NOVARTIS

Clinical Development – General Medicine

AIN457/Secukinumab

AIN457A2311 / NCT03668613

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

Statistical Analysis Plan (SAP)

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26-Apr-2019	Prior to week 16 dry run	Vital sign standard pediatric reference range assigned	Updated to reference ranges	2.8.4.2
04-Jun-2019	Prior to week 16 dry run	Clarification	Efficacy subgroups for summary stats defined in a table	2.2.2
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04-Jun-2019	Prior to week 16 dry run	To follow current process	Remove PD summary by major and minor classification	2.3.1

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04-Jun-2019	Prior to week 16 dry run	eGFR added clarification for liver function summaries Align to A2310-neutropenia (covered by important risk table) Align to A2310 liver related criterion	Added ranges for eGFR Summaries by visit will be presented Remove neutropenia separate neutropenia summary and listing Table 2.10 liver enzyme criteria updated to make consistent with 2310 criteria. No INR	2.8.3
04-Jun-2019	Prior to week 16 dry run	Align with A2310 amendment	Shift summaries added – at week 52 and every 52 weeks thereafter [redacted]	2.8.4.3
04-Jun-2019	Prior to week 16 dry run	Change treatment labels	Secukinumab reported as AIN457	
04-Jun-2019	Prior to week 16 dry run	Align with A2310 amendment	Cdc charts used Height, weight and BMI summaries by low/normal/high thresholds added	2.8.4.4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
04-Jun-2019	Prior to week 16 dry run	General clarification and improvements as needed		2.1.1.4, 2.3, 2.4.1.2, 2.5.1.1
[redacted]				
12-Sep-2019	Prior to week 16 dry run	Group all efficacy together	Moved other efficacy endpoint analysis from Section 2.13 to 2.7	2.7 and 2.13
30-Sep-2019	Prior to week 16 lock	Per HA discussions added further summaries	Summaries by age, body weight strata and disease severity strata Summaries by weight and dose for PK, AE and PASI/IGA response Summary of derived PK parameters AUC and Cmax	2.2.1, 2.5 to 2.8 1.2, 2.9

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Sep-2019	Prior to week 16 lock	Further to HA discussions added IA at week 24	Added week 24 IA. Summaries on entire treatment/study period	1.1, 2.8, 2.14
2-Oct-2019	Prior to week 16 lock	Ae tables by weight and dose	Additional outputs	2.8.1
2-Oct-2019	Prior to week 16 lock	Additional scope for DMC	Panel graphs for lab analytes added. AE figure added	2.8.1, 2.8.3
2-Oct-2019	Prior to week 16 lock	Clarify abnormality criteria for vital signs	New table added	2.8.4
2-Oct-2019	Prior to week 16 lock	Placebo prior finalized ahead of dbl	Table added documenting mixtures for placebo data	2.5.1
2-Oct-2019	Prior to week 16 lock	bayesian align text to the script	Rewording. Clarification on two models presented. Remove script from appendix and replace with model syntax	
2-Oct-2019	Prior to week 16 lock	AEs reported by weight and dose group	Additional table added for TEAEs	2.8.1
22-Oct-2019	Prior to week 16 lock	Updated notable VS table	align with AIN457 adult studies for age >=18	
1-July-2020	Prior to week 52 lock	Covid-19 pandemic impact	Additional outputs added	4
3-July-2020	Prior to week 52	ECG reporting	Report on-treatment/on-study	2.8.4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
6-July-2020	Prior to week 52 lock	Long term efficacy reporting	Primary method observed, and MI as sensitivity	2.5.3
20-June-2020	Prior to week 52	Per A2310 alignment	PASI score by subgroup dropped, efficacy analysis performed by dose and weight	2.7
8-July-2020	Prior to week 52	Drug taken at home due to covid, no longer required	Dropped home administration by visit outputs	2.4.1
8-July-2020	Prior to week 52 lock	General improvement	Remove internal hyperlinks and drop SOPs references. Further clarifications and tidy up.	

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body surface area
CHMP	Committee for medicinal products for human use
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report/record form
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FIR	First Interpretable Results
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase
HGB	Hemoglobin
IGA	Investigator's global assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IRT	Interactive response technology
LLN	Lower Limit of Normal
LLQ	Lower Level of Quantification
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
MAP	Meta-analytic-predictive
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
PsA	Psoriatic arthritis
PsO	Psoriasis
PD	Protocol deviation
PRO	Patient Reported Outcome
PT	Preferred Term
QTc	Corrected QT interval
QTcF	Fridericia corrected QTc
RMP	Risk Management Plan

SAS	Statistical analysis software
SAE	Serious adverse event
SPP	Safety Profiling Plan
SOC	System Organ Class
SMQ	Standardized MedDRA Query
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
ULQ	Upper Level of Quantification
WBC	White blood cell

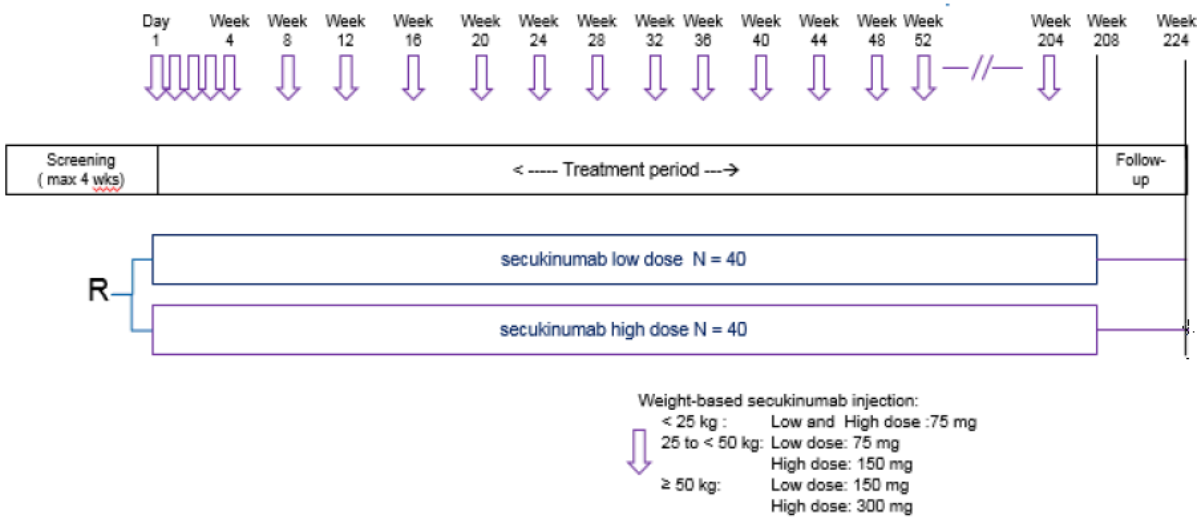
1 Introduction

Data will be analyzed by Novartis according to the data analysis section 9 of the protocol, which is available in Appendix 16.1.1 of the CSR.
This document contains the detailed statistical and analytical plans for full analyses of CAIN457A2311 study with reference to the study protocol and the project standard analysis plans AIN457A MAP.

1.1 Study design

This is an open-label, parallel-group, two-arm, multi-center trial in pediatric subjects aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis.

Approximately 80 subjects (at least 60 patients with moderate severity) will be enrolled. It is expected that subjects will be enrolled in about 40 centers worldwide. It will be targeted to have at least 5 subjects in the < 25 kg weight, and at least 10 subjects in each of the other two weight groups (25 - <50 kg and ≥50 kg). Subjects will receive the appropriate dose based on their body weight category. If a subject moves into a higher or lower weight group at two consecutive visits with weight measurements from Week 12 onwards, the subject will receive dosing according to the new (higher or lower) weight group respectively. The dose will be adapted starting from the visit of the second consecutive weight change.



The following study periods will be considered for analysis:

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

Treatment Period
The treatment period is defined as randomization to Week 208. In this period the endpoints are assessed and subjects are followed for long-term safety and efficacy. For safety analysis this is defined a last dose + 84 days exposure.

Follow-up Period
The treatment-free follow-up visits will be at Week 212, Week 216 and Week 224 (End Of Follow-up/EOF). Subjects who complete or discontinue treatment early are expected to perform the complete treatment-free follow-up period unless they start another systemic antipsoriatic treatment.

Of note: data from follow-up period for prematurely discontinued subjects will be included in the analysis of treatment period if appropriate.

Entire study period (Randomization to end of study (EOS)), including follow-up period (W212, W216 and W224 visits).

1.1.1 Randomization

Randomization will be stratified by body weight (< 25 kg, 25-< 50 kg, ≥ 50 kg) and disease severity collected at baseline (moderate, severe) (refer to Table 1-1). Subjects will be randomized using 1:1 ratio into one of the following treatment groups according to their baseline body weight:

- **AIN457 low dose:**
  - Subjects weighing < 50 kg at baseline will receive a dose of 75 mg administered as one injection of the 75 mg pre-filled syringe
  - Subjects weighing ≥50 kg at baseline will receive a dose of 150 mg administered as one injection of the 150 mg pre-filled syringe

- **AIN457 high dose:**
  - Subjects weighing < 25 kg at baseline will receive a dose of 75 mg administered as one injection of the 75 mg pre-filled syringe
  - Subjects weighing 25-<50 kg at baseline will receive a dose of 150 mg administered as one injection of the 150 mg pre-filled syringe
  - Subjects weighing ≥ 50 kg at baseline will receive a dose of 300 mg administered as one two injections of the 150 mg pre-filled syringes

Table 1-1 Disease severity definition by IGA and PASI score

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

PASI: Psoriasis Area and Severity Index; IGA: Investigator Global Assessment

1.2 Study objectives and endpoints

The primary objective of this study is to evaluate efficacy of AIN457 (low dose and high dose) compared to placebo (historical control) with respect to PASI 75 and IGA mod 2011 0 or 1 response rates at Week 12 in treatment of moderate to severe plaque psoriasis. Historical placebo data from qualifying trials will be used as the control for primary and key secondary efficacy endpoint analyses. Further details are provided in Section 2.5.

The secondary objectives for this study are as follows:

- To evaluate the efficacy of secukinumab in pediatric subjects with respect to PASI 90 at Week 12, compared to placebo (historical control)
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse event monitoring
- To evaluate the pharmacokinetics of secukinumab

This study will provide efficacy and safety data to support a submission for the indication of moderate to severe plaque psoriasis.

A summary of the primary, secondary [redacted] efficacy endpoints are listed in Table1-2.

Table 1-2 Primary, secondary [redacted] variables

Variable	Type
PASI 75 response at Week 12 (compared to historical placebo)	Co-primary
IGA 0/1 response at Week 12 (compared to historical placebo)	Co-primary
PASI 90 response at Week 12 (compared to historical placebo)	Key secondary
Height, weight, vital signs, laboratory evaluations , ECG over time	secondary
Adverse events	secondary
Secukinumab concentration in serum over time and derived PK parameters (AUC and Cmax)	secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

This document covers statistical and analytical plans for CAIN457A2311 with reference to study protocol and the project standard analysis plans (AIN457 MAP).

Novartis will be performing all analyses. Statistical software of R version 3.4.3 or later and SAS version 9.4 or later will be used.

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

All listings will be presented by treatment sequence.

Footnotes on outputs will be kept to a minimum also for outputs not covered in AIN457A MAP TFL shells.

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings in Appendix 16.2 can be presented on a separate page and do not have to be repeated as footnotes on each listing
- sorting order of categories, e.g. for sorting within MedDRA (Medical Dictionary for Regulatory Activities) hierarchy levels
- MedDRA version used for reporting of MedDRA coded data

Footnotes will generally NOT be given for

- units displayed on the output
- interpretation of results (e.g. “odds ratio larger 1 favors active treatment”)
- information that can be retrieved from the statistical section of the clinical study report (CSR) unless it is not identifiable from the output, e.g.
  - explanation of analysis model used unless results of more than one model are displayed on an output
  - derivations of variables (e.g. BMI (body mass index) will not be explained on a footnote)
- information that will be provided in the clinical study protocol and/or methods section of the CSR (e.g. baseline definition if this is specified in the statistical section of the CSR)

2.1.1 General definitions

2.1.1.1 Study treatment

The following study drugs will be used:

- Investigational treatment
  - Secukinumab 75 mg, 0.5 ml liquid formulation in a pre-filled syringe
  - Secukinumab 150 mg, 1 ml liquid formulation in a pre-filled syringe
  - Secukinumab 300 mg, 2 x 1 ml liquid formulation in a pre-filled syringe

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *Study Day 1* or *Day 1*.

All other study days will be labeled 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.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled

screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in [PDS].

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before randomization (day). All assessments obtained after randomization (day) are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before the first dose of study treatment. All assessments obtained after the first dose (day) of study treatment are considered as post-baseline unless otherwise specified.

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered.

In general, a baseline value refers to the last measurement made prior to administration of the first dose of study treatment. However, for patient reported outcomes, laboratory assessments and ECG if no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the electronic case report form (eCRF). The subject's exposure will be calculated considering the end of treatment period visit (e.g., treatment completion visit). If a subject discontinued early, then the last dose + 84 days or the last visit during the follow-up period whichever occurs earlier is considered.

2.2 Analysis sets

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

Randomized set: The randomized set will be defined as all subjects who were randomized at baseline visit. Unless otherwise specified, misrandomized subjects will be excluded from the randomized set.

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

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual randomization stratum is different to the assigned stratum in Interactive Response Technology system (IRT), the actual stratum will be used in analyses. Subjects reporting a severe GCP (good clinical practice) violation will be excluded from the FAS.

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

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. For safety summaries, subjects will be analyzed according to

treatment received. The treatment received will be set to the treatment randomized. But if a subject has received the wrong treatment during the entire study, the treatment received will be set to this wrong treatment. If a subject has received intermittent wrong treatment, the treatment received will be set to the original randomized treatment.

For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared flagging adverse events which occurred after the treatment deviation.

Protocol deviations leading to exclusion from analysis populations are defined in Table 5-2 in Section 5 Appendix.

The number of subjects in each analysis set will be presented for all treatment groups in efficacy and safety analyses, and for all subjects (total). The number of screened and screen failures subjects will also be shown for all subjects (total).

2.2.1 Subgroup of interest

The primary endpoint(s), selected secondary [redacted] endpoints and selected safety endpoints will be evaluated using the subgroups defined in Table 2-1 where appropriate. Subgroup analyses for the study endpoints are represented in Table 2.2. Analyses will be [redacted] presented as descriptive summaries.

Table 2-1 Subgroups definitions

Subgroup variables	Categories	Label for outputs	Suffix for outputs*
Randomization weight strata	body weight stratum (kg:<25, 25-<50, ≥50)	Weight strata	a
Randomization disease severity strata	Disease severity strata (moderate, severe)	Disease severity strata	b
Age group	(<12 years or ≥12 years)	Age group	c
Body weight and dose group	AIN457 75 mg and < 25 kg, AIN457 75 mg and 25--< 50 kg, AIN457 150 mg and ≥ 50 kg; AIN457 150 mg and 25-< 50 kg, AIN457 300 mg and≥ 50 kg	Body weight by dose group	d

Table 2-2 Subgroup endpoints

Endpoint/analysis	Randomization strata including weight and disease severity	Age	Weight and by dose group
[redacted]			
Adverse event	X	X	X
PK concentration data			X
Demography and backgroud characterics	X	X	

2.3 Patient disposition, demographics and other baseline characteristics

Summaries will be reported by the following treatment groups:

Treatment for analysis

- AIN457 low dose
- AIN457 high dose
- Total

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age in years (derived from year of birth and informed concent data, assuming date is July 1st since only year of birth is reported on the case report form (CRF))
- Height
- Weight
- Body mass index (BMI)

Categorical variables:

- Age categories (<12 years, 12 years and older)
- Gender
- Race
- Ethnicity

- Weight categories (<25 kg, 25-<50 kg, ≥50 kg)
- Disease severity (moderate or severe)

Psoriasis specific baseline characteristics and history of disease will be summarized as well: baseline PASI, baseline PASI (≤20, >20), baseline total body surface area (BSA), baseline IGA mod 2011 score (moderate, severe), severity of psoriasis (as defined at randomization), psoriatic arthritis (yes, no), time since diagnosis of psoriasis, time since diagnosis of psoriatic arthritis, previous exposure to biologic systemic psoriasis therapy, previous exposure to systemic psoriasis therapy, previous exposure to non-biologic systemic psoriasis therapy, previous failure to biologic systemic psoriasis therapy, previous failure to systemic psoriasis therapy, previous failure to non-biologic systemic psoriasis therapy (including phototherapy and photo-chemotherapy). Summaries above will be repeated and presented separately by age group and body weight by dose group.

Body Mass Index (*BMI*) will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

For BMI, height and body weight the last value prior to randomization is used. If there is no weight recorded prior to taking of study treatment, BMI will be missing.

Time since diagnosis of psoriasis (PsO) and time since diagnosis of psoriatic arthritis (PsA) will be calculated using the following formula:
Time since diagnosis = (inform consent date –first diagnosis date + 1)/365.25

The first diagnosis date of PsO or PsA will be imputed according to the imputation rules in Section 4.1 of MAP

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the randomized set.

Any condition entered on the *relevant medical history / current medical conditions* eCRF will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

Unless otherwise specified, analyses will be based on the randomized set.

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failure will be provided. The number and percentage of subjects in the randomized set who completed study periods (treatment period and treatment free follow period) and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated by randomized treatment groups on the FAS population. All substantial protocol deviations will be displayed in the outputs.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

The number of secukinumab injections will be summarized by treatment group by means of contingency tables.

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain time thresholds (any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, and thereafter every 4 weeks, so ≥ 8 weeks, ≥ 12 weeks, etc.) will be displayed.

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) 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 follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min ('end of treatment period' 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 reported for the treatment period up to Week 16 for the PEA, with the last category "≥16 weeks". Summaries on the entire treatment will be provided at Week 24 IA and thereafter.

Also, subjects who changed dose due to change of weight group will be listed if required.

2.4.1.1 Visit window

Visit-windows will be applied to data summarized by visit. These will be based on study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows are created to cover the complete range of days within the study. The visit windows are shown in Table 2-3. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments, and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.
When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 60

instead of on Day 29, it will be re-aligned to visit window *Week 12*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window, it is not assigned an analysis visit and will be listed under label "After Week xxx".

Table 2-3 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-141
Week 24	24	169	Day 142-197
Week 32	32	225	Day 198-253
Week 40	40	281	Day 254-309
Week 48	48	337	Day 310-351
Week 52	52	365	Day 352-407
Week 64	64	449	Day 408-491
Week 76	76	533	Day 492-575
Week 88	88	617	Day 576-673
Week 104	104	729	Day 674-771
Week 116	116	813	Day 772-855
Week 128	128	897	Day 856-939
Week 140	140	981	Day 940-1037
Week 156	156	1093	Day 1038-1135
Week 168	168	1177	Day 1136-1219
Week 180	180	1261	Day 1220-1303
Week 192	192	1345	Day 1304-1401
Week 208 (EOT)	208	1457	Day 1402-1471
Week 212	212	1485	Day 1472-1499
Week 216	216	1513	Day 1500-1541
Week 224 (EOF)	224	1569	Day 1542-1597

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments.

For parameters which are not collected at every visit (e.g. weight, laboratory [redacted]), visit windows defined in Table 2-3 will be combined. For example, if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 100 to Day 197 (combining Week 16 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.4.1.2 below are applied.

2.4.1.2 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 2-4).

For baseline assessment definition see Section 2.1.1.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. PASI 90 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-4 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

Timing of measurement	Type of data	Rule
		[redacted]
Post-baseline safety	Summary visit information (e.g. laboratory values, vital signs, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same day then take the average of these two results
Post-baseline safety	Notable abnormalities (e.g. vitals signs) and CTCAE grades for laboratory values	The most extreme measurement in the window will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by treatment group for the safety set unless otherwise specified. Concomitant treatments will be displayed for the treatment period.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes) and PT. Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment, and last dose plus 84 days or last (including follow-up visits) whichever occurs earlier will be a **concomitant** medication, including those which were started pre-baseline and continued into the treatment period.

Seperate psoriasis specific summaries of prior and/or concomitant medication will be presented as in Table 2-5, but as well for topical, phototherapy and photo chemotherapy (yes/no) using the randomized set.

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

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Further rules will be given in Section 5. Summaries will be based on the safety set.

Table 2-5 Subgroups based on the previous psoriasis therapy

Level 1 description	Level 1 outcome	Level 2 description	Level 2 outcome
previous therapy	yes/no		
systemic	no		
	yes	number	1
			2
			>=3
		failure*	no
			yes
biologic	no		
	yes	failure*	no
			yes
		type of previous biologic	
		anti-p40	no
			yes
		anti-TNF	no
			yes
non-biologic systemic	no		
	yes	failure*	no
			yes
		failure* to at least 2	no
			yes

only selected subgroups will be used for reporting

*: at least one therapy with lack of primary efficacy or lack of secondary efficacy or lack of tolerability

2.5 Analysis of the primary objective

The primary analysis of the study is a Bayesian analysis, chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data. Literature and internal Novartis pediatric and adult plaque psoriasis studies were reviewed to provide the basis for assessing efficacy compared to a historical placebo. All analyses included in this study are based on clinically appropriateness and alignment of definitions (endpoints, clinical disease population, and time point of assessment). Integrated in the analysis are data from four Novartis reported secukinumab adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric study CAIN457A2310. Pediatric placebo-controlled trial data from literature on other biologics at study level data will be utilized (Paller 2008, Landells et al 2015). A historical placebo control is obtained through the Bayesian meta-analytic-predictive (MAP) framework (Spiegelhalter et al 2004, Neuenschwander et al. 2010). Further details on the historical data included are provided in Section 3 and Table 3.1. Note, placebo response rates for study CAIN457A2310 will be available prior to the reporting of this study and therefore utilized in this analysis.

2.5.1 Primary endpoint

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. Analysis of the primary variable will be performed on each treatment group (AIN457 high vs. historical placebo and AIN457 low dose vs. historical placebo) separately on the FAS population.

2.5.1.1 Definition of PASI and related variables

The investigator or trained qualified designee will complete the PASI assessments. Whenever possible, the same evaluator should perform this assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 2-5. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

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

$$PASI = 0.1 (E_h + I_h + D_h)A_h + 0.2 (E_u + I_u + D_u)A_u + 0.3 (E_t + I_t + D_t)A_t + 0.4 (E_l + I_l + D_l)A_l,$$

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 2-6).

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The investigator is responsible for collecting the components or scoring signs and total regional area for all visits. PASI and total BSA calculations will be performed by investigator at screening and randomization only. The PASI scores will be calculated by Novartis and will be used in the analysis and for derivation of PASI response values (see below). [redacted]

Table 2-6 The PASI scoring system

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

* Percentage (not score) of body region (not whole body) affected will be entered in the eCRF.
† Neck is assessed as part of the Head (H) body region.
‡ Axillae and groin are assessed as part of the Trunk (T) body region.
§ Buttocks are assessed as part of the Lower limbs (L) body region.

The following definitions are possible efficacy evaluations that can be used in clinical trials in psoriasis (CHMP/EWP/2454/02, 2004):

- **PASI 75 response**: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders

[redacted]

[redacted]

[redacted]

2.5.1.2 Definition of IGA mod 2011 score and IGA mod 2011 0 or 1 response

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 2-7) has been developed based on a previous version of the scale used in secukinumab phase II studies, and has been updated in collaboration with health authorities (in particular the FDA). The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points. It is recommended that the same evaluator conducts the assessments throughout the study whenever possible.

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

Table 2-7 The IGA mod 2011 rating scale

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

Note: Involvement of nails is not part of the assessment.

Subjects require an IGA mod 2011 score at randomization of 3 or 4 in order to participate in the study. Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA mod 2011 scale compared to baseline.

2.5.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-8.

Table 2-8 Overview of analysis methods for efficacy variables

Variable(s)	Summary of time to event	Summary statistics for binary/ categorical data	Bayesian Analysis	Summary statistics for continuous data	Graphs
PASI 75 response at Week 12		X	X		X*
IGA 0/1 response at Week 12		X	X		X*
PASI 90 response at Week 12		X	X		X*
[redacted]					
Time to PASI 75/90 at week 12	X				X
	* dot plot; ** time course plot				

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis are that AIN457 high dose or AIN457 low dose is not superior to placebo from historical data in the proportion of subjects with PASI 75 response and IGA 0 or 1 response at Week 12. Data from four adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo controlled trials (Paller et al 2008, Landells et al 2015 and CAIN457A2310) will be used to estimate the historical placebo response rate.

The primary hypotheses of comparing AIN457 doses versus historical placebo data will be evaluated using a Bayesian model fitted to study level data. A Bayesian method has been chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data through a meta-analytic-predictive (MAP) prior. These historical data will include adult (data from repository CPOOL) and pediatric studies.

First, a logistic regression Bayesian mixed-effects model is fitted to the historical placebo data, including terms study and population. This is built to predict efficacy outcomes of a future pediatric trial taking into account between trial heterogeneity of the control response rate. The adult studies are assigned a smaller weight in comparison to the pediatric studies. This is achieved through allocation to two distinct exchangeability strata which share a common population response rate, but differ in their between-trial heterogeneity parameter $\tau_{s(h)}$. Moderate between-trial heterogeneity (with τ prior set as HalfNormal(0, 0.5)) was defined for pediatric trial data and substantial heterogeneity (with τ prior set as HalfNormal(0, 1)) was defined for adult trial data (Neuenschwander et al 2010), thus allowing pediatric trial data to be given a higher weight compared to adult trial data. From this model, the MAP prior is derived on the logit scale, and represents the predicted placebo log odds of the pediatric trial, which is used in this study as the comparator. For each endpoint the model was fit using MCMC and the resulting posterior distributions forming the MAP prior are approximated with a parametric

distribution for each endpoint. As parametric distribution a mixture of normal distributions is used, since mixtures can arbitrarily exact approximate any target distribution (West M 1993). The number of mixture components is chosen automatically using lowest Akaike Information Criteria (AIC) as the criterion. This step is performed prior to the first database lock, and results per endpoint from the best fitting mixture model are presented in Table 2-9.

Table 2-9 Information on placebo priors

Endpoint	Mixture component 1	Mixture component 2	Mixture component 3
IGA 0/1			
Weight	0.555	0.445	
Mean	-3.337	-2.741	
SD	1.0048	0.5311	
PASI 75			
Weight	0.361	0.351	0.288
Mean	-2.555	-2.101	-2.723
SD	0.3866	0.2910	0.9029
PASI 90			
Weight	0.774	0.226	
Mean	-3.487	-4.058	
SD	0.5944	1.0976	

A separate model for each endpoint is fitted on the log odds scale to active data from this study with the term treatment.

These data will be used to calculate the Bayesian posterior of the log odds ratio between AIN457 and placebo treatment response rate in this trial. For the log odds of the AIN457 treatment groups a non-informative prior will be used, whilst the placebo treatment group log odds response rate will be represented though the MAP prior as described above..

Both models described above are fitted separately on each efficacy endpoint (PASI 75, PASI 90 and IGA 0/1) using MCMC in Stan version 2.17.1. The MCMC non-convergence Rhat diagnostic (Gelman and Rubin 1992) will be monitored for all model parameters. Rhat values much greater than 1.0 indicate sampling problems and the overall number of model parameters with a Rhat value greater than 1.1 will be documented if observed. It is expected there will be zero divergent transitions during the sampling phase of the used hamiltonian monte-carlo (HMC) algorithm implemented in Stan (Upadhyay et al 2015).

The analysis will report the posterior of the mean log odds ratio as point estimate by its median, its 95% credible interval and the probability of a positive treatment effect which corresponds to the level of evidence for a positive treatment effect. Comparisons with placebo will be performed for the AIN457 low and high dose group separately on each of the efficacy endpoints at week 12.

Results from the posterior distribution will be plotted to provide a graphical representation.

Analysis of the co-primary variables and key secondary endpoint will be based on the Full Analysis Set (FAS).

Notation

Indexes

$i \in \{1,2,3\}$ labels endpoint PASI 75 (1), IGA 0/1 (2) or PASI 90 (3)

$j \in \{1,2\}$ labels AIN457 treatment arm low dose (1), high dose (2)

$h \in \{1, \ldots, H\}$ historical studies

$s(h) \in \{1,2\}$ population

pediatric historical studies have $s(h) = 1$

adult historical studies have $s(h) = 2$

Data

- r responders in placebo group
- $\tilde{r}$ responders in active group
- n patients in placebo group
- $\tilde{n}$ patients in active group

Parameters

- π responder rate placebo
- θ responder rate placebo, log-odds
- μ population response rate placebo
- τ between-trial heterogeniety of trial specific intercept for placebo
- $\tilde{\pi}$ responder rate active
- $\tilde{\theta}$ responder rate active, log-odds
- δ treatment effect as log-odds-ratio with respect to placebo control group

Model

Likelihood

$$r_{i,h}|\pi_{i,h}, n_{i,h} \sim \text{Binomial}(\pi_{i,h} = \text{logit}^{-1}(\theta_{i,h}), n_{i,h})$$

$$\tilde{r}_i \,|\, \tilde{\pi}_i \,, \tilde{n}_i \sim \text{Binomial}(\tilde{\pi}_i = \text{logit}^{-1}(\tilde{\theta}_i), \tilde{n}_i)$$

Hierarchical model (MAP)

$$\theta_{i,h}|\mu_i, \tau_{i,s(h)} \sim \text{Normal}(\mu_i, \tau^2_{i,s(h)})$$

$$\theta_{i,\star}|\mu_i, \tau_{i,1} \sim \text{Normal}(\mu_i, \tau^2_{i,1})$$

Treatment effect as log-odds ratio

$$\delta_i = \tilde{\theta}_i - \theta_{i,\star}$$

The final analysis will report for each endpoint i and treatment arm j the probability for a positive treatment effect $P(\delta_{i,j} > 0)$ and the median as a point estimate of the mean treatment difference of AIN457 low dose ($j = 1$) versus historical placebo and AIN457 high dose ($j = 2$) versus historical placebo, and the respective associated 95% credible interval of $\delta_{i,j}$.

Priors

- $\mu_i \sim \text{Normal}(0, 2^2)$ - overall intercept on log-odds scale
- $\tilde{\theta}_{i,j} \sim \text{Normal}(0, 2^2)$ - response rate for active on log-odds scale
- $\tau_{i,s(h)} \sim \text{HalfNormal}\left(0, s^2_{s(h)}\right)$ - between trial heterogeneity intercept
- $s_1 = 1/2$ - between trial heterogeneity pediatric data
- $s_2 = 1$ - between trial heterogeneity adult data

2.5.3 Handling of missing values/censoring/discontinuations

Pure non-responder imputation (pNRI) will be used as the primary missing data imputation method for both Bayesian analysis at week 12 and descriptive summaries up to week 52. Missing values with respect to response variables based on PASI score and IGA 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Subjects with missing baseline or those with all post-baseline missing will be imputed with non-response.

Missing data from this study for Bayesian analysis will be imputed in the SAS platform. A dataset with study level data is constructed in SAS and transferred to RBesT where the MAP analysis will be performed and the results transferred back to SAS for reporting activities.

2.5.4 Supportive analyses

No sensitivity analyses will be performed for Bayesian analysis.

Multiple imputation (MI) will be used as a supportive analysis for the descriptive summary of key efficacy endpoints (see Section 5.4.3) up to week 52. It is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. [redacted] In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

Of note: subjects with missing baseline or subjects with all post-baseline missing will be included in the multiple imputation analysis.

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

- Reponses variables based on PASI score and IGA mod 2011 categories will generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.
- Multiple imputation will be used as sensitivity method if appropriate. In general, data will be summarised up to the timepoint where 30-40% values are missing in total.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary efficacy endpoint of this study is the proportion of subjects with a PASI 90 response at Week 12.

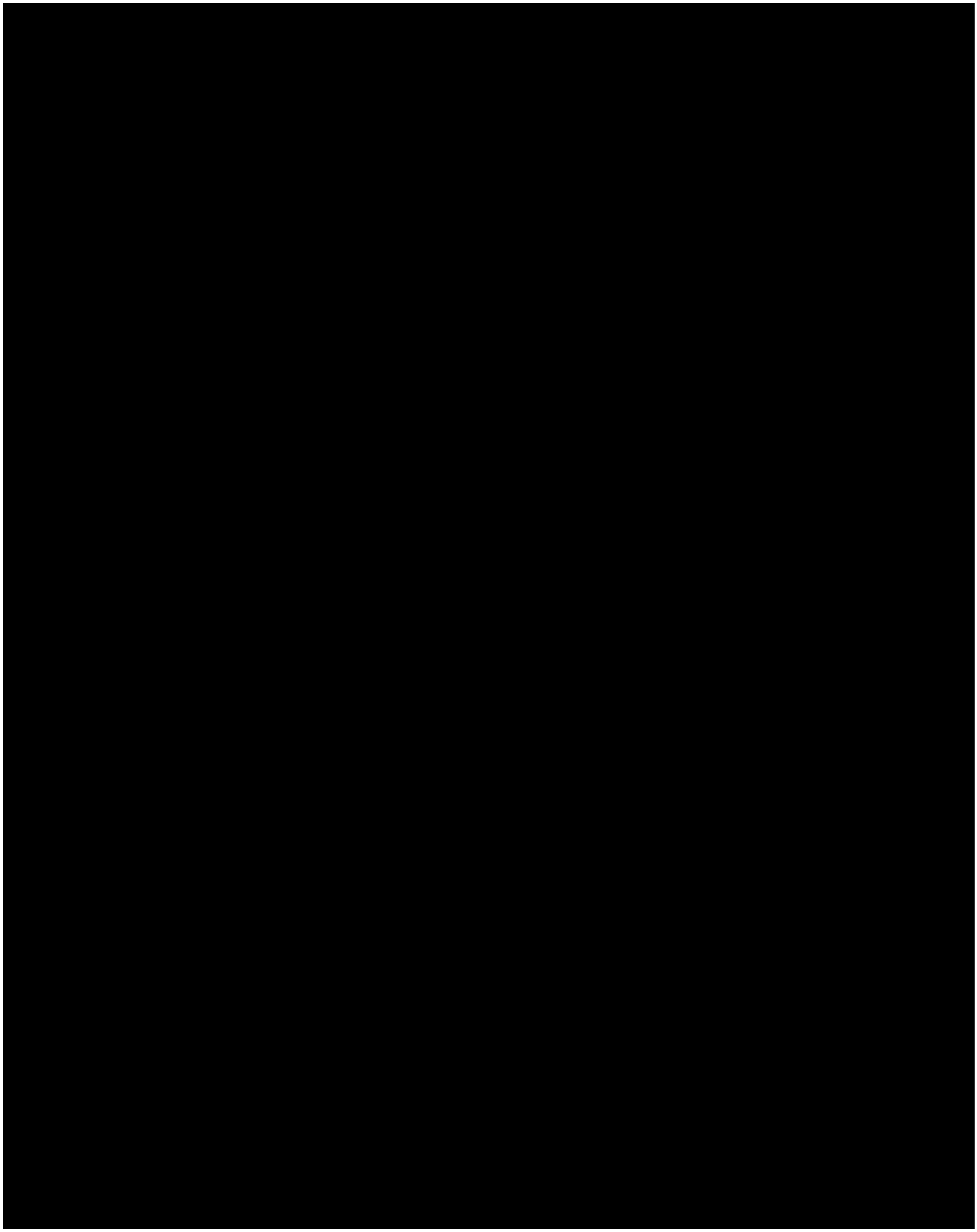
2.6.2 Statistical hypothesis, model, and method of analysis

These data will be analyzed in the same way as the primary endpoint though a Bayesian framework.

Efficacy of AIN457 low and high dose compared to historical placebo data will be performed separately. Analyses will be based on the FAS population, and historical placebo data will be incorporation into the analysis as before through the MAP framework.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data will be handled with the same methods as primary endpoint analysis. The bayesian analysis will use pure non-responder imputation and no sensitivity analysis will be performed. Multiple imputation will be used as a sensitivity analysis for the descriptive summary of key secondary endpoints.



2.8 Safety analyses

All safety analyses will be based on the safety set. Only those visits which were pre-planned in the protocol will be reported in tables and figures for safety variables.

The summaries of evaluation will be reported for the entire treatment period, and where appropriate on the entire study period as well.

Data will be presented by the following treatment groups:

- AIN457 low dose: all subjects who were randomized to AIN457 low dose
- AIN457 high dose: all subjects who were randomized to AIN457 high dose
- Any AIN457 dose: data on AIN457 groups above pooled together

Safety analyses will be performed on treatment received or actual treatment (See Section 2.2, Safety Set).

In general, the following guidelines are proposed for safety analysis unless stated otherwise:

- Adverse events: Only treatment emergent records are reported in the tables, and listings have the "treatment emergent" flag displayed.
- Laboratory data (including vital sign and ECG):
    - by period summary statistics tables: only include "on-treatment" records in the tables, i.e., Assessments within last dose plus 84 days cutoff. Listings have the "on-treatment" flag displayed.
    - by visit summary statistics tables: present all "on-treatment" visits, follow up visits (CRF visits) may be summarized separately if required.

In addition to the treatment emergent/on-treatment safety summary, extended entire treatment/ study period safety analysis will be provided for AE records up to EOS and for LABs by visit summary statistics up to EOS.

Additional listing will be provided for AE that started after last dose + 84 days through to EOS.

Entire treatment/study period

Entire treatment period = randomization to Week 208 (EOT); for safety analysis include FU period up to last dose + 84 days for early discontinued subjects.

Entire study period = randomization to end of study (EOS); includes follow up period (Week 212, 216 and 224)

For evaluation of entire treatment/study period, AIN457 treatment groups will be pooled to "any AIN457".

2.8.1 Adverse events (AEs)

Only treatment emergent adverse events are summarized. However all AEs are included in the listing with flags for treatment emergent. Non-treatment emergent adverse events may be summarized separately upon request.

Treatment emergent adverse events are defined as events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity on or after dosing based on preferred term and within last dose + 84 days (inclusive).

The crude incidence of treatment emergent adverse events will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in Section 5 Appendix. In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals may be provided, see also **Error! Reference source not found.**10.

Table 2-10 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP/RMP risks (special AE interest)	SAEs	AEs-SMQ	AEs by severity	study treatment related AEs, death & other significant AEs	notables (lab/vitals)
initial (Day 1 - week 16)	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire treatment period	• crude incidence • exp.time adjusted incidence	• crude incidence • exp.time adjusted incidence*	• crude incidence • exp.time adjusted incidence*	• crude incidence	• crude incidence • exp.time adjusted incidence*	• crude incidence
Entire study	• exp. time adjusted Incidence*	• exp. time adjusted Incidence*				

*Extended safety summary will be provided for pediatrics trials with FU of 16 weeks

* Please note that exposure adjusted incidence rates may be provided and follow the guideline as below:

- Primary SOC level for AE and SAE
- Level 1 for risks and SMQ
- PT level for SAE
- PT level for AE $\geq$ 2% or incidence rate per 100 subject years $\geq$ 5.0 in AIN457 low dose or AIN457 high dose treatment group (may be updated following review of dry run outputs).
- Other selected AEs of special interest on lower levels (e.g. PT or SMQ level 2), if appropriate

The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.4.2. In addition, exposure time-adjusted incidence rates may be provided for the treatment period including all data (see Section 5.4.5).

Adverse events will be summarized by presenting, for each treatment group (including any AIN457), the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). The relative frequencies and 95% confidence intervals within each system organ class will be presented for adverse event and serious adverse event in a panel graph (for DMC only).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

The crude incidence of treatment emergent AEs may be repeated and presented by age, disease severity strata and by body weight strata subgroups.

The exposure time-adjusted incidence rate of treatment emergent AEs, SAEs and important identified or potential risks (level 1) in entire treatment period will be summarized, where data permits. Data will be reported by SOC and PT and presented by age, disease severity strata and body weight strata. Crude rate will also be evaluated. Summary by body weight and dose group may be evaluated in addition to the above.

Adverse events will also be reported separately by standardized or customized MedDRA queries (SMQ or CMQ/NMQ). The MedDRA version used for reporting the study will be described in a footnote.

The most common adverse events reported (≥*z*% in any group for each preferred term in the SOC-PT table or ≥*z* % in any group for each grouping term table) will be presented in descending frequency according to its incidence in total AIN457 group (combining both AIN457 treatment groups) starting from the most common event. Here threshold value *z* is set to 2 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for study treatment related adverse events, death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment or interruption.

If for a same subject, 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 will be 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.

Algorithms for date imputations will be provided in Section 5 Appendix.

For SAEs occurred during screening a listing will be prepared for all subjects screened including screening failures.

For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared displaying all adverse events for that subject and flag AEs that occurred after the first treatment error.

To meet the requirements for posting results to ClinicalTrials.gov and EudraCT, two further tables are produced and final reporting. Treatment emergent adverse events which are not serious adverse events with an incidence greater than X% and a summary for treatment emergent serious adverse events and SAE suspected to be related to study treatment. Summaries are presented by system organ class and preferred term on the safety set population. Here, the threshold value X is set to 2-5 (%) and may be updated following review of the dry run outputs.

Other safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

Crude rate of important identified and potential risks from Case Retrieval Sheet will be provided for all (non-serious and serious) cases and for all serious cases. Exposure-time adjusted rates will be provided for treatment period including all data for all (non-serious and serious) cases and for all serious cases. In addition, listings will be provided for the related AE risks.

Risk measures and confidence intervals will be derived according to Section 5.

The version of the Case Retrieval Sheet used for the analyses will be described in a footnote. This includes MedDRA version and Novartis MedDRA Query (NMQ) dictionary date.

Important note: For the evaluation of risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.8.2 Deaths

Separate summary and listing will be provided for deaths.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry).

The general guideline for laboratory summaries (including vital signs and ECGs in Section 2.8.4.1 and 2.8.4.2) are as below:

- all the summary of laboratory outputs (newly occurring notables, maximum changes, shift tables, by visit summary statistics) will be reported on all data collected up until end of study. Any summary presented by period will use the on-treatment definition i.e., include all assessments within last dose plus 84 days.

- all records are displayed in the listing with the on-treatment flag. i.e., occurred within last dose plus 84 days- yes or no, as well as eCRF visits and period.

Descriptive summary statistics for the change from baseline to each study visit will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline within treatment period will be summarized analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-9: 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) and estimated glomerular filtration rate (eGFR).

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented. These summaries will be split into hematology and chemistry.

Table 2-11 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
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
eGFR	<LLN – 60ml/min/1.73m2	<60-30 ml/min/1.73m2	<30-15 ml/min/1.73m2	<15 ml/min/1.73m2

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed. Of note, baseline will be defined as last assessment prior to first dosing in treatment phase. If no pre-treatment value exists, also a value recorded after first dose can be used as baseline if it was collected on the same day as first dose, see Section 2.1.1.3.

The number and percentage of subjects with newly occurring or worsening after baseline (treatment emergent) liver enzyme abnormalities will be presented for the treatment period based on the event criteria given in Table 2-12. For pooled DMC analysis 95% confidence will be provided. Standard laboratory change from baseline tables of liver function test by visit will be produced.

Table 2-12 Liver-related events

Parameter	Criterion
ALT	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
AST	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>ULN; >1.5xULN, >2xULN
ALP	>ULN;>1.5xULN, >2xULN, >3xULN, >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >1.5xULN; ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN ALT or AST >10xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALP > 3x ULN & TBL > 2x ULN ALP > 5x ULN & TBL > 2x ULN ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law)** (ALT or AST > 3x ULN & TBL > 2x ULN & ALP < 2x ULN) or reported Hy's Law case

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.

Individual subject data listings will be provided for subjects with newly occurring or worsening abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

For the DMC, a panel graph will be presented to display shift from baseline to maximum evaluation for each of the liver function test (including ALT, AST, ALP and TBL) by treatment. Similarly a graphical presentation of each hematology parameter (including Leukocytes, neutrophils, lymphocytes and platelets) will be presented to display shift of baseline to minimum evaluation based on CTCAE grades.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The following quantitative variables may be summarized if requested: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Fridericia (QTcF) correction will be presented for QTc.

Notable abnormal QTc will summarized by computing the number and percentage of subjects (including 95% confidence intervals for pooled DMC analysis) with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- QTc changes from baseline > 30 msec
- QTc changes from baseline > 60 msec
- PR > 250 msec

Summary statistics will be presented for ECG variables by visit and treatment group based on the entire study period. In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-treatment/study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities (based on the treatment period/study period) will be provided, as well as a by-subject listing of all quantitative ECG parameters.

2.8.4.2 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post - baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

Vital signs will be summarized by visit based on the entire study period data. All vital signs will be listed with “on-treatment” flag displayed.
The number and percentage of subjects with newly occurring notable vital signs (within the treatment period) will be presented by treatment group. Subjects not meeting the following criteria at baseline but meeting at post-baseline are considered to be subjects with newly occurring abnormalities. Criteria for notable vital sign abnormalities are provided in Table 2-13 below:

Table 2-13 Criteria for notable vital signs in pediatric patients

Age group	Systolic BP(mmHg)	Diastolic BP(mmHg)	Pulse (bpm)
6 -11 yrs	90-130	50-80	50-105
12-17 yrs	90-145	55-90	45-95
18 yrs and over	90-139	60-89	60-100

If appropriate, data of subjects with newly occurring notable vital signs abnormalities will be listed in an additional listing.

Of note, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes), the average will be entered on the Vital Signs eCRF and will be used in the analysis.

2.8.4.4 Growth and Physical development

Body weight, height and BMI percentile will be summarized by treatment and visit.

Standard height, weight, and BMI curves will be obtained from the U.S. National Center of Health Statistics (www.cdc.gov/growthcharts) curves for ages up to 18 years. These growth curves will be used for all study subjects. The Center's files contain the L, M, and SD parameters needed to generate exact percentiles as follows:

$$z = \frac{\left(\frac{X}{M}\right)^{L} - 1}{L \times SD}$$

where X = physical measurement (e.g., patient's weight, height, and BMI)
M = median
SD= standard deviation
L = the power in the Box-Cox transformation

Percentiles for each patient at each time point will be calculated using the SAS function PROBNORM(z).

The number and percentages of subjects falling in low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95) growth percentiles will be summarized by treatment and visit. Shift from baseline in growth percentile categories, i.e., low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95), will be summarized by treatment and visit.

2.9 Pharmacokinetic endpoints

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 (BLQ) as well as missing data will be labeled as such in the concentration data listings. BLQ concentrations will be included in the summaries. Serum concentration data from patients who missed a dose or doses will be excluded at the following visit(s).
PK concentrations will be summarized by eCRF visit and treatment. PK concentrations will also be presented by visit (i.e., CRF visit), dose group (75 mg, 150 mg, 300 mg) and body weight categories at visit (<25 kg, 25 to <50kg, ≥50 kg). Per protocol, a subject will change into a higher or lower weight category and dose, when the subject's weight moves into a different weight category for two consecutive visits. This change is assessed from Week 12, then at week 16 and bimonthly until week 52 and at trimonthly visits in the extension phase. If such a change happens, in the PK summaries, at the concerned assessment points, the subject will be accounted in the new dose group (75 mg, 150 mg, 300 mg) and weight category 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. 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, elapse time since day of first secukinumab dose, reason excluding from analysis will be listed by treatment.

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

Pharmacokinetic derived parameters AUC84-112d, Tmax and Cmax will be summarized by treatment group (AIN457 low dose and AIN457 high dose). Descriptive summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. Derived pharmacokinetic parameters will be listed by treatment sequence.

2.10 PD and PK/PD analyses

Not applicable.

[redacted]

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

2.14 Interim analysis

A primary endpoint analysis of the data collected up until Week 16, including the co-primary endpoint (at Week 12) will be performed after the last subject completes their Week 16 visit. Efficacy and safety data up to Week 16 visit for all subjects will be summarized. AE listing will be presented on the entire treatment period i.e. reports AE data collected until last subject week 16 cut-off date.

To address comments from the health authorities an additional full analysis will be performed when all subjects have completed the Week 24 visit.

A full analysis will be performed when all subjects have completed the Week 52 visit, (or premature treatment discontinuation visit). Thereafter, efficacy and safety data collected after Week 52 until the end of study may be reported yearly in separate reports.

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

Trial modifications are not planned based on any interim analyses No aggregated statistical analysis will be performed by actual treatment group prior to W16 PEA.

3 Sample size calculation

The sample size for this study is calculated to ensure an adequate number of subjects for PK analyses and powered efficacy analyses. Approximately 80 pediatric subjects from 6 to less than 18 years of age at randomization will be recruited. Since a 15% screening failure rate is expected, approximately 95 patients will be screened. The study will aim to recruit at least 60 subjects with moderate severity and approximately 20 subjects with severe severity.

Power calculations were performed to support the co-primary endpoints PASI 75 and IGA 0 or 1 response at week 12, and secondary endpoint PASI 90 at week 12, versus placebo (historical control) for the low and high secukinumab dose regimens. The low dose arm with smaller treatment effect is being considered in the power/sample size calculation.

Data from four adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo controlled trials (Paller et al 2008,

Landells et al 2015) were used to estimate the historical placebo response rate. For study CAIN457A2310, a 10% response rate was assumed for PASI 75, IGA 0 or 1 and 8% for PASI 90 response for the placebo group. The 95% upper quantile of predicted number of responders are 7, 7 and 6 subjects, respectively. The assumed placebo response rates were derived accordingly with 40 pediatrics for study CAIN457A2310. Refer to table 3.1 below.

Table 3-1 Placebo response rates from historical secukinumab placebo controlled trials

Adult Placebo controlled trial	Endpoint	Number of subjects with response/ Number of subjects evaluable	Placebo response rate (%)
CAIN457A2302	IGA 0 or 1	6/246	2.4
	PASI 75	11/246	4.5
	PASI 90	3/246	1.2
CAIN457A2303	IGA 0 or 1	9/324	2.8
	PASI 75	16/324	4.9
	PASI 90	5/324	1.5
CAIN457A2308	IGA 0 or 1	0/59	0
	PASI 75	0/59	0
	PASI 90	0/59	0
CAIN457A2309	IGA 0 or 1	0/61	0
	PASI 75	2/61	3.3
	PASI 90	0/61	0
Pediatric Placebo controlled trial	**Endpoint**	**Number of subjects with response/ Number of subjects evaluable**	**Placebo response rate (%)**
Ustekinumab Dermatol 2015 (Age 12 to 17 years)	PGA 0 or 1	2/37	5.4
	PASI 75	4/37	10.8
	PASI 90	2/37	5.4
Etanercept NEJM 2008 (Age 12 to 17 years)	PGA 0 or 1	14/105	13
	PASI 75	12/105	11
	PASI 90	7/105	7
CAIN457A2310 (estimation Includes simulation uncertainty error)	IGA 0 or 1	7/40	17.5
	PASI 75	7/40	17.5
	PASI 90	6/40	15

The Meta-Analytic-Predictive (MAP) approach derives an informative prior from historical data which is discounted using a hierarchical model. When using the MAP approach to estimate the predicted placebo response rate, differential discounting was defined for two stratum: pediatric study data and adult study data. Moderate between-trial heterogeneity (with τ prior set as HalfNormal(0, 0.5)) was defined for pediatric trial data and substantial heterogeneity (with

τ prior set as HalfNormal(0, 1)) was defined for adult trial data (Neuenschwander et al.2010), thus allowing pediatric trial data to be given a higher weight compared to adult trial data. The prior distribution for the regression coefficient β was set as non-informative Normal (0, 2). The following Table 3-2 presents the summary statistics of the fitted mixtures of conjugate distribution to the sample.

All the calculations were performed in the R package RBesT (version 1.3.1) through the meta-analytical-predictive framework (Spiegelhalter et al. 2004, Neuenschwander et al. 2010).

Table 3-2 Predictive placebo response rates for this study from model of historical data

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

Based on confirmatory efficacy in the adult phase III program (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309), the PASI 75, IGA 0/1 and PASI 90 response rate at week 12 was assumed as 65%, 45% and 39% for secukinumab. Non-informative prior was set for secukinumab arm. A sample size of 40 pediatric patients from this study under each high or low secukinumab arm over predictive placebo response (Table 3-2) will lead to a power of approximately 99% for each co-primary endpoint and secondary endpoint. Details as following:

- A sample size of 40 pediatric patients per treatment group and true response rates of 65% for PASI 75 and 45% for IGA mod 2011 0 or 1 response for secukinumab was assumed. For each co-primary endpoint there is approximately 99% power to detect a posterior probability of the log odds ratio difference between placebo and secukinumab to exceed with at least 97.5%.
- Similarly, for the secondary endpoint of PASI 90 response there is approximately 99% power to provide a posterior probability of at least 97.5% that the PASI 90 response rate on secukinumab is greater than placebo. This assumes a response rate of 39% for secukinumab.

4 Change to protocol specified analyses

The following are changes to protocol specified analysis:

Following HA recommendadtion to impute subjects with all post-baseline missing values as non-responders according to the intention to treat principal and to remain consistent with the adult studies and pediatric data used within the MAP analysis, the primary analysis will be performed on pure non-responder imputation and the MI dropped. Modified non-responder analysis may still be performed upon request from HA. No sensitivity analysis will be provided for the Bayesian analysis. For the descriptive summary of key efficacy endpoints, results using pure non-responder imputation as well as multiple imputation will be provided.

Week 16 PEA analysis constitutes the scope for delivering to DMC and an extended FIR requirement, thus a full analysis will not be performed as planned. Further to recent communications with the health authorities, additional outputs and an interim analysis at Week 24 is added to support the pediatric submission. The following subgroup summaries are added to the planned analyses:

- Summaries by age subgroup:<12 years or ≥ 12 years
- Summaries by body weight strata:<25kg, 25-<50kg and ≥ 50kg
- Summaries by disease severity strata:moderate, severe
- Summaries by body weight and dose group:AIN457 – 75 mg and < 25 kg, AIN457 Low – 75 mg and ≥ 25 kg -< 50 kg, AIN457 Low – 150 mg and ≥ 50 kg;, AIN457 High – 150 mg and ≥ 25 kg -< 50 kg, AIN457 High – 300 mg and ≥ 50 kg;

Safety summaries for exposure adjusted incidence rates may be prepared.

Pandemic reporting (COVID-19)

Data collected in this trial that is affected by the COVID-19 situation, can be expected to lead to difficulties in interpretation in the trial's reporting. In recognition of these challenges, both FDA and EMA (and local regulatory authorities) have issued specific guidelines that request Novartis to collect the reasons for non-compliance and discontinuation of clinical trial elements related to COVID-19 in all ongoing trials.

In adherance to these guidences, specific protocol deviations were added to capture data necessary to provide a summary of impact for the pandemic.

The primary and key secondary objective of the study assesed at Week 12 are not impacted. These were reported prior to the pandemic, which emerged as the last few patients were reaching week 52 visit. Therefore, notably missing data are not expected and imputations are considered reasonable for evaluating efficacy up to week 52.

All protocol deviations for the study will be summarised together (i.e including COVID-19 specific PDs) as described in section 2.3.1. In addition, all protocol deviations from 1st March 2020, that is considered to be the starting point of COVID-19 period (as per internal guidance for those countries participating in this study) will capture whether there was any relation to COVID-19 including a precise relationship status in regard to COVID-19 virus (such as health status related, site issues, quarantine of patient/lockdown, drug supply issue, patient concern, other or no relationship to COVID-19). The relationship status will be presented in the listing. For patients with suspected/confirmed cases of COVID-19, separate listings may be provided for disposition, concomitant medications/proceduces and significant non drug therapies and adverse events (including COVID-19 testing with outcome results). Summaries of treatment emergent COVID-19 related adverse events may be presented if data permits.

5 Appendix

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

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

- The last day in the month and
- The end day of the corresponding epoch

5.1.2 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 + 140 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 + 140 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:

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

b. 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.

5.1.3 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.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.3.3 First diagnosis date (Pso, PsA) imputation

1. If the first diagnosis day/ month are missing and the year is non-missing:

a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).
b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).

2. If the first diagnosis day is missing and the month/year are non-missing:
a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).
b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.1.3.4 Other imputations

Only PASI and IGA mod 2011 based response variables are imputed with multiple imputation or non-response, other response variables [redacted] will be imputed with LOCF.

[redacted]

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

5.2 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote.

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Analysis of 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. If

applicable, means +/- SE will be plotted. [redacted]

5.4.2 Analysis of binary (and categorical) data

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. 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 for $p > 0, (L = 0 \text{ for } p = 0)$,

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

and the upper limit is for $p < 1, (U = 1 \text{ for } p = 1)$,

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

Figures will be provided for PASI 75 response (upper left) PASI 90 response (upper right), PASI 100 response (lower left) and IGA mod 2011 0 or 1 response (lower right) at Week 12 and Week 16 as dot plots displaying treatments on the x-axis and point estimates including 95% confidence intervals on the y-axis.

For time courses of response variables, the point estimate at each time point including 95% confidence interval will be plotted.

5.4.3 Multiple imputations for response variables

Descriptive summaries for PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visits will be analyzed using multiple imputation method.

In the multiple imputations analysis the response status will be imputed based on the individual treatment arm information.

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty.

Missing values for the 'change from baseline PASI score' and 'IGA mod 2011 score' will be imputed simultaneously based on an underlying joint normal distribution and using a Markov Chain Monte Carlo (MCMC) method. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. Assuming normality for the 'IGA mod 2011 score' is motivated by Schaefer (1997), where it was shown that the multivariate normal approximation for the imputation of incomplete categorical and binary data is robust.

The imputations will be done separately for each treatment group including baseline weight, failure to at least one previous biologic (yes/no), and number of previous systemic therapies as additional covariates.

Summary statistics for PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables with multiple imputations method.

The number of imputations will be set to 100, the seed for the random function will be set to 4572311 for this study. SAS proceduce MI will be used to generate the multiple imputed data sets. The SAS procedure MI can be used as follows:

The input data set <pasi_iga> should have one record per subject with baseline PASI score and IGA mod 2011 score as well as all changes from baseline PASI and post-baseline IGA mod 2011 score.

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi_iga> OUT=<impdata> SEED=457<studycode> NIMPUTE=100;
VAR <baseline weight> <failure to at least one biologic>
<number of previous systemic therapies>
<baseline PASI> <baseline IGA>
<change from baseline PASI week 1> - <change from baseline PASI week primary endpoint>
<IGA week1> - <IGA week primary endpoint>;
EM converge=1E-2 MAXITER=5000;
MCMC PRIOR=RIDGE=2 ;
BY <treatment group>;
RUN;
ODS LISTING;
```

Programming notes:
The SAS procedure MIANALYZE expects a variable called "_IMPUTATION_" which is generated by the MI procedure. It might be needed to set the SAS option "VALIDVARNAME=UPCASE" temporarily in the program before the MI call, this option should be reset after the MIANALYZE call to VALIDVARNAME=V6. In case there are no missings in one treatment group, the MI procedure does not impute any values. In this case the corresponding data need to be imputed manually outside PROC MI and added to the dataset <impdata>.
The imputed data are saved in data set <impdata>. The outcomes of interest, i.e. the PASI 50/75/90/100 response and IGA mod 2011 0 or 1 response will be calculated, e.g. as follows:

```
DATA <impdata2>;
SET <impdata>;
```

IF <change from baseline PASI week primary endpoint>/<baseline PASI>=0.75 THEN <PASI 75 response> =1;
ELSE <PASI 75 response>=0;
<…repeat for all PASI response…>
IF <baseline IGA> >=3 THEN DO;
IF <IGA week primary endpoint> < 1.5 THEN <IGA 0/1 response> =1;
ELSE IF <IGA week primary endpoint> >=1.5 THEN <IGA 0/1 response> =0;
ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE IF <baseline IGA>=2 THEN DO;
IF <IGA week primary endpoint> < 0.5 THEN <IGA 0/1 response> =1;
ELSE IF <IGA week primary endpoint> >=0.5 THEN <IGA 0/1 response> =0;
ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE <IGA 0/1 response> =0;
RUN;

5.4.4 Crude incidence and related risk estimates

5.4.4.1 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 p = 0 then L = 0 and if p = 1 then U = 1.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

5.4.5 Exposure adjusted incidence rate and related risk estimates

5.4.5.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or last dose plus 84 days whichever occur earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event. Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

5.4.6 Primary analysis

```
Example schematic code for Bayesian analysis of 2311 using dummy data
for PASI 75.

## model to fit placebo data

tau.prior <- rbind(c(0, 0.5), c(0, 1))

set.seed(345652)
analysis_pbo_mc_pasi <- gMAP(cbind(r, n-r) ~ 1 | trial,
                             tau.strata=stratum,
                             family=binomial,
                             data=final_data_pbo,
                             tau.dist="HalfNormal",
                             tau.prior=tau.prior,
                             beta.prior=rbind(c(0,2)))
```

```
## model to fit the data of A2311
set.seed(34535214)
analysis_A2311_mc_pasi75 <- gMAP(cbind(r, n-r) ~ 0 + TREATMENT,
                                 family=binomial,
                                 data=active,
                                 tau.dist="Fixed",
                                 tau.prior=1E-6,
                                 beta.prior=matrix(c(0,0,2,2), 2, 2))
```

5.4.7 Key secondary analysis

As per section 5.4.6 but on the PASI 90 endpoint.

5.4.8 Analysis of time-to-event data

Number and percentage of subjects with a clinical event based on the number of subjects in the analysis set at risk as denominator, will be provided by treatment group.

Subjects without PASI 75/90 response will be considered as censored at Week 12.

Median time to event and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation (PROC LIFETEST option conftype=log-log). The plot will include the number of subjects at risk for each treatment group at pre-specified timepoints, which are 0 to <= 4 weeks , >4 to <=8 weeks and 8 to <=12 weeks.

Subjects at risk, timepoint "0" and censoring will be defined as described in Table 5-1 below:

Table 5-1

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed*	Informative censoring
PASI 75/90 response	All subjects randomized with baseline and post-baseline data for PASI	Date of randomization	Date of 1st visit with PASI 75/90 response observed	Week 12 visit date/discontinuation date	Censor (if ConMed taken before the event)	No

Time-to-event will be derived as:

- date of event minus date of time=0 plus 1 day for subjects experiencing the event or
- date of censoring minus date of time=0 plus 1 day for subjects not experiencing the event

5.5 Rule of exclusion criteria of analysis sets

Protocol deviations for exclusion from analysis sets are defined in Table 5-2

Table 5-2 Subject classification rules

Analysis set	PD Categories Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
Randomization set	NA	Misrandomized subject
FAS (Full Analysis Set)	DVSPID: INCL01; OTH12	Misrandomized subject
Safety	DVSPID: INCL01; OTH12	Misrandomized subject Subjects who did not take any study treatment

INCL01: ICF missing or not signed; in the case where ICF was obtained after initiating study procedures, subjects will be included in all analysis sets

OTH12: Severe ICH-GCP non-compliance of study site

6 Reference

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NOVARTIS

Clinical Development – General Medicine

AIN457/Secukinumab

AIN457A2311 / NCT03668613

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

Statistical Analysis Plan (SAP) Amendment 1

Author: [redacted] (Trial Statistician)

Document type: SAP Documentation

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Number of pages: 56

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-Dec-2022	Prior to Final lock	Creation of final DBL SAP	Clarification on methods to address missing data beyond Week 52	2.7
14-Dec-2022	Prior to Final lock	Creation of final DBL SAP	Clarification on data presenting for patients with suspected/confirmed cases of COVID-19	4
15-Sept-2023	Prior to Final lock	Creation of amendment 1	Adjusted the definition of dose and weight subgroup for the final analysis	2.2.1
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body surface area
CHMP	Committee for medicinal products for human use
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report/record form
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FIR	First Interpretable Results
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase
HGB	Hemoglobin
IGA	Investigator's global assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IRT	Interactive response technology
LLN	Lower Limit of Normal
LLQ	Lower Level of Quantification
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
MAP	Meta-analytic-predictive
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
PsA	Psoriatic arthritis
PsO	Psoriasis
PD	Protocol deviation
PRO	Patient Reported Outcome
PT	Preferred Term
QTc	Corrected QT interval
QTcF	Fridericia corrected QTc
RMP	Risk Management Plan

SAS	Statistical analysis software
SAE	Serious adverse event
SPP	Safety Profiling Plan
SOC	System Organ Class
SMQ	Standardized MedDRA Query
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
ULQ	Upper Level of Quantification
WBC	White blood cell

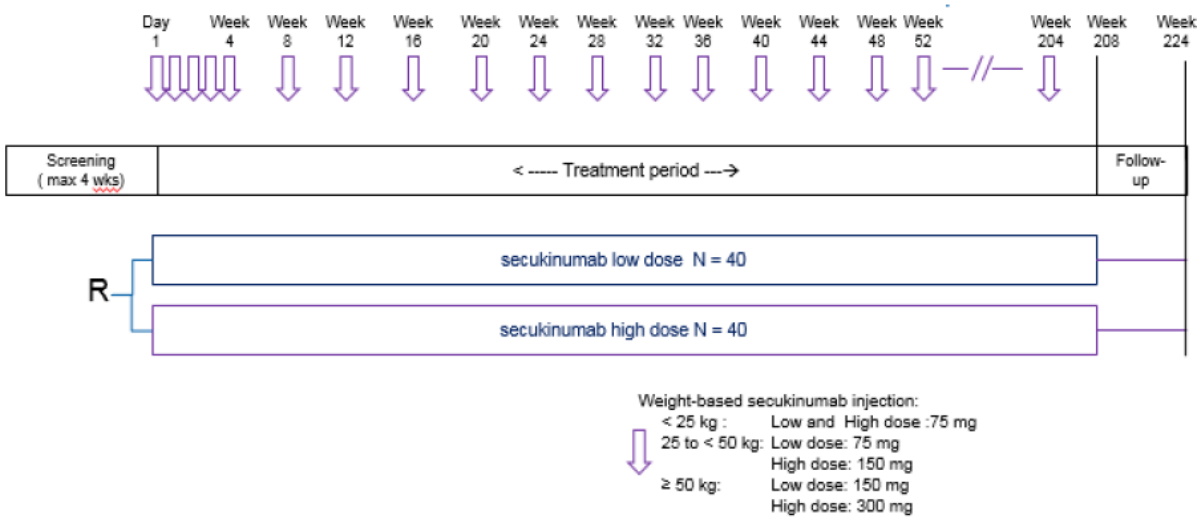
1 Introduction

Data will be analyzed by Novartis according to the data analysis section 9 of the protocol, which is available in Appendix 16.1.1 of the CSR.
This document contains the detailed statistical and analytical plans for full analyses of CAIN457A2311 study with reference to the study protocol and the project standard analysis plans AIN457A MAP.

1.1 Study design

This is an open-label, parallel-group, two-arm, multi-center trial in pediatric subjects aged 6 years to less than 18 years with moderate to severe chronic plaque psoriasis.

Approximately 80 subjects (at least 60 patients with moderate severity) will be enrolled. It is expected that subjects will be enrolled in about 40 centers worldwide. It will be targeted to have at least 5 subjects in the < 25 kg weight, and at least 10 subjects in each of the other two weight groups (25 - <50 kg and ≥50 kg). Subjects will receive the appropriate dose based on their body weight category. If a subject moves into a higher or lower weight group at two consecutive visits with weight measurements from Week 12 onwards, the subject will receive dosing according to the new (higher or lower) weight group respectively. The dose will be adapted starting from the visit of the second consecutive weight change.



The following study periods will be considered for analysis:

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

Treatment Period
The treatment period is defined as randomization to Week 208. In this period the endpoints are assessed and subjects are followed for long-term safety and efficacy. For safety analysis this is defined a last dose + 84 days exposure.

Follow-up Period
The treatment-free follow-up visits will be at Week 212, Week 216 and Week 224 (End Of Follow-up/EOF). Subjects who complete or discontinue treatment early are expected to perform the complete treatment-free follow-up period unless they start another systemic antipsoriatic treatment.

Of note: data from follow-up period for prematurely discontinued subjects will be included in the analysis of treatment period if appropriate.

Entire study period (Randomization to end of study (EOS)), including follow-up period (W212, W216 and W224 visits).

1.1.1 Randomization

Randomization will be stratified by body weight (< 25 kg, 25-< 50 kg, ≥ 50 kg) and disease severity collected at baseline (moderate, severe) (refer to Table 1-1). Subjects will be randomized using 1:1 ratio into one of the following treatment groups according to their baseline body weight:

- **AIN457 low dose:**
  - Subjects weighing < 50 kg at baseline will receive a dose of 75 mg administered as one injection of the 75 mg pre-filled syringe
  - Subjects weighing ≥50 kg at baseline will receive a dose of 150 mg administered as one injection of the 150 mg pre-filled syringe

- **AIN457 high dose:**
  - Subjects weighing < 25 kg at baseline will receive a dose of 75 mg administered as one injection of the 75 mg pre-filled syringe
  - Subjects weighing 25-<50 kg at baseline will receive a dose of 150 mg administered as one injection of the 150 mg pre-filled syringe
  - Subjects weighing ≥ 50 kg at baseline will receive a dose of 300 mg administered as one two injections of the 150 mg pre-filled syringes

Table 1-1 Disease severity definition by IGA and PASI score

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

4	12-< 20	Moderate
4	≥ 20	Severe

PASI: Psoriasis Area and Severity Index; IGA: Investigator Global Assessment

1.2 Study objectives and endpoints

The primary objective of this study is to evaluate efficacy of AIN457 (low dose and high dose) compared to placebo (historical control) with respect to PASI 75 and IGA mod 2011 0 or 1 response rates at Week 12 in treatment of moderate to severe plaque psoriasis. Historical placebo data from qualifying trials will be used as the control for primary and key secondary efficacy endpoint analyses. Further details are provided in Section 2.5.

The secondary objectives for this study are as follows:

- To evaluate the efficacy of secukinumab in pediatric subjects with respect to PASI 90 at Week 12, compared to placebo (historical control)
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, vital signs, clinical laboratory variables, electrocardiogram (ECG), and adverse event monitoring
- To evaluate the pharmacokinetics of secukinumab

[redacted]

This study will provide efficacy and safety data to support a submission for the indication of moderate to severe plaque psoriasis.

A summary of the primary, secondary [redacted] endpoints are listed in Table1-2.

Table 1-2 Primary, secondary [redacted] variables

Variable	Type
PASI 75 response at Week 12 (compared to historical placebo)	Co-primary
IGA 0/1 response at Week 12 (compared to historical placebo)	Co-primary
PASI 90 response at Week 12 (compared to historical placebo)	Key secondary
Height, weight, vital signs, laboratory evaluations , ECG over time	secondary
Adverse events	secondary
Secukinumab concentration in serum over time and derived PK parameters (AUC and Cmax)	secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

This document covers statistical and analytical plans for CAIN457A2311 with reference to study protocol and the project standard analysis plans (AIN457 MAP).

Novartis will be performing all analyses. Statistical software of R version 3.4.3 or later and SAS version 9.4 or later will be used.

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

All listings will be presented by treatment sequence.

Footnotes on outputs will be kept to a minimum also for outputs not covered in AIN457A MAP TFL shells.

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings in Appendix 16.2 can be presented on a separate page and do not have to be repeated as footnotes on each listing
- sorting order of categories, e.g. for sorting within MedDRA (Medical Dictionary for Regulatory Activities) hierarchy levels
- MedDRA version used for reporting of MedDRA coded data

Footnotes will generally NOT be given for

- units displayed on the output
- interpretation of results (e.g. “odds ratio larger 1 favors active treatment”)
- information that can be retrieved from the statistical section of the clinical study report (CSR) unless it is not identifiable from the output, e.g.
  - explanation of analysis model used unless results of more than one model are displayed on an output
  - derivations of variables (e.g. BMI (body mass index) will not be explained on a footnote)
- information that will be provided in the clinical study protocol and/or methods section of the CSR (e.g. baseline definition if this is specified in the statistical section of the CSR)

2.1.1 General definitions

2.1.1.1 Study treatment

The following study drugs will be used:

- Investigational treatment
  - Secukinumab 75 mg, 0.5 ml liquid formulation in a pre-filled syringe
  - Secukinumab 150 mg, 1 ml liquid formulation in a pre-filled syringe
  - Secukinumab 300 mg, 2 x 1 ml liquid formulation in a pre-filled syringe

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as *Study Day 1* or *Day 1*.

All other study days will be labeled 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.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of

screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in [PDS].

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before randomization (day). All assessments obtained after randomization (day) are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained (on or) before the first dose of study treatment. All assessments obtained after the first dose (day) of study treatment are considered as post-baseline unless otherwise specified.

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered.

In general, a baseline value refers to the last measurement made prior to administration of the first dose of study treatment. However, for patient reported outcomes, laboratory assessments and ECG if no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the electronic case report form (eCRF). The subject's exposure will be calculated considering the end of treatment period visit (e.g., treatment completion visit). If a subject discontinued early, then the last dose + 84 days or the last visit during the follow-up period whichever occurs earlier is considered.

2.2 Analysis sets

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

Randomized set: The randomized set will be defined as all subjects who were randomized at baseline visit. Unless otherwise specified, misrandomized subjects will be excluded from the randomized set.

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

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual randomization stratum is different to the assigned stratum in Interactive Response Technology system (IRT), the actual stratum will be used in analyses. Subjects reporting a severe GCP (good clinical practice) violation will be excluded from the FAS.

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

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. For safety summaries, subjects will be analyzed according to treatment received. The treatment received will be set to the treatment randomized. But if a subject has received the wrong treatment during the entire study, the treatment received will be set to this wrong treatment. If a subject has received intermittent wrong treatment, the treatment received will be set to the original randomized treatment.

For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared flagging adverse events which occurred after the treatment deviation.

Protocol deviations leading to exclusion from analysis populations are defined in Table 5-2 in Section 5 Appendix.

The number of subjects in each analysis set will be presented for all treatment groups in efficacy and safety analyses, and for all subjects (total). The number of screened and screen failures subjects will also be shown for all subjects (total).

2.2.1 Subgroup of interest

The primary endpoint(s), selected secondary [redacted] endpoints and selected safety endpoints will be evaluated using the subgroups defined in Table 2-1 where appropriate. Subgroup analyses for the study endpoints are represented in Table 2.2. [redacted]

Table 2-1 Subgroups definitions

Subgroup variables	Categories	Label for outputs	Suffix for outputs*
Randomization weight strata	body weight stratum (kg:<25, 25-<50, ≥50)	Weight strata	a
Randomization disease severity strata	Disease severity strata (moderate, severe)	Disease severity strata	b
Age group	(<12 years or ≥12 years)	Age group	c
Body weight and dose group*	AIN457 75 mg and < 25 kg, AIN457 75 mg and 25--< 50 kg, AIN457 150 mg and ≥ 50 kg; AIN457 150 mg and 25-< 50 kg, AIN457 300 mg and≥ 50 kg	Body weight by dose group	d

*In the final (Week 224) analysis, subjects will be accounted in their actual dose group and weight category group to evaluate doses adjusted to the body weight. Per protocol, a subject will change into a higher or lower weight category and dose, when the subject's weight moves into a different weight category for two consecutive visits. If such a change happens, starting from the next efficacy assessment after the dose change, the subject will be accounted in the new dose group (75 mg, 150 mg, 300 mg) and weight category group.

Table 2-2 Subgroup endpoints

Endpoint/analysis	Randomization strata including weight and disease severity	Age	Weight and by dose group
[redacted]			
Adverse event	X	X	X
PK concentration data			X
Demography and backgroud characterics	X	X	

2.3 Patient disposition, demographics and other baseline characteristics

Summaries will be reported by the following treatment groups:

Treatment for analysis

- AIN457 low dose
- AIN457 high dose
- Total

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age in years (derived from year of birth and informed concent data, assuming date is July 1st since only year of birth is reported on the case report form (CRF))
- Height
- Weight
- Body mass index (BMI)

Categorical variables:

- Age categories (<12 years, 12 years and older)
- Gender
- Race
- Ethnicity
- Weight categories (<25 kg, 25-<50 kg, ≥50 kg)
- Disease severity (moderate or severe)

Psoriasis specific baseline characteristics and history of disease will be summarized as well: baseline PASI, baseline PASI (≤20, >20), baseline total body surface area (BSA), baseline IGA mod 2011 score (moderate, severe), severity of psoriasis (as defined at randomization), psoriatic arthritis (yes, no), time since diagnosis of psoriasis, time since diagnosis of psoriatic arthritis, previous exposure to biologic systemic psoriasis therapy, previous exposure to systemic psoriasis therapy, previous exposure to non-biologic systemic psoriasis therapy, previous failure to biologic systemic psoriasis therapy, previous failure to systemic psoriasis therapy, previous failure to non-biologic systemic psoriasis therapy (including phototherapy and photo-chemotherapy). Summaries above will be repeated and presented separately by age group and body weight by dose group.

Body Mass Index (*BMI*) will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

For BMI, height and body weight the last value prior to randomization is used. If there is no weight recorded prior to taking of study treatment, BMI will be missing.

Time since diagnosis of psoriasis (PsO) and time since diagnosis of psoriatic arthritis (PsA) will be calculated using the following formula:
Time since diagnosis = (inform consent date –first diagnosis date + 1)/365.25

The first diagnosis date of PsO or PsA will be imputed according to the imputation rules in Section 4.1 of MAP

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the randomized set.

Any condition entered on the *relevant medical history / current medical conditions* eCRF will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

Unless otherwise specified, analyses will be based on the randomized set.

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failure will be provided. The number and percentage of subjects in the randomized set who completed study periods (treatment period and treatment free follow period) and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated by randomized treatment groups on the FAS population. All substantial protocol deviations will be displayed in the outputs.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

The number of secukinumab injections will be summarized by treatment group by means of contingency tables.

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain time thresholds (any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, and thereafter every 4 weeks, so ≥ 8 weeks, ≥ 12 weeks, etc.) will be displayed.

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) 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 follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min (‘end of treatment period’ 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 reported for the treatment period up to Week 16 for the PEA, with the last category “≥16 weeks”. Summaries on the entire treatment will be provided at Week 24 IA and thereafter.

Also, subjects who changed dose due to change of weight group will be listed if required.

2.4.1.1 Visit window

Visit-windows will be applied to data summarized by visit. These will be based on study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows are created to cover the complete range of days within the study. The visit windows are shown in

Table 2-3. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments, and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.
When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 60 instead of on Day 29, it will be re-aligned to visit window *Week 12*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window, it is not assigned an analysis visit and will be listed under label "After Week xxx".

Table 2-3 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-141
Week 24	24	169	Day 142-197
Week 32	32	225	Day 198-253
Week 40	40	281	Day 254-309
Week 48	48	337	Day 310-351
Week 52	52	365	Day 352-407
Week 64	64	449	Day 408-491
Week 76	76	533	Day 492-575
Week 88	88	617	Day 576-673
Week 104	104	729	Day 674-771
Week 116	116	813	Day 772-855
Week 128	128	897	Day 856-939
Week 140	140	981	Day 940-1037
Week 156	156	1093	Day 1038-1135
Week 168	168	1177	Day 1136-1219
Week 180	180	1261	Day 1220-1303
Week 192	192	1345	Day 1304-1401
Week 208 (EOT)	208	1457	Day 1402-1471

Week 212	212	1485	Day 1472-1499
Week 216	216	1513	Day 1500-1541
Week 224 (EOF)	224	1569	Day 1542-1597

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments.
For parameters which are not collected at every visit (e.g. weight, laboratory, [redacted], visit windows defined in Table 2-3 will be combined. For example, if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 100 to Day 197 (combining Week 16 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.4.1.2 below are applied.

2.4.1.2 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 2-4).

For baseline assessment definition see Section 2.1.1.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. PASI 90 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-4 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3
Post-baseline efficacy	All data [redacted]	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurement are taken on the same day then select the first one using eCRF visit number.

Timing of measurement	Type of data	Rule
[redacted]	[redacted]	If two measurement have been taken on the same day and same visit then select the worst. [redacted]
Post-baseline safety	Summary visit information (e.g. laboratory values, vital signs, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same day then take the average of these two results
Post-baseline safety	Notable abnormalities (e.g. vitals signs) and CTCAE grades for laboratory values	The most extreme measurement in the window will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by treatment group for the safety set unless otherwise specified. Concomitant treatments will be displayed for the treatment period.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes) and PT. Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment, and last dose plus 84 days or last (including follow-up visits) whichever occurs

earlier will be a **concomitant** medication, including those which were started pre-baseline and continued into the treatment period.

Seperate psoriasis specific summaries of prior and/or concomitant medication will be presented as in Table 2-5, but as well for topical, phototherapy and photo chemotherapy (yes/no) using the randomized set.

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

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Further rules will be given in Section 5. Summaries will be based on the safety set.

Table 2-5 Subgroups based on the previous psoriasis therapy

Level 1 description	Level 1 outcome	Level 2 description	Level 2 outcome
previous therapy	yes/no		
systemic	no		
	yes	number	1
			2
			>=3
		failure*	no
			yes
biologic	no		
	yes	failure*	no
			yes
		type of previous biologic	
		anti-p40	no
			yes
		anti-TNF	no
			yes
non-biologic systemic	no		
	yes	failure*	no
			yes
		failure* to at least 2	no
			yes

only selected subgroups will be used for reporting

*: at least one therapy with lack of primary efficacy or lack of secondary efficacy or lack of tolerability

2.5 Analysis of the primary objective

The primary analysis of the study is a Bayesian analysis, chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data. Literature and internal Novartis pediatric and adult plaque psoriasis studies were reviewed to provide the basis for assessing efficacy compared to a historical placebo. All analyses included in this study are based on clinically appropriateness and alignment of definitions (endpoints, clinical disease population, and time point of assessment). Integrated in the analysis are data from four Novartis reported secukinumab adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric study CAIN457A2310. Pediatric placebo-controlled trial data from literature on other biologics at study level data will be utilized (Paller 2008, Landells et al 2015). A historical placebo control is obtained through the Bayesian meta-analytic-predictive (MAP) framework (Spiegelhalter et al 2004, Neuenschwander et al. 2010). Further details on the historical data included are provided in Section 3 and Table 3.1. Note, placebo response rates for study CAIN457A2310 will be available prior to the reporting of this study and therefore utilized in this analysis.

2.5.1 Primary endpoint

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. Analysis of the primary variable will be performed on each treatment group (AIN457 high vs. historical placebo and AIN457 low dose vs. historical placebo) separately on the FAS population.

2.5.1.1 Definition of PASI and related variables

The investigator or trained qualified designee will complete the PASI assessments. Whenever possible, the same evaluator should perform this assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 2-5. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

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

$PASI = 0.1 (E_h + I_h + D_h)A_h + 0.2 (E_u + I_u + D_u)A_u + 0.3 (E_t + I_t + D_t)A_t + 0.4 (E_l + I_l + D_l)A_l,$

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 2-6).

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The investigator is responsible for collecting the components or scoring signs and total regional area for all visits. PASI and total BSA calculations will be performed by investigator at screening and randomization only. The PASI scores will be calculated by Novartis and will be used in the analysis and for derivation of PASI response values (see below). [redacted]

Table 2-6 The PASI scoring system

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

* Percentage (not score) of body region (not whole body) affected will be entered in the eCRF.
† Neck is assessed as part of the Head (H) body region.
‡ Axillae and groin are assessed as part of the Trunk (T) body region.
§ Buttocks are assessed as part of the Lower limbs (L) body region.

The following definitions are possible efficacy evaluations that can be used in clinical trials in psoriasis (CHMP/EWP/2454/02, 2004):

- **PASI 75 response**: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders

[redacted]

[redacted]

[redacted]

2.5.1.2 Definition of IGA mod 2011 score and IGA mod 2011 0 or 1 response

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 2-7) has been developed based on a previous version of the scale used in secukinumab phase II studies, and has been updated in collaboration with health authorities (in particular the FDA). The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points. It is recommended that the same evaluator conducts the assessments throughout the study whenever possible.

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

Table 2-7 The IGA mod 2011 rating scale

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

Note: Involvement of nails is not part of the assessment.

Subjects require an IGA mod 2011 score at randomization of 3 or 4 in order to participate in the study. Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA mod 2011 scale compared to baseline.

2.5.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-8.

Table 2-8 Overview of analysis methods for efficacy variables

Variable(s)	Summary of time to event	Summary statistics for binary/ categorical data	Bayesian Analysis	Summary statistics for continuous data	Graphs
PASI 75 response at Week 12		X	X		X*
IGA 0/1 response at Week 12		X	X		X*
PASI 90 response at Week 12		X	X		X*
[redacted]					
	* dot plot; ** time course plot				

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis are that AIN457 high dose or AIN457 low dose is not superior to placebo from historical data in the proportion of subjects with PASI 75 response and IGA 0 or 1 response at Week 12. Data from four adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo controlled trials (Paller et al 2008, Landells et al 2015 and CAIN457A2310) will be used to estimate the historical placebo response rate.

The primary hypotheses of comparing AIN457 doses versus historical placebo data will be evaluated using a Bayesian model fitted to study level data. A Bayesian method has been chosen to allow the direct incorporation into the analysis of information about placebo response rates from historical data through a meta-analytic-predictive (MAP) prior. These historical data will include adult (data from repository CPOOL) and pediatric studies.

First, a logistic regression Bayesian mixed-effects model is fitted to the historical placebo data, including terms study and population. This is built to predict efficacy outcomes of a future pediatric trial taking into account between trial heterogeneity of the control response rate. The adult studies are assigned a smaller weight in comparison to the pediatric studies. This is achieved through allocation to two distinct exchangeability strata which share a common population response rate, but differ in their between-trial heterogeneity parameter $\tau_{s(h)}$. Moderate between-trial heterogeneity (with τ prior set as HalfNormal(0, 0.5)) was defined for pediatric trial data and substantial heterogeneity (with τ prior set as HalfNormal(0, 1)) was defined for adult trial data (Neuenschwander et al 2010), thus allowing pediatric trial data to be given a higher weight compared to adult trial data. From this model, the MAP prior is derived on the logit scale, and represents the predicted placebo log odds of the pediatric trial, which is used in this study as the comparator. For each endpoint the model was fit using MCMC and the resulting posterior distributions forming the MAP prior are approximated with a parametric

distribution for each endpoint. As parametric distribution a mixture of normal distributions is used, since mixtures can arbitrarily exact approximate any target distribution (West M 1993). The number of mixture components is chosen automatically using lowest Akaike Information Criteria (AIC) as the criterion. This step is performed prior to the first database lock, and results per endpoint from the best fitting mixture model are presented in Table 2-9.

Table 2-9 Information on placebo priors

Endpoint	Mixture component 1	Mixture component 2	Mixture component 3
IGA 0/1			
Weight	0.555	0.445	
Mean	-3.337	-2.741	
SD	1.0048	0.5311	
PASI 75			
Weight	0.361	0.351	0.288
Mean	-2.555	-2.101	-2.723
SD	0.3866	0.2910	0.9029
PASI 90			
Weight	0.774	0.226	
Mean	-3.487	-4.058	
SD	0.5944	1.0976	

A separate model for each endpoint is fitted on the log odds scale to active data from this study with the term treatment.

These data will be used to calculate the Bayesian posterior of the log odds ratio between AIN457 and placebo treatment response rate in this trial. For the log odds of the AIN457 treatment groups a non-informative prior will be used, whilst the placebo treatment group log odds response rate will be represented though the MAP prior as described above..

Both models described above are fitted separately on each efficacy endpoint (PASI 75, PASI 90 and IGA 0/1) using MCMC in Stan version 2.17.1. The MCMC non-convergence Rhat diagnostic (Gelman and Rubin 1992) will be monitored for all model parameters. Rhat values much greater than 1.0 indicate sampling problems and the overall number of model parameters with a Rhat value greater than 1.1 will be documented if observed. It is expected there will be zero divergent transitions during the sampling phase of the used hamiltonian monte-carlo (HMC) algorithm implemented in Stan (Upadhyay et al 2015).

The analysis will report the posterior of the mean log odds ratio as point estimate by its median, its 95% credible interval and the probability of a positive treatment effect which corresponds to the level of evidence for a positive treatment effect. Comparisons with placebo will be

performed for the AIN457 low and high dose group separately on each of the efficacy endpoints at week 12.

Results from the posterior distribution will be plotted to provide a graphical representation.

Analysis of the co-primary variables and key secondary endpoint will be based on the Full Analysis Set (FAS).

Notation

Indexes

$i \in \{1,2,3\}$ labels endpoint PASI 75 (1), IGA 0/1 (2) or PASI 90 (3)

$j \in \{1,2\}$ labels AIN457 treatment arm low dose (1), high dose (2)

$h \in \{1, \dots, H\}$ historical studies

$s(h) \in \{1,2\}$ population

pediatric historical studies have $s(h) = 1$

adult historical studies have $s(h) = 2$

Data

- r responders in placebo group
- $\tilde{r}$ responders in active group
- n patients in placebo group
- $\tilde{n}$ patients in active group

Parameters

- π responder rate placebo
- θ responder rate placebo, log-odds
- μ population response rate placebo
- τ between-trial heterogeniety of trial specific intercept for placebo
- $\tilde{\pi}$ responder rate active
- $\tilde{\theta}$ responder rate active, log-odds
- δ treatment effect as log-odds-ratio with respect to placebo control group

Model

Likelihood

$$r_{i,h}|\pi_{i,h}, n_{i,h} \sim \text{Binomial}(\pi_{i,h} = \text{logit}^{-1}(\theta_{i,h}), n_{i,h})$$

$$\tilde{r}_i \,|\, \tilde{\pi}_i \,, \tilde{n}_i \sim \text{Binomial}(\tilde{\pi}_i = \text{logit}^{-1}(\tilde{\theta}_i), \tilde{n}_i)$$

Hierarchical model (MAP)

$$\theta_{i,h}|\mu_i, \tau_{i,s(h)} \sim \text{Normal}(\mu_i, \tau^2_{i,s(h)})$$

$$\theta_{i,\star}|\mu_i, \tau_{i,1} \sim \text{Normal}(\mu_i, \tau^2_{i,1})$$

Treatment effect as log-odds ratio

$$\delta_i = \tilde{\theta}_i - \theta_{i,\star}$$

The final analysis will report for each endpoint i and treatment arm j the probability for a positive treatment effect $P(\delta_{i,j} > 0)$ and the median as a point estimate of the mean treatment difference of AIN457 low dose ($j = 1$) versus historical placebo and AIN457 high dose ($j = 2$) versus historical placebo, and the respective associated 95% credible interval of $\delta_{i,j}$.

Priors

- $\mu_i \sim \text{Normal}(0, 2^2)$ - overall intercept on log-odds scale
- $\tilde{\theta}_{i,j} \sim \text{Normal}(0, 2^2)$ - response rate for active on log-odds scale
- $\tau_{i,s(h)} \sim \text{HalfNormal}\left(0, s^2_{s(h)}\right)$ - between trial heterogeneity intercept
- $s_1 = 1/2$ - between trial heterogeneity pediatric data
- $s_2 = 1$ - between trial heterogeneity adult data

2.5.3 Handling of missing values/censoring/discontinuations

Pure non-responder imputation (pNRI) will be used as the primary missing data imputation method for both Bayesian analysis at week 12 and descriptive summaries up to week 52. Missing values with respect to response variables based on PASI score and IGA 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Subjects with missing baseline or those with all post-baseline missing will be imputed with non-response.

Missing data from this study for Bayesian analysis will be imputed in the SAS platform. A dataset with study level data is constructed in SAS and transferred to RBesT where the MAP analysis will be performed and the results transferred back to SAS for reporting activities.

2.5.4 Supportive analyses

No sensitivity analyses will be performed for Bayesian analysis.

Multiple imputation (MI) will be used as a supportive analysis for the descriptive summary of key efficacy endpoints (see Section 5.4.3) up to week 52. It is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. [redacted] In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

Of note: subjects with missing baseline or subjects with all post-baseline missing will be included in the multiple imputation analysis.

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

- Reponses variables based on PASI score and IGA mod 2011 categories will generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.
- Multiple imputation will be used as sensitivity method if appropriate. In general, data will be summarised up to the timepoint where 30-40% values are missing in total.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary efficacy endpoint of this study is the proportion of subjects with a PASI 90 response at Week 12.

2.6.2 Statistical hypothesis, model, and method of analysis

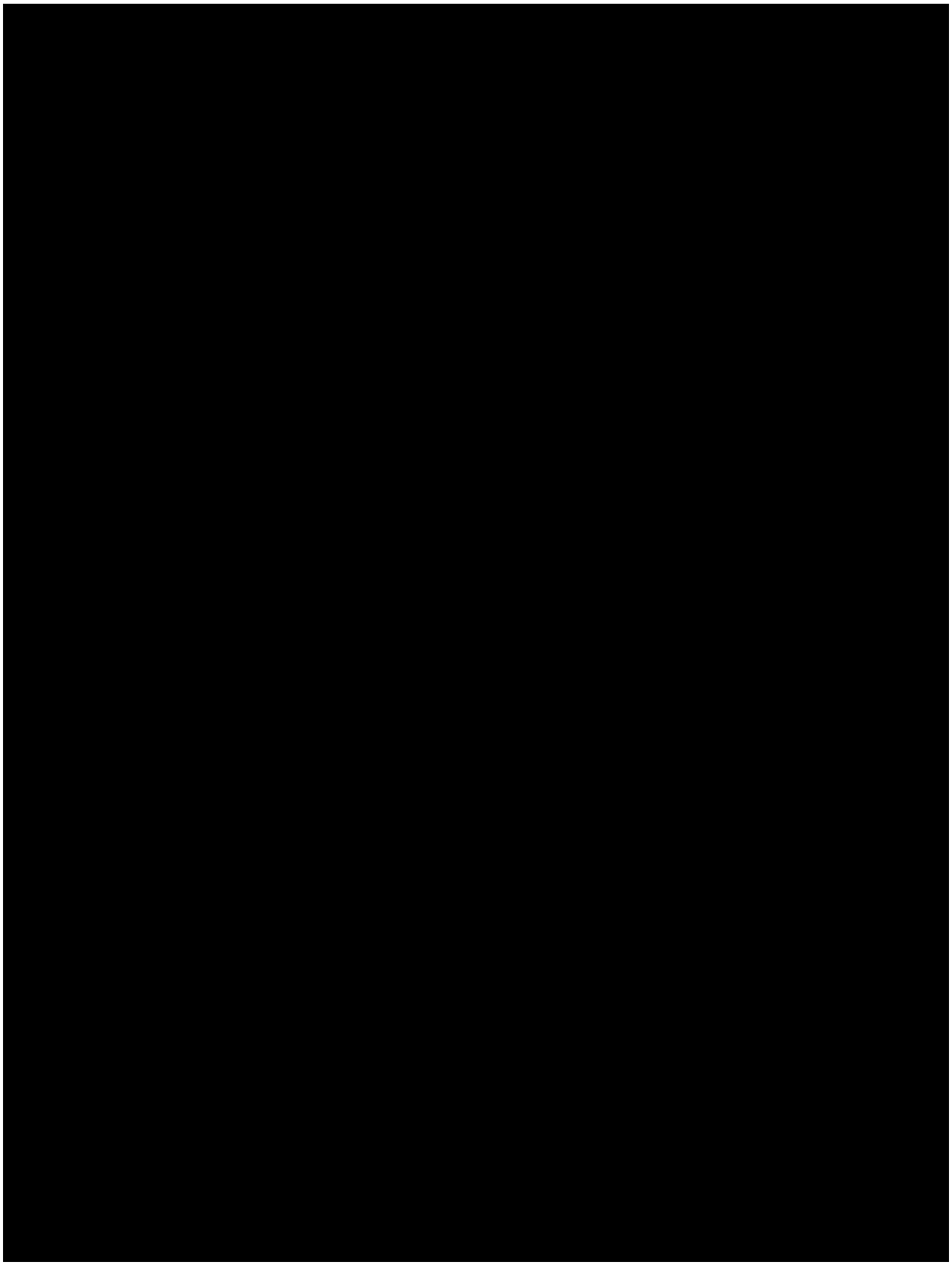
These data will be analyzed in the same way as the primary endpoint though a Bayesian framework.

Efficacy of AIN457 low and high dose compared to historical placebo data will be performed separately. Analyses will be based on the FAS population, and historical placebo data will be incorporation into the analysis as before through the MAP framework.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data will be handled with the same methods as primary endpoint analysis. The bayesian analysis will use pure non-responder imputation and no sensitivity analysis will be performed. Multiple imputation will be used as a sensitivity analysis for the descriptive summary of key secondary endpoints.

[redacted]



[redacted]

2.8 Safety analyses

All safety analyses will be based on the safety set. Only those visits which were pre-planned in the protocol will be reported in tables and figures for safety variables.

The summaries of evaluation will be reported for the entire treatment period, and where appropriate on the entire study period as well.

Data will be presented by the following treatment groups:

- AIN457 low dose: all subjects who were randomized to AIN457 low dose
- AIN457 high dose: all subjects who were randomized to AIN457 high dose
- Any AIN457 dose: data on AIN457 groups above pooled together

Safety analyses will be performed on treatment received or actual treatment (See Section 2.2, Safety Set).

In general, the following guidelines are proposed for safety analysis unless stated otherwise:

- Adverse events: Only treatment emergent records are reported in the tables, and listings have the "treatment emergent" flag displayed.
- Laboratory data (including vital sign and ECG):
    - by period summary statistics tables: only include "on-treatment" records in the tables, i.e., Assessments within last dose plus 84 days cutoff. Listings have the "on-treatment" flag displayed.
    - by visit summary statistics tables: present all "on-treatment" visits, follow up visits (CRF visits) may be summarized separately if required.

In addition to the treatment emergent/on-treatment safety summary, extended entire treatment/ study period safety analysis will be provided for AE records up to EOS and for LABs by visit summary statistics up to EOS.

Additional listing will be provided for AE that started after last dose + 84 days through to EOS.

Entire treatment/study period

Entire treatment period = randomization to Week 208 (EOT); for safety analysis include FU period up to last dose + 84 days for early discontinued subjects.

Entire study period = randomization to end of study (EOS); includes follow up period (Week 212, 216 and 224)

For evaluation of entire treatment/study period, AIN457 treatment groups will be pooled to "any AIN457".

2.8.1 Adverse events (AEs)

Only treatment emergent adverse events are summarized. However all AEs are included in the listing with flags for treatment emergent. Non-treatment emergent adverse events may be summarized separately upon request.

Treatment emergent adverse events are defined as events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity on or after dosing based on preferred term and within last dose + 84 days (inclusive).

The crude incidence of treatment emergent adverse events will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in Section 5 Appendix. In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals may be provided, see also Table 2-10.

Table 2-10 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP/RMP risks (special AE interest)	SAEs	AEs-SMQ	AEs by severity	study treatment related AEs, death & other significant AEs	notables (lab/vitals)
initial (Day 1 - week 16)	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire treatment period	• crude incidence • exp.time adjusted incidence	• crude incidence • exp.time adjusted incidence*	• crude incidence • exp.time adjusted incidence*	• crude incidence	• crude incidence • exp.time adjusted incidence*	• crude incidence
Entire study	• exp. time adjusted Incidence*	• exp. time adjusted Incidence*				

*Extended safety summary will be provided for pediatrics trials with FU of 16 weeks

* Please note that exposure adjusted incidence rates may be provided and follow the guideline as below:

- Primary SOC level for AE and SAE
- Level 1 for risks and SMQ
- PT level for SAE
- PT level for AE $\geq 2\%$ or incidence rate per 100 subject years ≥ 5.0 in AIN457 low dose or AIN457 high dose treatment group (may be updated following review of dry run outputs).
- Other selected AEs of special interest on lower levels (e.g. PT or SMQ level 2), if appropriate

The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.4.2. In addition, exposure time-adjusted incidence rates may be provided for the treatment period including all data (see Section 5.4.5).

Adverse events will be summarized by presenting, for each treatment group (including any AIN457), the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). The relative frequencies and 95% confidence intervals within each system organ class will be presented for adverse event and serious adverse event in a panel graph (for DMC only).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

The crude incidence of treatment emergent AEs may be repeated and presented by age, disease severity strata and by body weight strata subgroups.

The exposure time-adjusted incidence rate of treatment emergent AEs, SAEs and important identified or potential risks (level 1) in entire treatment period will be summarized, where data permits. Data will be reported by SOC and PT and presented by age, disease severity strata and body weight strata. Crude rate will also be evaluated. Summary by body weight and dose group may be evaluated in addition to the above.

Adverse events will also be reported separately by standardized or customized MedDRA queries (SMQ or CMQ/NMQ). The MedDRA version used for reporting the study will be described in a footnote.

The most common adverse events reported ($\geq z$% in any group for each preferred term in the SOC-PT table or $\geq z$ % in any group for each grouping term table) will be presented in descending frequency according to its incidence in total AIN457 group (combining both AIN457 treatment groups) starting from the most common event. Here threshold value z is set to 2 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for study treatment related adverse events, death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment or interruption.

If for a same subject, 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 will be 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.

Algorithms for date imputations will be provided in Section 5 Appendix.

For SAEs occurred during screening a listing will be prepared for all subjects screened including screening failures.

For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared displaying all adverse events for that subject and flag AEs that occurred after the first treatment error.

To meet the requirements for posting results to ClinicalTrials.gov and EudraCT, two further tables are produced and final reporting. Treatment emergent adverse events which are not serious adverse events with an incidence greater than X% and a summary for treatment emergent serious adverse events and SAE suspected to be related to study treatment. Summaries are presented by system organ class and preferred term on the safety set population. Here, the threshold value X is set to 2-5 (%) and may be updated following review of the dry run outputs.

Other safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

Crude rate of important identified and potential risks from Case Retrieval Sheet will be provided for all (non-serious and serious) cases and for all serious cases. Exposure-time adjusted rates will be provided for treatment period including all data for all (non-serious and serious) cases and for all serious cases. In addition, listings will be provided for the related AE risks.

Risk measures and confidence intervals will be derived according to Section 5.

The version of the Case Retrieval Sheet used for the analyses will be described in a footnote. This includes MedDRA version and Novartis MedDRA Query (NMQ) dictionary date.

Important note: For the evaluation of risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.8.2 Deaths

Separate summary and listing will be provided for deaths.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry).

The general guideline for laboratory summaries (including vital signs and ECGs in Section 2.8.4.1 and 2.8.4.2) are as below:

- all the summary of laboratory outputs (newly occurring notables, maximum changes, shift tables, by visit summary statistics) will be reported on all data collected up until end of study. Any summary presented by period will use the on-treatment definition i.e., include all assessments within last dose plus 84 days.

- all records are displayed in the listing with the on-treatment flag. i.e., occurred within last dose plus 84 days- yes or no, as well as eCRF visits and period.

Descriptive summary statistics for the change from baseline to each study visit will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline within treatment period will be summarized analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged. The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-9: 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) and estimated glomerular filtration rate (eGFR).

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented. These summaries will be split into hematology and chemistry.

Table 2-11 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
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
eGFR	<LLN – 60ml/min/1.73m2	<60-30 ml/min/1.73m2	<30-15 ml/min/1.73m2	<15 ml/min/1.73m2

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed. Of note, baseline will be defined as last assessment prior to first dosing in treatment phase. If no pre-treatment value exists, also a value recorded after first dose can be used as baseline if it was collected on the same day as first dose, see Section 2.1.1.3.

The number and percentage of subjects with newly occurring or worsening after baseline (treatment emergent) liver enzyme abnormalities will be presented for the treatment period based on the event criteria given in Table 2-12. For pooled DMC analysis 95% confidence will be provided. Standard laboratory change from baseline tables of liver function test by visit will be produced.

Table 2-12 Liver-related events

Parameter	Criterion
ALT	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
AST	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>ULN; >1.5xULN, >2xULN
ALP	>ULN;>1.5xULN, >2xULN, >3xULN, >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >1.5xULN; ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN;

	ALT or AST >8xULN & TBL >2xULN ALT or AST >10xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALP > 3x ULN & TBL > 2x ULN ALP > 5x ULN & TBL > 2x ULN ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**) (ALT or AST > 3x ULN & TBL > 2x ULN & ALP < 2x ULN) or reported Hy's Law case

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.

Individual subject data listings will be provided for subjects with newly occurring or worsening abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities will be listed in an additional listing.

For the DMC, a panel graph will be presented to display shift from baseline to maximum evaluation for each of the liver function test (including ALT, AST, ALP and TBL) by treatment. Similarly a graphical presentation of each hematology parameter (including Leukocytes, neutrophils, lymphocytes and platelets) will be presented to display shift of baseline to minimum evaluation based on CTCAE grades.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The following quantitative variables may be summarized if requested: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Fridericia (QTcF) correction will be presented for QTc.

Notable abnormal QTc will summarized by computing the number and percentage of subjects (including 95% confidence intervals for pooled DMC analysis) with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- QTc changes from baseline > 30 msec
- QTc changes from baseline > 60 msec
- PR > 250 msec

Summary statistics will be presented for ECG variables by visit and treatment group based on the entire study period. In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on-treatment/study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities (based on the treatment period/study period) will be provided, as well as a by-subject listing of all quantitative ECG parameters.

2.8.4.2 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post - baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

Vital signs will be summarized by visit based on the entire study period data. All vital signs will be listed with "on-treatment" flag displayed.
The number and percentage of subjects with newly occurring notable vital signs (within the treatment period) will be presented by treatment group. Subjects not meeting the following criteria at baseline but meeting at post-baseline are considered to be subjects with newly occurring abnormalities. Criteria for notable vital sign abnormalities are provided in Table 2-13 below:

Table 2-13 Criteria for notable vital signs in pediatric patients

Age group	Systolic BP(mmHg)	Diastolic BP(mmHg)	Pulse (bpm)
6 -11 yrs	90-130	50-80	50-105
12-17 yrs	90-145	55-90	45-95
18 yrs and over	90-139	60-89	60-100

If appropriate, data of subjects with newly occurring notable vital signs abnormalities will be listed in an additional listing.

Of note, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes), the average will be entered on the Vital Signs eCRF and will be used in the analysis.

2.8.4.4 Growth and Physical development

Body weight, height and BMI percentile will be summarized by treatment and visit.

Standard height, weight, and BMI curves will be obtained from the U.S. National Center of Health Statistics (www.cdc.gov/growthcharts) curves for ages up to 18 years. These growth curves will be used for all study subjects. The Center's files contain the L, M, and SD parameters needed to generate exact percentiles as follows:

$$z = \frac{\left(\frac{X}{M}\right)^{L} - 1}{L \times SD}$$

where X = physical measurement (e.g., patient's weight, height, and BMI)
M = median
SD= standard deviation
L = the power in the Box-Cox transformation

Percentiles for each patient at each time point will be calculated using the SAS function PROBNORM(z).

The number and percentages of subjects falling in low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95) growth percentiles will be summarized by treatment and visit. Shift from baseline in growth percentile categories, i.e., low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95), will be summarized by treatment and visit.

2.9 Pharmacokinetic endpoints

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 (BLQ) as well as missing data will be labeled as such in the concentration data listings. BLQ concentrations will be included in the summaries. Serum concentration data from patients who missed a dose or doses will be excluded at the following visit(s).
PK concentrations will be summarized by eCRF visit and treatment. PK concentrations will also be presented by visit (i.e., CRF visit), dose group (75 mg, 150 mg, 300 mg) and body weight categories at visit (<25 kg, 25 to <50kg, ≥50 kg). Per protocol, a subject will change into a higher or lower weight category and dose, when the subject's weight moves into a different weight category for two consecutive visits. This change is assessed from Week 12, then at week 16 and bimonthly until week 52 and at trimonthly visits in the extension phase. If such a change happens, in the PK summaries, at the concerned assessment points, the subject will be accounted in the new dose group (75 mg, 150 mg, 300 mg) and weight category 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. 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, elapse time since day of first secukinumab dose, reason excluding from analysis will be listed by treatment.

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

Pharmacokinetic derived parameters AUC84-112d, Tmax and Cmax will be summarized by treatment group (AIN457 low dose and AIN457 high dose). Descriptive summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. Derived pharmacokinetic parameters will be listed by treatment sequence.

2.10 PD and PK/PD analyses

Not applicable.

[redacted]

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

2.14 Interim analysis

A primary endpoint analysis of the data collected up until Week 16, including the co-primary endpoint (at Week 12) will be performed after the last subject completes their Week 16 visit. Efficacy and safety data up to Week 16 visit for all subjects will be summarized. AE listing will be presented on the entire treatment period i.e. reports AE data collected until last subject week 16 cut-off date.

To address comments from the health authorities an additional full analysis will be performed when all subjects have completed the Week 24 visit.

A full analysis will be performed when all subjects have completed the Week 52 visit, (or premature treatment discontinuation visit). Thereafter, efficacy and safety data collected after Week 52 until the end of study may be reported yearly in separate reports.

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

Trial modifications are not planned based on any interim analyses No aggregated statistical analysis will be performed by actual treatment group prior to W16 PEA.

3 Sample size calculation

The sample size for this study is calculated to ensure an adequate number of subjects for PK analyses and powered efficacy analyses. Approximately 80 pediatric subjects from 6 to less than 18 years of age at randomization will be recruited. Since a 15% screening failure rate is expected, approximately 95 patients will be screened. The study will aim to recruit at least 60 subjects with moderate severity and approximately 20 subjects with severe severity.

Power calculations were performed to support the co-primary endpoints PASI 75 and IGA 0 or 1 response at week 12, and secondary endpoint PASI 90 at week 12, versus placebo (historical control) for the low and high secukinumab dose regimens. The low dose arm with smaller treatment effect is being considered in the power/sample size calculation.

Data from four adult placebo-controlled trials (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309) and pediatric placebo controlled trials (Paller et al 2008, Landells et al 2015) were used to estimate the historical placebo response rate. For study CAIN457A2310, a 10% response rate was assumed for PASI 75, IGA 0 or 1 and 8% for PASI 90 response for the placebo group. The 95% upper quantile of predicted number of responders are 7, 7 and 6 subjects, respectively. The assumed placebo response rates were derived accordingly with 40 pediatrics for study CAIN457A2310. Refer to table 3.1 below.

Table 3-1 Placebo response rates from historical secukinumab placebo controlled trials

Adult Placebo controlled trial	Endpoint	Number of subjects with response/ Number of subjects evaluable	Placebo response rate (%)
CAIN457A2302	IGA 0 or 1	6/246	2.4
	PASI 75	11/246	4.5
	PASI 90	3/246	1.2
CAIN457A2303	IGA 0 or 1	9/324	2.8
	PASI 75	16/324	4.9
	PASI 90	5/324	1.5
CAIN457A2308	IGA 0 or 1	0/59	0
	PASI 75	0/59	0
	PASI 90	0/59	0

CAIN457A2309	IGA 0 or 1	0/61	0
	PASI 75	2/61	3.3
	PASI 90	0/61	0

Pediatric Placebo controlled trial	**Endpoint**	**Number of subjects with response/ Number of subjects evaluable**	**Placebo response rate (%)**
Ustekinumab Dermatol 2015 (Age 12 to 17 years)	PGA 0 or 1	2/37	5.4
	PASI 75	4/37	10.8
	PASI 90	2/37	5.4
Etanercept NEJM 2008 (Age 12 to 17 years)	PGA 0 or 1	14/105	13
	PASI 75	12/105	11
	PASI 90	7/105	7
CAIN457A2310 (estimation Includes simulation uncertainty error)	IGA 0 or 1	7/40	17.5
	PASI 75	7/40	17.5
	PASI 90	6/40	15

The Meta-Analytic-Predictive (MAP) approach derives an informative prior from historical data which is discounted using a hierarchical model. When using the MAP approach to estimate the predicted placebo response rate, differential discounting was defined for two stratum: pediatric study data and adult study data. Moderate between-trial heterogeneity (with τ prior set as HalfNormal(0, 0.5)) was defined for pediatric trial data and substantial heterogeneity (with τ prior set as HalfNormal(0, 1)) was defined for adult trial data (Neuenschwander et al.2010), thus allowing pediatric trial data to be given a higher weight compared to adult trial data. The prior distribution for the regression coefficient β was set as non-informative Normal (0, 2). The following Table 3-2 presents the summary statistics of the fitted mixtures of conjugate distribution to the sample.

All the calculations were performed in the R package RBesT (version 1.3.1) through the meta-analytical-predictive framework (Spiegelhalter et al. 2004, Neuenschwander et al. 2010).

Table 3-2 Predictive placebo response rates for this study from model of historical data

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

Based on confirmatory efficacy in the adult phase III program (CAIN457A2302, CAIN457A2303, CAIN457A2308 and CAIN457A2309), the PASI 75, IGA 0/1 and PASI 90 response rate at week 12 was assumed as 65%, 45% and 39% for secukinumab. Non-informative prior was set for secukinumab arm. A sample size of 40 pediatric patients from this

study under each high or low secukinumab arm over predictive placebo response (Table 3-2) will lead to a power of approximately 99% for each co-primary endpoint and secondary endpoint. Details as following:

- A sample size of 40 pediatric patients per treatment group and true response rates of 65% for PASI 75 and 45% for IGA mod 2011 0 or 1 response for secukinumab was assumed. For each co-primary endpoint there is approximately 99% power to detect a posterior probability of the log odds ratio difference between placebo and secukinumab to exceed with at least 97.5%.
- Similarly, for the secondary endpoint of PASI 90 response there is approximately 99% power to provide a posterior probability of at least 97.5% that the PASI 90 response rate on secukinumab is greater than placebo. This assumes a response rate of 39% for secukinumab.

4 Change to protocol specified analyses

The following are changes to protocol specified analysis:

Following HA recommendadtion to impute subjects with all post-baseline missing values as non-responders according to the intention to treat principal and to remain consistent with the adult studies and pediatric data used within the MAP analysis, the primary analysis will be performed on pure non-responder imputation and the MI dropped. Modified non-responder analysis may still be performed upon request from HA. No sensitivity analysis will be provided for the Bayesian analysis. For the descriptive summary of key efficacy endpoints, results using pure non-responder imputation as well as multiple imputation will be provided.

Week 16 PEA analysis constitutes the scope for delivering to DMC and an extended FIR requirement, thus a full analysis will not be performed as planned. Further to recent communications with the health authorities, additional outputs and an interim analysis at Week 24 is added to support the pediatric submission. The following subgroup summaries are added to the planned analyses:

- Summaries by age subgroup:<12 years or ≥ 12 years
- Summaries by body weight strata:<25kg, 25-<50kg and ≥ 50kg
- Summaries by disease severity strata:moderate, severe
- Summaries by body weight and dose group:AIN457 – 75 mg and < 25 kg, AIN457 Low – 75 mg and ≥ 25 kg -< 50 kg, AIN457 Low – 150 mg and ≥ 50 kg;, AIN457 High – 150 mg and ≥ 25 kg -< 50 kg, AIN457 High – 300 mg and ≥ 50 kg;

Safety summaries for exposure adjusted incidence rates may be prepared.

Pandemic reporting (COVID-19)

Data collected in this trial that is affected by the COVID-19 situation, can be expected to lead to difficulties in interpretation in the trial's reporting. In recognition of these challenges, both FDA and EMA (and local regulatory authorities) have issued specific guidelines that request

Novartis to collect the reasons for non-compliance and discontinuation of clinical trial elements related to COVID-19 in all ongoing trials.

In adherance to these guidences, specific protocol deviations were added to capture data necessary to provide a summary of impact for the pandemic.

The primary and key secondary objective of the study assesed at Week 12 are not impacted. These were reported prior to the pandemic, which emerged as the last few patients were reaching week 52 visit. Therefore, notably missing data are not expected and imputations are considered reasonable for evaluating efficacy up to week 52.

All protocol deviations for the study will be summarised together (i.e including COVID-19 specific PDs) as described in section 2.3.1. In addition, all protocol deviations from 1st March 2020, that is considered to be the starting point of COVID-19 period (as per internal guidance for those countries participating in this study) will capture whether there was any relation to COVID-19 including a precise relationship status in regard to COVID-19 virus (such as health status related, site issues, quarantine of patient/lockdown, drug supply issue, patient concern, other or no relationship to COVID-19). The relationship status will be presented in the listing. For patients with suspected/confirmed cases of COVID-19, separate summaries and/or listings may be provided for disposition, concomitant medications/proceduces and significant non drug therapies and adverse events (including COVID-19 testing with outcome results). Summaries of treatment emergent COVID-19 related adverse events may be presented if data permits.

5 Appendix

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

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

- The last day in the month and
- The end day of the corresponding epoch

5.1.2 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 + 140 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 + 140 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:

> a. If AE ‘month’ is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
>
> b. 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.

5.1.3 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.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.3.3 First diagnosis date (Pso, PsA) imputation

1. If the first diagnosis day/ month are missing and the year is non-missing:
   a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).

2. If the first diagnosis day is missing and the month/year are non-missing:
   a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.1.3.4 Other imputations

Only PASI and IGA mod 2011 based response variables are imputed with multiple imputation or non-response, other response variables ([redacted] will be imputed with LOCF.

[redacted]

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

5.2 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote.

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Analysis of 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. If applicable, means +/- SE will be plotted. [redacted]

5.4.2 Analysis of binary (and categorical) data

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. 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 for $p > 0, (L = 0 \text{ for } p = 0)$,

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

and the upper limit is for $p < 1, (U = 1 \text{ for } p = 1)$,

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

Figures will be provided for PASI 75 response (upper left) PASI 90 response (upper right), PASI 100 response (lower left) and IGA mod 2011 0 or 1 response (lower right) at Week 12 and Week 16 as dot plots displaying treatments on the x-axis and point estimates including 95% confidence intervals on the y-axis.

For time courses of response variables, the point estimate at each time point including 95% confidence interval will be plotted.

5.4.3 Multiple imputations for response variables

Descriptive summaries for PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visits will be analyzed using multiple imputation method.

In the multiple imputations analysis the response status will be imputed based on the individual treatment arm information.

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty.

Missing values for the 'change from baseline PASI score' and 'IGA mod 2011 score' will be imputed simultaneously based on an underlying joint normal distribution and using a Markov Chain Monte Carlo (MCMC) method. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. Assuming normality for the 'IGA mod 2011 score' is motivated by Schaefer (1997), where it was shown that the multivariate normal approximation for the imputation of incomplete categorical and binary data is robust.

The imputations will be done separately for each treatment group including baseline weight, failure to at least one previous biologic (yes/no), and number of previous systemic therapies as additional covariates.

Summary statistics for PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables with multiple imputations method.

The number of imputations will be set to 100, the seed for the random function will be set to 4572311 for this study. SAS proceduce MI will be used to generate the multiple imputed data sets. The SAS procedure MI can be used as follows:

The input data set <pasi_iga> should have one record per subject with baseline PASI score and IGA mod 2011 score as well as all changes from baseline PASI and post-baseline IGA mod 2011 score.

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi_iga> OUT=<impdata> SEED=457<studycode> NIMPUTE=100;
VAR <baseline weight> <failure to at least one biologic>
<number of previous systemic therapies>
```

```
<baseline PASI> <baseline IGA>
<change from baseline PASI week 1> - <change from baseline PASI week primary endpoint>
<IGA week1> - <IGA week primary endpoint>;
EM converge=1E-2 MAXITER=5000;
MCMC PRIOR=RIDGE=2 ;
BY <treatment group>;
RUN;
ODS LISTING;
```

Programming notes:
The SAS procedure MIANALYZE expects a variable called "_IMPUTATION_" which is generated by the MI procedure. It might be needed to set the SAS option "VALIDVARNAME=UPCASE" temporarily in the program before the MI call, this option should be reset after the MIANALYZE call to VALIDVARNAME=V6. In case there are no missings in one treatment group, the MI procedure does not impute any values. In this case the corresponding data need to be imputed manually outside PROC MI and added to the dataset <impdata>.
The imputed data are saved in data set <impdata>. The outcomes of interest, i.e. the PASI 50/75/90/100 response and IGA mod 2011 0 or 1 response will be calculated, e.g. as follows:

```
DATA <impdata2>;
SET <impdata>;
IF <change from baseline PASI week primary endpoint>/<baseline PASI>=0.75 THEN <PASI 75 response> =1;
ELSE <PASI 75 response>=0;
<…repeat for all PASI response…>
IF <baseline IGA> >=3 THEN DO;
IF <IGA week primary endpoint> < 1.5 THEN <IGA 0/1 response> =1;
ELSE IF <IGA week primary endpoint> >=1.5 THEN <IGA 0/1 response> =0;
ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE IF <baseline IGA>=2 THEN DO;
IF <IGA week primary endpoint> < 0.5 THEN <IGA 0/1 response> =1;
ELSE IF <IGA week primary endpoint> >=0.5 THEN <IGA 0/1 response> =0;
ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE <IGA 0/1 response> =0;
RUN;
```

5.4.4 Crude incidence and related risk estimates

5.4.4.1 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 p = 0 then L = 0 and if p = 1 then U = 1.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

5.4.5 Exposure adjusted incidence rate and related risk estimates

5.4.5.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or last dose plus 84 days whichever occur earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event.

Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

5.4.6 Primary analysis

```
Example schematic code for Bayesian analysis of 2311 using dummy data
for PASI 75.

## model to fit placebo data

tau.prior <- rbind(c(0, 0.5), c(0, 1))

set.seed(345652)
analysis_pbo_mc_pasi <- gMAP(cbind(r, n-r) ~ 1 | trial,
                             tau.strata=stratum,
                             family=binomial,
                             data=final_data_pbo,
                             tau.dist="HalfNormal",
                             tau.prior=tau.prior,
                             beta.prior=rbind(c(0,2)))



## model to fit the data of A2311
set.seed(34535214)
analysis_A2311_mc_pasi75 <- gMAP(cbind(r, n-r) ~ 0 + TREATMENT,
                                 family=binomial,
                                 data=active,
                                 tau.dist="Fixed",
                                 tau.prior=1E-6,
                                 beta.prior=matrix(c(0,0,2,2), 2, 2))
```

5.4.7 Key secondary analysis

As per section 5.4.6 but on the PASI 90 endpoint.

5.4.8 Analysis of time-to-event data

Number and percentage of subjects with a clinical event based on the number of subjects in the analysis set at risk as denominator, will be provided by treatment group.

Subjects without PASI 75/90 response will be considered as censored at Week 12.

Median time to event and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation (PROC LIFETEST option conftype=log-log). The plot will include the number of subjects at risk for each treatment group at pre-specified timepoints, which are 0 to <= 4 weeks , >4 to <=8 weeks and 8 to <=12 weeks.

Subjects at risk, timepoint "0" and censoring will be defined as described in Table 5-1 below:

Table 5-1

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed*	Informative censoring
PASI 75/90 response	All subjects randomized with baseline and post-baseline data for PASI	Date of randomization	Date of 1st visit with PASI 75/90 response observed	Week 12 visit date/discontinuation date	Censor (if ConMed taken before the event)	No

Time-to-event will be derived as:

- date of event minus date of time=0 plus 1 day for subjects experiencing the event or
- date of censoring minus date of time=0 plus 1 day for subjects not experiencing the event

5.5 Rule of exclusion criteria of analysis sets

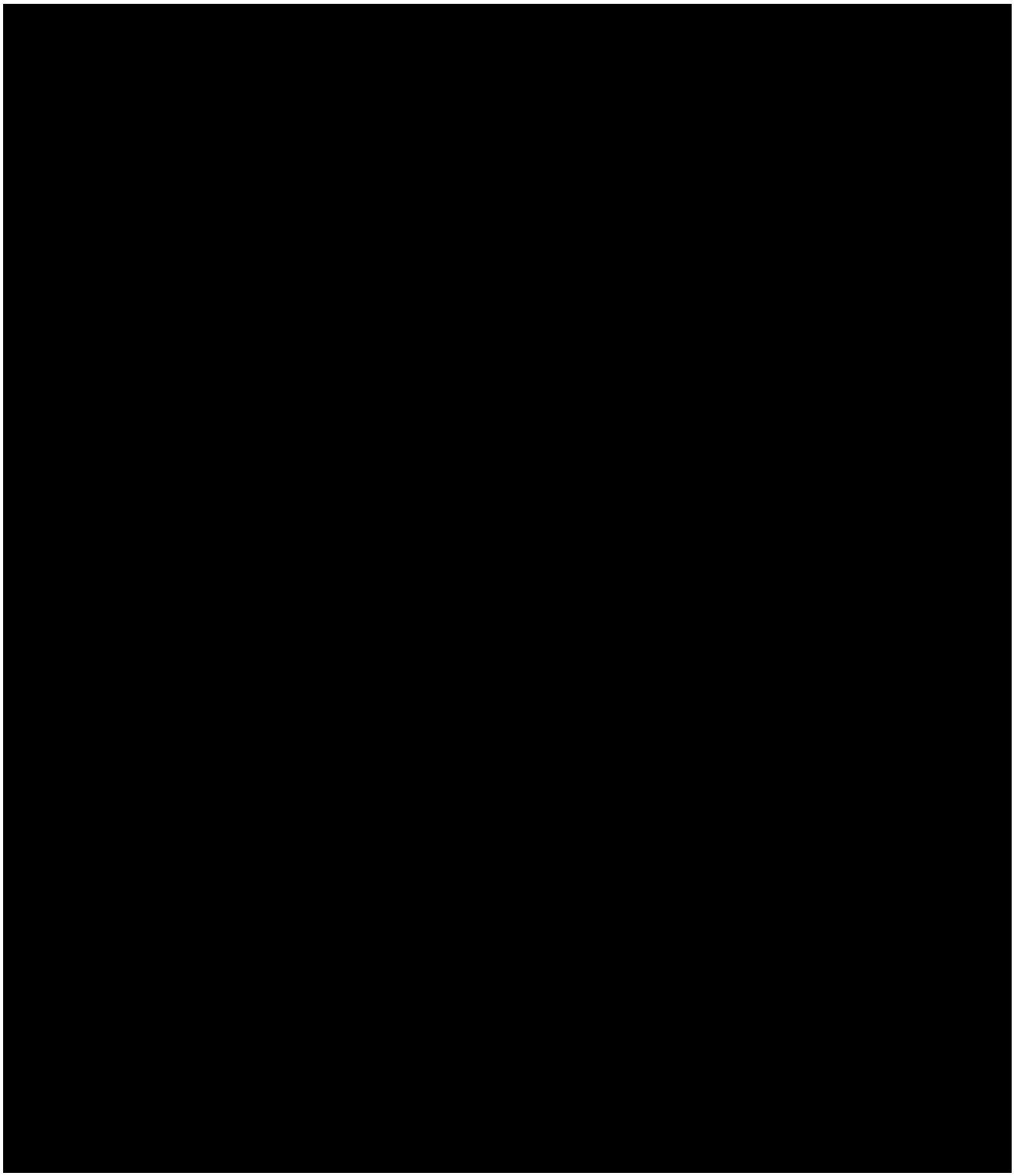
Protocol deviations for exclusion from analysis sets are defined in Table 5-2

Table 5-2 Subject classification rules

Analysis set	PD Categories Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
Randomization set	NA	Misrandomized subject
FAS (Full Analysis Set)	DVSPID: INCL01; OTH12	Misrandomized subject
Safety	DVSPID: INCL01; OTH12	Misrandomized subject Subjects who did not take any study treatment

INCL01: ICF missing or not signed; in the case where ICF was obtained after initiating study procedures, subjects will be included in all analysis sets

OTH12: Severe ICH-GCP non-compliance of study site



6 Reference

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