NOVARTIS

Clinical Development

CAIN457/Secukinumab/Cosentyx®

Clinical Trial Protocol [CAIN457F2304E1 / NCT03769168]

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

Statistical Analysis Plan (SAP)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
BMI	Body Mass Index
BP	Blood Pressure
CHAQ©	Childhood Health Assessment Questionnaire
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CV	coefficient of variation
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
JPsA	Juvenile Psoriatic Arthritis
LLN	Lower Limit Normal
LOCF	Last Observation Carried Forward
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mmHg	Millimeter mercury
PK/PD	Pharmacokinetics/Pharmacodynamic
PRO	Patient-reported Outcomes
PsA	Psoriatic Arthritis
QoL	Quality of Life
RA	Rheumatoid Arthritis
RAP	Report and Analysis Process
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation
SJC	Swollen Joint Count
SpA	Spondyloarthritis

SOC	System Organ Class
TFLs	Tables, Figures, Listings
TJC	Tender Joint Count
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

Data will be analyzed by [redacted] according to the data analysis section 12 of the study protocol CAIN457F2304E1 version 00. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

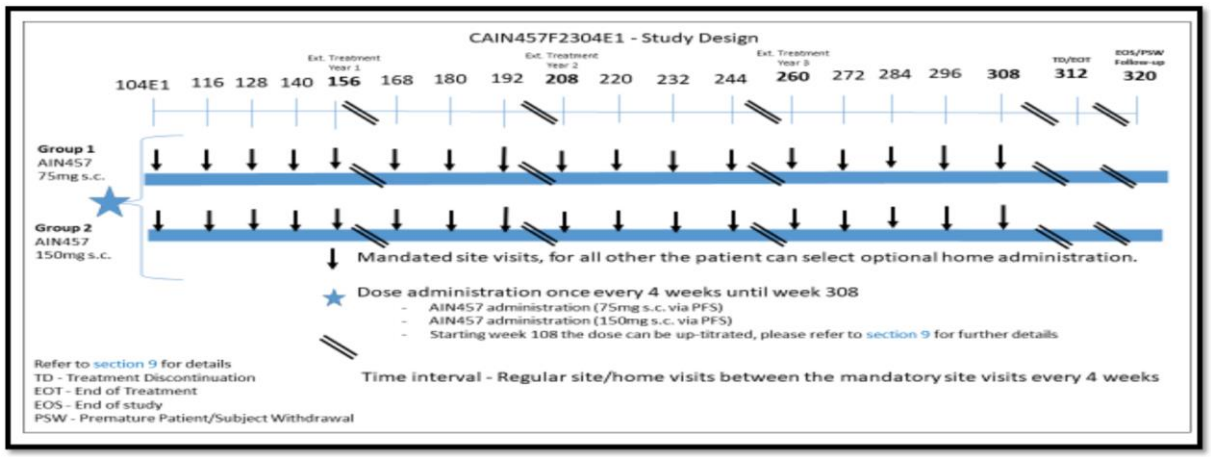
This document contains the detailed statistical and analytical plans for full analysis of CAIN457F2304E1 study.

1.1 Study Design

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

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

Figure 1-1 Study design



The following study periods will be considered for analysis:

- **Entire treatment period:** W104E1 (Extension trial start) to Week 312 (EOT), for safety analysis, exposure including follow-up period up to last dose + 84 days.
- **Entire study period:** W104E1(Extension trial start) to Week 320 (EOS), including follow-up period visits.

1.2 Study objectives and Endpoints

The primary objective of study is to evaluate the long-term efficacy of secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 312 in patients

with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.

Following are the secondary objectives

- To evaluate the long-term safety, tolerability and immunogenicity of secukinumab as assessed by vital signs, clinical laboratory variables and adverse events monitoring over time up to Week 312 and follow-up period
- To evaluate the long-term effect of secukinumab treatment for all patients and each JIA category with respect to:
  - JIA ACR 50/70/90/100
  - Each JIA ACR core component
  - Inactive disease status
  - Juvenile Arthritis Disease Activity Score (JADAS)
  - Total Enthesitis count
  - Total Dactylitis count
- To evaluate pharmacokinetics (PK) of secukinumab

[redacted]

- [redacted]
- [redacted]

A summary of primary, secondary [redacted] endpoints are included in Table 1-1 below.

Table 1-1 Primary, secondary [redacted] efficacy variables

Variable	Type
JIA ACR30 Response over time up to week 312	Primary
JIA ACR 50/70/90/100 over time up to week 312	Secondary
Each JIA ACR Core Components over time up to week 312	Secondary
Inactive Disease Status	Secondary
Change from baseline of JADAS Score	Secondary
Total Enthesitis count	Secondary
Total Dactylitis count	Secondary
Secukinumab serum concentrations and derived PK parameters	Secondary
[redacted]	

2 Statistical Methods

2.1 Data analysis general information

Data will be analyzed by the [redacted], using SAS version 9.4 or above.

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

Summary statistics for continuous variables will include the number of patients (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum.

For categorical or binary variables, the number and percent of patient in each category will be presented. The 95% confidence intervals will be provided as appropriate to evaluate the efficacy of the treatment regimens.

Baseline from core study (CAIN457F2304) and Week 104E1 visit data will be presented, as appropriate.

All listings will be presented by treatment sequence.

2.1.1 Study Day 1 and other study days

The first day of administration of study treatment (first dose) in extension study is defined as Study Day 1 or Day 1 (i.e. Week 104E1).

All other study days will be labelled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose] +1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor “Day 0” will not be used.

2.1.2 Baseline, and post-baseline definitions

In general, a *baseline* value refers to the core study and is the last measurement made prior to administration of the first dose of study treatment in core. Baseline information will be presented appropriately in the “by visit” summaries in both safety and efficacy tables.

A post-baseline value refers to a measurement taken after the first dose of study treatment in core study.

For early discontinuation visit mapping in different assessments, the early discontinuation week will be the next visit of corresponding assessment based on the patients’ last scheduled visit.

2.1.3 Day of last dose of study treatment

The date of last dose will be collected via the CRF. The subject’s exposure will be calculated considering the end of treatment period visit. The end of treatment period will be defined as the last dose plus 84 days or last visit whichever occurs earlier. i.e., for subjects who discontinued

or have their last visit earlier than last dose plus 84 days, the end of study treatment exposure will be the date of the last study visit in the corresponding treatment period.

On-treatment event is defined as assessments within last dose plus 84 days, for safety analysis (i.e., Lab, Vitals, and ECG).

2.1.4 Visit windows

During extension trial, only nominal planned CRF visits will be considered for analysis of efficacy and safety by visit summary tables. Unplanned visits will not be included in summaries.

2.2 Analysis sets and treatments

2.2.1 Analysis Sets

The following analysis sets will be used for the data analysis:

Full Analysis Set (FAS): The Full Analysis Set (FAS) will consist of all patients who enrolled in the extension trial.

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

[redacted]

2.2.2 Treatment groups

Treatment groups for efficacy and safety will be used as follows:

Endpoint	Table/Figure/Listing	Assigned Treatment group	Actual Treatment group sequence	Additional comment
Disposition, Protocol deviations, Demographic and Baseline Characteristics	Table	AIN457 75 mg	AIN457 75 mg AIN457 150 mg AIN457 300 mg Total	Treatment group along with sequence will be used for summaries
		AIN457 150 mg	AIN457 150 mg AIN457 300 mg Total	
		Any AIN457	AIN457 75 mg AIN457 150 mg AIN457 300 mg Total	This includes number of subjects treated with 75 mg or 150 mg or 300 mg dose group at least once

Endpoint	Table/Figure/Listing	Assigned Treatment group	Actual Treatment group sequence	Additional comment
Efficacy	Tables	AIN457 75 mg		For efficacy tables, we will report assigned and actual treatment groups
		AIN457 150 mg		
		AIN457		As pooled treatment group [total of assigned treatment group at start of extension trial (AIN457 75 mg + AIN457 150 mg)].
	Figures	AIN457 75 mg (Total)	75 mg to 75 mg	Treatment group along with sequence will be used for figures [redacted]
			75 mg to 150 mg	
			75 mg to 150 mg to 300 mg	
		AIN457 150 mg (Total)	150 mg	
			150 mg to 300 mg	
	Listing	AIN457 75 mg		Original treatment group
		AIN457 150 mg		
AEs, SAEs, and Concomitant medication	Tables	Any AIN457 75 mg		This includes number of subjects treated with 75 mg dose group at least once
		Any AIN457 150 mg		This includes number of subjects treated with 150 mg dose group at least once
		Any AIN457 300 mg		This includes number of subjects treated with 300 mg dose group at least once
		Any AIN457		This includes number of subjects treated with 75 mg or 150 mg or 300 mg dose group at least once

Endpoint	Table/Figure/Listing	Assigned Treatment group	Actual Treatment group sequence	Additional comment
Lab and Vital signs by visit	Tables	AIN457 75 mg	AIN457 75 mg	Treatment received at that visit.
			AIN457 150 mg	
			AIN457 300 mg	
			Total	
		AIN457 150 mg	AIN457 150 mg	
			AIN457 300 mg	
			Total	
	Listings	AIN457 75 mg		Assigned treatment group at start.
		AIN457 150 mg		

2.3 Subject disposition, background and demographic characteristics

2.3.1 Subject disposition

The number of subjects enrolled in the extension will be presented. The number and percentage of subjects in the FAS who completed the period up to week 312 and/or the follow up visit and who discontinued the treatment or study prematurely (including the reason for discontinuation) will be presented for each treatment group. Also, separate disposition summary report will be created [redacted].

For each protocol deviation (PD), the number and percentage of subjects for whom the PD applies will be tabulated.

2.3.2 Demographic and baseline characteristics

Demographics and baseline characteristics will be presented for FAS.

The following common background and demographic variables will be analyzed according to the treatment group or sequence (when dose escalation occurs).

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (2 - < 6 years, 6 - < 12 years and 12 - < 18 years)
- Gender
- Race

- Ethnicity
- Weight categories (< 50 kg or >= 50 kg)
- Smoking status at baseline

Patient demographic and baseline characteristics will be derived from the core study data and demographics captured in the extension database will not be summarized.

2.4 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. Data collected for core study will be used for the extension as well. Data will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Disease history and baseline characteristics will be presented by treatment group.

Unless otherwise specified, analyses will be based on the extension FAS.

2.5 Study medication

The analysis of study treatment data will be based on the safety set. The number of active injections will be summarized by dose received. The duration of exposure to study treatment will also be summarized by dose groups. In addition, the number and percentage of subjects with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Duration of exposure will be calculated as time from first dose of secukinumab in extension study to the minimum of (last dose of the treatment + 84 days) and (last visit date).

Duration of exposure (days) = min (last visit date, last dose date +84) – first dose date +1

Duration of exposure (years) = duration of exposure (days) / 365.25

Duration of exposure (100 subject years) = duration of exposure (years) / 100

The analyses of duration of exposure described above will be done for each AIN457 dose level and also for the entire study treatment period.

2.6 Concomitant medication

2.6.1 Concomitant medication in extension

Concomitant medications in extension will be summarized by dose groups based on Safety Set. Any medication given at least once between the start of the first dose in this extension trial and the date of the last study visit + 84 days in the extension study, will be a concomitant medication, including those which were started before Week 104E1 visit and continued into the extension study where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and preferred term according to the Novartis Drug and Therapy Dictionary (NovDTD). Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular preferred term.

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

Prior surgeries and procedures are defined as surgeries and procedures executed prior to the first study dose. Any surgeries and procedures started between the day of the first dose of study treatment in this extension trial and within 84 days after the last dose will be concomitant surgeries and procedures, including those which were started pre-baseline and continued into the period where study treatment is administered.

2.7 Analysis of Primary Variable(s)

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

2.7.1 Handling of missing data

For the calculation of JIA ACR, partially missing data for JIA ACR components will be imputed by Last Observation Carried Forward (LOCF).

Missing data for JIA ACR30 variables will not be imputed and observed data except JIA ACR components will be used in all analysis.

2.7.2 Statistical model, hypothesis, and method of analysis

No formal hypotheses are planned for this study.

The proportion of patients meeting the JIA ACR30 criteria will be descriptively summarized and presented graphically for all patients by treatment groups, and by JPsA and ERA subtypes, as appropriately. Treatment efficacy will be evaluated by the 95% confidence interval of the proportion of patients responding to treatment according to the JIA ACR criteria.

Results will be presented for the FAS.

2.8 Analysis of secondary [redacted] variables

Secondary variables include:

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

[redacted]

- [redacted]

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

All these above efficacy variables will be analyzed on the FAS (unless otherwise specified) for all applicable analysis visits based on the observed data. The summary table will display in assigned treatment and actual treatment in JPsA, ERA, and total categories. Additionally, data from the assigned AIN457 treatment groups will be pooled (AIN457 75 mg + AIN457 150 mg) and reported as "AIN457" for each visit, for efficacy outputs.

For binary variables, the proportion of responders along with the 95% CI will be presented by dose groups over analysis visits.

For continuous variables, the change from baseline (baseline of core) when available, will be summarized.

Additionally, observed data tables will summarize the JIA ACR30, ACR50, ACR70, ACR90 and ACR100 response following dose escalation when assessed. Results will be illustrated in line plots.

Also, individual subject listings of the JIA ACR components as well as for the JIA ACR30/50/70/90/100 response will be given.

[redacted]

Graphical presentation using line plot or bar charts of secondary [redacted] will also be included as appropriate.

[redacted]

2.9 Efficacy evaluation

2.9.1 Description of efficacy variables

2.9.1.1 JIA ACR response criteria

Standard ACR pediatric Criteria (JIA ACR criteria) consist of 6 core components which will be assessed as scheduled in [Table 8-1 of the protocol]. 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 patient's overall wellbeing on a 0-100 mm VAS from 0 mm = very well to 100 mm = very poor.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ©)
- Number of active joints using the ACR definition (any joint with swelling or in the absence of swelling, limitation of motion accompanied by either pain on motion or tenderness not due to deformity)
- Number of joints with limited range of motion
- Laboratory measure of inflammation: CRP (local) (mg/L)

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

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

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

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

2.9.1.3 Parent's/patient's Global Assessment of patients 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.

2.9.1.4 Childhood Health Assessment Questionnaire (CHAQ©)

The Childhood Health Assessment Questionnaire (CHAQ©), [Protocol Section 16.6], will be used to assess physical ability and functional status of patients as well as quality of life. The disability dimension consists of multiple choice and VAS items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from four response categories, ranging from 'without any difficulty' to 'unable to do'.

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

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. If AEs or SAEs are

confirmed, then the physician must record the events as per instructions given in [Section 10.1.1] and [Section 10.1.2 of the protocol]. Investigators should not encourage the patients and/or parents to change the responses reported in the PRO questionnaires.

2.9.1.5 Active joint count

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

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

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

2.9.1.6 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 [Protocol Section 8.3.1.7] will also be assessed for limitation of motion excluding the 2 sternoclavicular, 2 acromioclavicular joints as well as the 2 sacroiliac joints.

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

2.9.1.7 C-reactive Protein (CRP)

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

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

2.9.1.8 Tender and Swollen Joint Count

Tender 75 joint counts (TJC)

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

- Temporomandibular joints: 2
- Sternoclavicular joints: 2
- Acromioclavicular joints: 2
- Shoulders: 2
- Elbows: 2
- Wrists: 2
- Hands:

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

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

2.9.1.9 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.

2.9.1.10 Inactive Disease Status

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

- No joints with active arthritis
- No uveitis
- CRP (local) value within normal limits for the laboratory where tested or, if elevated, not attributable to 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 ≤ 10mm)

The absence of patient-reported morning stiffness attributable to JPsA or ERA lasting ≥15 minutes.

2.9.1.11 Juvenile Arthritis Disease Activity Score (JADAS)

The Juvenile Arthritis Disease Activity Score (JADAS) is a composite disease activity score developed and validated for juvenile idiopathic arthritis (JIA). JADAS consists of four components: physician global assessment of disease activity on a 10 cm VAS (0=no activity, 10=maximum activity); parent/patient global assessment of well-being on a 10 cm VAS (0=very well, 10=very poor); number of joints with active disease; and an inflammatory marker (ESR) (Consolaro, 2009).

The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (MCP) (from first to third), proximal interphalangeal (PIP) joints, hips, knees, and ankles.

The JADAS-71 includes the following joints: cervical spine, temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, MCP, PIP, Distal interphalangeal, hip, knee, ankle, subtalar, tarsometatarsal – *replaced by intertarsal in our study*, metatarsophalangeal, foot interphalangeal.

The JADAS is calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0–57, 0–101 for the JADAS-27 and JADAS-71 respectively.

JADAS-CRP is adapted by substituting ESR with CRP as the inflammatory marker (Nordal 2012). CRP is truncated to a 0–10 scale according to the following formula: (CRP (mg/l) − 10)/10, similar to the truncated ESR used in JADAS. Before calculation, CRP values <10 mg/l will be converted to 10 and CRP values >110 mg/l will be converted to 110.

The following formula to calculate the JADAS27 using CRP (mg/L) will be used:

JADAS27-CRP = (27 AJC)* + Physician Global Assessment of Disease Activity (0-10cm) + Parent's or Patient's Global Assessment of Patient's overall well-being (0-10cm) + CRP (standardized in mg/dl unit (=CRP/10).

27 AJC=Active joints count based on 27 joints list (see Table 2-1 below)

The following formula to calculate the JADAS71 using CRP (mg/L) will be used:

JADAS71-CRP = (71 AJC)* + Physician Global Assessment of Disease Activity (0-10cm) + Parent's or Patient's Global Assessment of Patient's overall well-being (0-10cm) + CRP (standardized in mg/dl unit (=CRP/10).

71 AJC=Active joints count based on 71 joints list (see Table 2-1 below)

The corresponding score will be calculated only when all components are available.

[redacted]

Table 2-1 Joints Identification for Disease Activity Scores and Indexes

*Table: Joints index

	In CRF	Side	71-joint	27-joint
Cervical spine	Yes		+	+
Temporomandibular	Yes	R/L	+	–
Sternoclavicular	Yes	R/L	+	–

	In CRF	Side	71-joint	27-joint
Acromioclavicular	Yes	R/L	+	–
Shoulder	Yes	R/L	+	–
Elbow	Yes	R/L	+	+
Wrist	Yes	R/L	+	+
Metacarpophalangeal (MCP)				
1	Yes	R/L	+	+
2	Yes	R/L	+	+
3	Yes	R/L	+	+
4	Yes	R/L	+	–
5	Yes	R/L	+	–
Proximal interphalangeal (PIP)				
1	Yes	R/L	+	+
2	Yes	R/L	+	+
3	Yes	R/L	+	+
4	Yes	R/L	+	+
5	Yes	R/L	+	+
Distal interphalangeal				
2	Yes	R/L	+	–
3	Yes	R/L	+	–
4	Yes	R/L	+	–
5	Yes	R/L	+	–
Hip	Yes	R/L	+	+
Knee	Yes	R/L	+	+
Ankle	Yes	R/L	+	+
Subtalar	Yes	R/L	+	–
Tarsometatarsal	INTERTARSAL	R/L	+	–
Metatarsophalangeal				
1	Yes	R/L	+	–
2	Yes	R/L	+	–
3	Yes	R/L	+	–
4	Yes	R/L	+	–
5	Yes	R/L	+	–
Foot interphalangeal (Toe)				
1	Yes	R/L	+	–
2	Yes	R/L	+	–
3	Yes	R/L	+	–
4	Yes	R/L	+	–
5	Yes	R/L	+	–

2.9.1.12 Assessment of duration of morning stiffness

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

2.9.1.13 Assessment of Uveitis due to JIA

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

2.9.1.14 Total enthesitis count

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

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

2.9.1.15 Total dactylitis count

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

[redacted]

2.10 Safety evaluation

Safety analyses will be summarized descriptively on the safety set.

Subjects who switch treatment during the study (e.g. dose escalation) will be counted to both groups using the appropriate start and stop exposure date.

Patient status of COVID-19 will be included in AE and Protocol deviation summary and listings.

2.10.1 Adverse events

Treatment emergent adverse events (i.e. events started after the first dose of secukinumab in extension study, or events present prior to the first dose of secukinumab but increased in severity based on preferred term and within 84 days after last dose of secukinumab) will be summarized. All AEs will be included in the listing, with flags for treatment emergent.

A separate treatment emergent adverse events summary report will be created [redacted].

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

[redacted]

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

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

The safety analyses that will be performed for treatment emergent AEs, LABS and Vital signs for each analysis period is described in the table below.

An overview of the safety analyses and which will be performed for each analysis period is described in Table 2-2

Table 2-2 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/lab criteria
Entire treatment period	crude incidence [redacted]	crude incidence	crude incidence	crude incidence [redacted]	crude incidence [redacted]	crude incidence

[redacted]

The tables will include data from the extension part of the trial.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than X% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

Here, the threshold value X is set to 2-5 (%) but it may be updated following review of the dry run outputs.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.10.2 Laboratory data

The summary of lab data will only include on-treatment data, which are defined as those lab assessments after the first dose of secukinumab in extension study and on or before last dose + 84 days.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry, and urinalysis). In addition to the individual laboratory parameters the ratio “total cholesterol / HDL” will be derived and summarized.

For urinalysis, frequency tables across visits will be presented.

Descriptive summary statistics for the absolute value at study visits as well as the change from baseline to extension study visits will be presented in tabular fashion. These descriptive summaries will be presented by laboratory test and treatment dose, dose sequence. Change from baseline will only be summarized for subjects with both baseline (from core study) and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

The maximum change (maximum decrease and maximum increase) from baseline for each lab parameter, will also be analyzed. These summaries will be presented by laboratory test and treatment dose, dose sequence.

In addition, shift tables will be provided for all parameters to compare a patient’s baseline laboratory evaluation relative to the visit’s observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether the baseline value was normal, low, or high These summaries will be presented by laboratory test for all patients by dose groups and/or possibly by JPsA and ERA subtypes. Shifts will be presented by visit as well as for most extreme values post-baseline.

Reported laboratory assessments with either a less than or greater than sign (“<” or “>”) will be used for analysis after removal of the sign and conversion to standard unit. These laboratory data will be displayed in listings using the standard unit with the reported sign (“<” or “>”).

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-3: hemoglobin,

platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in the initial treatment phase of the core study. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Table 2-3 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Life-threatening consequences: urgent intervention indicated
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - <=LLN
  - <0.8 x LLN
- LDL, cholesterol, triglycerides:
  - >=ULN
  - >1.5 x ULN
  - >2.5 x ULN

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-4:

Table 2-4 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.
Notes:1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria	

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g. a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

2.10.3 Vital signs

The summary of vital signs will only include on-treatment data, which are defined as those vital sign measurements after the first dose of extension study treatment and on or before last dose + 84 days.

Analysis in vital sign measurement, using descriptive summary statistics for the change from baseline for each post-baseline visit in extension, will only be presented for subjects with both a baseline (of core study) and post baseline values. These descriptive summaries will be presented by vital sign and treatment dose, dose sequence. Change from baseline will be calculated as:

change from baseline = post-baseline value – baseline value

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

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-5 below.

Table 2-5 Criteria for notable vital sign abnormalities

Age group	Systolic BP(mmHg)	Diastolic BP(mmHg)	Pulse (bpm)
2-5 yrs	76-120	45-80	55-120
6 -11 yrs	90-130	50-80	50-105
12-17 yrs	90-145	55-90	45-95
18 yrs and over	90-140	60-90	60-100

Note: The age is the age at the time of the visit. It will be derived as follows:

Integer part of ((assessment date – birth date) / 365.25)

Individual subject listing of vital signs and a listing for the newly occurring notably abnormalities will be provided.

Additionally, age and body weight over visit related analysis will be performed [redacted].

2.10.4 Electrocardiogram (ECG)

ECG information was collected locally at the site and not collected in the database for extension study and will not be analyzed for the study.

2.10.5 Immunogenicity

Summary statistics will be provided for the percent of subjects with blood samples for immunogenicity (anti-AIN457 antibodies). The summary statistics will include extension study immunogenicity summary.

2.10.6 Compound specific safety evaluation

Safety topics of interest, such as risks defined in the Safety Profiling Plan (SPP), Risk Management Plan or Safety topics of interest regarding signal detection or routine analysis are defined in the most recent version of Program Case Retrieval Sheet and can be retrieved via the "SP" flag.

The crude incidence [redacted] for potential compound and class-related risks and routine risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

2.11 Pharmacokinetics

All 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 as well as 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 (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. n(log) is the number of patients with non-zero concentrations. The formula for deriving the geometric mean and CV (%) is as following:

- CV (%) = (SD/mean) *100,
- geometric mean=exp ((sum of log transformed data) / number of non-missing data points after log transformation),
- geometric CV = sqrt (exp (variance of log-transformed data)-1) *100.

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed by treatment sequence.

Values below lower limit of quantification/below detection limit will be imputed by 0.

3 Sample size calculation

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

4 Change to protocol specified analyses

Prior and concomitant therapies will be reported based on the Safety Set (instead of FAS specified in the protocol), since Safety Set is the standard analysis set for reporting prior and concomitant therapies.

[redacted]

ECG information was collected locally and not collected in the database. So, no analysis will be performed for ECG parameters.

[redacted]

Updated the Full Analysis Set (FAS) definition as per the study requirement.

Corrected the typo in “Figure 1-1 Study design” diagram, Week 168 appears two times, so corrected visit information as Week 168 and Week 180.

[redacted]

6 Appendix

6.1 Imputation rules

6.1.1 Study drug

Any partial dates will be imputed as follows:

The earlier day will be taken from below

- The last day in the month and
- The end day of the corresponding Treatment Period

6.1.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 31DECYYYY, date of death).
2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death).
3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

1. If the AE start date 'year' value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date 'year' value is less than the treatment start date year value, the AE started before treatment. Therefore:

   If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).

   Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

6.1.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JULYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

6.2 Statistical methodology and assumptions

6.2.1 Analysis of continuous data

6.2.1.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group.

6.2.2 Analysis of binary (and categorical) data

6.2.2.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well based on the score method including continuity correction Newcombe (1998):

With z as (1-alpha/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$

Then the lower limit is

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

Note: if $L > p$ then $L = p$ and if $U < p$ then $U = p$. For percentages multiply p, L and U by 100.

6.2.3 Crude incidence and related risk estimates

6.2.3.1 Crude incidence and 100*(1-α) % confidence interval

For n subjects, each at risk to experience a certain event with probability π, the crude incidence is estimated as p=x/n, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With z as (1-α/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$.

Then the lower limit is:

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

Note: if L > p then L = p and if U < p then U = p.

[redacted]

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