NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457M2301E1 / NCT04179175

A Multicenter, Double-blind, Randomized Withdrawal extension study of subcutaneous secukinumab to demonstrate long-term efficacy, safety and tolerability in subjects with moderate to severe hidradenitis suppurativa

Statistical Analysis Plan (SAP) Amendment 3

Author: [redacted]

Document type: SAP Documentation

Document status: Final

Release date: 22-Jun-2023

Number of pages: 55

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Aug-2022		*Creation of Amendment 1*	*Adding estimand and details of PEA*	*1.2.1, 2.3, 2.7.3, 2.7.5*
17-Apr-2023		*Creation of Amendment 2*	• *Review of analysis visit windows.* • *Specifying in scope analyses for the interim lock.* • *Removing missed doses from the estimand.* • *Adding one sensitivity analyses associated with the primary endpoint.* • *Aggregating regions for the primary endpoint analysis.* • [redacted] • *Treatment groups for safety analysis over the entire study period.* • *Considering the PD OTH10 (false LOR declaration) as censoring.* • *Definition of HiSCR non-responders analysis set.* • *Removing the subsection related to AESI.* • *Removing the evaluation of newly occurring notable vital signs and newly occurring abnormal laboratory values.*	*1,1.1, 1.2,* *2.1, 2.2, 2.3, 2.4, 2.5.1, 2.7.3, 2.7.4, 2.7.5, 2.7.6, 2.8 2.13, 2.14, 4, 5.4.2.2, 5.6*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			• *Representing exposure according to the visit schedule.* • *Adding specification on the impact of serious GCP violation in the core studies.* • [redacted] • [redacted]	
22-Jun-2023		*Creation of amendment 3*	• *Aligning the naming convention of treatment groups with the core studies CSR* • *Reviewing the Analysis sets: (i) distinguishing between responders and non-responders in randomized and full analysis set; (ii) excluding mis-randomized subjects only from the full analysis sets; (iii) not excluding subjects with serious GCP violation in the extension study from any of the analysis sets.* • *Clarifying the definition of the end of the RWP for the primary, secondary and efficacy endpoints analyses.* • *Clarifying how we analyze the subjects with missed or false LOR declaration in IRT.* • *Clarifying what will be displayed as baseline and disease history characteristics.* • *In the safety analysis, we evaluate the Adverse Events that are part of the Safety Topics of Interest instead of the Risk Management Plan.*	*1.2.1, 2.2, 2.3, 2.4,2.5.1, 2.5.1.1, 2.7,2.8.1,2.13, 5.4.2.2,5.6,2.10*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			• *Adding sensitivity analysis 2 to assess the impact of missed triggered reassessment in IRT and missed reassessment.* • [redacted]	

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AN	Abscesses and inflammatory nodules
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BCC	Basal cell carcinoma
CRF	Case Report Form
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
EOT	End of Treatment
HLT	High Level Term
HS	Hidradenitis suppurativa
[redacted]	[redacted]
IRT	Interactive Response Technology
LOR	Loss of response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
[redacted]	[redacted]
OL	Open Label
[redacted]	[redacted]
PE	Primary endpoint
PFS	Pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
[redacted]	[redacted]
Q2W	Once every two weeks
Q4W	Once every four weeks
RAP	Report and Analysis Process
RWP	Randomized Withdrawal Period
SAP	Statistical Analysis Plan
SCC	Skin squamous cell carcinoma
s.c.	Subcutaneous
SAE	Serious adverse event
SOC	System Organ Class
TFLs	Tables, Figures, Listings

WHO	World Health Organization

1 Introduction

Data will be analyzed by Novartis according to the data analysis Section 12 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

This document covers statistical and analytical plans for the primary endpoint analysis, i.e after all subjects have completed the visit at Week 104 or have discontinued from the study and also the final analysis, i.e., after all subjects have completed four years of treatment with reference to the study protocol.

1.1 Study design

This is a four-year multicenter, double blind, randomized withdrawal extension study of the two phase III studies CAIN457M2301 and CAIN457M2302 (collectively referred as 'core studies'). Total treatment time of core and extension is up to five years.

This study includes a blinded and an open-label (OL) part. The blinded part includes a placebo-controlled period lasting up to 52 weeks (between Week 52 and Week 104) to provide data for randomized withdrawal analysis. The primary endpoint (PE) is assessed at the end of the Randomized Withdrawal Period (RWP) (End of Treatment (EOT) -1). The duration of the RWP for each subject is determined by the timepoint at which a subject has lost a clinical response (LOR) or reaches Week 104, whichever occurs first. After LOR has been attained or Week 104 has been reached, the subject receives Open Label (OL) treatment with secukinumab and continues in the study for the maximum duration of 260 weeks of treatment plus 8 weeks of the post-treatment follow-up period, or until secukinumab is commercially available in the country of study conduct. For this statistical analysis plan, years refers to the number of extension years (not core + extension), unless otherwise specified.

It is expected that subjects who complete the four years of treatment receive their final dose of study medication at Week 256 for subjects receiving secukinumab 300 mg Q4W dose regimen or at Week 258 for subjects receiving secukinumab Q2W dose regimen. Week 260 is the end of the open label treatment (EOT-2) followed by 8 weeks of the post treatment follow up period ending up at Week 268/F8 visit.

The study population includes subjects who have completed the entire treatment period in the core studies. Subjects will be defined as HiSCR responders or non-responders as follows:

- **HiSCR responders** (subjects who achieved at least 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and in the number of draining fistulae) compared to the weighted average of the baseline and screening visits of the core studies, or
- **HiSCR non-responders** (subjects who did not achieve at least 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and

in the number of draining fistulae) compared to the weighted average of the baseline and screening visits of the core studies.

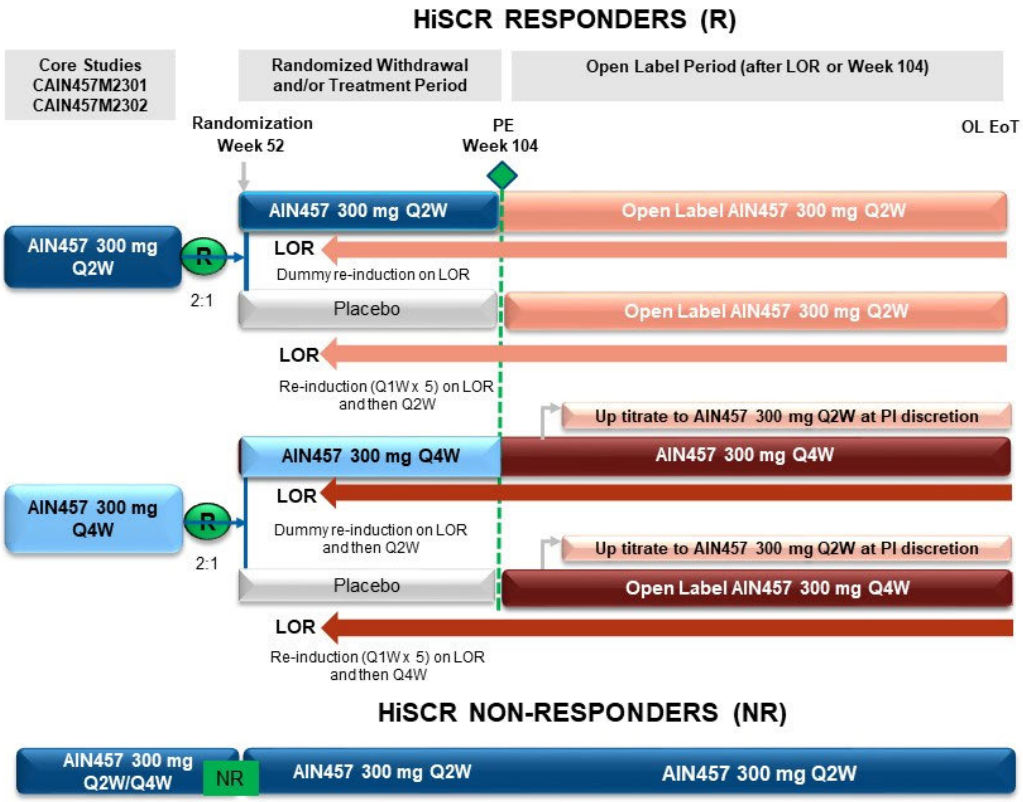
The definition of weighted average is given in Section 2.1.1.2.

The study design for HiSCR responders and non-responders is different.

The Week 52 visit in the core studies will be the randomization visit for CAIN457M2301E1 (extension study).

An outline of the study design is presented in Figure 1-1.

Figure 1-1 Study design



HiSCR responders will be randomized into a secukinumab arm or a placebo arm. Depending on the treatment received by the subject in the core study, they will be either randomized to AIN457 300 mg Q2W or placebo, or to AIN457 300 mg Q4W or placebo (see Figure 1-1). Additionally, the randomization will be stratified by body weight (<90kg, >=90kg) and geographical region (see Table 1-1).

Table 1-1 Geographical regions used for stratified randomization

Geographical Region	Country
Japan	Japan
AMEA (Asia pacific, middle East & Africa)	Australia, India, Korea, Lebanon, Malaysia, Philippines, Singapore, South Africa, Taiwan, Turkey, Vietnam
RE (Region Europe)	Austria, Belgium, Bulgaria, Croatia, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Lithuania, Netherlands, Poland, Portugal, Russia, Slovakia, Spain, Switzerland, UK
LaCAN (Latin America and Canada)	Argentina, Canada, Colombia, Guatemala, Mexico
US	US

Note: Japan may be combined with AMEA region and US may be combined with LaCAN region for analysis.

HiSCR non-responders will not be randomized and will be assigned to the open-label AIN457 300 mg Q2W regimen.

The primary endpoint analysis is planned after all subjects have completed the visit at Week 104 or have discontinued from the study. At the time of the primary endpoint analysis, subjects, investigators and site staff and Novartis Clinical Trial Team (CTT) will be unblinded to study treatment in the randomized withdrawal treatment period.

At the end of the study, a final analysis of all data collected will be performed when all subjects have completed their last visit in the study. Additional interim analysis may be conducted at various time points for publications or health authority requests.

1.2 Study objectives and endpoints

The objectives and related endpoints presented in Table 1-2 will be evaluated in subjects with moderate to severe HS.

Table 1-2 Objective and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the efficacy of secukinumab (300 mg q4w or 300 mg q2w) in subjects with moderate to severe HS who were HiSCR responders at Week 52 of the core studies, with respect to loss of response by Week 104, compared to placebo.	• Time to loss of response (LOR) up to Week 104 (Randomized Withdrawal period) in subjects who were HiSCR responders at Week 52 in the core studies. HiSCR response is defined as at least 50% decrease in Abscess and inflammatory Nodule (AN) number with no increase in the number of abscesses and in the number of draining fistulae. Loss of response is defined as: • at least a 50% increase in AN (abscess and/or nodules) count at a regular or unscheduled visit compared to the average AN count from 3 previous visits or at Week

Objective(s)	Endpoint(s)
	52, whichever is lower, with an increase of at least 3. • If at a regular or unscheduled visit, the subject experiences at least a 30% increase in AN count compared to the average AN count from the 3 previous visits or at the Week 52 visit, whichever is lower, with an increase of at least 2 , the subject should be reassessed within 2-4 weeks. A further increase in the AN count of at least 2 would be considered a LOR also. Note: If the 3 previous visits include visits from core studies, the AN count from the core studies will be included in the average. Furthermore, if the 3 previous visits include a reassessment, the AN count from the reassessment will be included as well.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the long-term safety and tolerability of secukinumab in subjects with moderate to severe HS.	• Adverse events, laboratory values, vital signs

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

1.2.1 Primary Estimand

The primary clinical question of interest is: What is the effect of secukinumab vs. placebo on the time to loss of response (LOR) up to Week 104 in subjects with moderate to severe hidradenitis suppurativa who were HiSCR responders at Week 52 of the core studies.

The primary estimand is described by the following attributes:

1. **Population:** Subjects with moderate to severe hidradenitis suppurativa, who completed Treatment period 2 (52 weeks) of the core studies while receiving treatment with secukinumab and have been defined as HiSCR responders (see Section 1.1 and Section 2.1.1.2).
2. **Endpoint:** time to LOR up to Week 104. LOR is declared at the first visit when:
   - two criteria are satisfied: (i) at least a 50% increase in abscess and inflammatory nodule (AN) count is recorded, compared to the minimum value between the average AN count from the 3 previous visits and the AN count at Week 52; (ii) at least a 3 AN count increase is recorded, compared to the minimum value between the average AN count from the 3 previous visits and AN count at Week 52; or
   - three criteria are satisfied: (i) at least a 30% increase in abscess and inflammatory nodule (AN) count is recorded, compared to the minimum value between the average AN count from the 3 previous visits and the AN count at Week 52; (ii) at least a 2 AN count increase is recorded, compared to the minimum value between the average AN count from the 3 previous visits and AN count at Week 52; (iii) if criteria (i) and (ii) are met, the subject should be re-assessed within the next 2-4 weeks. At the reassessment visit, at least a 2 AN count increase is recorded with respect to the previous assessment.

   If the 3 previous visits include visits from the core studies, the AN count from the core studies will be included in the average. Furthermore, if the 3 previous visits include a reassessment, the AN count from the reassessment will be included as well.

   The evaluation of time to LOR relies on the AN count assessments at nominal visits. No analysis visit window is applied for the LOR evaluation. Data reported in Electronic Data Capture (EDC) system will be used for the analysis. For subjects with an OTH11 Protocol Deviation, PD, (missed LOR in IRT), the LOR is declared at the date of the PD. Subjects with an OTH10 PD (false LOR in IRT) are censored at the date of the PD. IRT is the Interactive Response Technology.
3. **Treatment of interest:** The randomized study treatment (secukinumab 300 mg in two different dosing regimens Q2W and Q4W, or placebo).
4. **The summary measure:** hazard ratio of secukinumab dose regimens versus placebo.

Handling of intercurrent events:

1. Intake of prohibited medications: ignore events (treatment policy).
2. Intake of rescue medication: consider the event as LOR (composite strategy).
3. Missing 2 or more than 2 consecutive assessments: censor the subject at the last assessment (hypothetical strategy).
4. Discontinuation of study treatment due to adverse events or lack of efficacy: consider the event as LOR (composite strategy).

5. Discontinuation of study treatment due to any reason (except for adverse event and lack of efficacy): censor the subject at the last recorded visit (hypothetical strategy).
6. COVID-19 related events:
    a) Missed at least one dose due to COVID-19.
    b) Discontinued treatment due to COVID-19.

   Ignore such events (treatment policy).

2 Statistical methods

2.1 Data analysis general information

Novartis will be performing the analysis. Statistical software 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.

If not otherwise specified, p-values will be presented as one-sided for hypothesis testing and as two-sided for other analyses. The level of significance will be set to 2.5% (one-sided, family-wise type-I-error). 95% confidence intervals will be displayed but will not be used for decision making; they will only be used for estimation and will therefore always be two-sided.

All listings will be presented by treatment arms.

Footnotes in the outputs will be kept to a minimum.

Footnotes will 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 NOT be given for:
- units displayed on the output;
- interpretation of results (e.g. “hazard ratio larger than 1 favor 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 in an output;
    - derivations of variables (e.g. BMI will not be explained in 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 Day 1 and other study days

Study day is defined with respect to the core studies. The first day of administration of randomized study treatment (first dose) in the core studies 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 an event date is calculated as Date of event – [Day 1] + 1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For event dates before Day 1, study day for an event date is calculated as Date of event – [Day 1], 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.

2.1.1.2 Screening, baseline and post-baseline definitions

There is no official screening period for this extension trial. Screening period is the duration between signing the informed consent form (ICF) and randomization registered with Interactive Response Technology (IRT). The screening will occur during the core studies. Further information will be found in Study Programming Dataset Specifications (PDS).

For the identification of HiSCR responders at Week 52, for each component (AN count, number of abscesses and of draining fistulae), a weighted average of the values recorded at the baseline, screening 2 and screening 1 visits of core studies is computed.

Baseline and screening visits of core studies are obtained before the first dose of study treatment in the core studies (including the two screening visits).

As reported in Section 1.1, a subject is identified as HiSCR responder if: (i) at least 50% decrease in Abscess and Inflammatory Nodule (AN) count compared to the weighted average of the AN count among screening 1, screening 2 and baseline of the core studies is recorded; (ii) no increase in the number of abscesses compared to the weighted average of the number of abscesses among screening 1, screening 2 and baseline of the core studies is recorded; (iii) no increase in the number of draining fistulae compared to the weighted average of the number of abscesses among screening 1, screening 2 and baseline of the core studies is recorded;

For each component, the method for calculating the weighted averages is as follows:

1. If the values at the first screening visit, the second screening visit, and at baseline are available, weights will be W1=1/6, W2=2/6, W3=3/6.
2. If the values at the first screening visit and at baseline are available, weights will be W1=1/4, W2=0, W3=3/4.
3. If the values at the second screening visit and at baseline are available, weights will be W1=0, W2=2/5, W3=3/5.
4. If the values at the first screening visit and at the second screening visit are available, weights will be W1=1/3, W2=2/3, W3=0.
5. If only the values at the first screening visit are available, weights will be W1=1, W2=0, W3=0.

6. If only the values at the second screening visit are available, weights will be W1=0, W2=1, W3=0.
7. If only the values at baseline are available, weights will be W1=0, W2=0, W3=1.

The weighted average is applied only for the identification of HiSCR responders at Week 52 for randomization purposes into the extension study.

[redacted]

Baseline of the extension study is the visit performed at Week 52 in the core studies, when the first dose of the extension study treatment is given to the subject.

When calculating the change from baseline of safety and efficacy exploratory endpoints, the baseline value of the core studies will be used, if not stated otherwise. The choice of analyzing the data with respect to the core baseline is made for consistency and continuity with respect to the assessments provided for the core studies analyses.

2.1.1.3 Day of last dose of study treatment

The date of last dose will be collected via the CRF.

The subject's exposure will be calculated considering the last visit or the last dose + 84 days whichever occurs earlier.

2.2 Analysis sets

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

The **Randomized Analysis Set of HiSCR responders (RAS-R)** consists of all HiSCR responders that are randomized. Subjects will be analyzed according to the treatment they are assigned to at randomization. Subjects with a Serious GCP violation in the core study and whose data were excluded from the core study randomized set are also excluded from the extension study randomized sets.

The **Randomized Analysis Set of HiSCR non-responders (RAS-NR)** consists of all HiSCR non-responders that are assigned to treatment. Subjects with a Serious GCP violation in the core study and whose data were excluded from the core study randomized set are also excluded from the extension study randomized sets.

The **Full Analysis Set of HiSCR responders (FAS-R)** comprises of all HiSCR responders to whom study treatment has been assigned at randomization. Subjects will be analyzed according to the treatment assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS-R. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject. If the actual stratum is different to the assigned stratum (i.e., region and weight) in IRT, the actual stratum will be used in the analyses. Subjects with a Serious GCP violation in the

core study and whose data were excluded from the core study full analysis set are also excluded from the extension study full analysis sets.

The **Full Analysis Set of HiSCR non-responders (FAS-NR)** comprises all HiSCR non-responders to whom study treatment has been assigned. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS-NR. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject. If the actual stratum is different to the assigned stratum (i.e., region and weight) in IRT, the actual stratum will be used in analyses. Subjects with a Serious GCP violation in the core and whose data were excluded from the core study full analysis set are also excluded from the extension study full analysis sets.

The **Safety Set (SAF)** includes all subjects (HiSCR responders and non-responders) who received at least one dose of study treatment in the extension study. Subjects will be analyzed according to the study treatment received. Treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received (subject received the wrong treatment during the entire study).

2.2.1 Subgroups of interest

The primary endpoint will be evaluated using the randomization strata subgroups: body weight stratum (<90 kg, ≥90kg) and geographical region (see Table 1-1).

2.3 Analysis period and treatment groups

2.3.1 Randomized withdrawal period

All efficacy analyses within the Randomized Withdrawal Period (RWP) – where only HiSCR responders are included – will be conducted using the following treatment groups:

- AIN457 Q2WR-Q2W (HiSCR responders at Week 52 who were on secukinumab Q2W in the core studies and randomized to secukinumab Q2W in the extension).
- AIN457 Q2WR-PBO (HiSCR responders at Week 52 who were on secukinumab Q2W in the core studies and randomized to placebo in the extension).
- AIN457 Q4WR-Q4W (HiSCR responders at Week 52 who were on secukinumab Q4W in the core studies and randomized to secukinumab Q4W in the extension).
- AIN457 Q4WR-PBO (HiSCR responders at Week 52 who were on secukinumab Q4W in the core studies and randomized to placebo in the extension).

The efficacy analyses performed in the RWP will address the primary endpoint [redacted]

All safety analyses within the RWP – where only HiSCR responders will be included – will be conducted using the treatment groups that have been previously defined for the efficacy analyses within the RWP.

In order to properly map the subject's exposure to treatment for the safety and efficacy exploratory analyses, the RWP ends at the 1st intake of OL dose if the subjects continues into the OL period, otherwise the RWP ends at the date of discontinuation. In this way we are able to define the RWP consistently also for cases that deviate from the standard (i.e., subjects with OTH10 or OTH11 PD or subjects with discrepant dates between LOR reported in EDC and in IRT). For example, if a subject meets LOR on 5-Dec-2021 in EDC and LOR is declared in IRT on 12-Dec-2021 because the OL treatment was delivered on 12-Dec-2021, we will consider the end of the RWP as 12-Dec-2021 for safety analysis and for efficacy exploratory analysis. On the contrary, for the PEA we will consider the LOR date reported in EDC.

A summary of this section is reported in Table 2-1 and Table 2-2 (see rows related to 'RWP').

Table 2-1 Treatment groups by subject groups for efficacy analysis

Evaluation of	Analysis Period	Treatment group label (order as listed)	Analysis
Subjects who were HiSCR responders at Week 52	RWP	AIN457 Q2WR-Q2W AIN457 Q2WR-PBO AIN457 Q4WR-Q4W AIN457 Q4WR-PBO	Primary endpoints: time to Loss of response [redacted]
Subjects who were HiSCR non-responders at Week 52	Up to Week 104	AIN457 Q2WNR-Q2W AIN457 Q4WNR-Q2W	[redacted]

Table 2-2 Treatment groups by subject groups for safety analysis

Evaluation of	Analysis Period	Treatment group label (order as listed)
Subjects who were HiSCR responders at Week 52	RWP	AIN457 Q2WR-Q2W AIN457 Q2WR-PBO AIN457 Q4WR-Q4W AIN457 Q4WR-PBO
All subjects	Entire study period	Any AIN457 Q4W Any AIN457 Q2W Any AIN457 AIN457 NR

2.3.2 Open label part and entire study period

The entire study period for the Week 104 interim lock starts at Week 52 and it ends at the cut-off date.

The exploratory efficacy analyses will be conducted over the RWP on the FAS-R and up to the Week 104 visit on the FAS-NR. The evaluation of exploratory endpoints on the OL period will be performed at the final analysis and not at the Week 104 interim lock since the focus is on the efficacy until Week 104, and the OL exposure time for the HiSCR responders can be highly

variable (from a minimum of 0 days for those who reached Week 104 without LOR to 10 months for those who met the LOR at Week 60). The safety analyses will be conducted over the RWP and over the entire study period on the SAF. See Section 2.14 for further details on the scope of the interim analysis.

The safety analyses within the entire study period (from Week 52 up to the cut-off date for the Week 104 interim analysis) – where both HiSCR responders and non-responders are included, after taking any dose of secukinumab – will be conducted using the following treatment groups:

- Any AIN457 Q4W (all subjects that have been exposed to Q4W in the extension study). In this group we include:
  - HiSCR responders in AIN457 Q4WR-Q4W that either discontinued during the RWP or continued to Q4 in the OL period. The exposure starts at Week 52 and ends at the discontinuation date or at the 1st dose of up-titration (if it happened) or at the cut-off date or at the end of study date.
  - HiSCR responders in AIN457 Q4WR-PBO that switched to Q4W in the OL period. The exposure starts at the 1st intake of OL treatment and ends at the 1st dose of up-titration, if it happened, or at the cut-off date or at the end of study date.
- Any AIN457 Q2W (all subjects that have been exposed to Q2W in the extension study, regardless of responder status at Week 52, including those who up-titrated). In this group we include:
  - HiSCR responders in AIN457 Q2WR-Q2W that either discontinued during the RWP or continued to Q2W in the OL period. The exposure starts at Week 52 and ends at the discontinuation date or at the cut-off date or at the end of study date.
  - HiSCR responders in AIN457 Q2WR-PBO that switched to Secukinumab Q2W in the OL. The exposure starts at the 1st intake of OL treatment and ends at the cut-off date or at the end of study date.
  - HiSCR responders in AIN457 Q4WR-Q4W or in AIN457 Q4WR-PBO that are up-titrated to Q2W at the LOR date or during the OL. The exposure starts at the 1st dose of up-titration and ends at the cut-off date or at the end of study date.
  - HiSCR non-responders (group AIN457 NR reported below). The exposure starts at Week 52 and ends at the cut-off date or at the end of study date.

- Any AIN457 (all subjects exposed to Secukinumab in the extension study regardless of the assigned drug regimen, and regardless of responder status). This group is the combination of 'Any AIN457 Q2W' and 'Any AIN457 Q4W' groups.
- AIN457 NR (all subjects who are HiSCR non-responders, AIN457 Q4WNR-Q2W and AIN457 Q2WNR-Q2W). The analysis period starts at Week 52 and ends at the cut-off date or at the end of study date.

A summary of the treatment groups over different treatment periods for the Week 104 interim lock is reported in Table 2-1 and Table 2-2.

2.3.3 Final analysis

Final analysis will be conducted when all subjects have completed the final visit of the study.

The final analysis will target the secondary [redacted] objectives in Table 1-2.

2.4 Subject disposition, demographics and other baseline characteristics

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age (at core baseline)
- Weight (at core and extension baseline)
- Body mass index (BMI) (at core and extension baseline)

Categorical variables:

- Age categories (<20, [20, 30), [30, 50), ≥50) (at core baseline)
- Age categories (<30, [30, 40), [40, 65), ≥65) (at core baseline)
- Weight categories (<70 kg, [70 kg, 90 kg), ≥ 90kg) (at core and extension baseline)
- Weight categories (<90 kg, ≥ 90kg) (at core and extension baseline)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Smoking status at core baseline (Current, Former, Never)

Hidradenitis suppurativa specific baseline characteristics and history of disease (before the core studies) will be summarized as well.

Lesion counts (i.e., nodules, abscesses, AN, draining fistulae) at core and extension study baseline will be reported. [redacted] Hurley Stage, Time since diagnosis of HS, time since HS symptom(s) onset, family history of HS, previous surgery for HS, previous exposure to systemic biologic therapy, previous exposure to systemic antibiotics, previous exposure to non-biologic and non-antibiotic systemic therapy will be reported at core study baseline.

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

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

For BMI, and body weight, the last value prior to first dose in the extension study will be used as a baseline value. If there is no weight at extension study baseline or height at core study baseline, BMI will be missing.

Time since diagnosis of hidradenitis suppurativa will be calculated using the following formula:

Time since diagnosis = (informed consent date –first diagnosis date + 1)/365.25

Time since hidradenitis suppurativa symptom(s) onset will be calculated using the following formula:

Time since onset = (informed consent date – Symptom(s) onset date + 1)/365.25

The first diagnosis date of hidradenitis suppurativa and hidradenitis suppurativa symptom(s) onset will be based on the core study baseline and will be imputed according to the imputation rules in Section 5.1.4. The informed consent for enrolling into the extension study is used in the above formulae.

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment arm and for all subjects (total) in the RAS-R and RAS-NR sets. The number and percentage of subjects in each category will be presented for categorical variables for each treatment arm and all subjects (total) in the RAS-R and RAS-NR.

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

2.4.1 Subject disposition

The number and percentage of subjects in the RAS-R who completed the RWP , the OL period, and who discontinued the treatment prematurely (including the reason for discontinuation) in the respective treatment period will be presented for each treatment group and all subjects. The following treatment periods and groups will be considered:

- RWP: The same groups as in the primary endpoint analysis are used. Details about subjects who completed the RWP with LOR are reported.
- OL: The same groups as in the primary endpoint analysis are used.

For the RAS-NR, the following groups will be considered over the entire treatment period:

- AIN457 Q2WNR-Q2W (HiSCR non-responders who were on secukinumab Q2W in the core studies and stay on Q2W in the extension).
- AIN457 Q4WNR-Q2W (HiSCR non-responders who were on secukinumab Q4W in the core studies and are up-titrated to Q2W in the extension).

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

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

2.5.1 Study treatment / compliance

The analysis of study treatment data will be based on the Safety Set.

The number of secukinumab and placebo doses will be summarized by treatment group by means of contingency tables.

The duration of exposure to study treatment in extension will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain times will be displayed using the following categories: "any exposure", "≥8 weeks", "≥16 weeks", "≥24 weeks", "≥32 weeks", "≥40 weeks", "≥48 weeks", "≥52 weeks", "≥56 weeks", "≥68 weeks" and so on with an increase of time threshold by 12 weeks beyond 68 weeks until there are no subjects in the category or the last category "≥208 weeks" is presented.

Duration of exposure for each period will be calculated using the first dose day and the end date in the extension study.

- For the RWP, end date is defined as the 1st dose of the OL period.
- For the OL period, end date is defined as the end of study date or the cut-off date.
- For the entire study period, end date is defined as the end of study date or the cut-off date.

Duration of exposure (days) = min (end 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

2.5.1.1 Visit windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. Study day 1 is defined as the first randomized dose date in the core studies (or date of randomization if no dose is taken).

These visit windows do not apply for the primary endpoint (time to LOR) because we do not summarize these data by visit but assess the time until LOR (time between the first randomized dose date in the extension study, or date of randomization if no dose is taken, and the LOR date).

For any other assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. In this table, the days are counted since the first dose of study treatment in the core studies (study day 1). These visit windows apply to measurements taken at every visit (see Table 2-3 and Table 2-4). The visit windows for the representation of eDiaries (collected on a monthly basis) are reported in Table 2-5 (for the RWP) and in Table 2-6 (for the entire study period). Of note, the RWP is defined only for the HiSCR Responders, and it ends at the date of discontinuation, of Week 104 visit or of LOR, whichever happens first.

For reporting the core studies' baseline and Week 52 information, the core studies' database will be used. All the other assessments recorded after the intake of the 1st dose of the extension study treatment are derived from the extension study database, [redacted]

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 60 visit of a subject is delayed and occurs on Day 460 instead of on Day 421, it will be re-aligned to visit window Week 68. 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 in Section 2.5.1.2.

Table 2-3 Assessment windows for scheduled visits for the analyses performed within the RWP

Analysis Visit	Week	Scheduled Day	Visit Window
Core baseline	BSL	1	
Week 52	52	365	Day 352-379
Week 60	60	421	Day 380-449
Week 68	68	477	Day 450-505
Week 76	76	533	Day 506-561
Week 84	84	589	Day 562-617
Week 92	92	645	Day 618-673
Week 100	100	701	Day 674-715
Week 104	104	729	Day 716-(minimum between day 743 and Week 104 dosing day)

Table 2-4 Assessment windows for scheduled visits for the analyses performed within the entire study period

Analysis Visit	Week	Scheduled Day	Visit Window
Core baseline	BSL	1	
Week 52	52	365	Day 352-379
Week 60	60	421	Day 380-449
Week 68	68	477	Day 450-505
Week 76	76	533	Day 506-561
Week 84	84	589	Day 562-617
Week 92	92	645	Day 618-673
Week 100	100	701	Day 674-715
Week 104	104	729	Day 716-743
Week 108	108	757	Day 744-799
Week 120	120	841	Day 800-883
Week 132	132	925	Day 884-967
Week 144	144	1009	Day 968-1051

Analysis Visit	Week	Scheduled Day	Visit Window
Week 156	156	1093	Day 1052-1135
Week 168	168	1177	Day 1136-1219
Week 180	180	1261	Day 1220-1303
Week 192	192	1345	Day 1304-1387
Week 204	204	1429	Day 1388-1471
Week 216	216	1513	Day 1472-1555
Week 228	228	1597	Day 1556-1639
Week 240	240	1681	Day 1640-1723
Week 252	252	1765	Day 1724-1793
Week 260	260	1821	Day 1794-1849
F-U Week 268/ F8	268	1877	Starting from Day 1850

Table 2-5 Assessment windows for eDiary within the Randomized Withdrawal Period

Analysis visit	Week	Scheduled Day	Visit Window
Core baseline	BSL	1	
Week 52	52	365	Day 352-379
Week 60	60	421	Day 380-435
Week 64	64	449	Day 436-463
Week 68	68	477	Day 464-491
Week 72	72	505	Day 492-519
Week 76	76	533	Day 520-547
Week 80	80	561	Day 548-575
Week 84	84	589	Day 576-603
Week 88	88	617	Day 604-631
Week 92	92	645	Day 632-659
Week 96	96	673	Day 660-687
Week 100	100	701	Day 688-715
Week 104	104	729	Day 716-(minimum between day 743 and Week 104 dosing day)

Table 2-6 Assessment windows for eDiary within the entire study period

Analysis visit	Week	Scheduled Day	Visit Window
Core baseline	BSL	1	
Week 52	52	365	Day 352-379
Week 60	60	421	Day 380-435
Week 64	64	449	Day 436-463
Week 68	68	477	Day 464-491
Week 72	72	505	Day 492-519
Week 76	76	533	Day 520-547

Analysis visit	Week	Scheduled Day	Visit Window
Week 80	80	561	Day 548-575
Week 84	84	589	Day 576-603
Week 88	88	617	Day 604-631
Week 92	92	645	Day 632-659
Week 96	96	673	Day 660-687
Week 100	100	701	Day 688-715
Week 104	104	729	Day 716-743
Week 108	108	757	Day 744-771
Week 112	112	785	Day 772-799
Week 116	116	813	Day 800-827
Week 120	120	841	Day 828-855
Week 124	124	869	Day 856-883
Week 128	128	897	Day 884-911
Week 132	132	925	Day 912-939
Week 136	136	953	Day 940-967
Week 140	140	981	Day 968-995
Week 144	144	1009	Day 996-1023
Week 148	148	1037	Day 1024-1051
Week 152	152	1065	Day 1052-1079
Week 156	156	1093	Day 1080-1107
Week 160	160	1121	Day 1108-1135
Week 164	164	1149	Day 1136-1163
Week 168	168	1177	Day 1164-1191
Week 172	172	1205	Day 1192-1219
Week 176	176	1233	Day 1220-1247
Week 180	180	1261	Day 1248-1275
Week 184	184	1289	Day 1276-1303
Week 188	188	1317	Day 1304-1331
Week 192	192	1345	Day 1332-1359
Week 196	196	1373	Day 1360-1387
Week 200	200	1401	Day 1388-1415
Week 204	204	1429	Day 1416-1443
Week 208	208	1457	Day 1444-1471
Week 212	212	1485	Day 1472-1499
Week 216	216	1513	Day 1500-1527
Week 220	220	1541	Day 1528-1555
Week 224	224	1569	Day 1556-1583
Week 228	228	1597	Day 1584-1611
Week 232	232	1625	Day 1612-1639
Week 236	236	1653	Day 1640-1667
Week 240	240	1681	Day 1668-1695

Analysis visit	Week	Scheduled Day	Visit Window
Week 244	244	1709	Day 1696-1723
Week 248	248	1737	Day 1724-1751
Week 252	252	1765	Day 1752-1779
Week 256	256	1793	Day 1780-1807
Week 260	260	1821	Starting from Day 1808

For parameters which are not collected at every visit (e.g. weight, [redacted]), visit windows defined in Table 2-3, Table 2-4, Table 2-5 and in Table 2-6 and in will be combined. The following rules are used to determine the visit window for an applicable visit post baseline: "Lower limit" = "upper limit of prior applicable visit" + 1. "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2. For example, if a parameter is measured at Week 76 and Week 104 only, Week 76 visit window will extend from Day 380 to Day 631, and Week 104 will extend from Day 632 to Day 743. If more than one assessment falls into the interval, the rules defined in Section 2.5.1.2 are applied.

The analysis visit will be used for listing of visit and period for both safety and efficacy data. If a visit falls after the last visit window (after Day 1849) it is not assigned to an analysis visit and will be listed under label "After Week 260".

All the efficacy and safety evaluation will rely on the analysis visit windows (including Week 52) except for the Primary Endpoint Analysis [redacted]

2.5.1.2 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 2-7).

For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the scheduled day 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, [redacted] the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-7 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Core Baseline	All data	See Section 2.1.1.2.

Timing of measurement	Type of data	Rule
[redacted]		
From Week 52 (safety)	Summary visit information (e.g. laboratory values, vital signs, etc.)	The (non-missing) measurement closest to the scheduled 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.
From Week 52 (safety)	Notable abnormalities (e.g. vitals signs) and CTCAE grades for laboratory values	The most extreme measurement in the period will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period.

2.5.2 Prior and concomitant therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior medications will not be re-summarized for extension. They have been summarized in the core studies. 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 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 5.1.3.

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). 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.

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

2.6 Protocol deviations

A summary of all protocol deviations will be provided, including COVID-19 related PDs.

2.7 Analysis of the primary objective

The primary aim of the study is to demonstrate the efficacy of secukinumab (300 mg Q4W or 300 mg Q2W) in subjects with moderate to severe HS who were HiSCR responders at Week 52 of the core studies, with respect to loss of response up to Week 104, compared to placebo.

2.7.1 Primary endpoint

The primary endpoint of the study is the time to loss of response up to Week 104 (Randomized Withdrawal Period) in subjects who were HiSCR responders at Week 52 in the core studies. HiSCR responder definition is reported in Section 1.1 and Section 2.1.1.2.

Loss of response is declared if:

- two criteria are satisfied: (i) at least a 50% increase in abscess and inflammatory nodule (AN) count is recorded, compared to the minimum value between the average AN count from the 3 previous visits and the AN count at Week 52; (ii) at least a 3 AN count increase is recorded, compared to the minimum value between the average AN count from the 3 previous visits and AN count at Week 52; or
- three criteria are satisfied: (i) at least a 30% increase in abscess and inflammatory nodule (AN) count is recorded, compared to the minimum value between the average AN count from the 3 previous visits and the AN count at Week 52; (ii) at least a 2 AN count increase is recorded, compared to the minimum value between the average AN count from the 3 previous visits and AN count at Week 52; (iii) if criteria (i) and (ii) are met, the subject should be reassessed within the next 2-4 weeks. At the reassessment visit, at least a 2 AN count increase is recorded.

If the 3 previous visits include visits from core studies, the AN count from the core studies will be included in the average. Furthermore, if the 3 previous visits include a reassessment, the AN count from the reassessment will be included as well.

The evaluation of time to LOR relies on the AN count assessments at nominal visits. No analysis visit window is applied for the LOR evaluation. Data reported in the Electronic Data Capture (EDC) system will be used for the analysis. For subjects with an OTH11 PD (missed LOR in IRT), the LOR is declared at the date of the PD. Subjects with an OTH10 PD (false LOR in IRT) are censored at the date of the PD.

The analysis of the primary endpoint will be based on the FAS-R.

2.7.2 Statistical hypothesis, model, and method of analysis

The statistical hypotheses are that the hazard rate for loss of response up to Week 104 (RWP) in subjects who were HiSCR responders at Week 52 in the core studies is greater or not different in the secukinumab 300 mg Q2W group compared to the corresponding placebo group, as well as in the secukinumab 300mg Q4W group compared to the corresponding placebo group.

Let us assume the following:

- λ_T^{q2w} denotes the hazard rate for loss of response in the secukinumab 300 mg Q2W (AIN457 Q2WR-Q2W).
- λ_P^{q2w} denotes the hazard rate for loss of response in the placebo group (secukinumab 300 mg Q2W in the core studies, AIN457 Q2WR-PBO).
- λ_T^{q4w} denotes the hazard rate for loss of response in the secukinumab 300 mg Q4W (AIN457 Q4WR-Q4W).
- λ_P^{q4w} denotes the hazard rate for loss of response in the placebo group (secukinumab 300 mg Q4W in the core studies, AIN457 Q4WR-PBO).

The following hypotheses will be tested

- $H_{01}: \frac{\lambda_T^{q2w}}{\lambda_P^{q2w}} \geq 1$ versus $H_{A1}: \frac{\lambda_T^{q2w}}{\lambda_P^{q2w}} < 1$,
- $H_{02}: \frac{\lambda_T^{q4w}}{\lambda_P^{q4w}} \geq 1$ versus $H_{A2}: \frac{\lambda_T^{q4w}}{\lambda_P^{q4w}} < 1$

In other words

- H_{01}: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg Q2W group relative to the placebo group.
- H_{02}: The hazard rate of loss of response up to Week 104 is greater or equal in the Secukinumab 300 mg Q4W group relative to the placebo group.

The number and percentage of subjects who experienced loss of response based on the number of randomized subjects in the FAS-R at risk as the denominator, will be provided by treatment groups.

A stratified log-rank test will be performed to assess the treatment effect on the risk of reaching LOR, for testing each hypothesis ($H_{01,}$ H_{02}) separately. The strata are based on region (see Table 1-1) and body weight (<90 kg, ≥ 90kg). The hazard ratios associated with the treatment and their corresponding 95% confidence intervals will be estimated using a stratified Cox proportional hazards regression model with the treatment group of extension study as explanatory variable and stratified by region and body weight (<90 kg, ≥ 90kg). Analogously to the stratified log-rank tests, two separate stratified Cox models will be fitted.

Separate analyses will be performed for comparison of secukinumab 300 mg Q2W with placebo and secukinumab 300 mg Q4W with placebo. The two placebo groups will not be pooled for this analysis.

The Kaplan-Meier estimates of the probability of not having a LOR will be plotted for each treatment group. We will display two plots, one per each treatment stratum from core (AIN457 Q2WR-Q2W vs AIN457 Q2W-PBO and AIN457 Q4WR-Q4W vs AIN457 Q4WR-PBO). The plots will include the number of subjects at risk for each treatment group at pre-specified time points.

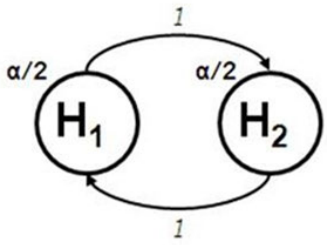
The number and the cumulative number of subjects with LOR, number of subjects in the analysis set, estimate of cumulative rate up to Week 104, median event time, and its estimated 95% confidence interval, as estimable will be provided for each treatment group. In addition, for pre-specified time intervals (e.g., 8-week intervals) the following will be presented for each

treatment group and time interval: number of subjects at risk, subjects with loss of response, subjects with loss of response divided by number of subjects at risk, cumulative number of subjects with event and cumulative event probability including 95% confidence interval.

Testing strategy

The familywise error will be set to α=2.5% (one-sided). The two hypotheses H_{01} (referring to 300 mg Q2W) and H_{02} (referring to 300 mg Q4W) will be tested at α/2=1.25% (one-sided). In case, a null hypothesis has been rejected for one regimen, but not for the other regimen, the alpha can be shifted to the other regimen and the null hypothesis can be retested at level α=2.5% (one-sided). The graphical approach of Bretz et al (2009) for sequentially rejective testing procedures is used to illustrate the testing strategy (Figure 2-1):

Figure 2-1 Testing strategy



2.7.3 Handling of intercurrent events

The following intercurrent events (ICEs) will be considered:

1. Intake of prohibited medication/treatment (medication/treatment with possible confounding effect defined as biologics, topical and systemic antibiotics if taken for more than 14 days, or any major HS-related surgery other than those allowed as rescue therapy): a treatment policy strategy will be applied. We will ignore such events and will consider all observed values.
2. Intake of rescue medication: a composite strategy will be applied. If this event occurs, we will consider it as LOR.
3. Missing 2 or more than 2 consecutive assessments: a hypothetical strategy will be applied, and the subject will be censored at the last recorded visit.
4. Discontinuation of study treatment due to adverse events or lack of efficacy: a composite strategy will be applied. If this event occurs, we will consider it as LOR.
5. Discontinuation of study treatment due to any reason (except for adverse event and lack of efficacy): a hypothetical strategy will be applied. The subject will be censored at the last recorded visit.
6. COVID-19 related events such as:
   a) Missed at least one dose due to COVID-19 (identified via TRT08 and TRT09 PD).
   b) Discontinuation of study treatment due to COVID-19 (identified via OTH15 PD).

A treatment policy strategy will be applied.

Intercurrent events are handled on the day it occurs and onwards. If multiple ICEs occur to the same subject over the treament period, only the first one is considered. If multiple ICEs occur on the same day for a subject, the ICE with composite strategy is considered; if not applicable, the ICE with hypothetical policy is considered; if still not applicable, the ICE with treatment policy is considered.

Justification of the applied strategies with regards to the intercurrent events

1. Intake of prohibited medication (medication/treatment with possible confounding effect defined as biologics, antibiotics if taken over a period of more than 14 days, or any major HS-related surgery other than allowed as a rescue therapy): if a prohibited treatment is used during the study, the subject should discontinue the use of the prohibited treatment if he/she wishes to continue in the study. Taking into consideration the primary endpoint, intake of prohibited medications or major HS-related surgery is unlikely to accelerate the time to LOR hence using a treatment policy strategy to handle this intercurrent event is considered to be an appropriate approach.
2. Intake of rescue medication: it indicates that the patient has signs and symptoms of HS that are not controlled by current therapy, thus implying LOR. Hence, a composite strategy is considered to be the appropriate way to handle this ICE.
3. Missing 2 or more than 2 consecutive assessments: could undermine the validity of the PEA, therefore we censor the subjects with 2 or more than 2 consecutive missing assessments at the last recorded visit.
4. Discontinuation of study treatment due to adverse events or lack of efficacy: permanent discontinuation of study treatment due to lack of efficacy implies LOR; discontinuation due to adverse event represents an unfavorable outcome; therefore, both these ICEs are handled using the composite strategy.
5. Discontinuation of study treatment due to reasons other than adverse events or lack of efficacy: subjects discontinuing their randomized study treatment for other reasons than adverse events or lack of efficacy (reasons that are unrelated to the study treatment) could theoretically have continued on their assigned treatment without being put at undue risk.
6. COVID-19 related cases: COVID-19 related cases are common occurrences and are unlikely to impact the primary outcome of this trial. Hence, consistently with health authorities feedback on the core studies, a treatment policy strategy is used for the assessment of the primary endpoint, including study treatment discontinuation due to Covid-19.

2.7.4 Handling of missing values not related to intercurrent events

Incorrect declaration of LOR and incorrect open-label transfer (due to data reconciliation issues) leads to an automatic censoring of the subject. Censoring is declared on the date of the incorrect LOR assessment. These subjects are identified via OTH10 protocol deviation.

Missed LOR declaration in IRT is identified via OTH11 protocol deviation. LOR for these subjects is declared at the PD date.

No missing values to assess LOR will be imputed and only observed data will be analyzed (see also Section 4).

2.7.5 Supportive analyses

In our primary analysis, we chose a specific way to handle different ICEs. This can be considered a conservative approach because we try to put as few assumptions in our analysis as possible. To assess the possible effect of these assumptions on the PEA we will do supportive analyses additionally.

Supportive analysis 1

In Supportive analysis 1, we analyze the PE with the same estimand described in Section 2.7.3, except for the ICE related to ≥2 consecutive missing assessments. If a loss of response is observed at the first assessment after ≥2 consecutive missing assessments, we report the observed LOR. Otherwise, it will be assumed that no LOR happened during the missed assessments. We apply a treatment policy strategy, instead of a hypothetical strategy.

Estimand for supportive analysis 1

1. Intake of prohibited medication: ignore (treatment policy).
2. Intake of rescue medication: consider the event as LOR (composite strategy).
3. Missing 2 or more than 2 consecutive assessments: ignore (treatment policy).
4. Discontinuation of study treatment due to adverse events or lack of efficacy: consider the event as LOR (composite strategy).
5. Discontinuation of study treatment due to any reason (except for adverse event and lack of efficacy): censor the subject at the last recorded visit (hypothetical strategy).
6. COVID-19 related events:
   a) Missed at least one dose due to COVID-19 (identified via TRT08 and TRT09 PD).
   b) Discontinue of study treatment due to COVID-19 (identified via OTH15 PD).

   Ignore such events (treatment policy).

Supportive analysis 2

In Supportive analysis 2, we analyze the PE with the same estimand described in Section 2.7.3, except for the ICE related to study treatment discontinuation (for any reason, except for adverse event and lack of efficacy). Indeed, subjects who permanently discontinued study treatment (for any reason, except for adverse event and lack of efficacy) will be considered as loss of response (composite strategy instead of hypothetical strategy).

Estimand for supportive analysis 2

1. Intake of prohibited medication: ignore (treatment policy).
2. Intake of rescue medication: consider the event as LOR (composite strategy).
3. Missing 2 or more than 2 consecutive assessments: censor at the last recorded assessment (hypothetical strategy).
4. Discontinuation of study treatment due to adverse events or lack of efficacy: consider the event as LOR (composite strategy).

5. Discontinuation of study treatment due to any reason (except for adverse event and lack of efficacy): consider the event as LOR (composite strategy).
6. COVID-19 related events:
    a) Missed at least one dose due to COVID-19 (identified via TRT08 and TRT09 PD).
    b) Discontinue of study treatment due to COVID-19 (identified via OTH15 PD).

   Ignore such events (treatment policy).

For both Supportive analyses 1 and 2, the same analyses described for the PEA in Section 2.7.2 will be performed.

2.7.6 Sensitivity analysis 1

A sensitivity analysis will be done to evaluate the effect of the AN count recorded at Week 52 on the time to LOR. Specifically, we will fit a stratified Cox proportional hazard model, with weight (<90 kg, >=90 kg) and region as strata, adjusted for the treatment and the AN count recorded at Week 52. For this analysis, we apply only the primary estimand.

Separate analyses will be performed for comparison of secukinumab 300 mg Q2W with placebo and secukinumab 300 mg Q4W with placebo. The two placebo groups will not be pooled for this analysis.

2.7.7 Sensitivity analysis 2

A sensitivity analysis will be done to assess the impact of:

- a missed re-assessment visit after re-assessment was correctly declared in IRT.
- a missed re-assessment declaration by IRT.

Re-assessment is declared in IRT if the subject experiences at least a 30% increase in AN count compared to the average AN count from the 3 previous visits or at the Week 52 visit, whichever is lower, with an increase of at least 2. After the re-assessment is declared, the subject should come back for an unscheduled visit in the next 2-4 weeks for re-assessing LOR. If the subject does not come back for the LOR re-assessment, the PD OTH02B is filed. If IRT missed to declare the re-assessment even if the criteria were met, the PD OTH19 is filed.

In this sensitivity analysis, we will impute a LOR for the subjects who have at least one confirmed OTH02B or OTH19 PD. The LOR will be imputed 4 weeks after the re-assessment was declared (PD OTH02B) or was missed to be declared (PD OTH19). If a subject presents multiple PDs OTH19 and OTH02B, only the first one will be considered for the LOR imputation. We will fit a stratified Cox proportional hazard model, with weight (<90 kg, ≥90 kg) and region as strata, adjusted for the treatment. A stratified log-rank test will be performed to assess the treatment effect on the risk of reaching LOR. Same strata of the Cox model are used for the stratified log-rank test. For this analysis, we apply only the primary estimand and if an ICE is recorded before the LOR imputation date, we will consider it following the rules described in Section 2.7.3.

Separate analyses will be performed for comparison of secukinumab 300 mg Q2W with placebo and secukinumab 300 mg Q4W with placebo. The two placebo groups will not be pooled for this analysis.

2.8 Analysis of secondary objective

2.8.1 Safety endpoints

All safety evaluations will be performed on the Safety Set. In general, summaries will be provided for extension study, i.e after first dose of study medication in the extension study. Baseline from the core studies will be used for all change from baseline analyses.

Analysis of adverse events will be based on treatment emergent events, which are defined as events that started on or after the first dose of extension study treatment or events that were present prior to the first dose of study treatment but that increased in severity, based on preferred term and on or before the end of treatment or the last taken dose +84 days.

In addition, for subjects who discontinue study treatment but continue with study participation, an additional AE listing will be prepared displaying which events occurred after the study treatment discontinuation.

Other safety variables will be evaluated based on treatment emergent events, which are defined as any events that happened after first dose of extension study treatment and on or before last dose +84 days.

Safety analysis will be performed on actual treatment. The safety analysis will be performed for the Randomized Withdrawal Period and the entire study period, separately, using the groups defined in Section 2.3.

Adverse events

Adverse events (AEs) will be coded by primary system organ class (SOC) and preferred term (PT) according to the MedDRA version 25.1 or later.

For AEs and other binary safety variables crude incidence will be derived as described below and summarized in Table 2-8.

All AEs and SAEs will be listed with “treatment emergent” flag displayed.

Table 2-8 Overview of analyses on some safety endpoints

Analysis period	AEs, SAEs & Safety topics of interest AEs	AEs by severity	Study treatment related AEs, death	notables (lab/vitals)
RWP and Entire study period	• crude incidence • exp.time adjusted incidence	• crude incidence	• crude incidence	• crude incidence

Risks defined in the Safety Profiling Plan are defined in the Program Case Retrieval Sheet (CRS). Safety topics of interest, such as risks defined in the Risk Management Plan (RMP) or

topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

The crude incidence and exposure-adjusted incidence rates for the safety topics of interest AEs will be summarized. In addition, separate listings will be provided for SAEs and discontinuations from safety topics of interest AEs.

The crude incidence of treatment emergent adverse events will be summarized by treatment, by primary SOC and PT. 95% confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.4.2.1. In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having at least one AE, having an AE in each primary SOC and having each individual AE (PT). Summaries will also be presented for AEs by severity and by treatment association (IMP 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 AE with the same PT, the AEs with the greatest severity will be presented. If a subject reported more than one AE within the same primary SOC, the subject will be counted only once with the greatest severity at the SOC level, where applicable. AEs by severity will be provided by SOC and AEs by severity and PTs may be provided if required at ad-hoc basis.

The most common adverse events reported (≥ 2 % in any treatment group by PT) will be presented in descending frequency according to its incidence in AIN457 NR group starting from the most common event. Based on the findings of the core studies, the threshold value is set to 2 % but it may be updated following review of the dry run outputs.

Separate summaries will be provided for deaths, AEs suspected to be related to study drug, SAEs, AEs leading to discontinuation, and AEs requiring concomitant medication.

In addition, for the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not SAEs, with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by PT.

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 has 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.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Algorithms for AE date imputations will be provided in Section 5.1.2.

2.8.2 Deaths

Separate summary and listing will be provided for deaths.

2.8.3 Laboratory evaluations

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

Descriptive summary statistics for the change from core study baseline to each extension study visit will be presented by laboratory test and treatment group. Change from core study 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

All laboratory data will be listed with "on-treatment" flag displayed.

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

In addition, shift tables will be provided for all parameters to compare a subject's core study baseline laboratory evaluation relative to the most extreme laboratory test value within the period of interest. 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 for each period of interest. Boxplots over time will be presented for all lab parameters. 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).

Table 2-9 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Number is not applicable*
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

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
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

* Life-threatening consequences;urgent intervention indicated.

Shift tables will be presented comparing core study baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment period under evaluation. Liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-10.

Table 2-10 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
TBL	>1xULN;>1.5xULN; >2xULN; >3xULN,
ALP	>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 >20xULN & TBL >2xULN;
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Potential Hy's Law) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP >2xULN may not result in severe DILI. ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Potential Hy's Law) or reported Hy's Law case Note: "Hy's Law case" is a lower level term in MedDRA (10070546) and may be reported as AE.

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>5xULN.

For urin alysis, all parameter collected will be listed.

2.8.4 Other safety data

2.8.4.1 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from cores studies baseline for each extension study visit will be performed by vital sign parameters 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

All vital signs will be listed with "on-treatment" flag displayed.

Criteria for notable vital sign abnormalities are provided in Table 2-11 below.

Table 2-11 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

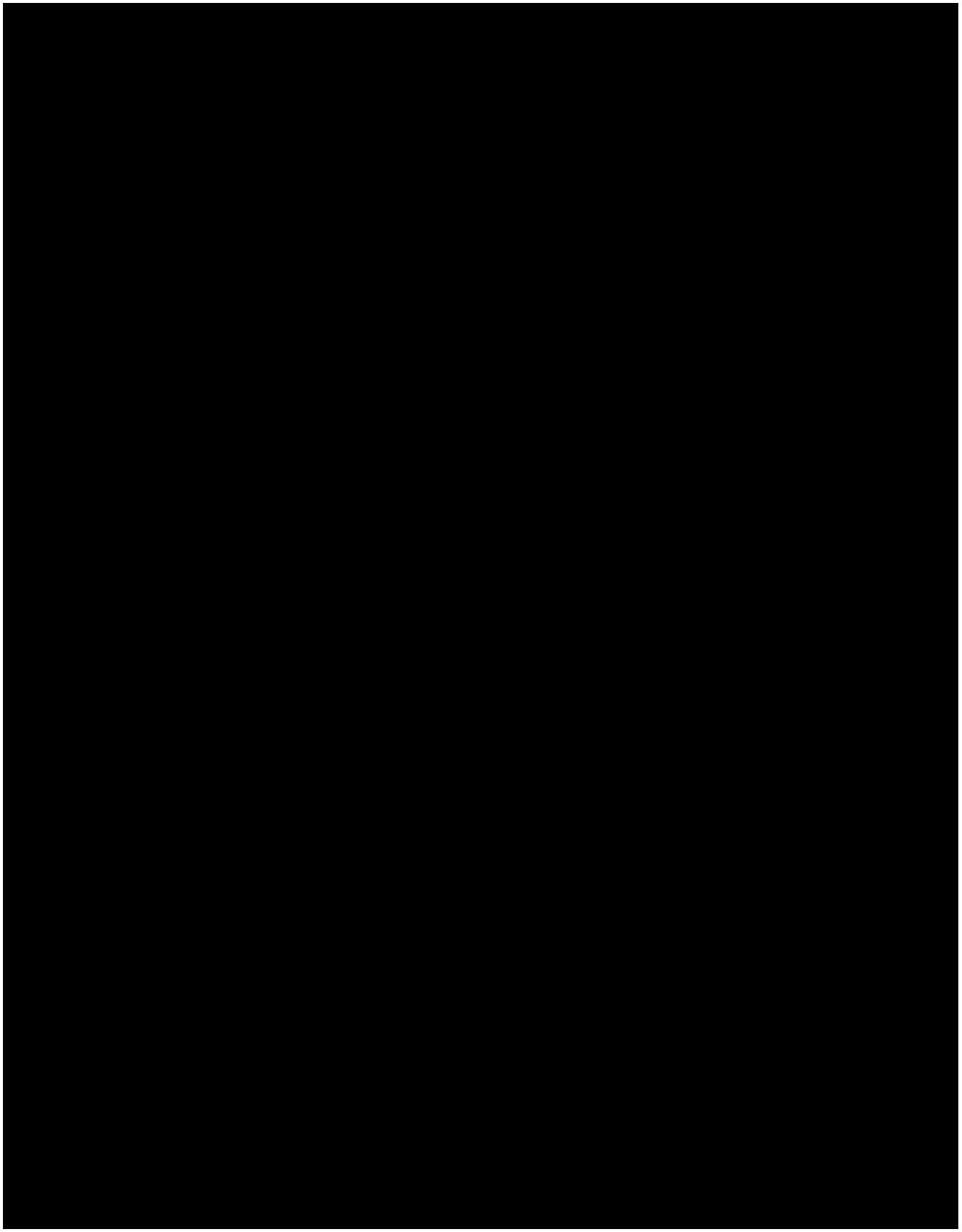
[redacted]

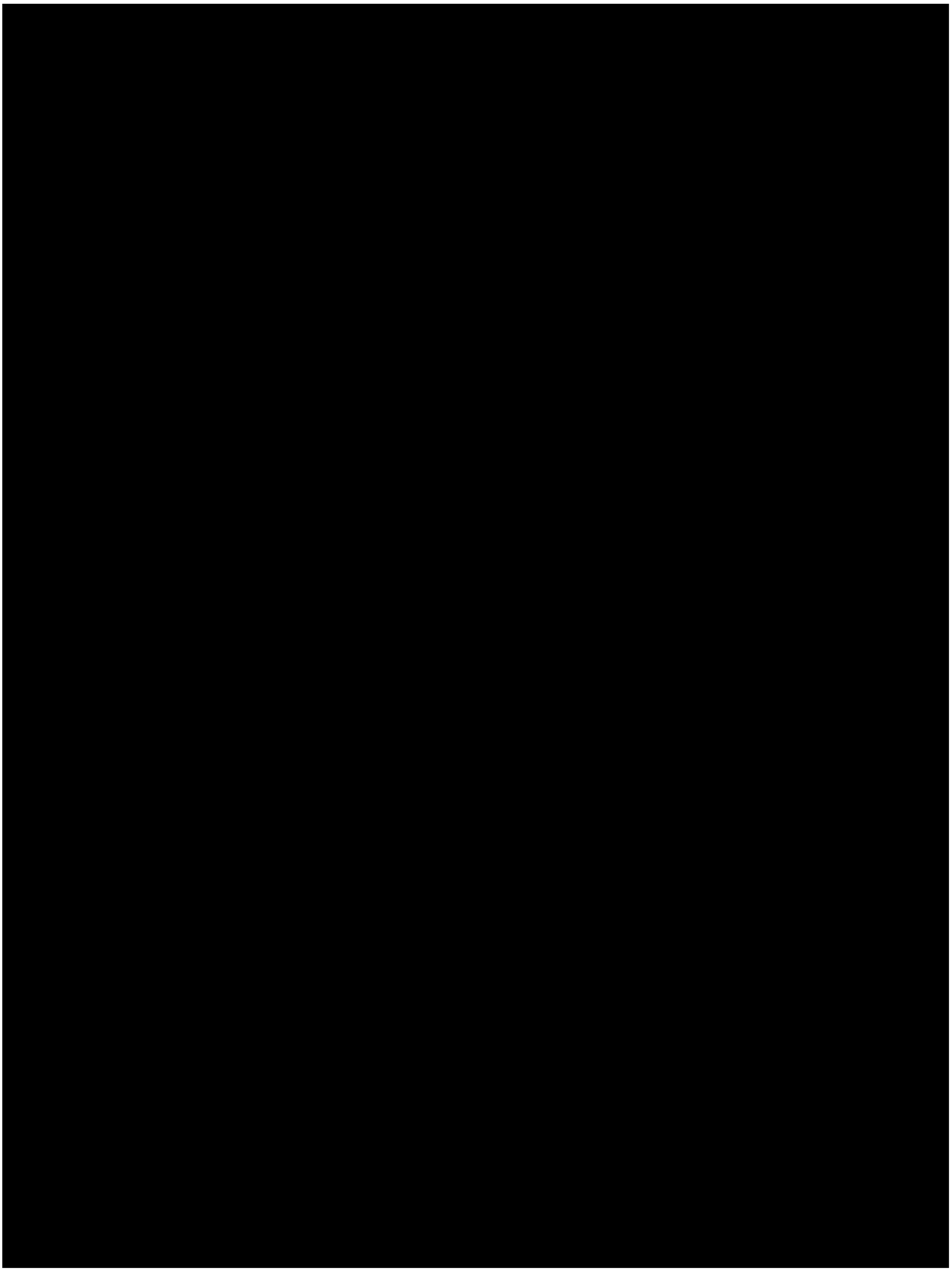
2.10 PD and PK/PD analyses

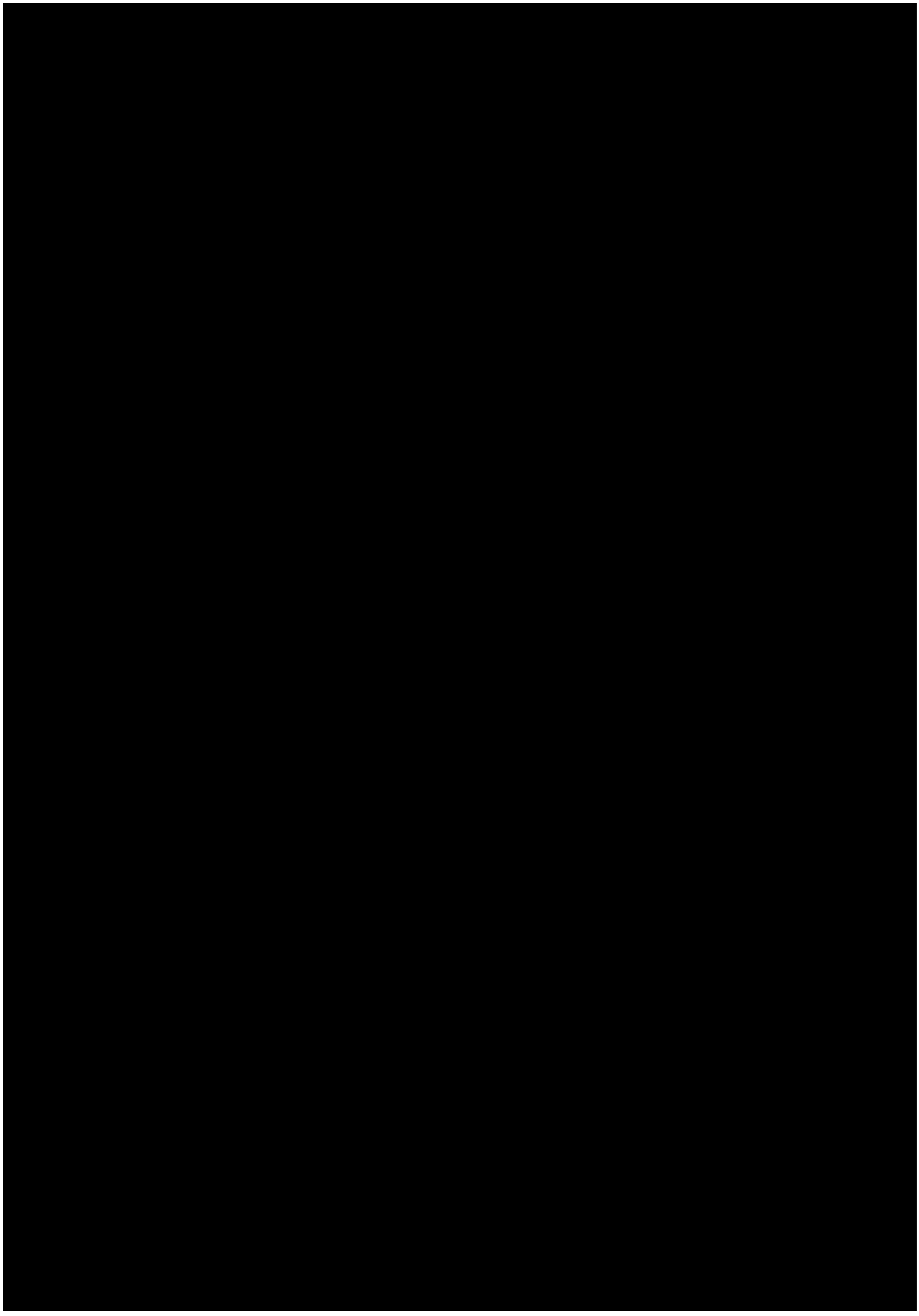
Not applicable.

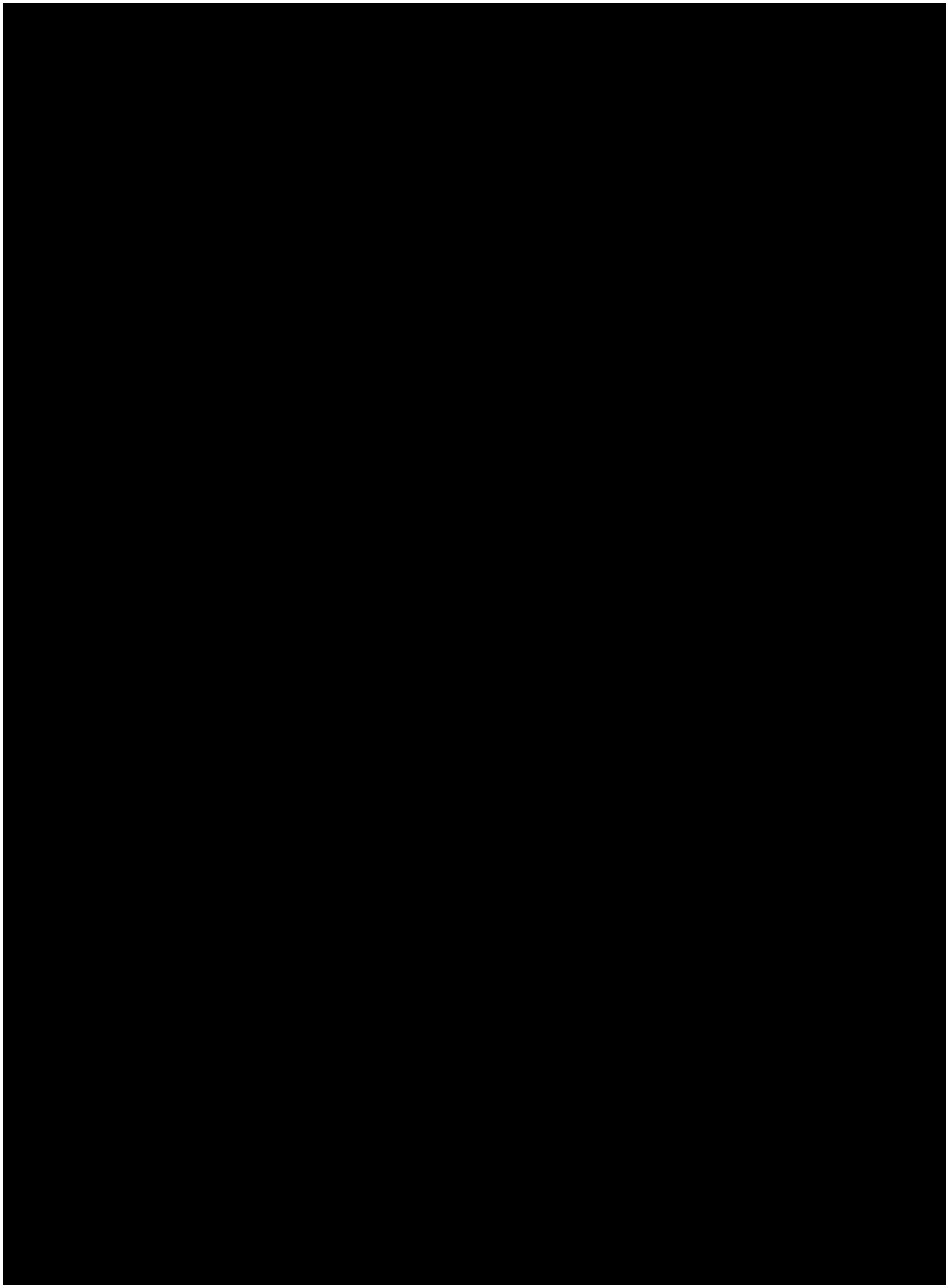
2.11 Immunogenicity

Not applicable.









[redacted]

2.14 Interim analyses

A PEA is planned to be performed when all enrolled subjects have completed Week 104 or have discontinued the study treatment.

For efficacy analyses, all data collected up to the Week 104 visit will be analyzed.

[redacted]

For safety analyses, all data collected up to the data cut-off date will be considered.

Additional interim analysis may be conducted at various time points for publications or health authority requests. The study procedures will not be modified as a result of these interim analyses.

3 Sample size calculation

Primary endpoint(s)

Assumptions for the number of subjects eligible for entering randomized withdrawal:

- Drop-out rate up to Week 52 in core studies: 21%
- HiSCR response rate at Week 52 on secukinumab 300 mg q2w in core studies: 45%. Same for secukinumab 300 mg q4w.
- Type-I-error rate is defined to one-sided 2.5%
- Drop-out rate from Week 52 to Week 104: 20%

With these assumptions it is estimated to have 168 subjects eligible per core study regimen (AIN457 300 mg Q2W and AIN457 300 mg Q4W) to enter the randomized withdrawal, therefore a total sample size of 336 for this study. Within each core study regimen there will be a randomization ratio of 2:1, this would be 112 subjects on secukinumab regimen and 56 subjects on placebo for the two extension randomized withdrawal regimens. If we assume 25% of the subjects in secukinumab arm and 50% in placebo arm would experience loss of response by Week 76 (from Humira data), with about 160 subjects the study would have more than 85% power to detect a difference. The sample power calculation was done in East 6.

Recruitment affected due to pandemic in the core studies, sample size allowed to increase by 15% by a protocol amendment. Therefore, the total sample size for the study may be 387 subjects.

4 Change to protocol specified analyses

No multiple imputation will be performed.

Up-titration is not allowed during RWP, by study design. Up-titration from Q4W to Q2W is allowed only at LOR or during the OL period.

Switching from placebo to secukinumab is not allowed during the RWP, because this would lead to the end of the RWP and the beginning of the OL period, by study design. We amended the supportive analyses accordingly.

The evaluation of HiSCR75/90/100 [redacted] is added.

[redacted]

The objective of Supportive Analysis 1 is to assess the robustness of the primary endpoint results with a change in the strategy for handling the ICE related to consecutive missing assessments or doses. For instance, imputing the date of a missing assessment used in the

primary analysis (as described in the protocol) can add unnecessary uncertainty to this evaluation. Consequently, we evaluate a treatment policy strategy for handling this ICE in Supportive Analysis 1 ("If a loss of response is observed at the first assessment after ≥2 consecutive missing assessments or doses, we report the observed LOR").

In order to consider the same factors in the Cox model and in the stratified log-rank test, we fit a stratified Cox model (same strata of the log-rank test) and we adjust only for the treatment. In the protocol we pre-specified a Cox model that is adjusted for treatment and AN count at Week 52. We will provide this as sensitivity analysis.

[redacted]

According to the extension study protocol, eDiaries should be collected monthly starting from Week 56. However, due to an error in the data collection by [redacted] the eDiaries have been collected starting from Week 60. This deviation from protocol is documented in FIRST (Facilitated Issue and Risk Surveillance Tool) and in the Clinical Trial Team meeting minutes. In the SAP, we reflect the current situation in the analysis windows definition.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows.

The earlier day will be taken from below:

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

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

Impute AE start date:

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

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

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

5.1.4 First diagnosis date and Symptom(s) onset date imputation

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

5.1.5 Other imputations

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 be coded according to MedDRA dictionary. The MedDRA version used for reporting the adverse events will be described in a footnote.

5.3 Laboratory parameters derivations

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

Liver Function and Related Variables

Alanine transaminase (ALT) (SGPT): > 3 x Upper Limit of Normal (ULN)

Aspartate transaminase (AST) (SGOT): > 3 x ULN

Total bilirubin: > 2 x ULN

Alkaline phosphatase: > 2.5 x ULN

Renal Function

Creatinine (serum): > 1.5 x ULN

Hematology

Hemoglobin: ≥ 20 g/dl decrease from core study baseline

Platelet count: < Lower Limit of Normal (LLN)

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN

Eosinophils: > 1.1 x ULN

Lymphocytes: > 1.1 x ULN

Urinalysis

Protein urine dipstick: ++*

* ++ is ≥ 100 mg/dl

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. If appropriate, summary statistics will also be derived for absolute and percentage changes from baseline.

5.4.2 Analysis of binary (and categorical) data

5.4.2.1 Summary statistics for 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-α/2)-quantile of the standard normal distribution (SAS: z = PROBIT(1-α/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 $p < 1, (U = 1 \text{ for } p = 1)$,

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

For response variables (e.g. HiSCR, [redacted]) the response rates (risk difference) including 95% confidence interval will be derived by visit.The Fisher's exact test

will be performed using the SAS procedure PROC FREQ with the option FISHER and RISKDIFF to calculate Risk difference and 100*(1-α)% confidence interval.

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

5.4.2.2 Log rank test and stratified Cox proportional hazards regression model

When the last subject reached the end of the randomized withdrawal period (by either having a Loss of Response or by reaching Week 104 or by discontinuing the study treatment), the primary analysis can be conducted. A log rank test, stratified by region and body weight stratum, will be applied to compare the survival functions between secukinumab treatment groups versus placebo. PROC LIFETEST will be used to implement the test.

The hazard ratios for these comparisons for loss of response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group of extension study as explanatory variable and stratified by region and body weight stratum.

The hazard ratio will be calculated such that an hazard ratio <1 is favorable for secukinumab. Using PROC PHREG to calculate the confidence interval for the hazard ratios assumes asymptotic normality of the Wald estimate for the regression coefficient.

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

In both log-rank test and Cox model, the geographical region Japan will be combined with AMEA region and US will be combined with LaCAN region. Region Europe will be kept separately. The same approach is applied in the supportive, sensitivity and subgroup analysis and in the demographics representation.

If the stratified cox regression model does not converge, the following steps will be performed:

1. If convergence not reached, remove the stratification variable region
2. If convergence not reached, remove the body weight stratum variable.

5.4.3 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 $(j = 1, \ldots, n)$ 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 $\lambda = D/T$, 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 $100(1 - \alpha)\%$ confidence interval for a Poisson variable

with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact $100(1-\alpha)\%$ confidence interval for $\lambda = D/T$ will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

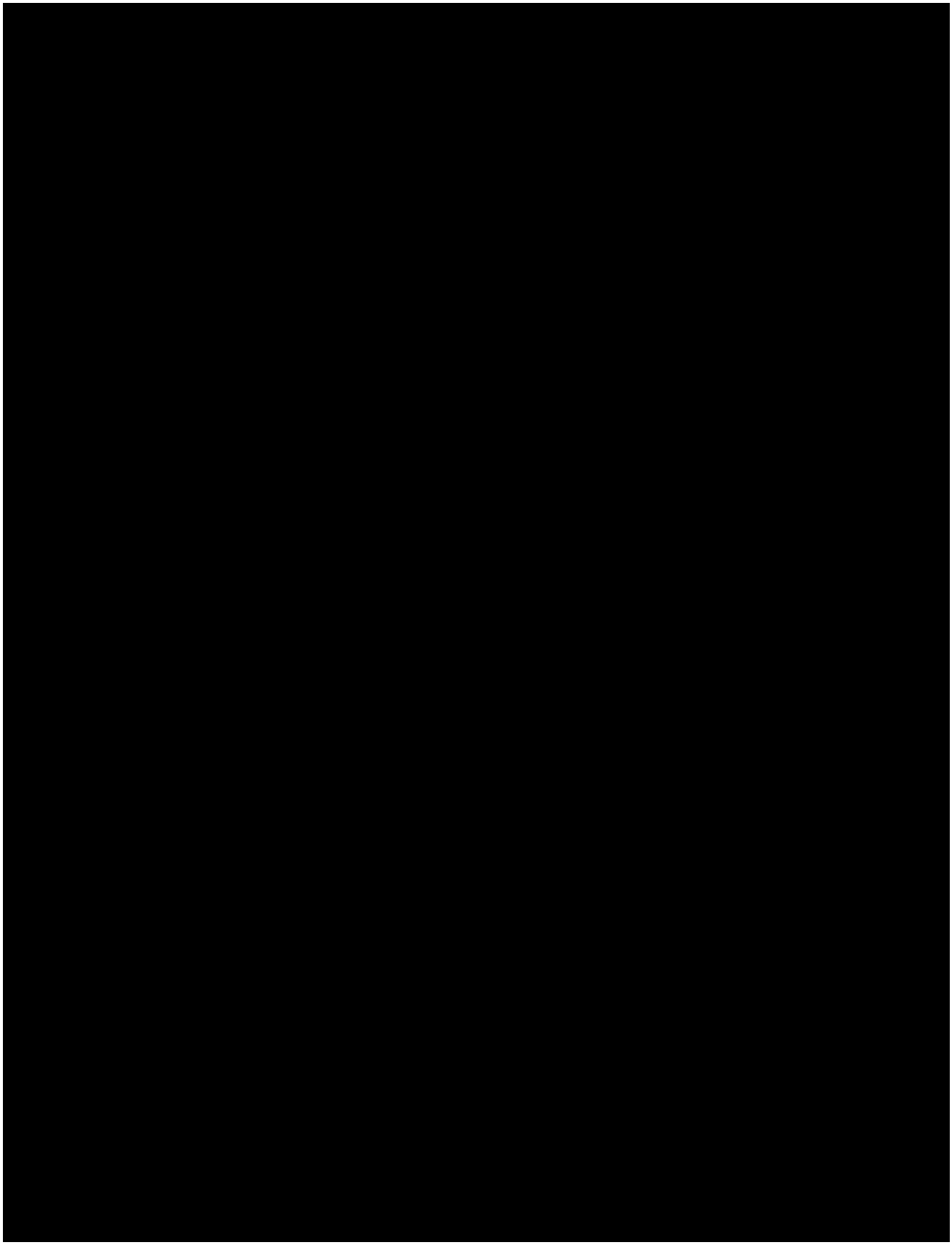
where $\chi_{\alpha,k}$ is the α-th quantile of the Chi-square distribution with k degrees of freedom.

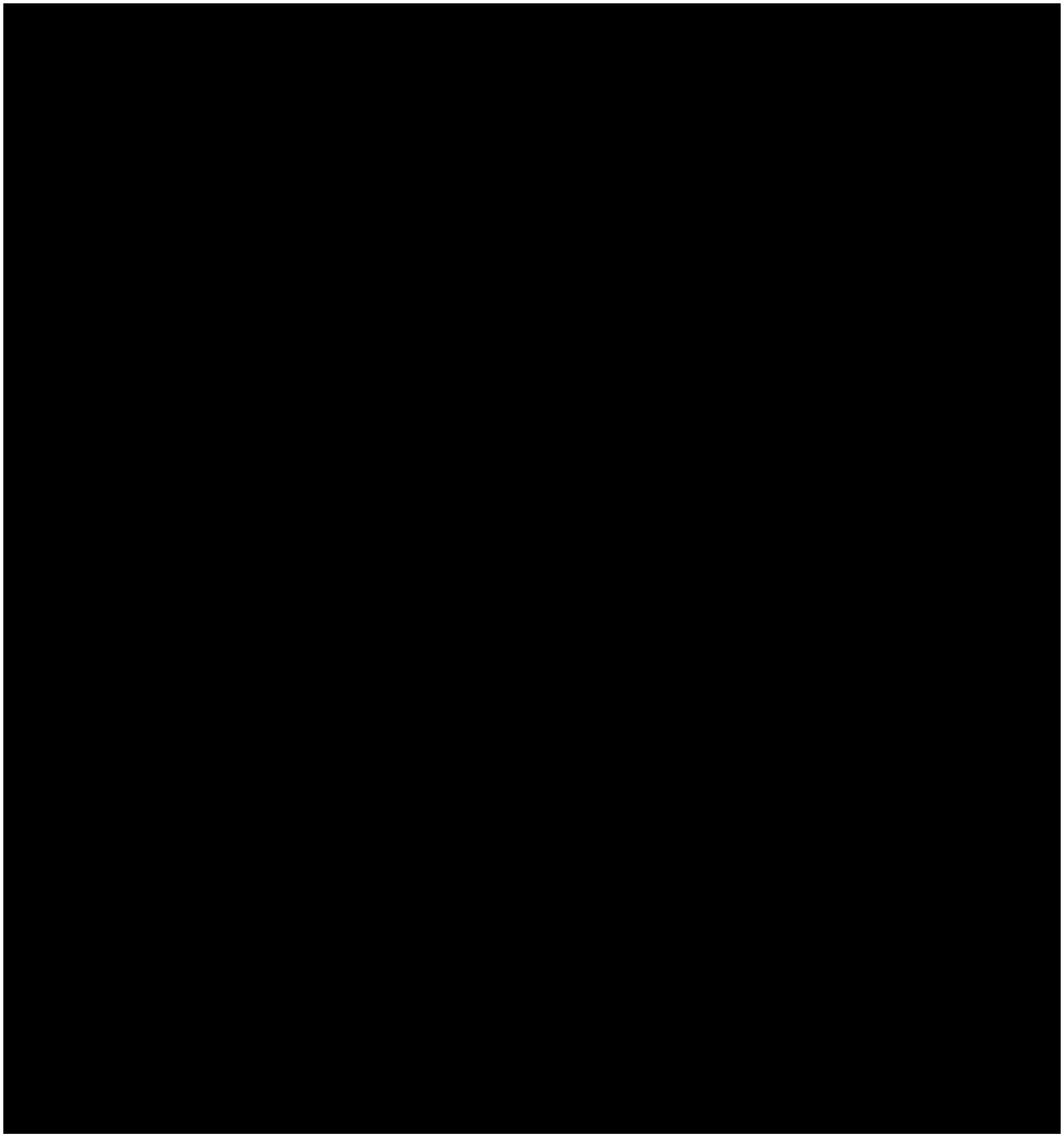
The example below shows how this should be handled for cases where subjects switch treatment. In particular for summarizing 'Any AIN' as a group, one should take into consideration the sequence of treatments while calculating exposure time for subjects.

Table 5-1 Examples for calculating exposure time for incidence rates (IR)

1st treatment	1st exposure	2nd treatment	2nd exposure	Event days (in terms of study day)	Exposure for IR
Placebo	100 days	150 mg	200 days	50 (1st trt) 110 (10 days into 2nd trt)	Placebo: 50 days (event) 150 mg: 10 days (event) Any AIN: 10 days (event)

[redacted]





5.6 Rule of exclusion criteria of analysis sets

Table 5-2 presents the rules of exclusion criteria of analysis sets. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject. . Subjects with serious GCP violation in the core studies that led to exclusion from the FAS and RAS of the core studies will be part only of the Safety Set of the extension study.

If subjects are incorrectly stratified as HiSCR non-responder or responder (PD OTH016 or PD OTH07, respectively), they will be assessed as per their assigned strata (HiSCR non-responder or HiSCR responder, respectively). PDs are raised for subject mis-classification (PD OTH016 and PD OTH07) and for subject mis-randomization (PD OTH17).

Table 5-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAS-R	INCL01*;	Subjects with serious GCP-violation in the core studies (PD OTH-07 from core studies)
FAS-R	INCL01*; M-OTH17	Subjects with serious GCP-violation in the core studies (PD OTH-07 from core studies)
RAS-NR	INCL01*	Subjects with serious GCP-violation in the core studies (PD OTH-07 from core studies)
FAS-NR	INCL01*; M-OTH17	Subjects with serious GCP-violation in the core studies (PD OTH-07 from core studies)
SAF	INCL01*	No study drug taken

* Written informed consent must be obtained before any assessment is performed.

6 Reference

Biostatistical Guidance on Analysis Sets in Clinical Trials, available in Cabinets/CREDI TABULU/B&SR/CIS Process Documentation/Guidances (outside of ESOPS)/Others

Bishop YMM, Fienberg SE, Holland PW (1991) Discrete multivariate analysis. Cambridge MA, 11th ed. The MIT Press

Bretz F, Maurer W, Brannath W, Posch M (2009). A graphical approach to sequentially rejective multipletest procedures. Statistics in Medicine; 28: 586-604.

Bretz F, Maurer W, Xi D (2018). Replicability, reproducibility and multiplicity in drug development.

Ratitch, Bohdana & Lipkovich, Ilya & Shannon Erickson, Janelle & Zhang, Lu & Mallinckrodt, Craig. (2018). Points to consider for analyzing efficacy outcomes in long‐term extension clinical trials. Pharmaceutical Statistics. 10.1002/pst.1888.

Carpenter JR, Roger JH, Kenward MG (2013). Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat p. 1352-71.

CSR template available in the CREDI template area: Cabinets/CREDI Templates /CTD

Garwood, F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

Kimball AB, Okun MM, Williams DA, et al (2016) Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N. Engl. J. Med. p. 422-34.

Little, R.J.A and Rubin, D.B. (2002). Statistical Analysis with Missing Data. Wiley Series in Probabiliy and Statistics, Chapter 10.

Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.

Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: Wiley.

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867

Schaefer, J.L. (1997). Analysis of Incomplete Multivariate Data, Chapman&Hall.

Ulm K (1990). A simple method to calculate the confidence interval of a standard mortality ratio. American Journal of Epidemiology, 131(2); 373-375