disease Activity Score (JADAS) • Total enthesitis count • Total dactylitis count 2. To evaluate withdrawal effect of secukinumab treatment for all patients and each JIA category during and at the end of Treatment Period 2 with respect to: • JIA ACR 30/50/70/90/100 and inactive disease status 3. To evaluate Pharmacokinetics (PK) of secukinumab and confirm the predicted dose in Treatment Period 1 4. To evaluate the safety/tolerability and immunogenicity of Secukinumab
Study design	This is a double-blind, placebo-controlled, event-driven randomized withdrawal study to investigate the efficacy and safety of secukinumab treatment in the JIA categories of JPsA and ERA. The study is divided into 3 parts (plus a post-treatment follow-up period) consisting of open-label, single-arm active treatment in Treatment Periods 1 and 3 and a randomized, double-blind, placebo controlled, event-driven withdrawal design in Treatment Period 2.
Population	Male and female patients aged from ≥ 2 years to < 18 years who are diagnosed with either enthesitis-related arthritis (ERA) based on fulfilling the ILAR (International League of Associations for Rheumatology) JIA

[redacted]

	classification criteria or JPsA based on fulfilling a modified ILAR JIA classification criteria and who are naïve to biologic treatments.
Key Inclusion criteria	1. Males and females ≥ 2 years old and < 18 years old at the time of screening. 2. Confirmed diagnosis of ERA according to the ILAR classification criteria or JPsA according to the modified ILAR classification criteria that must have occurred at least 6 months prior to Screening. 3. Active disease (ERA or JPsA) defined as having both: • ≥ 3 active joints (swollen or if not swollen must be both tender and limited range of motion) at Baseline. • ≥1 site of active enthesitis at Baseline or documented by history 4. Inadequate response (≥ 1 month) or intolerance to ≥ 1 NSAID (Non-Steroidal Anti-inflammatory Drug) 5. Inadequate response (≥ 2 months) or intolerance to ≥ 1 DMARD (Disease Modifying Anti-rheumatic Drugs) 6. No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of the following agents which must remain at stable dose during trial Treatment Periods 1 and 2. • Stable dose of methotrexate (maximum of 20 mg/ m^2 BSA (body surface area)/ week) for at least 4 weeks prior to the baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the center) • Stable dose of SSZ (Sulfasalazine) (ERA patients only) $\leq$ 50 mg/kg/day with max of 3000 mg/day for at least 4 weeks prior to the baseline visit • Stable dose of an oral corticosteroid (CS) at a prednisone equivalent dose of $\leq$ 0.2 mg/kg/day or up to 10 mg/day maximum, whichever is less, for at least 7 days prior to baseline • Stable dose of no more than 1 NSAID for at least 1 week prior to baseline 7. Negative QuantiFERON (QF) test. Negative Purified Protein Derivative (PPD) test is also acceptable if either required by local guidelines or if the patient is < 5 years of age. A positive PPD is defined as $\geq$ 15mm induration for children $\geq$ 4 years and $\geq$ 10mm for children < 4 years.
Key Exclusion criteria	1. Use of other investigational drugs within 4 weeks or 5 half-lives of Baseline, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer. 2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes. 3. Subjects who have ever received biologic immunomodulating agents, including but not limited to TNFα (Tumor Necrosis Factor alpha) inhibitors, T-cell costimulatory, Anti-IL6 (interleukin), Anti-IL1, cell-depleting therapies including but not limited to anti-CD20 (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), secukinumab or other biologic drugs directly targeting IL-17 or IL-17 receptor or any investigational immunomodulating agent. 4. Subjects taking any non-biologic DMARD except for MTX (Methotrexate) (or sulfasalazine [SSZ] for ERA patients only). 5. Patients fulfilling any ILAR diagnostic JIA category other than ERA or JPsA.

	6. Patients taking medications prohibited by the protocol. 7. Any intramuscular/intravenous/intra-articular corticosteroid treatment within 4 weeks before baseline. 8. Active or recurrent bacterial, fungal or viral infection including known infection with Human Immunodeficiency Virus (HIV), Hepatitis B, and Hepatitis C at baseline. 9. History or evidence of active tuberculosis (TB) or evidence of Latent TB (positive QuantiFERON or PPD at screening) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with secukinumab. 10. Pregnant or nursing (lactating) females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG (human chorionic gonadotropin) laboratory test. 11. Female patients (< 18 years of age) of childbearing potential (menarchal or becoming menarchal during the study) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in the protocol.
Study treatment	Investigational treatment • Secukinumab 150mg/1mL, liquid formulation provided in 1 mL PFS (Pre-filled syringe) • Secukinumab 75mg/0.5mL, liquid formulation provided in 0.5 mL PFS Reference treatment • Placebo, liquid formulation in a 1 mL and 0.5 mL PFS
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 subject's 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] • JADAS score • Total dactylitis count • Total enthesitis count [redacted]

[redacted]

	[redacted]
Key safety assessments	• Adverse events/serious adverse events (AE/SAE) • Electrocardiogram (ECG) • Laboratory evaluations • Immunogenicity
Other assessments	• Secukinumab levels
Data analysis	The primary objective for Treatment Period 2 of the study is to show superiority of Secukinumab over placebo regarding the primary variable in Treatment Period 2. The following statistical hypothesis will be tested once the required number of flares has been observed and the study has been stopped: H0: $1\text{-}S_{A\,N}(t) \geq 1\text{-}\ S_{Pla}(t)$ HA: $1\text{-}S_{A\,N}(t) < 1\text{-}\ S_{Pla}(t)$ at each time point t, with $S_{AIN}(t)$ and $S_{Pla}(t)$ being the survivor functions in the Secukinumab and placebo treatment group at time t. The two treatment groups will be compared using a one-sided stratified Logrank test with the stratification factor of JIA category (ERA or JPsA) at the 2.5% level of significance. Hazard ratios and their associated 95% confidence intervals will be estimated based on a Cox proportional hazards model with treatment and stratification factor as explanatory variables. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs.
Key words	JIA, JPsA, ERA, Secukinumab, ILAR

[redacted]

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 seven JIA categories characterized by different clinical presentations:

- Polyarticular (Rheumatoid Factor (RF) positive);
- Polyarticular (RF negative);
- Oligoarticular;
- Juvenile psoriatic Arthritis (JPsA);
- Enthesitis-related Arthritis (ERA) and;
- Systemic
- Undifferentiated

Of the seven 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) respectively.

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 (Horneff 2009, Martini 2003, 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 (> 6-9 years old) with a lower extremity arthritis, enthesitis and, in a minority of patients, axial involvement, and are often HLA-B27 positive. (Human Leukocyte Antigen)

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%–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 (Beuckelman et al 2011). 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 intraarticular 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 IL-17A and neutralizes activity. Secukinumab treatment has demonstrated significant and clinically meaningful efficacy in treating adults with ankylosing spondylitis (AS) and psoriatic arthritis (PsA), both approved indications.

The adult AS and PsA secukinumab data support the proposed secukinumab study in children with similar pediatric spondyloarthritic conditions: ERA and JPsA. This study will investigate secukinumab treatment in children ≥ 2 to < 18 years of age with active JPsA or ERA JIA using a pediatric dose equivalent to the adult 150mg dose. To ensure children with a more SpA-like condition (Martini 2012) are not excluded, the ILAR diagnostic criteria for JPsA are modified NOT to exclude those who are:

- HLA–B27-positive male beginning after the 6th birthday;
- those who have AS, 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.

This 2-year study consists of 3 parts plus a post-treatment follow-up period: The initial Treatment Period 1 will entail open-label secukinumab administered subcutaneously every week for the first 4 weeks (loading dose period) and at Week 8. Responders (minimum JIA ACR30 response) at the end of Treatment Period 1 (Week 12) will enter into Treatment Period 2 and be randomized 1:1 at Week 12 to either continue secukinumab or begin placebo in a blinded fashion every 4 weeks. Non-responders will not be dosed and will undergo an end of study visit on the same day and enter the Post-treatment follow-up period. Treatment Period 2 will continue until 33 patients experience a disease flare (as per American College of Rheumatology (ACR) flare definition). Patients experiencing a flare and those who remain (in

Treatment Period 1 or 2) when Treatment Period 2 completes will enter Treatment Period 3 to receive open-label secukinumab every 4 weeks until week 100. A total study duration of 104 weeks at the patient level is reached. A Post-treatment follow-up visit is performed 12 weeks after last study treatment administration for all patients unless the patient enters the extension trial.

All patients who successfully complete the study (104 weeks) will be eligible to continue secukinumab treatment in an extension trial.

1.2 Purpose

The purpose of this study is to demonstrate the efficacy and safety of secukinumab treatment in children ≥2 to <18 years of age with active ERA and JPsA categories of JIA and to demonstrate the sustained efficacy of secukinumab by using a flare prevention design in a double-blind placebo control treatment withdrawal part of the trial. Additionally, this study will evaluate predicted pediatric doses to achieve secukinumab level equivalency of adult 150mg dosing.

2 Study objectives and endpoints

2.1 Primary objective(s)

To demonstrate that the time to flare in Treatment Period 2 is longer with secukinumab for combined ERA and JPsA groups than with placebo.

2.2 Secondary objective(s)

1. To evaluate effect of secukinumab treatment for all patients and each JIA category in Treatment Period 1 up to Week 12 (end of Treatment period 1) with respect to:
   - JIA ACR 30/50/70/90/100 and inactive disease status
   - Each JIA ACR core component
   - Change from baseline Juvenile Arthritis Disease Activity Score (JADAS)
   - Total enthesitis count
   - Total dactylitis count
2. To evaluate withdrawal effect of secukinumab treatment for all patients and each JIA category during and at the end of Treatment Period 2 with respect to:
   - JIA ACR 30/50/70/90/100 and inactive disease status
3. To evaluate Pharmacokinetics (PK) of secukinumab and confirm the predicted dose in Treatment Period 1
4. To evaluate the safety/tolerability and immunogenicity of Secukinumab

[redacted]

[redacted]

[redacted]

2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

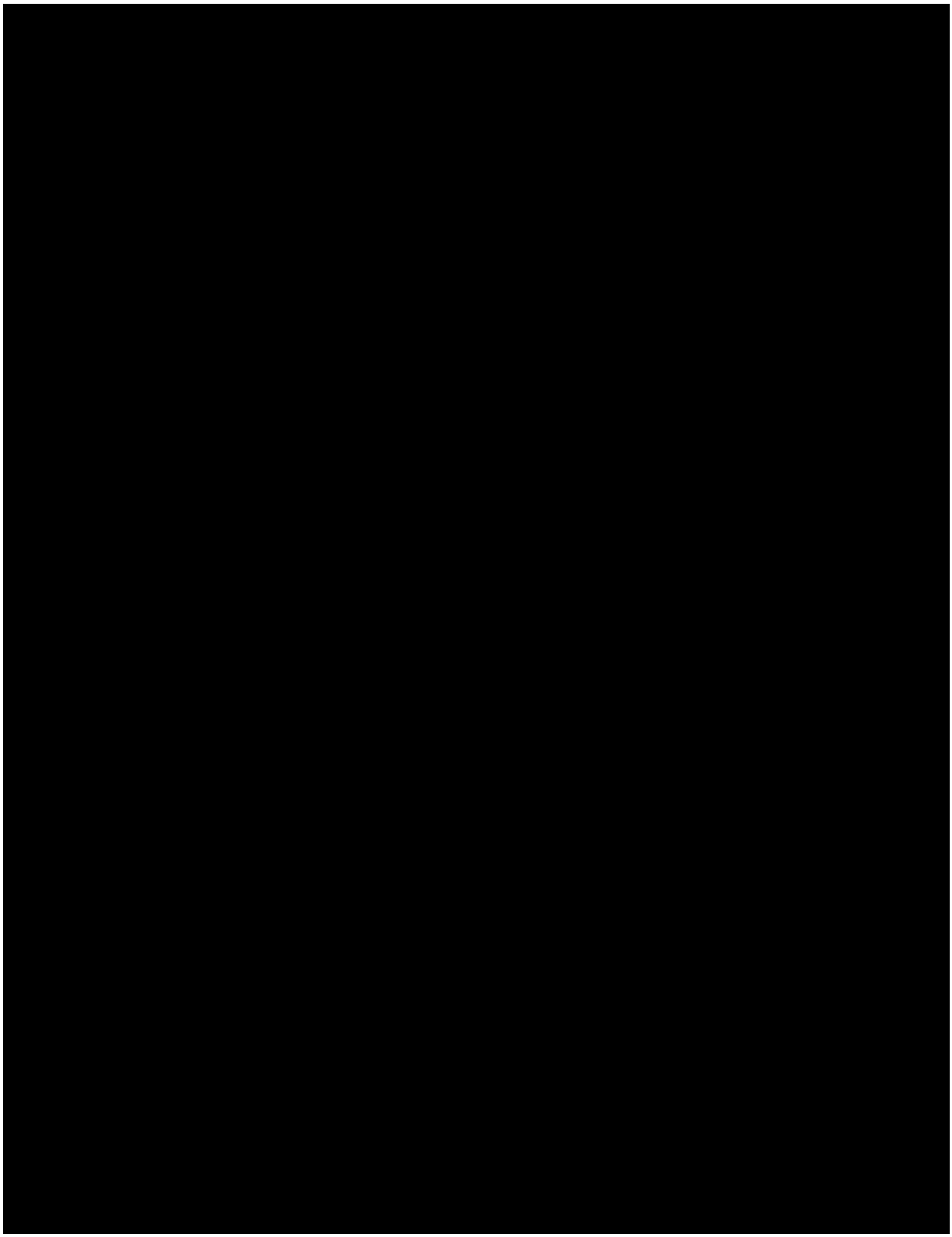
OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Primary		
To demonstrate that the time to flare in Treatment Period 2 is longer with secukinumab for combined ERA and JPsA groups than with placebo	Time to disease flare (active vs. control). Flare definition (see Appendix 8)	Section 9.4.1
	Timeframe: Treatment Period 2	
Secondary		
1. To evaluate the effect of secukinumab treatment for all patients and each JIA category in Treatment Period 1 up to Week 12		Section 9.4.2

[redacted]

(end of Treatment Period 1) with respect to:		
• JIA ACR 30/50/70/90/100 and inactive disease status	• JIA ACR 30/50/70/90/100 (see Appendix 9) • inactive disease status	
• Each JIA ACR core component	JIA ACR core components	
• Change from baseline JADAS score	JADAS score	
• Total enthesitis count	Total enthesitis count	
• Total dactylitis count	Total dactylitis count	
	Timeframe: Treatment Period 1	
2. To evaluate withdrawal effect of secukinumab treatment for all patients and each JIA category during and at the end of Treatment Period 2 with respect to: • JIA ACR 30/50/70/90/100 and inactive disease status	• JIA ACR 30/50/70/90/100 (see Appendix 9) • inactive disease status	
	Timeframe: Treatment Period 2	
3. To evaluate PK of secukinumab and confirm the predicted dose	Secukinumab serum concentrations and derived PK parameters	
	Timeframe: Treatment Period 1	
4. To evaluate the safety/tolerability and immunogenicity of secukinumab	AEs, laboratory values, vital signs, Anti-Drug Antibodies (ADA)	
	Timeframe: Entire study	

[redacted]

[redacted]



3 Investigational plan

3.1 Study design

This is a double-blind, placebo-controlled, event-driven randomized withdrawal study to investigate the efficacy and safety of secukinumab treatment in the JIA categories of JPsA and ERA. The study is divided into 3 parts (plus a post-treatment follow-up period) consisting of open-label, single-arm active treatment in Treatment Periods 1 and 3 and a randomized, double-blind, placebo controlled, event-driven withdrawal design in Treatment Period 2, as described below:

Treatment Period 1: A maximum 8-week screening period is used to assess patient eligibility. All eligible patients will enter Treatment Period 1 to receive 12-weeks of open-label secukinumab at a dose predicted to achieve secukinumab serum levels equivalent to adults administered a 150 mg dose regimen (see Section 3.3 for details). Secukinumab will be administered subcutaneously (s.c.) weekly for the first 4 weeks (Baseline, Weeks 1, 2, 3, 4) and then every 4 weeks thereafter. Clinical response (JIA ACR 30) will be assessed at Week 12. Responders will advance to Treatment Period 2 and non-responders must exit the trial (early termination visit and enter into the Post-treatment follow-up period).

Treatment Period 2: Patients with a clinical response (JIA ACR30) at Week 12 will enter double-blind withdrawal Treatment Period 2 to be randomized 1:1 to either secukinumab or placebo on that visit. Treatment Period 2 is event driven and will close when 33 patients experience a disease flare as per JIA definition (Appendix 8). If Treatment Period 2 is closed when a patient becomes eligible to enter Treatment Period 2, the patient will skip Treatment Period 2 and advance directly to Treatment Period 3. When the 33rd flare is observed, all investigators will be informed that Treatment Period 2 is closed and all remaining patients will enter Treatment Period 3 at their next scheduled visit. Because Treatment Period 2 is event driven, it is possible that a patient remains in Treatment Period 2 for the duration of the study (Week 104) before 33 disease flares are observed. Such patients will complete the study without having entered Treatment Period 3.

Treatment Period 3: Patients experiencing a disease flare in Treatment Period 2 will immediately enter Treatment Period 3 to receive open label secukinumab every 4 weeks until total study duration of 104 weeks for that patient is achieved. Additionally, when Treatment Period 2 closes, all remaining patients in Treatment Period 2 will enter Treatment Period 3 at their next scheduled visit and all remaining Treatment Period 1 patients who become eligible to enter Treatment Period 2 will skip Treatment Period 2 and enter Treatment Period 3 directly. Consequently, the starting time point of Treatment Period 3 for each patient may be different.

Post-treatment follow-up: All patients completing the study (Week 104) or who discontinue early will enter the Post-treatment follow-up period lasting 12 weeks from the last study drug dose administration. Only patients who qualify and enter the secukinumab extension trial without interruption of secukinumab treatment will not require this Post-treatment follow-up visit.

Due to the event driven design of Treatment Period 2, the lengths of Treatment Periods 2 and 3 will be variable and patient-specific. Based on the study design, a patient may participate in:

1. **Treatment Period 1 only** if the patient is a non-responder at the end of Treatment Period 1 and must discontinue from the study.
2. **Treatment Periods 1, 2, and 3**.
3. **Treatment Periods 1 and 2 only** if the patient never experiences a disease flare after randomization into Treatment Period 2 and reaches a total study duration of 104 weeks before a total 33 flares in Treatment Period 2 are observed.
4. **Treatment Periods 1 and 3 only** if 33 flares are observed in Treatment Period 2 prior to or at the time the patient reaches Week12 (end of Treatment Period 1) and is eligible to enter Treatment Period 2. In this situation, the patient will enter Treatment Period 3 directly from Treatment Period 1 to receive open-label secukinumab.

All patients will participate in the Post-treatment follow up period, except for those entering the extension study.

Enrollment will be staggered such that enrollment will be held in each dose weight group (< or ≥50kg) when 10 patients in that weight group have enrolled. Patients discontinued before Week 12 may be replaced. In order to confirm the predicted pediatric dosing regimen, a Pharmacokinetics (PK) interim analysis (IA) will be conducted for each of these 2 weight dose groups after completion of the Week 12 visit. Separate PK IAs may be performed for each dose weight group depending on enrollment rate in each. When the adequacy of the predicted dose is confirmed, enrollment for that weight group will reopen until full enrollment is reached. The interim analysis for one or both dose weight groups may not be necessary if the adequacy of the secukinumab dose is confirmed by evidence obtained in an ongoing pediatric psoriasis study.

The primary analysis is planned when 33 disease flares in Treatment Period 2 have been observed (Treatment Period 2 is completed).

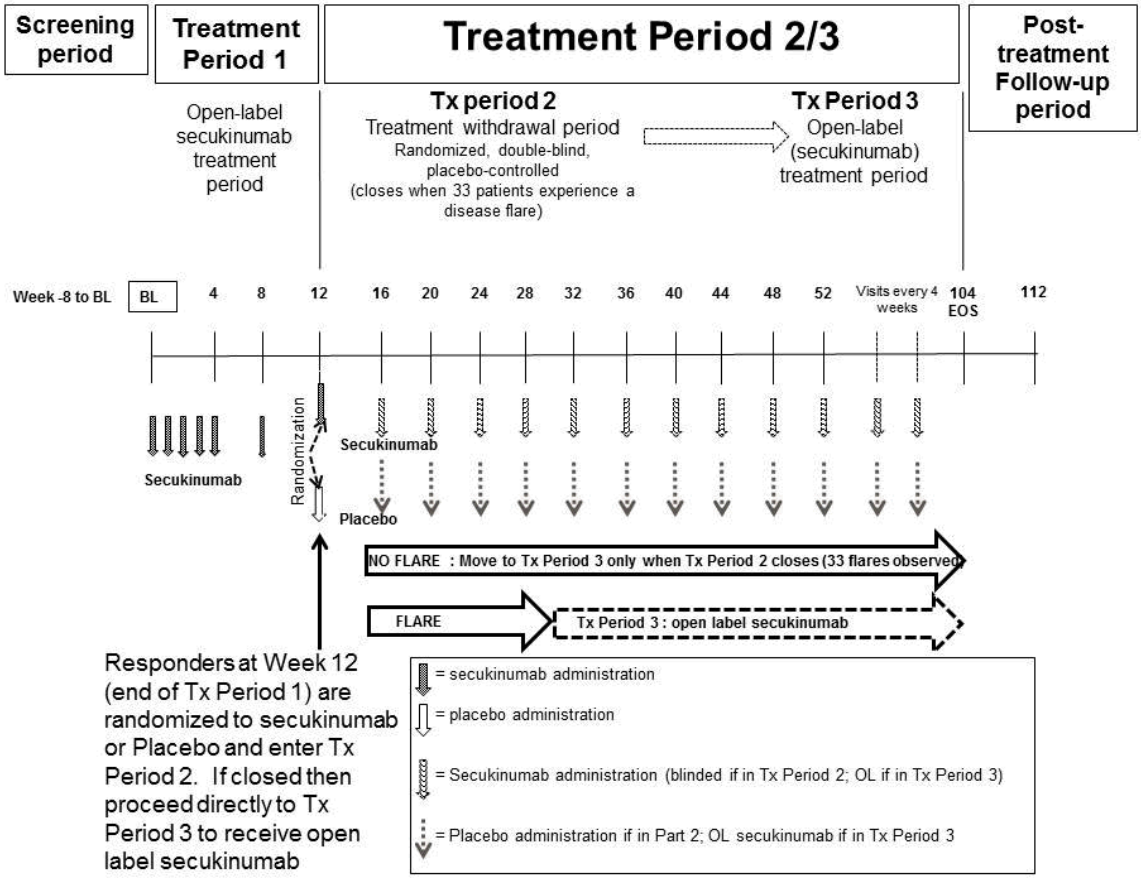
Treatment: Secukinumab prefilled syringes (PFS), available as a 150mg/1mL PFS and as a 75mg/0.5mL PFS, and matching placebo will be used in the study.

- Treatment Period 1 open-label: Secukinumab 75 mg (< 50kg, 0.5 mL PFS) or 150 mg (≥50 kg, 1 mL PFS) s.c will be administered at Baseline, Weeks 1, 2, 3, 4, and 8. The end of Treatment Period 1 visit at Week 12 will determine if the patient continues directly into Treatment Period 2 *at that visit* (minimum JIA ACR30 response) to begin blinded study drug administration or is not a responder and must have the early termination visit performed and enter directly into the Post-treatment follow-up period without any further study drug administration.
- Treatment Period 2 treatment withdrawal: Patients who are a responder (minimum JIA ACR30) at the end of Treatment Period 1 visit at Week 12, will move directly into Treatment Period 2 *at that same visit* to be randomized 1:1 to receive blinded secukinumab (75mg for < 50kg [0.5 mL PFS] or 150 mg for ≥ 50 kg [1mL PFS] or matching placebo administered in Treatment Period 2 and then every four weeks until either experiencing a disease flare or completion of Treatment Period 2 (33 disease flares observed in the overall study population). For patients who are eligible to enter Treatment Period 2, but it has closed (because 33 disease flares were observed), they will skip Treatment Period 2 and enter directly into Treatment Period 3 *at that visit* to begin open-label secukinumab administration.

[redacted]

- Treatment Period 3 open-label: Secukinumab 75 mg (< 50 kg, 0.5 mL PFS) or 150 mg (≥ 50 kg, 1mL PFS) s.c will be administered every 4 weeks until Week 100 included.

Figure 3-1 Study design



The time point for entering Treatment Period 3 will be either when the patient experiences a disease flare, or on/after the completion of Treatment Period 2. Consequently, the duration in Treatment Period 2 will be up to 92 weeks for patients without a disease flare if Treatment Period 2 does not close before the patient reaches 104 weeks of total study participation. Patients could enter Treatment Period 3 at any point from Week 12 to Week 104.

All patients completing the Week 104 visit or who discontinue early will have a Post-treatment follow-up visit 12 weeks from the last study drug dose. Only patients who enter the extension trial without interruption of their secukinumab treatment will not require this Post-treatment follow-up visit.

3.2 Rationale for study design

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 favourable benefit risk was established in adult ankylosing spondylitis and psoriatic arthritis patients and approved for these indications in multiple countries including the European Union 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 paediatric arthritic population to study secukinumab treatment is children aged ≥ 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 present 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 paediatric 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 paediatric population.

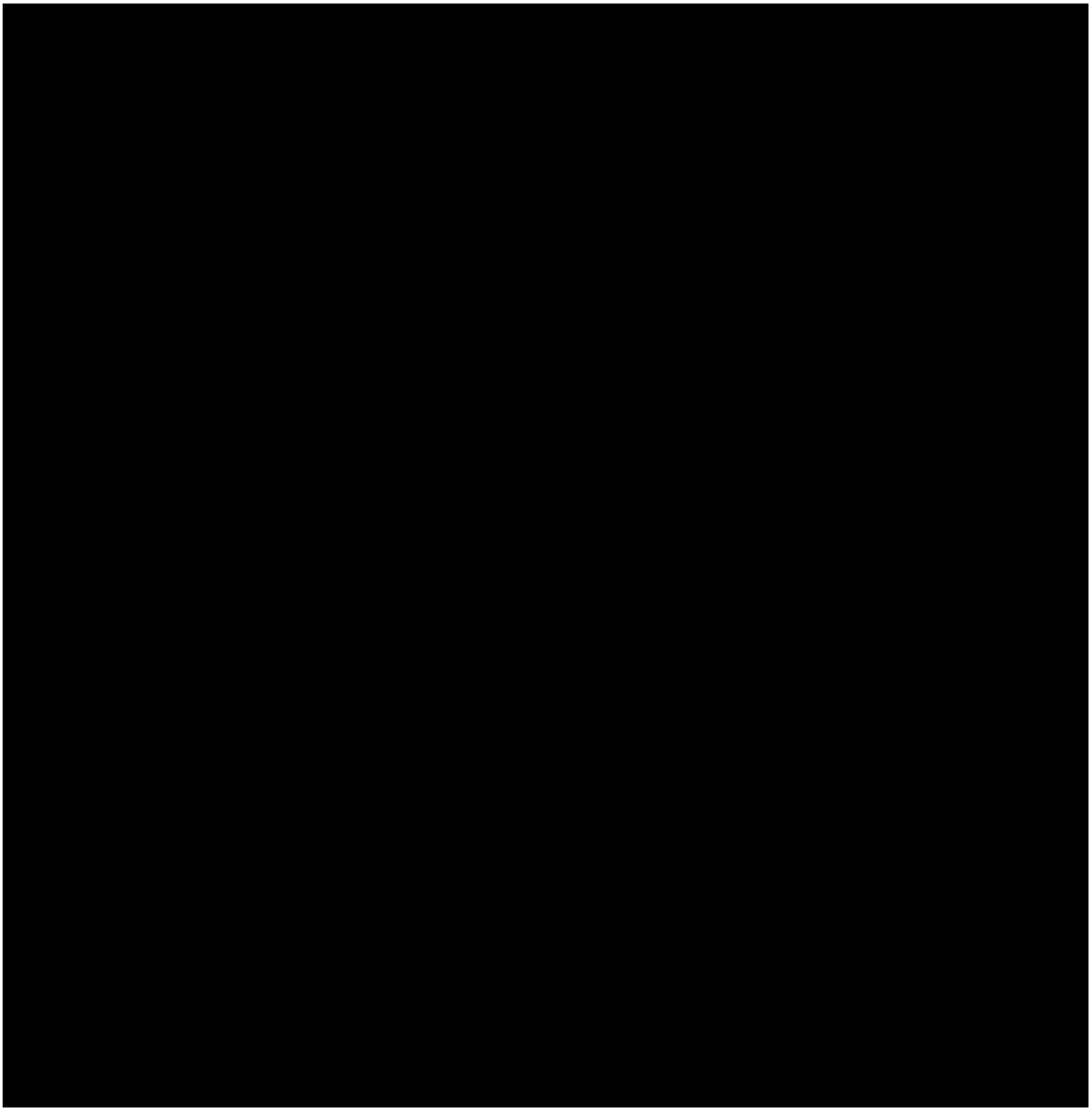
The patient population will be described in more detail in the Section 4 below.

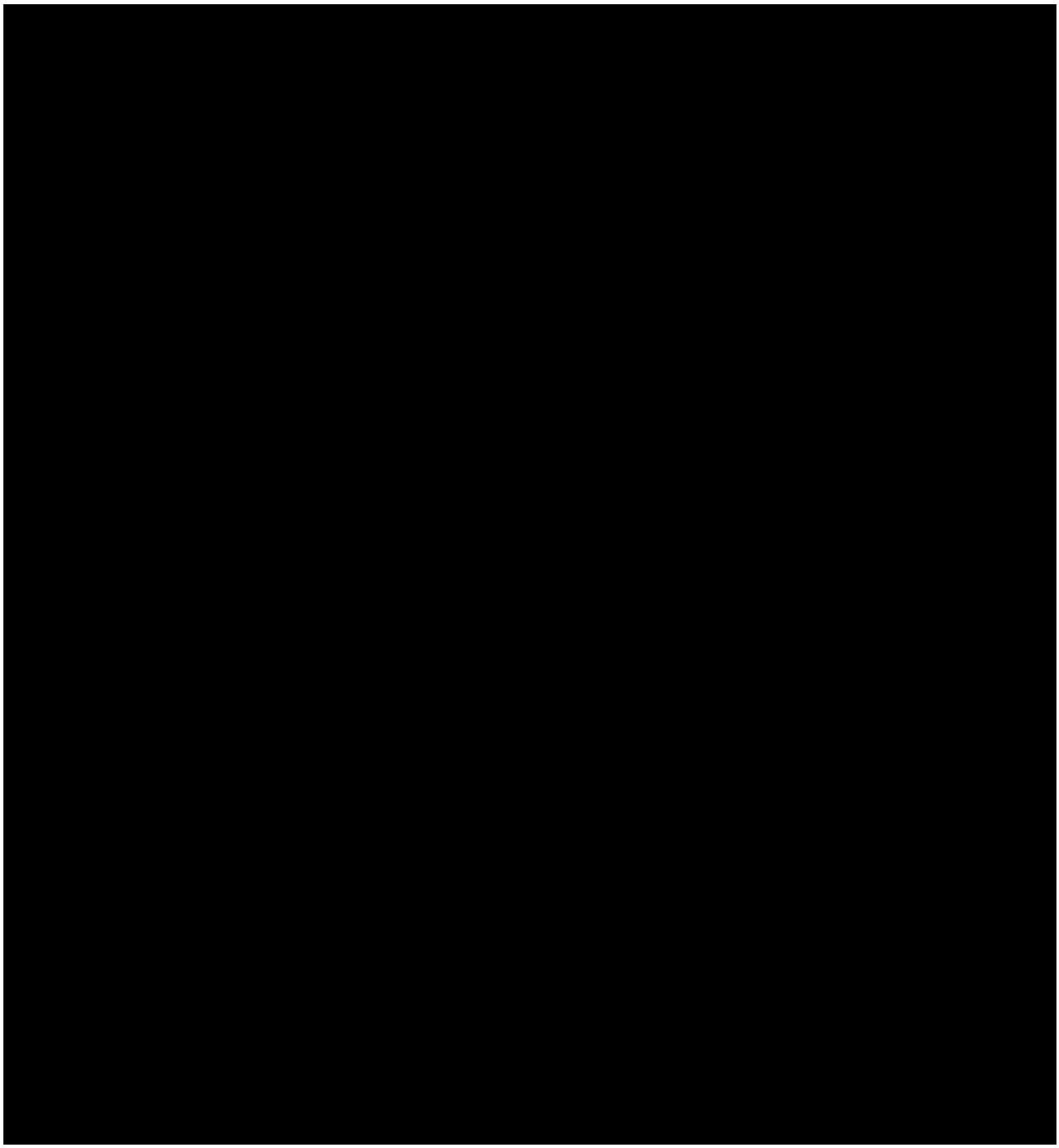
3.3 Rationale for dose/regimen, route of administration and duration of treatment

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 TNF inhibitor. For both indications, the recommended dose in 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)

[redacted]

[redacted]





3.4 Rationale for choice of comparator

A placebo group is included in this study at Week 12. Due to the nature of the disease and the primary outcome measure used (JIA ACR30 response), a placebo group is necessary to obtain reliable efficacy measurements for comparison between the active treatment and placebo groups in a controlled fashion. This is in accordance with health authority guidelines, including (EMA 2015). Placebo exposure is kept to a minimum by advancing all patients who experience a disease flare in Treatment Period 2 to Treatment Period 3 where they receive

open-label secukinumab and by stopping Treatment Period 2 when 33 flares occur and advance all remaining patients to Treatment Period 3 to receive open-label secukinumab.

3.5 Purpose and timing of interim analyses/design adaptations

A PK interim analysis will be conducted for the first 10 patients enrolled in each weight dose group (< or ≥50kg) after completion of the Week 12 visit in order to confirm the predicted pediatric dosing regimen.

Enrollment will be held in each dose weight group (< or ≥ 50kg) when 10 patients in that group have entered Treatment Period 1. Patients discontinued before Week 12 may be replaced. Separate PK IAs may be performed depending on enrollment rate in each weight dose group. When the adequacy of the predicted exposure is confirmed, recruitment for that weight group will reopen until the planned study population is fully enrolled. The interim analysis for one or both dose weight groups may not be necessary if the secukinumab dose is confirmed by evidence obtained in ongoing Secukinumab pediatric studies. Any change in the dose regimen to be implemented based on the PK IA results or available data from the ongoing pediatric psoriasis study will be communicated in written format from Novartis.

3.6 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 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 (ADA) 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 subjects 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 Brochure (IB) for Secukinumab. Based on overall risk-benefit assessment, the current trial with secukinumab is justified.

4 Population

The study population will consist of male and female patients aged from ≥2 years to <18 years at screening who are diagnosed with either enthesitis-related arthritis (ERA) based on fulfilling the ILAR JIA classification criteria or JPsA based on fulfilling a modified ILAR JIA classification criteria. Every effort will be made in order to randomize at least 20 patients from each JIA category to Treatment Period 2. A 1:1 stratified randomization for Treatment Period 2, will be put in place ensuring an equal number of patients from each JIA category (JPsA and ERA) will receive either secukinumab or placebo treatment. Patients included must be biologic treatment naïve and have active disease despite current or previous NSAID and DMARD therapy.

All non-biologic DMARDs except MTX (or sulfasalazine [SSZ] for ERA patients only) are to be withdrawn with adequate washout before Baseline (see Table 5-1).

Concomitant therapy with MTX, (or SSZ for ERA patients only) and oral corticosteroids (CS) will be acceptable at stipulated maximum doses, but the dose and route of administration must have been stable for at least four weeks prior to Baseline for the DMARD and 7 days for the CS and remain at that dose during the study Treatment Period 1, while dose adjustments will be permitted according to investigator's judgement in Treatment Period 2 only after 3 consecutive months of minimum ACR50 response or at any time in Treatment Period 3.

A total of approximately 80 patients to Treatment Period 1 in approximately 40 – 50 centers worldwide is anticipated to enroll in order to reach the minimum required sample size of 60 patients in Treatment Period 2 (see also section 9.6). Depending on the responder rate in Treatment Period 1 and the dropout rate in Treatment Periods 1 and 2, more patients may need to be enrolled in Treatment Period 1 to reach the 33 flares in Treatment Period 2. A 20% screen failure rate is anticipated which will then require approximate 100 children to be screened.

4.1 Inclusion criteria

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

1. Parent's or legal guardian's written informed consent and child's assent, if appropriate, must be obtained before any study related activity or assessment is performed. Of note, if the subject 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).
2. Males and females ≥2 years old and <18 years old at the time of screening.
3. Confirmed diagnosis of ERA according to the ILAR classification criteria or JPsA according to the **modified** ILAR classification criteria (See Appendix 7) that must have occurred at least 6 months prior to Screening.
4. Active disease (ERA or JPsA) defined as having both:
   - ≥ 3 active joints (swollen or if not swollen must be both tender and limited range of motion) at Baseline
   - ≥1 site of active enthesitis at Baseline or documented by history
5. Inadequate response (≥1 month) or intolerance to ≥1 NSAID.
6. Inadequate response (≥2 months) or intolerance to ≥ 1 DMARD.

[redacted]

7. No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of the following agents which must remain at stable dose during trial Treatment Periods 1 and 2 (See Section 5.5.7 for additional details and for required wash-out period):
   - Stable dose of methotrexate (maximum of 20 mg/ m^2 BSA/ week) for at least 4 weeks prior to the Baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the center)
   - Stable dose of SSZ (ERA patients only) ≤50 mg/kg/day with max of 3000 mg/day for at least 4 weeks prior to the Baseline visit
   - Stable dose of an oral corticosteroid (CS) at a prednisone equivalent dose of ≤0.2 mg/kg/day or up to 10 mg/day maximum, whichever is less, for at least 7 days prior to Baseline
   - Stable dose of no more than one NSAID for at least 1 week prior to Baseline
8. Negative QuantiFERON (QF) test. Negative Purified Protein Derivative [PPD] test is also acceptable if either required by local guidelines or if the patient is <5 years of age. A positive PPD is defined as ≥15mm induration for children ≥4 years and ≥10mm for children <4 years.
   - Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated and for a minimum of 4 weeks before Baseline.
   - In the absence of local guidelines the US CDC (Centers for Disease Control and Prevention) guidelines for treatment of latent TB must be followed i.e. INH (isonicotinylhydrazide) treatment for 9 months. Patients diagnosed with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study.

4.2 Exclusion criteria

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

1. Use of other investigational drugs within 4 weeks or 5 half-lives of Baseline, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
3. Patients with active uncontrolled inflammatory bowel disease or active uncontrolled uveitis.
4. Patients who have ever received biologic immunomodulating agents, including but not limited to TNFα inhibitors, T-cell costimulatory, Anti-IL6, Anti-IL1, cell-depleting therapies including but not limited to anti-CD20 (e.g., alemtuzumab, anti-CD4, anti-CD5, anti-CD3, and anti-CD19), secukinumab or other biologic drugs directly targeting IL-17 or IL-17 receptor or any investigational immunomodulating agent.

[redacted]

5. Patients taking any non-biologic DMARD except for MTX (or sulfasalazine [SSZ] for ERA patients only) (see Section 5.5.7 and Table 5-1 for additional details).
6. Patients fulfilling any ILAR diagnostic JIA category other than ERA or JPsA.
7. Patients taking medications prohibited by the protocol (see Section 5.5.8, Table 5-1) (e.g., topical corticosteroids or ultraviolet (UV) therapy at screening). The washout periods to be observed before Baseline are given in Table 5-1.
8. Patients taking high potency opioid analgesics (morphine equianalgesic or higher) including but not limited to methadone, hydromorphone and morphine.
9. Any intramuscular/intravenous/intra-articular corticosteroid treatment within 4 weeks before Baseline.
10. Active or recurrent bacterial, fungal or viral infection including known infection with Human Immunodeficiency Virus (HIV), Hepatitis B, and Hepatitis C at Baseline.
11. History or evidence of active tuberculosis (TB) or evidence of Latent TB (positive QuantiFERON or PPD at screening) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with secukinumab.
12. History or current diagnosis of Electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
13. Pregnant or nursing (lactating) females, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
14. Female patients (< 18 years of age) of childbearing potential (menarchal or becoming menarchal during the study) who do not agree to abstinence or, if sexually active, do not agree to the use of contraception as defined in Section 6.5.7.
15. Active ongoing inflammatory diseases other than JPsA / ERA that might confound the evaluation of the benefit of secukinumab therapy.
16. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in a study with an immunomodulatory treatment.
17. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension and uncontrolled diabetes (can be discussed on a case-by-case basis with Novartis).
18. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:

[redacted]

a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to baseline, to rule out lab error.
b. If the total bilirubin (TBL) concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L).

19. Screening total white blood cell (WBC) count < 3 000/µL, or platelets < 100 000/µL or neutrophils < 1 500/µL or hemoglobin < 8.5 g/dL (85 g/L).
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
21. Current severe progressive or uncontrolled disease which in the judgment of the clinical Investigator renders the subject unsuitable for the trial.
22. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
23. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol (can be discussed on a case-by-case basis with Novartis).
24. History or evidence of ongoing alcohol or drug abuse, within the last six months before Baseline.
25. Plans for administration of live vaccines during the study period or within 6 weeks preceding Baseline.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study drugs:

Investigational treatment

- Secukinumab 150 mg/1 mL, liquid formulation provided in 1 mL PFS
- Secukinumab 75 mg/0.5 mL, liquid formulation provided in 0.5 mL PFS

Reference treatment

- Placebo, liquid formulation in a 1 mL and 0.5 mL PFS

Secukinumab 75 mg/0.5 mL and 150 mg/1 mL pre-filled syringes and matching placebo pre-filled syringes will be provided in a double blind fashion and have identical appearance

All study drugs will be labeled accordingly:

For the open-label parts (Treatment Periods 1 and 3):

[redacted]

- AIN457 150 mg/1 mL
- AIN457 75 mg/0. 5mL

For the double-blind part (Treatment Period 2):

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

For detailed instructions on storage of the study drugs, please refer to Section 5.5.3

5.1.2 Additional treatment

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

5.2 Treatment arms

Patients will enter Treatment Period 1 to receive 12-weeks open label active treatment of either s.c. secukinumab 75 or 150 mg, based on their body weight (< 50 kg or ≥ 50 kg) at each dosing visit starting at Baseline. They will receive further doses at Weeks 1, 2, 3, 4, and 8.

At the End of Treatment Part 1 visit at Week 12, efficacy assessments must be performed and ACR response criteria evaluated to determine future patient disposition in the study. Patients who are assessed as a responder (minimum JIA ACR30 response) will enter Treatment Period 2 at that same visit to be randomized to either continue their active treatment or matching placebo every 4 weeks, in a blinded manner, in a 1:1 ratio until 33 patients experience a disease flare and Treatment Period 2 is completed. If Treatment Period 2 is closed at the time of the Week 12 visit, the patient will skip Treatment Period 2 and enter Treatment Period 3 directly to receive open-label secukinumab. Patients who are not a responder at the Week 12 visit will have the early termination visit done on the same day and enter into the Post-treatment follow-up period at that visit without receiving any further study drug administration.

Patients will enter Treatment Period 3 from Treatment Period 2 because of either experiencing a flare or when 33 flares in Treatment Period 2 are overall observed and Treatment Period 2 is closed. Patients in Treatment Period 1 when Treatment Period 2 closes will skip Treatment Period 2 and advance directly into Treatment Period 3 after successfully completing Treatment Period 1. During Treatment Period 3, patients will receive open-label secukinumab (either 75 or 150 mg, based on body weight) every 4 weeks until study Week 100 is reached.

5.3 Treatment assignment and randomization

All patients fulfilling all entry criteria will be assigned to AIN457/secukinumab 75 or 150 mg, based on body weight (< 50 kg or ≥ 50 kg) and continue to receive an appropriate secukinumab dose at each visit based on their weight at that visit. At the Week 12 visit, all responders will be eligible to enter Treatment Period 2 where they will be randomized via Interactive Response Technology (IRT) to one of the two treatment arms, active as secukinumab 75 or 150 mg, or matching placebo based on their weight at that visit.

In Treatment Period 2, patients will be randomized by each JIA category (strata: JPsA and ERA) in a 1:1 ratio to receive AIN457 or placebo so that approximately an equal number from each category will receive either active or placebo.

At each subsequent dosing visit body weight will be checked and the patients will be assigned the correct blinded dose based on their weight at that visit.

The Investigator or his/her delegate will contact the IRT after confirming that the patient fulfills the response criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

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

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

5.4 Treatment blinding

Patients/parents, Investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment (Treatment Period 2) from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the bioanalyst, independent statistician, programmer and DMC (Data Monitoring Committee) members.

(2) The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, administration route and appearance.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and after the primary efficacy analysis.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The Investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the Electronic Data Capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated.

If for any reason the subject is a screen failure, the subject may be rescreened. There is no restriction on the number of times a potential subject may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening. If a subject rescreens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. For all subjects, the investigator/qualified site staff will record if the subject was rescreened on the rescreening CRF page and any applicable screening numbers the subject was issued prior to the current screening number.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to placebo or active treatment. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, Investigator staff will detach the tear-off part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number. For delivery of IMP to a participant's home, the pharmacist/qualified site personnel will dispense, via IRT, the investigational treatment package and detach outer part of the label from the packaging and affix it to the source document for that patient's unique subject number.

During a major health care disruption (e.g., COVID 19 pandemic/epidemic) that limits or prevents on-site study visits, delivery of IMP directly to a participant's home would be permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Delivery of IMP directly to a participant's home would be permitted only during the duration of the health care disruption and for patients whom the Investigator deems that delaying/skipping a dose is not an option. The shipment/provisioning will be for a maximum quantity covering a 1-month supply.

In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed; prior to drug shipment and just before dosing) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participant can again visit the site. Where home dosing is performed, patient's body weight will be collected and transmitted to the site prior to shipment. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be conducted after

the dose is administered. Scheduled efficacy assessments are not required for home administration.

The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Home administration can be performed by the patient or parent/guardian/caregiver, provided they are familiar or have been trained on how to inject with the PFS as per investigators judgment. The patient/parent/guardian/caregiver should be provided with the PFS Instructions For Use.

It must be noted that subjects 12-<18 years of age can self-inject only under Parent/Guardian/Caregivers or health care professional supervision. Subjects < 12 years of age should not self –inject.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (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/subjects 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.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (secukinumab 75 mg, 150 mg or placebo) will be administered by s.c. PFS throughout the study. Administration of study treatment will occur at the study site for the whole study duration (104 weeks), except in cases of a major healthcare disruption that impedes on-site drug administration. Apart for the exceptional circumstances created by the current pandemic that may apply to some cases, administration of study treatment must occur

only after the study assessments for the visit have been completed, and with the timing indicated in Table 6-1 (Assessment Schedule).

The first study treatment administration will occur at the Baseline visit only after eligibility criteria have been confirmed, all study baseline assessments have been performed, and the scheduled blood samples have been drawn. At each subsequent visit, all study assessments (as applicable per Table 6-1) 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 6-1).

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

During a major health care disruption (e.g., COVID 19 pandemic / epidemic) that limits or prevents on-site study visits, delivery of IMP directly to a participant's home would be permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Delivery of IMP directly to a participant's home would be permitted only during the duration of the health care disruption and for patients whom the Investigator deems that delaying/skipping a dose is not an option. The shipment/provisioning will be for a maximum quantity covering a 1-month supply.

In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed; prior to drug shipment and just before dosing) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participant can again visit the site. Where home dosing is performed, patient's body weight will be collected and transmitted to the site prior to shipment. Appropriate safety assessments (e.g., evaluation of AEs and SAEs) should be conducted after the dose is administered. Scheduled efficacy assessments are not required for home administration.

The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Home administration can be performed by the patient or parent/guardian/caregiver, provided they have been trained on how to inject with the PFS as per investigators judgment. The patient/parent/guardian/caregiver should be provided with the PFS Instructions For Use.

It must be noted that subjects 12-<18 years of age can self-inject only under Parent/Guardian/Caregivers or health care professional supervision. Subjects < 12 years of age should not self –inject.

For the visits where a urine pregnancy test is required or deemed necessary, if the patient cannot visit the site to have urine pregnancy test done, the urine pregnancy test kit can be provided to the patient/parent/guardian/caregiver or shipped directly to the their home (e.g., together with the study drug). After appropriate instruction, patient/parent/guardian/caregiver

can perform the urine pregnancy test at home and report the result to the site. It is important that a negative pregnancy test is confirmed prior to the administration of the study drug.

The patient/parent/guardian/caregiver will record the date of administration and will return the packaging at their next visit to the site. Used syringes should be disposed immediately after use in a sharps container OR according to the regulatory requirements in the respective country.

Site staff are to transcribe this information into the appropriate Dosage Administration Record eCRF. The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

In case a flare is suspected between two scheduled visits in Treatment Period 2, the patient can be evaluated at that time by the investigator during an unscheduled visit. If a flare is confirmed at that visit, he/she will advance to Treatment Period 3 and receive open-label secukinumab at a dose according to their body weight. Subsequent visits will be carried out 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).

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. For subjects who are unable to tolerate the protocol-specified dosing scheme (including subjects who in the opinion of the Investigator are at significant safety risk unless dosing is temporarily interrupted), study treatment interruption is permitted in order to keep the subject on study drug. In such cases, study treatment should be interrupted only during the time that a risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks.

Any study treatment interruption must be recorded on the corresponding eCRF page.

5.5.6 Rescue medication

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

Use of rescue medication is prohibited. Please see Section 5.5.7 and Section 5.5.8 for details on concomitant medications. Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, subjects will be discontinued from the study if treated with prohibited medications (as described in Section 5.5.8) 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, subjects who are deemed by the Investigator not to be benefiting from study treatment, or for any reason on the subject'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.

5.5.7 Concomitant medication

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 after the patient was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies eCRF page.

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.

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment before study Baseline, a drug wash-out of 8 weeks must be performed. However, another wash-out procedure can be considered. Cholestyramine may be given orally at a dose of 8 g three times daily (t.i.d) to wash-out leflunomide. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in subjects who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days, the subject can be safely enrolled 4 weeks after the beginning of the 11-day treatment period.

Non-biologic DMARDs (limited to MTX or SSZ)

All non-biologic DMARDs, with the exception of stable dose of SSZ (for ERA patients only), or MTX are prohibited as concomitant medications and must undergo a washout period before Baseline administration, as indicated in Table 5-1.

Concomitant MTX (maximum of 20 mg/ m^2/ BSA week) and folic/folinic acid supplementation (according to standard medical practice of the center), or SSZ (only for ERA patients, stable dose of $\leq$ 50 mg/kg/day and up to max 3000 mg/day) treatment may be used if the dose and route of administration are stable for at least 4 weeks before the Baseline visit and remain stable for the duration of the study. Dose reductions are permitted only in case of adverse events.

Systemic corticosteroids

Treatment with oral corticosteroids $\leq$ 0.2 mg/kg/day (or maximum 10 mg/day whichever is lower) of oral prednisone (or equivalent) is permitted if the dose was stable at least 7 days preceding Baseline visit and remains stable. Otherwise a washout period of 1 week prior to Baseline is needed.

Corticosteroids can be tapered down to discontinuation beginning in Treatment Period 2 based on investigator clinical judgment for patients with at least 3 consecutive months of minimum

ACR50 response and at any time in Treatment Period 3 based on investigator clinical judgment. No corticosteroid dose tapering will be allowed in Treatment Period 1.

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

Intra-articular corticosteroid injections are not permitted within 4 weeks prior to Baseline or at any time in Treatment Period 1 or 2. Intra-articular corticosteroid injections will be permitted in Treatment Period 3. 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.

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

Subjects are permitted to enter the trial using regular dose of a single NSAID for their arthritis. The dose must be stable for at least 1 week before the baseline visit and remain at this dose during the trial. 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 subject must refrain from intake of the PRN medication during at least 24 hours before a visit with a disease activity assessment.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 is NOT allowed after screening due to their confounding effect and/or safety interactions.

Note: Live vaccination is NOT allowed within 6 weeks before baseline and until after 3 months following 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 5-1 Prohibited medication

Medication	Prohibition period / washout before baseline	Action taken
Any biologic drugs, including but not limited to TNFα inhibitors, secukinumab, or other biologic drug directly targeting IL-17 or IL-17 receptor, any biological DMARD (bDMARDs)	Previous exposure at any time: exclusion criterion	Discontinue investigational treatment
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].	Previous exposure at any time: exclusion criterion	Discontinue investigational treatment
Conventional DMARDs (except SSZ (for ERA only) or MTX)	4 weeks	Discontinue investigational treatment

[redacted]

Medication	**Prohibition period / washout before baseline**	**Action taken**
including apremilast		
Leflunomide	8 weeks	Discontinue investigational treatment
Leflunomide with cholestyramine washout	4 weeks	Discontinue investigational treatment
Any investigational treatment or participation in any interventional trial	4 weeks, or until the expected pharmacodynamics effect has returned to baseline or 5 half-lives (whichever is longer)	Discontinue investigational treatment
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN	2 weeks	
Systemic corticosteroids at a prednisone equivalent dose of ≤0.2 mg/kg/day or up to 10 mg/day maximum, whichever is less, is permitted if the dose is stable at least 7 days before baseline. *Corticosteroid dose can be tapered down to discontinuation in Treatment Period 2 for patients with 3 consecutive months of minimum ACR50 response or at any time in Treatment Period 3 based on investigator judgment. No changes in corticosteroid dose will be allowed in Treatment Period 1.	1 week	If administered due to a medical urgency unrelated to the patient's arthritis, study treatment should be interrupted until the steroid is discontinued – if not medical urgency or if related to the patient's arthritis, then discontinue from the study may be required on a case by case basis.
Intra-articular corticosteroids are not permitted within 4 weeks prior to baseline or at any time in Treatment Period 1 or 2. Intra-articular corticosteroid injections will be permitted in Treatment Period 3 but 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. The joints injected with intra-articular corticosteroids will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.	4 weeks	Discontinue investigational treatment, (see Section 5.5.7)
Intramuscular or intravenous corticosteroid treatment are not permitted	4 weeks	Discontinue investigational treatment or from study may be required on a case

[redacted]

Medication	Prohibition period / washout before baseline	Action taken
		by case basis.
Live vaccinations	6 weeks	Discontinue investigational treatment for 12 weeks and patient should remain in the study and follow visit schedule.
Oral or topical retinoids	4 weeks	Discontinue investigational treatment
Photochemotherapy (e.g. PUVA)	4 weeks	Discontinue investigational treatment
Phototherapy (UVA or UVB)	2 weeks	Discontinue investigational treatment
Topical skin treatments (except in face, eyes, scalp and genital area during screening period only, and if topical corticosteroids, only those with mild to moderate potency)	2 weeks	Discontinue investigational treatment may be required on a case by case basis.

5.5.9 Emergency breaking of assigned treatment code

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

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject/guardian must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study drug must be discontinued in Treatment Period 2 after emergency unblinding.

The possibility to enroll a patient after an emergency break in Treatment Period 2 into an extension study, if available, will be evaluated on a case-by-case basis.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has received a maximum of 104 weeks of study treatment and completed all of the scheduled study assessment and procedures up to and including the Week 112 visit. All patients who complete the scheduled study assessments and procedures up to and including Week 104 will be eligible to enter an extension trial to continue secukinumab treatment without interruption. Patients who enter the extension study will be considered study completers at Week 104 and the follow-up visit at Week 112 will not be performed.

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

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

5.6.2 Discontinuation of study treatment

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

Study treatment must be discontinued under the following circumstances:

- Patient/Guardian wish /withdrawal of informed consent
- Pregnancy (see Section 6.5.7 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse events:
  - Any severe or serious AE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication
  - Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  - Life-threatening infection
  - Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the Investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1).
- Use of any biologic immunomodulating agent except secukinumab
- Any protocol deviation that results in a significant risk to the subject's safety.

If permanent discontinuation of study treatment prior to Week 100 occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic 4 weeks after last study drug administration, for a premature discontinuation visit and 12 weeks after "last study drug administration" for a Post-treatment follow-up visit. Assessments performed at these two visits are detailed in the "premature discontinuation visit" and "Post-treatment follow-up visit" respectively in Table 6-1 and should be completed and recorded in the appropriate eCRF page. The Investigator must determine the primary reason for the patient's premature discontinuation of study and record this information on the Dosage Administration eCRF page and also contact the IRT to register the patient's discontinuation from study treatment.

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 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.

[redacted]

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 6-1.

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a premature subject withdrawal (PSW) (see Table 6-1). 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 will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" or an "s" when the visits are performed. The "x" indicates data collected on the eCRF page, the "s" indicates data collected in the source documents only.

Patients must be seen for all visits on the designated day, or as close to it as possible.

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).

- For visits scheduled through Week 4, the study treatment should not be administered less than 5 days from the previous administration.
- For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration, except in case of a flare in Treatment Period 2.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit 4 weeks after last study drug administration, at which time all of the assessments listed for the Week 104/PSW visit) will be performed and a visit 12 weeks after last study drug administration at which time all of the assessments listed for the Week 104/Post-Treatment safety follow up visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the eCRF page.

If patients/guardians refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Attempts to contact the patient/guardian should be recorded in the source

documentation. Patients/guardians will be contacted for safety evaluations during the 12 weeks following the last administration of study treatment.

In the event of a major health care disruption (e.g., pandemic, epidemic) that limits or prevents on-site study visits, regular phone calls or virtual contacts (every 4 weeks or more frequently, if needed) will occur until the subject can again visit the site. Events qualifying for being reported in the case report form (e.g., AE, procedure) should be entered as appropriate. Special effort should be made to collect information related to TD/PSW visits. If it is not feasible to conduct the TD or the PSW visit on-site, phone calls should be attempted instead.

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have duration of up to 8 weeks, during which time, after signature of ICF, the subject be evaluated for eligibility and allowed sufficient time for potential medication washout (see Table 5-1, in addition to all other assessments indicated in Table 6-1).

Screening will consist of two consecutive visits. During the first screening visit, initial assessments will be performed as outlined in Table 6-1. At that visit the duration of the washout period will be determined. The second screening visit will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to Screening visit 2 on the same day and complete all assessments within the next 4 weeks prior to Baseline.
- If the washout period is more than 4 weeks, the patient/guardian will be instructed to initiate necessary washout regimen and return for Screening visit 2 within 4 weeks prior to Baseline to complete all assessments prior to Baseline.

The rationale is that in all cases screening visit 2 must occur within the 4 weeks prior to Baseline.

All patients evaluated at Screening visits 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before Baseline.

If for any reason the patient is a screen failure, the patient may be rescreened. There is no restriction on how much time must pass from the date of screen failure and the date of rescreening, but > 1 rescreens must be approved by Novartis on a case by case basis (see also Section 5.5.1).

For rescreened patients, a new ICF has to be obtained. The date of the new informed consent signature must be entered on the Informed consent CRF page to correspond to the new screening subject number. Informed Consent for a rescreened subject must be obtained prior to performing any study related assessment or collecting any data for the Screening Visit.

For rescreening, all screening assessments must be performed as per protocol, except for the tuberculosis (TB) work up, if applicable, if performed within 12 weeks of Baseline. However, the subject must repeat the QuantiFERON test.

[redacted]

At the discretion of the investigator, laboratory assessments at Baseline visit need not to be performed if screening laboratory assessments were performed within 7 days from Baseline. Urine pregnancy for appropriate female patients and local CRP assessments should be performed at Baseline.

Suggested order of assessments:

Suggested guidelines for conduct of the visit assessments are below:

- Laboratory sample collection, including local CRP sample
- Parent/Guardian/Subject to complete patient reported outcomes (PRO) at the study site prior to any other study assessments.
- Investigator to complete investigator assessments
  - ACR components sent centrally for ACR derivation/flare occurrence - results must be reviewed prior to Week 12/Treatment Period 2 administration of study treatment
- Physical exam (at applicable visits)
- All remaining study visit procedures (e.g. vital signs measurements) must be completed prior to study treatment dosing.
- Contact IRT to register the subject visit, as applicable
- Administration of study treatment, as applicable

[redacted]

Table 6-1 Assessment schedule

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
Informed consent and optional PG informed consent	X																			
Inclusion/exclusion criteria	X[2]	X[2]	X[2]																	
Demography	X																			
JPsA/ ERA date of diagnosis	X																			
Cardiovascular History	X	X[2]	X[2]																	
Smoking History	X	X[2]	X[2]																	
Relevant Medical History / current medical conditions	X	X[2]	X[2]																	
Prior / Concomitant Medications and non-drug therapies	X	X	Update as necessary																	
Surgeries and non-drug procedures	X	X	Update as necessary																	
Washout evaluation instruction	S																			
Physical Examination	S		S	S	S	S	S	S	S	S							S	S	S	
Height		X	X								X		X		X		X		X	
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	For correct

[redacted]

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
																				dose assignment
Vital signs: BP and pulse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Quantiferon (or PPD skin test if required by local regulation)	X																			Results to be available prior to BL
Hepatitis B, C and HIV serology[3] (only in countries where it is required)	S																			Results to be available prior to BL
ECG	X		X						X				X				X		X	
Contact IRT	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Randomization via IRT									X											Only responders will be randomized
Study Drug administration[4,5]			X	X	X	X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]		X[5]		If flare confirmed at an unscheduled Tx Period 2 visit, patient will receive Tx Period 3 OL secukinumab and continue to next scheduled visit

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
PK sampling (pre-dose)[6]			X		X		X	X	X		X		X		X		X	X[6]	X	
Immunogenicity[7]			X						X				X				X	X[7]	X	
[redacted]																				
Central laboratory Hematology/ Clinical Blood chemistry/ urinalysis (local)		X	X		X		X	X	X	X	X	X	X	X	X	X	X		X	Results to be available prior to BL. If screening labs are <7 days prior to BL, then repeat labs at BL are not necessary
Lipids (fasting)			X								X		X		X		X			
CRP (local lab)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Results to be available prior to BL
Serum pregnancy test (for females of		X																		

[redacted]

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
childbearing potential)																				
Urine pregnancy test (for females of childbearing potential)			X								X		X		X		X		X	May also be performed at the investigator's discretion at any time during the study
AEs / SAEs (incl. injection site reaction)	X	X	Update as necessary															X	X	
Physician global assessment of disease activity (PGA) VAS[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CHAQ©			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		CHAQ© includes the parent/patient's global assessment of subject's overall well-being (VAS).
Active joint count • TJC/SJC • Joint count with limited range of			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
motion																				
Tot. Dactylitis count			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tot. Enthesitis count			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]																				
Assessment of Uveitis			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]																				

[redacted]

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																		
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	
[redacted]																				
Treatment period 1 completion form									X											
Treatment period 2 completion form										X	X	X	X	X	X	X	X	X		To be performed at the completion of Tx Period 2.
Study Treatment Completion form																	X			
Follow-up period Completion form																			X	

Scheduled visits in Treatment Periods 2 and 3 are every 4 weeks.

X = assessment to be recorded in clinical data base; **S** = assessment to be recorded in source documentation;

BL= baseline; **Tx** = Treatment; **TD** = study treatment discontinuation; **PSW** = Premature subject withdrawal

[redacted]

	Screening[1]		Treatment Period 1							Treatment Period 2 / 3 (Primary Treatment Period) (Note: a patient enters Tx Period 3 in case of flare or when Tx Period 2 completes)								Unscheduled visit	Post-Treatment Safety follow-up	Notes
	1	2																	
Week	**Up to -8**	**-4 to BL**	**BL**	**1**	**2**	**3**	**4**	**8**	**12/ PSW**	**16 to 20**	**24**	**28 to 48**	**52**	**56 to 72**	**76**	**80 to 100**	**104 / TD/ PSW**		**12 Weeks after last study drug dosed**	

1. Screening will consist of two consecutive visits. During the first screening visit, initial assessments will be performed as outlined in Table 6-1. At that visit the duration of the washout period will be determined. The second screening visit will be performed as follows:
   - Washout period is ≤4 weeks: proceed directly to Screening visit 2 that same day and complete all assessments within the next 4 weeks prior to BL.
   - Washout period is > 4 weeks: initiate necessary washout regimen and return for Screening visit 2 within 4 weeks prior to BL to complete all assessments prior to BL.
2. Should be updated as necessary at each screening visit and at Baseline
3. Hepatitis B, hepatitis C and/or HIV serology testing performed by local lab during screening only if required as per local medical practice/regulation prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRFs
4. Study drug is administered after all assessments are completed. Open label secukinumab is administered in Treatment Periods 1 and 3. At Week 12 all responders will switch to double-blind study drug administration on that visit day.
5. Blinded study drug (active or placebo) is administered in Tx Period 2. If a disease flare is confirmed at an unscheduled Tx Period 2 visit, the subject will receive open-label secukinumab at that visit, complete the Tx Period 2 completion form and continue in Tx Period 3 with the next scheduled visit.
6. PK samples should be obtained prior to study drug administration. PK sample is also obtained at any visit (scheduled or unscheduled) with a confirmed disease flare in Treatment Period 2.
7. An immunogenicity sample is also obtained at any visit (scheduled or unscheduled) with a confirmed disease flare in Treatment Period 2

[redacted]

10. In order to prevent bias, the physician's global assessment of disease activity (VAS) should be completed prior to the Investigator reviewing the parent/patient's assessment of disease activity (which is completed as part of the CHAQ).

[redacted]

[redacted]

6.1 Information to be collected on screening failures

All patients from whom informed consent was obtained but did not enter into the next study period will have the study completion page for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data. Subject may discontinue from the study prior to first study drug administration. These subjects are considered screening failures. All subjects who have signed informed consent and have received the first study drug administration will have all AEs occurring after informed consent is signed recorded on the Adverse Event eCRF page. If a patient discontinued prior to Baseline IRT provider must be notified within 5 days and the reason for patient not being enrolled in Treatment Period 1 will be entered on the screening page disposition CRF page.

6.2 Patient demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects and recorded in the eCRFinclude:

- Age, gender, race, ethnicity and source of subject referral.
- Relevant JPsA/ERA JIA and relevant medical history/current medical condition data until the start of study treatment, such as date of diagnosis of JPsA / ERA, previous JPsA / ERA therapies, cardiovascular medical history, smoking history, and surgical history including sterilization for females, if applicable.

Whenever possible, diagnoses and not symptoms will be recorded.

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

6.3 Treatment exposure and compliance

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

Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

The study treatment will be administered by the study staff directly at the site (except in case of healthcare disruption, such as the COVID-19 pandemic/epidemic-refer to Section 5.5.4), thus compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 5.5.5. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.4 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 subject's overall well-being (VAS included within CHAQ©)
- Childhood Health Assessment Questionnaire (CHAQ©)
- Active joint count
- Joint count with limited range of motion
- CRP (local)
- Inactive disease status
- JADAS score
- Total dactylitis count
- Total enthesitis count

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

6.4.1 JIA ACR response criteria

Standard ACR paediatric Criteria (JIA ACR criteria) consist of 6 core components which will be assessed as scheduled in Table 6-1. JIA ACR 30/50/70/90/100 are defined as 30%, 50%, 70%, 90% and 100% improvement from baseline 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 Subject'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 (mg/L)

The respective response variables listed above will be used by a central vendor to determine ACR Pediatric response, responder status at Week 12, and flare occurrence in Treatment Period 2. These results will be communicated to the investigator prior to the patient leaving the study site. Additionally, these components will be used to determine JADAS and inactive disease status (Wallace et al. 2011) as part of secondary [redacted] analyses.

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

The physician will rate the patient's current condition on a 0-100 mm VAS (Appendix 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.

6.4.3 Parent's/patient's Global Assessment of subject's overall well-being (VAS)

The parent's or patient's 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.

6.4.4 Childhood Health Assessment Questionnaire (CHAQ^{Copyright})

The Childhood Health Assessment Questionnaire, CHAQ© (Appendix 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. Subjects 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 6-1. 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 7.1 and Section 7.2 of the protocol. Investigators should not encourage the patients and/or parents to change the responses reported in the PRO questionnaires.

6.4.5 Active joint count

The number of joints with active arthritis at each visit will determined by applying the ACR definition to the number of joints with swelling, tenderness and limited range of motion at

[redacted]

each scheduled visit for all patients throughout the study (see Section 6.4.6 and Section 6.4.8 for more detail).

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.

6.4.6 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 6.4.8) 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.

6.4.7 C-reactive Protein (CRP)

C-reactive Protein (CRP) will be determined at each scheduled visit for all patients throughout the study and during unscheduled visits where efficacy is assessed.

CRP is used as an inflammation marker, to determine its severity, and to monitor response to treatment.

CRP (mg/L) will be measured at the local lab, including during unscheduled visit for flares, and the actual sample collection date, time and result will be collected.

6.4.8 Tender and Swollen Joint Count

Tender 75 joint count (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:
  - distal interphalangeal
  - 10 proximal interphalangeal
  - 10 metacarpophalangeal
- Hip: 2

- Knee: 2
- Ankle: 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.

[redacted]

6.4.10 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 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).

6.4.11 Total dactylitis count

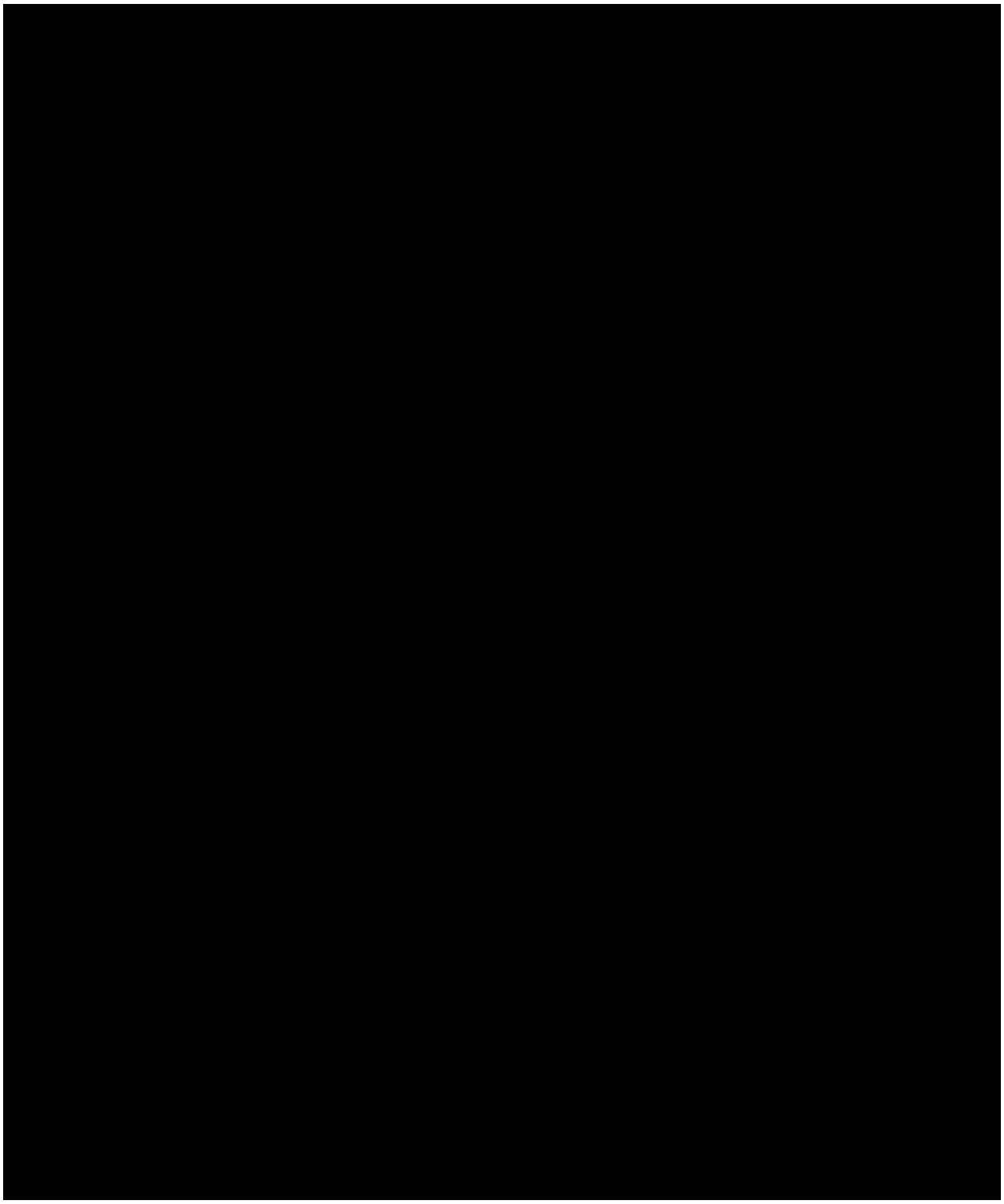
The dactylitis count is the number of fingers and toes presenting with dactylitis, with a range of 0-20.

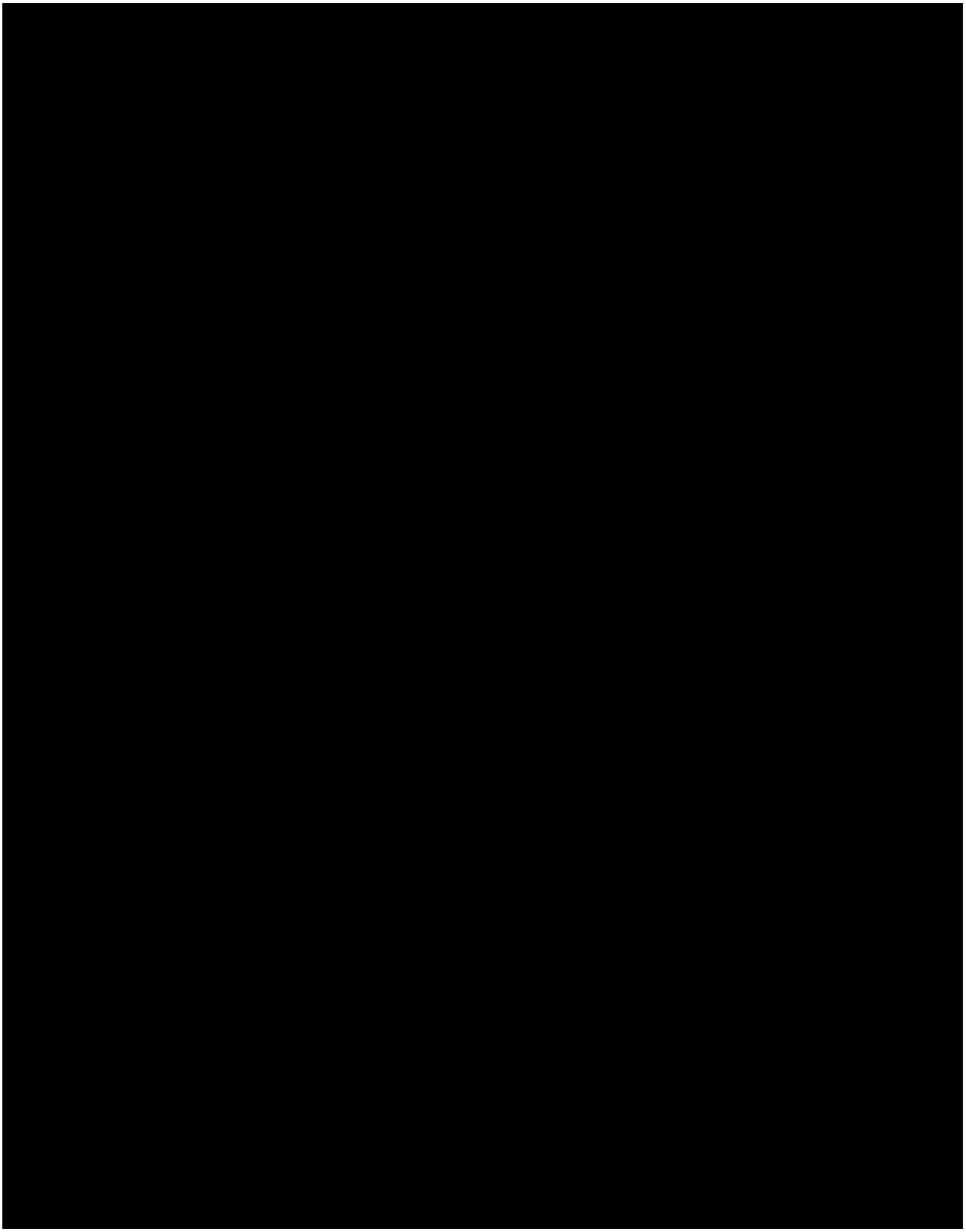
6.4.12 Total enthesitis count

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

[redacted]

- 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.





[redacted]

6.4.20 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;
- CRP (local)

[redacted]

[redacted]

[redacted]

6.4.22 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 value within normal limits for the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score ≤ 10mm
- Duration of morning stiffness attributable to JIA ≤15 min

[redacted]

6.5 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
- QuantiFERON TB-Gold test (or PPD skin test if <5 years of age or required by local regulation)
- Hepatitis B, Hepatitis C and HIV serology (screening for patients who require it by local regulation)

[redacted]

- Electrocardiogram
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- Immunogenicity

6.5.1 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.

6.5.2 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 Appendix 1.

6.5.3 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.

6.5.4 QuantiFERON TB-Gold test or PPD skin test

A QuantiFERON TB-Gold test (**or** a PPD skin test if patient < 5 years of age or required by local regulations) must be performed at either Screening visit 1 or 2 and the results have to be known prior to Baseline to determine the subject's eligibility for the trial. The QuantiFERON TB-Gold test will be performed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

If a PPD skin test is required based on age or local regulations, it can be performed at either Screening visit 1 or 2, and read before Baseline visit to determine the subject's eligibility for the trial. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD

extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48 - 72 hours to develop, the subjects must return to the study site within that time for evaluation of the injection site. This will determine whether the subject has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 15 mm for children ≥ 4 years and ≥ 10 mm for children < 4 years of age (or according to local practice/guidelines) is interpreted as a positive result.

Subjects with a positive test (QuantiFERON TB-Gold test or PPD skin test) may participate in the study if (1) active TB is ruled out and (2) the patient is willing and able to complete a minimum of 4 weeks of latent TB treatment prior to initiating treatment with secukinumab and (3) the patient is willing to continue and complete the latent TB treatment (according to local guidelines) in parallel with study treatments. In the absence of local guidelines the US CDC guidelines for treatment of latent TB must be followed i.e. INH treatment for 9 months. Patients diagnosed with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study.

6.5.5 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 Appendix 1. All subjects 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.

6.5.5.1 Hematology

Hemoglobin, platelets, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits as per Table 6-1.

6.5.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT (Gamma-glutamyl transferase), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin and uric acid will be measured at scheduled visits as per Assessment Schedule in Table 6-1.

6.5.5.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments at scheduled visits as per Table 6-1. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page.

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

6.5.5.4 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol, and triglycerides will be measured from a fasting blood sample that will be collected at Baseline and at visits indicated in Table 6-1.

6.5.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1. All ECGs must be performed on the ECG machines provided for the study. 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 Fridericia QT correction formula (QTcF) should be used for clinical decisions.

All ECGs will be centrally and independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG Investigator manual.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of investigational treatment. Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions eCRF page as appropriate.

6.5.7 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 in all women of childbearing potential at Screening visit 2. Urine pregnancy tests are performed at Baseline and at visits indicated in Table 6-1 in all female subjects of childbearing 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 subject 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:

- Abstinence
- Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK (United Kingdom): with spermicidal foam/gel/film/cream/vaginal suppository
- Use of established oral, injected or implanted hormonal methods of contraception**,** intrauterine device (IUD) or intrauterine system (IUS)

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

6.5.8 Tolerability of secukinumab

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

6.5.9 Immunogenicity

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 6-1.

In addition, if a subject 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.

[redacted]

Table 6-4 IG sample log

Week	IG Sample log
0	301
12	302
52	303
104	304
112	305

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

6.5.10 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/subject population. Quantiferon or PPD testing at screening is performed to rule out the presence of active tuberculosis. The frequency of the visits and the close medical monitoring will ensure possible safety concerns are properly addressed.

6.6 Other assessments

6.6.1 Resource utilization

No measures of Healthcare Resource Utilization (RU) will be collected in the study.

6.6.2 Pharmacokinetics

PK samples will be obtained for all subjects 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 6-1.

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.

[redacted]

PK samples should be collected at treatment Period 2 visits where a disease flare is confirmed. If a flare is confirmed at an unscheduled visit, the sample number will be 1001 as described in Table 6-5.

Table 6-5 PK sample log

Week	Time	Sample number	Dose reference ID
0 [1]	pre-dose	10	1
2 [1]	pre-dose	20	1
4 [1]	pre-dose	30	1
8 [1]	pre-dose	40	1
12 [1]	pre-dose	50	1
16 [2]	pre-dose	51	1
20 [2]	pre-dose	52	1
24 [1]	pre-dose	60	1
28 [2]	pre-dose	61	1
32 [2]	pre-dose	62	1
36 [2]	pre-dose	63	1
40 [2]	pre-dose	64	1
44 [2]	pre-dose	65	1
48 [2]	pre-dose	66	1
52 [1]	pre-dose	70	1
56 [2]	pre-dose	71	1
60 [2]	pre-dose	72	1
64 [2]	pre-dose	73	1
68 [2]	pre-dose	74	1
72 [2]	pre-dose	75	1
76 [1]	pre-dose	80	1
80 [2]	pre-dose	81	1
84 [2]	pre-dose	82	1
88 [2]	pre-dose	83	1
92 [2]	pre-dose	84	1
96 [2]	pre-dose	85	1
100 [2]	pre-dose	86	1
104 [1,3]	672h (Any time at visit)	90	2
112 [1,3]	2016h (Any time at visit)	100	2
Unscheduled[4]	Pre-dose	1001	

1. Required samples in every subject
2. PK sample only taken only from subjects with flare at that visit
3. Scheduled time is relative to last dose given at Week 100
4. Sample collected for subjects with confirmed flare in Treatment Period 2 occurring at an unscheduled visit.

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

[redacted]

[redacted]

[redacted]

7 Safety monitoring

7.1 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 subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

The occurrence of adverse events must be sought by non-directive questioning of the 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.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in 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 Appendix 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

[redacted]

- 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 7.2.1 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 7.2.1 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 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.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

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

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E2D Guideline).

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

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

7.2.2 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 subject 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.

[redacted]

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 Drug Safety and Epidemiology Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events 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 (S)AE):

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

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

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

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

[redacted]

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 on appropriate CRF pages, including the liver event overview CRF pages.

7.4 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 ≥24h) increase in serum creatinine of ≥25% compared to baseline 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 15-1 in Appendix 3 should be followed up by the Investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, 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.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF page irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Treatment Errors

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

7.6 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. Where possible, 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.

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

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of 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 CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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.

8.2 Data collection

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

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

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

8.3 Database management and quality control

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

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

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

[redacted]

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

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

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

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

[redacted]

8.4 Data Monitoring Committee

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

The DMC will periodically review patient disposition and safety data throughout the study as specified in the DMC Charter to ensure the safety of the patients. The DMC will be composed of external individuals with experience and expertise in the management of pediatric patients, including those with autoimmune conditions.

An independent statistician and statistical programmer will prepare the information for the DMC. Members of the DMC will not share any unblinded or partially-blinded information with anyone outside of the DMC. The Sponsor will remain fully blinded to any results throughout the study unless the DMC recommends changes in the conduct of the study (for example, early termination due to negative safety findings).

Details regarding the DMC process, responsibilities and membership will be described in the DMC charter.

8.5 Adjudication Committee

Not required.

[redacted]

9 Data analysis

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.

This trial is conducted as a three-part study. Data summaries may be presented separately for each study part and for combined study parts where appropriate.

Unless otherwise stated, all statistical tests will be two-sided at the 5% significance level and accompanied by two-sided 95% confidence intervals where appropriate.

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

The trial follows the recommendation of the Consolidated Standards of Reporting Trials (CONSORT) statement and results are reported for the intention-to-treat population (Schulz et al 2010).

9.1 Analysis sets

The following analysis sets will be used in this trial:

The randomized set will be defined as all subjects who were randomized in Treatment Period 2. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given in Treatment Period 2.

The Full Analysis Set (FAS) Treatment Period 2 will consist of all randomized patients who received at least one dose of study drug in Treatment Period 2. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization in Treatment Period 2.

The FAS Treatment Period 1 will consist of all patients who received at least one dose of study drug in Treatment Period 1.

The FAS Treatment Period 3 will consist of all patients who received at least one dose of study drug in Treatment Period 3. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization in Treatment Period 2.

The Safety Set for a treatment period will consist of all patients that received at least one dose of study drug in that treatment period. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

[redacted]

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized descriptively for the FAS for Treatment Period 1 and Treatment Period 2 by treatment group and overall. Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, 25% and 75% quantiles, and number of patients with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

Comparability of treatment groups in Treatment Period 2 with respect to the demographic and baseline characteristics will be assessed descriptively.

Relevant medical history/current medical conditions will be listed and summarized by system organ class and preferred term of the MedDRA dictionary.

9.3 Treatments

Study treatment

The exposure to study drug (number of injections) and duration of exposure (days) will be summarized and listed.

The number and percentage of patients taking medication and non-drug therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary (which employs the Anatomical Therapeutic Chemical classification system). Separate summaries will be provided for therapies that ended prior to Treatment Period 1 (prior therapies) and were active after the start of Treatment Period 1 (concomitant therapies).

The FAS corresponding to the study periods summarized will be used.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary efficacy endpoint will be time to disease flare event in Treatment Period 2, which is defined as the interval between the date of randomization to the date of first occurrence of disease flare event. The analysis of the primary efficacy endpoint will be based on the FAS Treatment Period 2.

All subjects who enter Treatment Period 2 will be followed until the sooner of either experiencing a disease flare or the end of Treatment Period 2 when 33 flare events are observed. Subjects who have not experienced flare event at the end of Treatment Period 2 data (as defined in Section 3.1) or discontinue prematurely from Treatment Period 2 before it closes for reasons other than experiencing a disease flare will be censored at the date of the last efficacy evaluation in Treatment Period 2.

Statistical model, hypothesis, and method of analysis

The primary objective for Treatment Period 2 of the study is to show superiority of secukinumab over placebo regarding the primary variable in Treatment Period 2.

The following statistical hypothesis will be tested once the required number of flares has been observed and the study has been stopped:

H_0: $1\text{-}S_{AIN}(t) \geq 1\text{-}\ S_{Pla}(t)$

H_A: $1\text{-}S_{AIN}(t) < 1\text{-}\ S_{Pla}(t)$

at each time point t, with $S_{AIN}(t)$ and $S_{Pla}(t)$ being the survivor functions in the secukinumab and placebo treatment group at time t.

The two treatment groups will be compared using a one-sided stratified Logrank test with the stratification factor of JIA category (ERA or JPsA) at the 2.5% level of significance. Hazard ratios and their associated 95% confidence intervals will be estimated based on a Cox proportional hazards model with treatment and stratification factor as explanatory variables.

The Kaplan-Meier estimates of the proportion of patients with the flare event at selected landmark points, along with its 95% confidence intervals using Greenwood's formula, will be provided. The primary analysis will be based on the FAS for Treatment Period 2.

Handling of missing values/censoring/discontinuations

All patients in Treatment Period 2 will have a value of time to flare either by having an event or being censored.

Supportive analyses

For sensitivity purposes, the primary analysis will be repeated using an unstratified log-rank test.

The primary analysis will be repeated where patients discontinuing the study for any reason will be considered as having flare at the time of study discontinuation.

Subgroup analyses for the primary efficacy variable will be performed for stratification factor: JIA category (ERA or JPsA).

Analysis of secondary variables

9.4.2 Efficacy variables

The analysis of secondary variables is descriptive only for FAS. Summary statistics will be presented. Summary statistics for continuous variables include N, mean, standard deviation, minimum, median, maximum, 25% and 75% quantiles, and number of patients with non-missing data. For binary or discrete variables the number of subjects in each category and relative frequencies will be provided.

The following secondary efficacy endpoints will be analyzed for all patients and each JIA category by descriptive statistics in Treatment Period 1:

- JIA ACR 30/50/70/90/100 and inactive disease status
- Each JIA ACR core component
- Change from baseline Juvenile Arthritis Disease Activity Score (JADAS) score
- Total enthesitis count
- Total dactylitis count

[redacted]

The following secondary efficacy endpoints will be analyzed for all patients and each JIA category by descriptive statistics in Treatment Period 2, and/or other periods, as appropriate:

- JIA ACR 30/50/70/90/100 and inactive disease status

[redacted]

9.4.4 Safety variables

The analysis of safety data may be provided for each Treatment Period separately and all periods combined, as appropriate. The analysis of safety data will be conducted on the Safety Set, which includes subjects who receive any study treatment and have at least one post-baseline safety assessment. All data will be analyzed according to the treatment actually received.

The safety variables to be analyzed include Adverse events (AEs), clinical laboratory tests (hematology and chemistry), physical examination results, ECGs, and deaths. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

9.4.4.1 Adverse events

Adverse events will be coded using the MedDRA dictionary that provides the primary system organ class and preferred term information. Adverse events will be presented in two parts:

- Adverse events (including infections)
- Infectious adverse events

Adverse events will be summarized by presenting, for each study period and each treatment group, the number and percentage of patients having any adverse event, having any adverse event in each primary system organ class and having each individual adverse event based on the preferred term. All other information collected (e.g. severity, relationship to study drug) will be tabulated and listed as appropriate.

Deaths, serious adverse events, and adverse events leading to discontinuation of study drug will be summarized by primary system organ class and preferred term and listed.

9.4.4.2 Vital signs

Vital signs data will be summarized by presenting descriptive statistics for the absolute values and changes from baseline. All information collected will be listed by patient and abnormal values (see Appendix 1) will be flagged.

9.4.4.3 Laboratory evaluations

Laboratory data will be summarized in the same way as vital signs. In addition, shift tables based on normal ranges and incidence rates of notable abnormalities (see Appendix 1) will be presented.

Pharmacokinetics

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

[redacted]

9.5 Interim analyses

A PK interim analysis is planned at the end of Treatment Period 1 in the first 10 patients enrolled in each weight category (< and ≥ 50kg) in order to confirm the predicted doses. This will be done by using previously developed population PK model [AIN457 in RA – Population PK modeling report] and comparing predicted individual PK profiles with actual PK observations (e.g., superimposing the data with simulations from the model). Only Treatment Period 1 PK data for these patients will be included in this interim analysis thus Treatment Period 2 data will remain blinded. No alpha level adjustment will be necessary.

The PK interim analysis for both weight category subgroups may not be necessary if data from currently ongoing pediatric psoriasis study is available.

Novartis will perform the primary efficacy analysis of Treatment Period 2 (time to flare) when Treatment Period 2 is completed. No alpha level adjustment will be necessary.

Interim safety review

The DMC will review unblinded safety data as described in Section 8.4. These results will only be available to DMC members and the independent statistician and statistical programmer who will generate the output for DMC review. All unblinded individuals will keep results confidential up to final clinical data base lock and unblinding.

9.6 Sample size calculation

It is assumed that the Flare-free time follows an exponential distribution with a constant hazard ratio.

The hazard ratio of flare events for the secukinumab group relative to placebo group is estimated to be 0.32 in Treatment Period 2. The hazard ratio of 0.32 was used to establish the sample size necessary in Treatment Period 2 and consequently Treatment Period 1 (derived from the median time to disease flare for ETANERCEPT and placebo in LOVELL et. al. 2000). With the hazard ratio assumed to be 0.32, 33 flares are necessary to detect a statistically significant difference between secukinumab and placebo assuming 90% power and a 1-sided significance level of 0.025. No data is available to estimate the placebo hazard rate beyond 6-months. Given that uncertainty and a maximum 21-month follow-up in Treatment Period 2, the total sample size necessary to achieve 33 flares in Treatment Period 2

[redacted]

is estimated to be at least 60 and at most 80 patients. Assuming approximately 70% to 85% of patients respond in Treatment Period 1, the estimated minimum number of patients treated in Treatment Period 1 is between 70 and 86. Under the assumption of 12 months of accrual duration, the total maximum expected study duration is 33 months. The expected number of flare events is 12 and 21 respectively for secukinumab and placebo group in Treatment Period 2.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), 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/REB approval.

Women 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.

[redacted]

[redacted]

10.3 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/guardians. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

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.

[redacted]

11.1 Protocol Amendments

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

12 References (available upon request)

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13 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,
  - ≥1.5xULN,
  - ≥ 2xULN
- ALP
  - >ULN
  - ≥1.5xULN,
  - ≥2xULN,
  - ≥3x ULN
  - ≥5xULN
- ALT and/or AST >3x-, 5x-, 10x ULN accompanied by TBL >2xULN
- ALT or AST >3x ULN and TBL >2x-, and ALP >2 x ULN.
- ALP >3x ULN and TBL >2x ULN

- Gamma-Glutamyltransferase (GGT):
  - >ULN
  - ≥3 x ULN
  - ≥5 x ULN
- 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) (Schwartz et al 2009).

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

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

[redacted]

- 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 13-1 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

[redacted]

Table 13-2 Recommended dimensions for blood pressure cuff bladders

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

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

[redacted]

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

Table 14-1 Liver Event and Laboratory Trigger Definitions

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

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

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

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

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

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

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

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

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

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline and is above ULN	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline and is above the ULN	Follow up within 24-48h 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 24-48h 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 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.

Table 16-1 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

17 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

[redacted]

18 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

19 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 6th 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.

20 Appendix 8: ACR definition of flare for JIA

Both criteria 1 and 2 must be fulfilled to meet the definition of a disease flare. Criteria changes described are relative to the End of Treatment Period 1 (Week 12 visit).

1. ≥ 30% worsening in at least 3 of the 6 ACR response variables
   - Physician global assessment of overall disease activity
   - Parent or patient global assessment of overall well-being
   - Functional ability (CHAQ©)
   - Number of joints with active arthritis
   - Number of joints with limited range of motion
   - Index of inflammation: CRP
2. ≥ 30% improvement in no more than 1 of the 6 ACR response variables

Contingencies:

- if the Physician or Parent Global Assessment is one of the 3 response variables used to define flare, worsening of ≥ 20 mm (1-100mm visual analogue scale) must be present;
- if the number of active joints or joints with limitation of motion is one of the 3 response variables used to define flare, worsening in ≥ 2 joints must be present;
- if CRP is one of the 3 response variables to define flare it must be above normal range.

21 Appendix 9: 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 components with no more than one component 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 Subject'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 (mg/L)

22 Appendix 10: Criteria for defining clinical inactive disease

Criteria for defining clinical inactive disease in ERA/JPsA

Inactive disease:

- No joints with active arthritis
- CRP 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
- No Uveitis

Adapted from Wallace CA, et al (2011).