NOVARTIS

Global Medical Affairs- Immunology

AIN457A/Secukinumab/Cosentyx®

CAIN457A2322 / NCT03020199

A randomized, multicenter STudy to evaluate the Effect of secukinumab 300 mg s.c. administered during 52 weeks to subjects suffering from new-onset moderate to severe plaque Psoriasis as early Intervention compared to standard treatment with narrow-band UVB (STEPIn study)

Statistical Analysis Plan (SAP)

Author: [redacted] (Trial Statistician)

Document type: SAP Documentation

Document status: Amendment 10

Release date: 18-Aug-23

Number of pages: 70

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Sep-2020	Prior Week 16 dry run	Due to protocol amendment , Covid pandemic, Week 16 IA	Further details added as per protocol amendment version 2 and analysis related to Covid pandemic is also added Further details related to Week 16 IA also added First diagnosis date imputation rule is added.	2.4, 2.5, 2.6, 2.7,2.8, 2.12 , 2.14
26-Mar-2021	Prior Week 16 DBL	Address comments received during dry run	[redacted] PASI 75 is added.	2.13.1.2, 2.3.2.2,2.3.2
03-July-21	Prior Week 52 DBL	CTT discussion	Week 52 Mechanistic sub study is added	2.14
23-11-21	Prior Week 52 DBL for main analysis	CTT discussion	Modified full analysis set is created.	2.2
30-11-2021	Prior Week 52 DBL for main analysis	CTT discussion	List of Adverse events of special interest / grouping of AEs is updated	Table 2.4
28-02-2022	Prior Week 104 Interim Analysis	As per requirement by CTT in Week 52 Analysis	If require, analysis repeated for mFAS set	2.3.1, 2.3.2
08-09-2022	Prior Week 104 Interim Analysis	As per data from W104 dry run , Statistical analysis method updated for low response data	Statistical analysis method updated with required statistical tests and conditions.	2.6.2, 2.13.2.1, 2.13.4
05-05-2023	Prior Week 104 Interim analysis (Mechanistic sub-study)	additional analysis for Main study , additional outputs in Mechanistic Sub-study for Week 104.	Additional analysis for Main study and updates to analyze treatment separately for mechanistic sub-study New section 2.15 added as additional analysis of Main study.	2.1, 2.3.1, 2.5.4, 2.12, 2.13.4 New section 2.15 added

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
12-06-2023	Prior Week 104 Interim analysis (Mechanistic sub-study)	Updates in analysis plan of mechanistic sub study	Disposition summary output updates. [redacted] skin biopsy output limited up to 52 and listings to display. PASI categorical score to analyze with NRI method.	2.3.1, 2.3.2, 2.10, 2.12, 2.13
18-08-2023	Prior to Week 208 Final DBL	Updates in analysis plan of Main study Updates in analysis plan of Mechanistic sub-study for final analysis.	1. Analysis to display up to Week 208 based on observed data and for imputed data to display upto Week 104. 2.Analysis based on MMI approach also to display for LOCF / NRI approach. Additional analysis to perform upto Week 208 and to consider for main CSR. 3.Subgroup analysis not to perform for additional analysis. Dispositon summary output updates. 4.Details on Early Termination added. 5. Analysis to perform at Week 152 scheduled visit instead of Week 156. 6. Listings to display only for final analysis of Mechanistic study 7. An additional output for absolute PASI score < 3	2.1, 2.3, 2.4.2, 2.5.4, 2.7.1, 2.8 2.12, 2.13, 2.14, 2.15

Table of contents

List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
[redacted]	[redacted]
BSA	Body surface area
[redacted]	[redacted]
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
FAS	Full analysis set
GCP	Good clinical practice
[redacted]	[redacted]
IEC	Independent ethics committee
IGA	Investigator's global assessment
IRB	Institutional review board
IRT	Interactive response technology
LLN	Lower limit of normal
MedDRA	Medical dictionary for regulatory activities nb-UVB
NIBR	Novartis Institutes for BioMedical Research
mFAS	Modified full analysis set
PASI	Psoriasis area and severity index
[redacted]	[redacted]
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan
[redacted]	[redacted]
SOC	System Organ Class
s.c.	Subcutaneous
TB	Tuberculosis
ULN	Upper limit of normal
[redacted]	[redacted]

1 Introduction

This statistical analysis plan (SAP) describes the statistical methodologies which will be used in the Phase IV clinical study CAIN457A2322. This is an open label, randomized, multicenter study in 67 sites worldwide.

The purpose of this study is to determine whether early intervention with subcutaneous secukinumab 300 mg in subjects with new-onset moderate to severe plaque psoriasis may lead to prolonged symptom-free periods by preventing reactivation of old lesions or ultimately totally hindering the occurrence of new lesions, i.e., changing the natural course of the disease. In addition, a sub-study is included which aims to mechanistically understand the impact of early and late short- or long-term intervention with secukinumab on skin biomarkers.

Any deviations or changes from this SAP with rationale will be described in the CSR.

1.1 Study design

According to the study protocol, subjects will be allocated to 3 main treatment arms:

- Arm A (subjects with new-onset plaque psoriasis to be treated with secukinumab 300 mg s.c.): composed of Arm A1 (A1a and A1b) and Arm A2
- Arm B1 (subjects with new-onset plaque psoriasis to be treated with narrow band –UVB): composed of Arm B1a and Arm B1b
- Arm C (subjects with chronic plaque psoriasis to be treated with secukinumab 300 mg s.c.): composed of Arm C1 and Arm C2

An overview of the treatment arms is summarized in Table 1-1.

Table 1-1 Summary information for study arms

Arm	Psoriasis duration	Study part	Treatment	Treatment duration
A1a	new-onset	Main	Secukinumab	52 weeks
A1b	new-onset	Main and mechanistic	Secukinumab	52 weeks
A2	new-onset	Mechanistic	Secukinumab	104 weeks
B1a	new-onset	Main	nb-UVB	52 weeks
B1b	new-onset	Main and mechanistic	nb-UVB	52 weeks
C1	Chronic	Mechanistic	Secukinumab	52 weeks
C2	Chronic	Mechanistic	Secukinumab	104 weeks

The design consists of a Main Study and a Mechanistic Sub-study.

The Main Study will be multicenter, randomized, 2-treatment-arm (secukinumab and nb-UVB), parallel-group and open-label. It will include 3 clinical epochs (Screening Phase, Treatment Phase, and Follow-up Phase) involving all subjects in Arms A1 (A1a and A1b) and B1 (B1a and B1b).

The Mechanistic Sub-study will be open-label and comprise 5 treatment arms (A1b, A2, B1b, C1, and C2) comprising of subjects who have agreed to provide biopsy samples for investigation. It will include 2 phases (Screening Phase and Treatment Phase) for subjects in

Arms A2, C1 and C2. Subjects from Arms A1b and B1b will undergo the 3 clinical phases of the Main Study.

Screening Phase

Subject's eligibility for the study will be assessed at the Screening visit (Day -28 to Day -1 before Baseline) and at the Baseline visit.

Main study treatment Phase

At the Baseline Visit (Visit 1), eligible subjects will be randomized to one of the following treatment arms (see Figure 1-1 below):

- **Arm A1**: Subjects with new-onset plaque psoriasis will receive 300-mg secukinumab by s.c. injection at Baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 48, inclusive.
- **Arm B1**: Subjects with new-onset plaque psoriasis will receive either 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles (subjects with PASI 90 at Week 40 will not receive a second treatment cycle). Only during the first 4 weeks of each cycle, nb-UVB treatment will be given in combination with topical calcipotriol 50 µg/g and betamethasone 0.5 mg/g.

Follow-up Phase

At the end of the Treatment Phase at Week 52, all subjects with ≥ PASI 50 response from Arm A1 and Arm B1 will enter the Follow-up Phase. Subjects who do not achieve a PASI 50 response, will have all assessments of end of study (EOS) and be discontinued from the study.

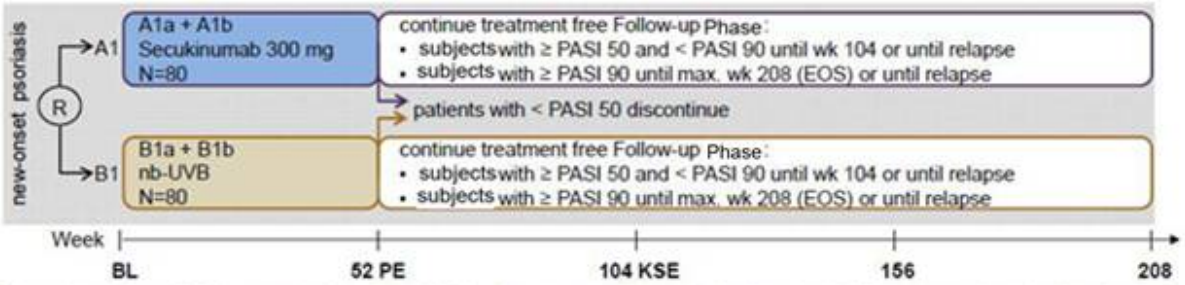
During the Follow-up Phase, subjects will not receive study treatment; they will be observed maximally until Week 208, and compared regarding the proportion of them who achieve PASI 90 response at Week 104.

Subjects who relapse (those who experience a loss of 50% of the maximum improvement in PASI score achieved during the Treatment Phase) will have all assessments of EOS and be discontinued from the study.

If no relapse occurs, subjects who achieve < PASI 90 at Week 52 in Arms A1 (A1a and A1b) and B1 (B1a and B1b) will be followed until Week 104, while subjects who achieve ≥ PASI 90 at Week 52 will be followed until Week 208.

The investigator should provide ongoing adequate care for subjects who relapse. If the investigator decides to continue treating the subjects with secukinumab, a new loading dose of commercially available secukinumab could be considered. The treatment with secukinumab after relapse will be out of scope of the study.

Figure 1-1 Study design – Main study



BL = baseline, EOS = end of study, KSE = key secondary endpoint, nb-UVB=narrow-band ultraviolet B, PASI = psoriasis area and severity index, PE = primary endpoint, R = randomization.

Mechanistic Sub-study

A separate informed consent will be obtained from study subjects who agree on having skin biopsies taken and therefore become eligible for this Mechanistic Sub-study. Besides the biopsies, subjects will undergo the same assessments as in the Main Study.

Treatment Phase

At the Baseline Visit, eligible subjects will be allocated to one of the treatment arms of the mechanistic Sub-study (see Figure 1-1):

- Arm A1b: secukinumab 300 mg s.c. administered at Baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 48 inclusive (last dose administered Week 48)
- Arm A2: secukinumab 300 mg s.c. administered at Baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 100 inclusive (last dose administered at Week 100)
- Arm B1b: 1 or 2 cycles of nb-UVB of 12 weeks each with a maximum break of 28 weeks between cycles
- Arm C1: secukinumab 300 mg s.c. administered at Baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 48 inclusive (last dose administered at Week 48)
- Arm C2: secukinumab 300 mg s.c. administered at Baseline, once weekly at Weeks 1, 2, 3 and 4; and thereafter every 4 weeks until Week 100 inclusive (last dose administered at Week 100)

Arm C1 and Arm C2 with subjects having chronic psoriasis, will serve as control groups in the Mechanistic Sub-study.

Skin biopsies will be taken from all subjects who participate as described in below schedule:

Table 1-2 Schedule for the collection of skin biopsies

	Collection time				
Arm	Baseline	Week 16	Week 52	Week 104	Week 208
A1b	X	X	X	X [a]	X [a]
A2	X	X	X	X	X [a]
B1b	X	X	X	X [a]	X [a]
C1	X	X	X		
C2	X	X	X	X	

a) Only subjects eligible for the Follow-up Phase will have biopsies taken at the marked time points

Follow-up Phase

At the end of the Treatment Phase, all subjects with ≥ PASI 50 response from Arm A1b and Arm B1b will enter the Follow-up Phase. Subjects who do not achieve a PASI 50 response, will have all assessments of EOS and be discontinued from the study.

During the Follow-up Phase, subjects will not receive study treatment; they will be observed maximally until Week 208, and compared regarding the proportion of them who achieve PASI 90 at Week 104.

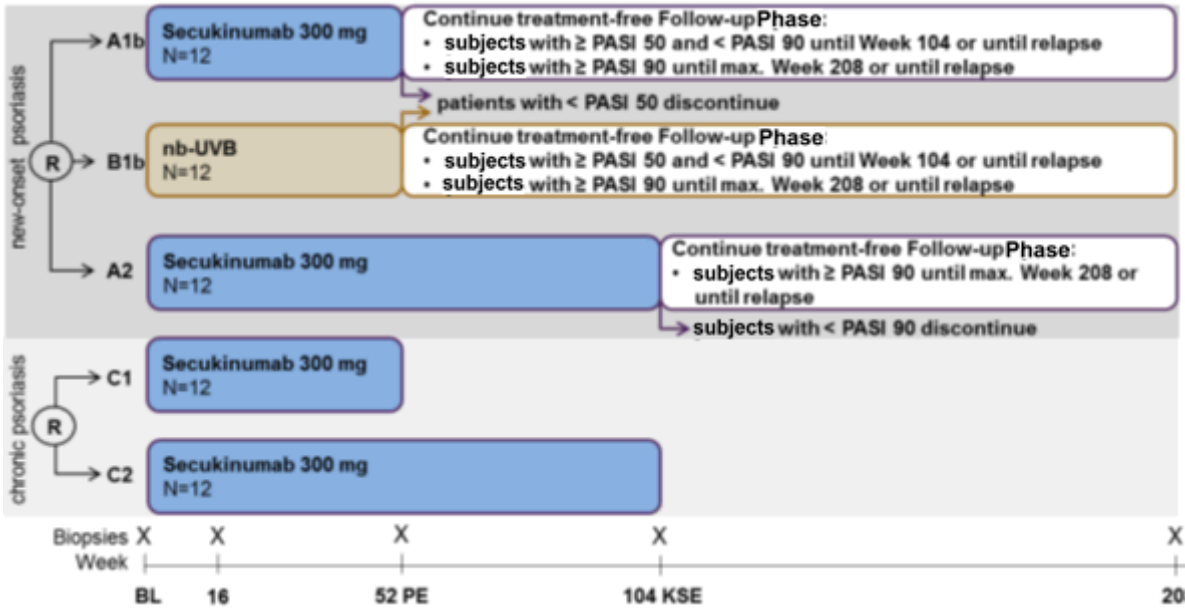
Subjects who relapse (those who experience a loss of 50% of the maximum improvement in PASI score achieved during the Treatment Phase) will have all assessments of EOS and be discontinued from the study.

If no relapse occurs, subjects who achieve < PASI 90 at Week 52 in Arms A1b and B1b will be followed until Week 104, while subjects who achieve ≥ PASI 90 at Week 52 will be followed until Week 208.

For Arm A2, subjects who achieve < PASI 90 at Week 104 will have their EOS assessment and stop participating in the study, while those who achieve ≥ PASI 90 will be followed until Week 208.

Subjects at Arms C1 and C2 will not be followed up.

Figure 1-2 Study design – Mechanistic Sub-study



BL = Baseline, EOS = end of study, KSE = key secondary endpoint, nb-UVB=narrow-band ultraviolet B, PASI = psoriasis area and severity index, PE = primary endpoint, R = randomization.

A primary endpoint [redacted] is planned after all subjects complete the visit at which the primary endpoint is assessed i.e. Week 52 or discontinue from the study earlier, or are lost to follow-up.

A key secondary endpoint analysis is planned after all subjects have reached Week 104 or discontinue from the study earlier, or are lost to follow-up.

An interim analysis for the Mechanistic Sub-study will be performed at Week 16. Only subject data of treatment arms A1b, A2, B1b, C1, C2 will be analyzed. The Week-16 Interim analysis will be conducted after all subjects have either completed Week-16 visit or discontinued from the study, or are lost to follow up prior to Week 16.

Another interim analysis for the Mechanistic Sub-study will be performed at Week 52 which is similar to week 16.

1.2 Study objectives and endpoints

1.2.1 Primary objective

To demonstrate that early treatment with secukinumab 300 mg s.c. (Arm A1) is superior to standard of care treatment with nb-UVB (Arm B1) in subjects with new-onset moderate to severe plaque psoriasis with respect to subjects achieving ≥ 90% improvement (reduction) in psoriasis area and severity index (PASI 90) response at Week 52.

1.2.2 Key secondary objective

To evaluate the superiority of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized subjects who achieve at least PASI 90 at Week 104.

1.2.3 Additional secondary objective

To evaluate the effects of early treatment with secukinumab (Arm A1) compared with nb-UVB (Arm B1) based on the proportion of all randomized subjects who achieve at least investigator's global assessment (IGA mod 2011) 0/1 response at Week 52.

1.2.4 Exploratory objectives

[redacted]

4. To explore the effects of treatment with secukinumab compared with nb-UVB based on the proportion of subjects who achieve at least investigator's global assessment (IGA mod 2011) 0/1 response at Week 104

[redacted]

[redacted]

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed using the Statistical Analysis Software (SAS) Version 9.4 or higher, according to the data analysis section (Section 9) of the protocol. This information will also be available in Appendix 16.1.1 of the Clinical Study Report (CSR). Additional important information as appropriate will be given in listings and the CSR. Final study CSR document will include the reports of Main study, mechanistic study and additional analysis.

Unless otherwise specified, the statistical hypothesis tests will be conducted against 1-sided alternative hypothesis, employing a 2.5% level of significance. For other analyses, p-values will be presented as 2-sided, employing a 5% level of significance. Two-sided 95% confidence intervals will be displayed.

Efficacy, safety, and other data will be summarized descriptively as follows:

- for continuous variables, descriptive summary statistics (number of subjects (n), mean, standard deviation (SD), median, minimum, maximum and lower/upper quartiles) for absolute and change (absolute and relative) from Baseline values will be reported by treatment arms (of the Main Study and of the Mechanistic Sub-study, as applicable).
- for categorical variables, frequency (n) and percentage (%) will be presented by treatment arms (of the Main Study and of the Mechanistic Sub-study, as applicable). Percentages will be calculated with respect to the number of evaluable subjects (m) out of the total number of subjects in the analysis set (N) of interest.

For Mechanistic Sub-study at time of final analysis or Week 104 interim analysis (if required) treatment arms are presented by duration of psoriasis for each treatment arm separately as;

New-onset : Arm A1b , Arm A2 and Arm B1b.
Chronic : Arm C1 and Arm C2
Total (wherever required).

In Main Study, after Week 104 subjects continued into the study are low, hence if statistical analysis where missing data is handled using Imputation method then analysis will be performed upto Week 104 unless mentioned otherwise. However, In Mechanistic Sub-study

due to limited number of subjects after Week 104 , listings will be only provided including disposition summary for the final analysis.

2.1.1 General definitions

2.1.1.1 Study treatment

2.1.1.1.1 Investigational and control drugs

Study treatment

Secukinumab (AIN457) 300 mg will be administered in an open-label fashion according to label as 2 s.c. injections of secukinumab 150 mg (1-mL liquid formulation in a pre-filled syringe). Each 300-mg dose will be provided as 2 pre-filled syringes of 150-mg secukinumab in a single box. Each syringe is labeled as AIN457 150 mg/1 mL.

Reference treatment

Narrow-band UVB applied in 1 or 2 cycles, each comprising a period of 12 weeks with 2 to 3 treatment sessions per week totaling 24 to 36 sessions per cycle. The application will be performed according to the investigational site's protocol, taking into account the subject's skin type. A maximum dose of 3 J/cm2 on the body and 1 J/cm2 on the face is recommended.

Additional treatment

The subjects in Arm B1 may use topical treatment with calcipotriol 50 µg/g and betamethasone 0.5 mg/g applied once daily (50 grams will be the maximum amount that can be applied per week) in addition to nb-UVB during the first 4 weeks of each cycle.

2.1.1.2 Study day

The day of first dose administration of the randomized treatment (Visit 1) will be considered as study day 1. All other study day will be labeled relative to study day 1. The descriptor "study day 0" will not be used.

The day for a particular event on or after the study day 1 will be calculated as:

(Date of event) – (Date of first dose) + 1.

For example study day 2, study day 3 … will be one day, two days… after study day 1, and respectively.

During the Screening phase the day before study day 1 will be calculated as:

(Date of event) – (Date of first dose).

For example study day -1, study day -2,…, will be one day, two days,…, before study day 1 respectively.

2.1.1.3 Screening, Baseline, and post-Baseline assessments

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

performing any study related activity. The date of signing informed consent is the start date of Screening period. Any assessment obtained during the Screening period will be labeled as Screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in Study Programming Dataset Specifications (PDS).

For both efficacy and safety analyses, Baseline assessments are defined as the last assessment (including unscheduled assessment) taken on or before the first dose of randomized study treatment, which is typically the last assessment taken before study drug administration at Visit 1. If the Baseline assessments are missing, then the last available measurement on or before the first dose of randomized study treatment (that is from the Screening visit, if available) will be considered as Baseline.

All the assessments taken after first dose of study treatment will be considered as post- Baseline assessments.

2.1.1.4 Day of last dose of randomized study treatment

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

For safety analysis on-treatment is defined as assessments from the first dose to last dose plus 84 days.

2.1.1.5 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. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-1. These apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Week 16 visit of a subject is delayed and occurs on Day 146 instead of on Day 129, say, it will be re -aligned to visit window Week 24. 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 2.1.1.5.1.

In general, if 2 consecutive visits Vt and Vs are x days apart, the upper limit of the visit window for Vt will be Vt+x/2 and the lower limit for the visit Vs will be Vs-x/2 (if x is even, the lower limit for Vs will be Vs-x/2+1, and the upper limit for Vt will be Vt+x/2). The algorithm needs to ensure that visit windows are not overlapping and that there are no gaps, such that each assessment can be uniquely allocated to one visit window, e.g., if Week 16 visit is scheduled for day 113, Week 24 is scheduled at day 169 and Week 36 is scheduled at day 253, then the visit window for Week 24 extends from Day 142 to Day 211. Of note, subjects are allowed to have gaps in visits.

Table 2-1 Assessment windows for scheduled visits

Treatment Arms	Analysis visit	Week	Scheduled day	Visit Window
ALL: A1, B1, A2, C1 and C2	Baseline	BL	1	-28 days to Day 1
	Week 16	16	113	Day 2-141
	Week 24	24	169	Day 142-211
	Week 36	36	253	Day 212-309
	Week 52	52	365	Day 310 – 421*/407*
A2 and C2 only	Week 68	68	477	Day 422-533
	Week 84	84	589	Day 534-645
	Week 100	100	701	Day 646-715
	Week 104	104	729	Day 716-771**
A1 and B1 only	Week 64	64	449	Day 408-491
	Week 76	76	533	Day 492-575
	Week 88	88	617	Day 576-659
	Week 100	100	701	Day 660-715
A1, B1 only Arm A2 from Week 105 on	Week 104	104	729	Day 716-771
	Week 116	116	813	Day 772-855
	Week 128	128	897	Day 856-939
	Week 140	140	981	Day 940-1023
	Week 152	152	1065	Day 1024-1107
	Week 164	164	1149	Day 1108-1191
	Week 176	176	1233	Day 1192-1275
	Week 188	188	1317	Day 1276-1359
	Week 200	200	1401	Day 1360-1443
	Week 208/EOS	208	1457	Day 1444-1541***

* For Arm C1, If a visit falls after the last visit window (after Day 421) it is not assigned an analysis visit and will be listed under label “After Week 52”.

*For Arm A1 and B1, the Week 52 visit window will have 407 as a upper limit days

*For Arm A2 and C2, the Week 52 visit window will have 421 as a upper limit days

** For Arm C2, If a visit falls after the last visit window (after Day 771) it is not assigned an analysis visit and will be listed under label “After Week 104”.

*** For Arms A1, A2 and B1, If a visit falls after the last visit window (after Day 1541) it is not assigned an analysis visit and will be listed under label “After Week 208”.

The following visit window convention will be followed for schedule for the collection of skin biopsies (Table 2-2). Assessments, performed between the visits windows, will only be listed.

Table 2-2 Assessment windows for skin biopsies

Treatment Arms	Analysis visit	Week	Scheduled day	Visit Window
A1b, B1b, A2,C1 and C2	Baseline	BL	1	-28 days to Day 1
	Week 16	16	113	Day 99-141
	Week 52	52	365	Day 337-393
A1b, B1b, A2, and C2	Week 104	104	729	Day 701-757
A1b, B1b, and A2	Week 208	208	1457	1429-1541

2.1.1.5.1 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.

For Baseline assessment definition see Section 2.1.1.3.

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

- for quantitative variables, the closest to the actual visit is chosen (if 2 assessments have the same distance, then the earlier one will be chosen);
- for qualitative variables, the worst record is selected. It is noted that in the analyses performed, worst case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. PASI 90 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-3 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.2.
Post-baseline efficacy	All data except for [redacted]	The measurement closest to the target day will be used. In the event 2 measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If 2 measurements are taken on the same day, then select the first one using eCRF visit number. If 2 measurements have been taken on the same day and same visit then select the worst.

Timing of measurement	Type of data	Rule
[redacted]	[redacted]	[redacted]
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	The (non-missing) measurement closest to the target day will be used. In the event 2 measurements are taken equally apart (e.g. 1 day before target date and 1 day after) the first one will be used. If 2 measurements are taken on the same day then select the first one (using the time). If 2 measurements are taken on the same date/time then use the first visit number (assuming this is the planned visit). If 2 measurements are taken on the same date/time/eCRF visit number then use the average of 2 assessments
Post-baseline safety	Notable abnormalities (e.g. vital signs) and CTCAE grading for laboratory values	The most extreme measurement in the window will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period

2.2 Analysis sets

The following analysis sets will be used:

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

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

Full analysis set (FAS): The FAS will be comprised of all subjects who were randomized to the study. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned at Baseline.

Modified full analysis set (mFAS): The mFAS includes all subjects who are randomized and took at least one dose of study treatment during the Treatment Phase, subjects will be analyzed according to the treatment assigned at Baseline.

Safety set (SAF): The safety set includes all subjects who took at least one dose of study treatment during the Treatment Phase, whether or not they were randomized. Subjects will be analyzed according to the treatment received.

Section 2.15.2 define the analysis set used for additional analysis.

Protocol deviations leading to exclusion from analysis sets are defined in Section 5.7.

The treatment arms for the analyses of data will have the following distribution of subjects:

Main Study (Planned number)

- Eighty subjects from Arm A1 (i.e., A1a(68)+A1b(12))
- Eighty subjects from Arm B1 (i.e., B1a(68)+B1b(12))

Mechanistic Sub-study (Planned number)

- Twelve subjects from ArmA1b
- Twelve subjects from Arm A2
- Twelve subjects from Arm B1b
- Twelve subjects from Arm C1
- Twelve subjects from Arm C2

2.2.1 Subgroups of interest

The following subgroups of analysis will be explored for the primary and the key secondary analysis (Arms A1 and B1) :

- Weight (≤ 90 kg, >90 kg)
- BMI (< 25, 25-< 30, >= 30)
- Onset of psoriasis time (0-6 months, 6-12 months)
- Age (< 18-30, 31-50)
- Concomitant medication in UVB arm (yes, no)
- Previous psoriasis therapy (biologic systemic therapy, non-biologic systemic therapy , Topical, phototherapy and Photochemotherapy – yes/no)

2.3 Subject disposition, demographics and other Baseline characteristics

2.3.1 Subject disposition

The data of subject disposition will be summarized separately for the Main study as below, unless additional details are stated for the mechanistic sub-study treatment and follow-up phase

will be presented. All tables and listings mentioned in this section will be based on the Randomized set. If required, analysis will be also repeated for the mFAS analysis set.

Screening Phase disposition: The number and percentage of subjects screened, completed and discontinued at Screening with the reasons for screen failures will be presented for all enrolled subjects as captured in the Screening log page of the eCRF.

Since multiple attempts of rescreening are allowed, the rescreening data will be handled in the following approach to ensure that an overestimation of the number of screened subjects is not reported:

- If a subject completes after one or more rescreening attempts and is randomized, he/she will be counted only once as screened and Screening completed and not as a screen failed (as he/she has ultimately met the eligibility criteria and entered the treatment phase)
- If a subject fails after one or more rescreening attempts, He/She will be counted only once as screened and once as screen-failed (although he/she might have failed Screening 2 or more times)
- if a subject is rescreened, only the last available Screening data will be reported.

Treatment and follow-up phase disposition: The number and percentage of subjects in the FAS who completed or discontinued the study periods (i.e., treatment phase at Visit 5 including the reason for discontinuation as captured in the eCRF will be presented by treatment.

Study treatment phase completion:

- Subjects who discontinue at Week 52 (for Arm A1 and Arm B1) due to PASI < 50 and at Week 104 (for Arm A2) due to PASI < 90 will be assumed as treatment phase completers and will not enter into the follow-up period
- Subjects who achieve PASI between 50 and 90 at Week 52 (for Arm A1 and Arm B1) will be assumed as treatment phase completers and enter follow-up period till Week 104.

Subjects who complete treatment phase at Week 52 (for Arm A1 and Arm B1) and Week 104 (for Arm A2) but discontinue before entering follow up phase (despite PASI 50/PASI 90 requirement met) will be assumed as treatment phase completers. The Investigator or Staff will fill additional follow-up disposition eCRF with the reason for discontinuation from the study. In this manner, all the reasons for subjects discontinuation from the study will be captured.

In the Main study for final analysis, subject disposition status with reasons for discontinuation as per CRF will be calculated for duration of Baseline – Week 52. Whereas , for follow-up epoch the duration is Week 52 – Week 104 , Week 104 – Week 152 and Week 152 – Week 208 and for entire follow-up epoch duration Week 52- Week 208. An analysis will be performed for Randomized set and follow-up efficacy analysis set.

For the follow-up epoch, an analysis will be repeated from subgroup of subjects who entered follow-up phase , percentage calculations based on the subject entered follow-up phase. Subject disposition in the follow-up phase for the above mentioned duration (Week 52 – Week 104, Week 104 – Week 152, Week 152 – Week 208) is also performed with respect to the PASI categories (PASI 50-89, PASI 75, PASI 90 and PASI 100) at Week 52. An analysis will be performed for mFAS.

For the mechanistic sub-study, subjects disposition over Screening, treatment and follow-up phase are summarized similarly in separate tables at time of Week 52 interim analysis. However, at time of final analysis and if required at time of Week 104 interim analysis treatment arms are presented separately as per section 2.1. For W104 IA and Final analysis subject disposition status with reasons for discontinuation will be calculated for duration of Baseline – Week 52 , Baseline – Week 104 and Week 52 – W104 for Treatment epoch (Arm A2: Week 104) . Whereas , for follow-up epoch the duration is Week 52 – Week 104 (Arm A1 and B1) , Week 104 – Week 152 , Week 152 – Week 208 and Week 52 – Week 208. For the follow-up epoch, an analysis will be repeated for the subgroup of subjects who entered follow-up phase , percentage calculations based on all the subject entered follow-up phase.

Median time to event (i.e. discontinuation) and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation (PROC LIFETEST option conftype=log-log). Completers will be treated as censored. If any subject whose PASI score is not collected at analysis visit week 52 the subject will be not considered for Time to discontinuation analysis.

In addition, the number and percentage of subjects with protocol deviations will be tabulated by each treatment and deviation category, separately for Main study and Mechanistic sub-study. Subjects excluded from analysis set(s) due to defined Protocol deviations will be tabulated in the same. The number and percentages of subjects in each analysis set will be summarized by each treatment for the FAS, separately for Main study and Mechanistic sub-study. In Mechanistic study for final analysis protocol deviation will be listed only for FAS set. . Covid-19-specific protocol deviations will be tabulated separately in a similar way. Listing will also be produced separately for Covid-19 related protocol deviations.

Caution will be taken in the interpretation of the percentages of subject disposition and protocol deviations due to the overlap of subjects between study arms (A1 and B1) in the Main study and Mechanistic sub-study, as data of these 2 arms will be included in both of the study outputs.

All subjects data related to disposition, protocol deviation and analysis sets will also be listed.

Any possible implications of study changes due to COVID-19 on the interpretation of study subject data will be tabulated and listed.

2.3.2 Demographics and Baseline characteristics

For the Main study and Mechanistic sub-study, summary statistics will be presented for continuous demographic and Baseline characteristic variables by treatment for all subjects in the FAS.

Similarly for categorical variables, the number and percentage of subjects in each category will be presented by each treatment arm for all subjects in the FAS. If required, analysis will be also performed for mFAS.

In Mechanistic substudy at the time of Week 104 IA and Final analysis, only listings will be presented for Demogrphics and Baseline disease characteristics based on FAS. The corresponding summary tables were already included earlier IAs (EX: Week 52 IA).

2.3.2.1 Demographics

Continuous demographic variables captured either at Screening or at Baseline include:

- age (in years; calculated in the eCRF from date of birth and Visit 1 date)
- height at Screening (in centimeters)
- weight at Baseline (in kilograms)
- body mass index (BMI, in kg/m²) = (body weight at Baseline in kilograms) / (height at Screening in centimeters/100)²

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

Categorical demographic variables captured either at Screening or at Baseline include:

- age categories (18-30, 31-50)
- gender (male, female)
- race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- ethnicity (Hispanic or Latino, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed, Not Reported, Unknown, Other)
- child-bearing potential (able to bear child, premenarche, post-menopausal, sterile - of child bearing age)
- skin type (I, II, III, IV, V, VI)
- smoking status at Baseline (never, current, former)
    - estimated number of pack-years (The estimated number of pack years is defined as the total years of smoking multiplied by cigarette packs smoked per day (e.g.10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.). The number of pack years will be analyzed as recorded on the eCRF.)
    - Time since last date of tobacco use (for former category) = (Date of Visit 1 – Date of last use of tobacco + 1)/365.25.
- Presence of cardiovascular history (Yes/No)

2.3.2.2 Disease history and Baseline characteristics

In addition, the following variables collected at Baseline (Visit 1) will be summarized by treatment:

- 12-lead electrocardiogram (ECG)vital signs
    - sitting pulse (beats/min)
    - Mean of sitting blood pressure (systolic/diastolic) (mmHg)

[redacted]

- serum pregnancy test (only for women of child bearing potential)

[redacted]

[redacted]

- PASI total score
- PASI categories (< 10, 10 - ≤ 20, > 20)
- BSA (affected %)
- IGA mod 2011 score
- Time since the first diagnosis (by a physician) of plaque-type psoriasis (Years) (Visit 1 date is reference date)
- Presence of psoriatic arthritis (Yes/No)
- Time since the diagnosis of psoriatic arthritis (Years) (Visit 1 date is reference date)

  Onset of psoriasis time in years will be calculated as:

  Treatment start date - date of first diagnosis (by physician) of plaque psoriasis/psoriatic arthritis+1)/365.25

  The first diagnosis date will be imputed according to the imputation rules in Section 5.3.3.3

  Visit 1 Date is nothing but treatment start date. If treatment start date is missing then randomization date will considered as a reference start date.

2.3.2.3 Relevant medical history / Current medical conditions

Any condition entered as medical history or current medical conditions at Baseline will be coded using the MedDRA dictionary version 26 or later. Medical history will be summarized for all subjects in the FAS by SOC and PT . Summaries for psoriasis-specific medical history will be provided separately. Cardiovascular medical history assessed prior to randomization will also be summarized.

This medical history data will also be listed with ongoing treatments flagged.

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

2.4.1 Exposure to study treatment and overall compliance

AIN 300mg

The analysis of study treatment data will be based on the SAF."DOSAGE ADMINISTRATION RECORD" and nb-UVB (Cycle 1, Cycle 2) eCRF page and will be used for below analysis.

The number of secukinumab 300 mg injections will be summarized for Main study and Mechanistic sub-study by treatment arms by means of contigency tables. For Main Study treatment arms are A1a, A1b and for Mechanistic sub-study treatment arms are A1b, A2, C1 and C2.

Duration of exposure to study treatment will be summarized by treatment arms.

In addition, the number of subjects with exposure of at least certain time thresholds will be displayed.

The following categories will be presented: "any exposure", "≥ 1 week", "≥ 2 weeks", "≥ 3 weeks", "≥ 4 weeks", "≥ 8 weeks", "≥ 12 weeks", "≥ 16 weeks", and so on with an increase of time threshold by 4 weeks until there are no subjects in the category or the last category "≥ 48 weeks" is presented for Arm A1 in main study and for Arm C1 in mechanistic study Similarly last category "≥ 100 weeks" is presented for Arm A2 and Arm C2 in mechanistic study.

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier. i.e., for subjects who discontinued or have their last visit earlier than 84 days, the end of study treatment exposure will be the date of the last study visit in the follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min ('end of treatment period' date, last dose date +84) – first dose date +1

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

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

The cumulative actual dose of secukinumab is defined as the sum of all doses of secukinumab taken across a treatment phase of the study. The cumulative assigned dose of secukinumab is defined as the sum of all doses of secukinumab assigned to a subject across a treatment phase of the study.

Cumulative actual dose administered in mg upto Week 16, Week 52 form arms A1a, A1b and C1 and up to Week 104 for arms A2 and C2 will be summarized.

Compliance for secukinumab is defined as actual cumulative dose divided by cumulative assigned dose. Treatment compliance for subjects will be summarized for subjects for 16 weeks, 52 weeks and for A2 104 weeks.

nb-UVB

Subjects in B1a and B1b receive nb-UVB.

The number of sessions in Cycle 1 and Cycle 2 will be categorized into < 24, 24-36 and count in each category will be presented, number of subjects exposed to treatment with nb-UVB to whole body or partial body will also be summarized. The number of subjects required a second cycle also will be presented.

On-treatment exposure to the study treatment will be defined (in days) time (from first dose to the time to the last dose of treatment+84) . Duration of exposure in Cycle 1 and Cycle 2 will be summarized.

2.4.2 Prior and concomitant medications

Prior treatments are defined as treatments taken and stopped prior to the first dose of study treatment.

Any treatment given at least once between the day of first dose of randomized study treatment (Baseline) and 84 days after the last dose of study treatment or last visit (including follow-up visits) will be a concomitant treatment, including those which were started pre-Baseline and continued into the Treatment Phase.

Concomitant medications and prior medications taken within the 6 months preceding study enrollment will be captured at the Screening visit, and updated at Baseline, with ongoing or not ongoing information. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Further rules are given in section 5.3.3.

Prior and concomitant treatments will be summarized by treatment arms in separate tables for the SAF and for the Treatment Phas and follow-up period (, separately. Treatments 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 treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

In addition, previous psoriasis therapy

- any “previous < biologic systemic /non-biologic systemic> therapy” (yes/no)
- previous biologic systemic therapy (yes/no, with embedded subgroup “Failure”* – yes/no),
- previous non biologic systemic therapy (yes/no, with embedded subgroup “Failure”* – yes/no),
- Previous topical (yes/no), previous phototherapy (yes/no), previous photochemotherapy (yes/no) and
- “Failure to at least 2 previous psoriasis therapy (biologic systemic, non-biologic systemic, topical, phototherapy and photochemotherapy)” (yes/no will also be summarized in a similar manner.

(* at least one therapy with lack of primary efficacy or lack of secondary efficacy or lack of tolerability).

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized. “Surgical and Medical Procedures” eCRF page will be used to get this information.Concomitant Medications - Topical Corticosteroid will also be summarized similarly. Concomitant Medications - Topical Corticosteroid eCRF page will be used to get this information.

Previous psoriasis therapy will be availabel for chronic subjects only.

2.5 Analysis of the primary objective

The primary objective of this study is to demonstrate the superior efficacy of secukinumab 300 mg s.c. compared to nb-UVB in subjects with new-onset moderate to severe plaque psoriasis with respect to subjects achieving PASI 90 response at Week 52.

2.5.1 Primary variable

The primary efficacy variable is the proportion of subjects who achieve PASI 90 at Week 52. The analysis for the primary objective will be based on the FAS and mFAS.

2.5.2 Statistical hypothesis, model, and method of analysis

For the primary analysis, the following hypothesis testing will be performed:

$$H_{01}: p_{sec} = p_{nbUVB} \; versus \; H_{A1}: p_{sec} > p_{nbUVB}$$

where p_{sec} and p_{nbUVB} are the proportion of PASI 90 responders in the secukinumab 300 mg s.c. (Arm A1) and nb-UVB (Arm B1) groups, respectively.

The primary analysis method for PASI 90 response at Week 52 will use a logistic regression model with treatment as an explanatory variable and significant covariates among Baseline PASI score, age, and BMI. The best subset of the significant covariates will be selected using a forward selection method based on the likelihood ratio test. Interaction terms with treatment will also be considered, if significant, among the best subset of selected covariates and the treatment term.

Statistical significance will be evaluated at a 1-sided alpha level of 0.025. The estimated adjusted odds ratio for Arm A1 versus Arm B1 will be displayed along with the associated 2-sided 95% confidence interval (equivalent to the 1-sided 97.5% confidence interval) and p-value.
If there are issues related to the convergence of the logistic regression model, the above hypothesis will be tested using a 1- sided Wald test.

The primary analysis is not expected to be influenced by the use of topical treatment within the first 4 weeks since, any effect will be worn off by Week 52.

The detailed testing strategy including the primary endpoint analysis is provided in Section 2.6.2

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will be handled with a modified multiple imputation method. Subjects who discontinued the study before Week 52 because of lack of efficacy or AEs will be considered non-responders. Missing values for other reasons will be inserted by means of the multiple imputation method.

The multiple imputation method is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates (i.e., under the assumptions of missing at random (MAR)), creating multiple completed data sets, which can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty.

Missing values for the "change from Baseline PASI score" will be imputed simultaneously based on an underlying normal distribution and using the data augmentation procedure of Markov Chain Monte Carlo (MCMC) method. The change from Baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. The imputations will be done separately for each treatment group (Arm A1 and Arm B1). For Arm A1and B1, the imputation will also include Baseline PASI score, age, Baseline BMI as additional variable.

2.5.4 Supportive analyses

Sensitivity analysis will be performed on the primary analysis method for PASI 90 response at Week 52 by repeating the logistic regression model with treatment as an explanatory variable and all three covariates Baseline PASI score, age, and BMI. Interaction terms with treatment also will be considered.

If logistic regression model does not converge the following steps will be performed:

1. Run the PROC GENMOD procedure with EXACT statement;
2. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with continuous covariates (i.e., baseline BMI by replacing with BMI stratum (< 25, 25-< 30, >= 30), and then baselines PASI score), followed by removing categorical covariates (i.e., BMI stratum etc.,);
3. If convergence not reached, perform 1 sided Wald test.

It should be noted that this model might not converge if response rates are too low.

The impact of missing data on the analysis results of PASI 90 at Week 52 will be assessed as well by repeating the logistic regression model using different ways to handle missing data.

- Non-responder imputation
- Tipping point analysis
- Last observation carry forward (LOCF)

A non-responder imputation will be used as a supportive analysis of the primary variable using logistic regression (forward selection method) as described in primary analysis method. In this analysis, a missing value of PASI 90 response at Week 52 will be imputed with non - response regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues).

Assuming significance is shown for the primary analysis using non-responder imputation, the tipping point analysis will investigate if, and at which point, significance is not achieved anymore as subjects imputed as non-responders are increasingly reclassified as responders independently for each treatment group.

For PASI 90 response, missing values will be replaced by LOCF. Baseline values will not be carried forward. Similar analysis will be performed using logistic regression (forward selection method) as described in primary analysis method.

An additional analysis might be considered including Week 52 assessments performed later than per visit windowing due to covid.

Scatter plot will be produced for study day analysis for Week 52 time window (Day 310 to 421) and PASI score stratified by pre pandemic and during pandemic phase. In Y axis PASI score and in X axis study day will be plotted.

For the figures with pre-pandemic and during pandemic phase, the definition is:

If the treatment period end date was before pandemic start, the pandemic phase is defined as "pre-pandemic", otherwise defined as "during pandemic". If a subject discontinued from treatment in treatment period and the discontinued date from study was before pandemic start, then the pandemic phase defined as "pre-pandemic", otherwise defined as "during pandemic". Pandemic start is defined as – 01MAR2020

Observed PASI score at Week 52 will be listed by pandemic phase (pre- and during-pandemic).

Descriptive analysis of absolute value of PASI scores (observed data) at Weeks 16, 24, 36, 52 up to Week 208 for all treatment arms will be provided. Descriptive analysis of absolute value of PASI score with MI method will be performed up to Week 104 only, where the missing PASI score will be imputed using multiple imputation. Graphical representation will be done using Dot plot and time course plot for PASI 90 response at week 52 and PASI score over time respectively. Percent change from baseline PASI score (multiple imputation) over time will be presented graphically for individual subjects through Spaghetti plots.

Follow-up phase visits where number of subjects in treatment group are very low it may give large imputed values and the covariance matrix in MCMC process can not be computed, hence, the analysis tables and graphs will be presented up to Week 104. Additionally, same analysis tables and graphs will be also repeated LOCF (for continuous endpoints) or NRI (for binary endpoints) . upto Week 104 Data beyond week 104 and upto Week 208 will only be summarized as observed data. All analysis will be performed using mFAS set.

A Separate Time course plot will be generated to display the Percentage (%) of patients with Total PASI absolute score < 3 with (NRI) approach upto Week 104.

For Mechanistic sub-study the summary statistics for PASI absolute score and change from baseline to post-baseline visits is summarized for FAS. Time course plot for percentage change from baseline PASI score and absolute PASI score will be provided for each treatment group separately. At time of Final analysis PASI score will be listed for FAS set.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary variable

The key secondary variable is the proportion of all randomized subjects who achieve PASI 90 at Week 104. In order to reduce selection bias, all subjects who do not achieve PASI 90 at Week 52 will also be included in the analysis at Week 104 using the PASI improvement obtained at Week 104 only.

A subject who fails to achieve PASI 90 response at Week 104, irrespective of the responses over the past visits will be considered non-responder. Similarly, subjects who achieved PASI 90 response at Week 104, but not at any of the past visits will be considered responder.

This would mean that if a subject achieves PASI 85 (85% improvement in PASI score compared to Baseline) at Week 52, and the improvement in PASI increases to 90% at Week 104, the subject will be considered responder in the analysis at Week 104.

2.6.2 Statistical hypothesis, model, and method of analysis

For the key secondary analysis, the following hypothesis testing will be performed:

$$H_{02}: p^*_{sec} = p^*_{nbUVB} \; versus \; H_{A2}: p^*_{sec} > p^*_{nbUVB}$$

where p^*_{sec} and p^*_{nbUVB} are the proportion of subjects who achieve PASI 90 response at Week 104 in the secukinumab 300 mg s.c. (Arm A1) and nb-UVB (Arm B1) arms respectively. This testing will be performed using an exact logistic regression analysis similar to the primary analysis, with the strategy below under consideration. In case of no covariates is significant, exact logistic regression analysis will be performed using onlyTreatment as fixed effect factor.

Missing data will be handled similarly as for the primary endpoint analysis. Subjects who relapse will be considered non-responders in addition to those who discontinue the study before Week 104 because of lack of efficacy or AEs.

Testing strategy

Since the primary and the key secondary hypotheses are not mutually independent, an adjustment for multiplicity is considered here to control the alpha level (Type I error) i.e., familywise error rate.

This adjustment will be made using a hierarchical testing procedure which states that first H_{01} will be tested at 1-sided α=2.5% level of significance. The obtained p-value from the fitted logistic regression model will be divided by 2 and this resultant p-value needs to be considered. If the resultant p-value is smaller than 0.025, H_{01} is rejected at 2.5% significance level, concluding that there is strong evidence to consider that secukinumab is performing better than nb-UVB at Week 52. However, if this resultant p-value is greater than 0.025, H_{01} is not rejected at 2.5% significance level, concluding that the evidence obtained from the observed sample is not strong enough to say that any one of the treatment arms is performing better than the other. “PASI score” eCRF page will be used to get above information.

The testing sequence will continue to test H_{02} at α=2.5% (1-sided), only if H_{01} is rejected.

2.6.3 Handling of missing values/censoring/discontinuations

As specified in Section 2.5.3, the method of handling missing responses for the key secondary variable will also be the modified multiple imputation method, similarly as for the primary endpoint analysis. Subjects who relapse (a loss of 50% of the maximum improvement in PASI score) or who do not achieve a PASI 50 response at Week 52, will be considered non-responders in addition to those who discontinue the study before Week 104 because of lack of efficacy or AEs.

2.7 Analysis of additional secondary objective(s)

2.7.1 IGA mod 2011 0 or 1 response

The secondary efficacy variable is the proportion of all randomized subjects who achieve at least IGA 0/1 response at Week 52. Subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA mod 2011 scale compared to Baseline.

IGA mod 2011 0 or 1 response at Week 52 will be analyzed using a logistic regression model similar to the primary analysis, with treatment as an explanatory variable and significant variables among Baseline IGA mod 2011 score, age, and BMI, and their interactions with treatment. Forward selection procedure based on the likelihood ratio test would be used to select the best subset of covariates. The estimated adjusted odds ratio for Arm A1 versus Arm B1 will be displayed along with the associated 95% confidence interval.

If there are issues related to the convergence of the logistic regression model, we will use a 1-sided Wald's test will be performed.This analysis will be based on the FAS and mFAS.

Time course plot for IGA mod 2011 0/1 response rates at scheduled visits upto Week 104 for imputed data and upto Week 208 based on observed data.

Handling of missing data

Missing IGA 0/1 response values will be imputed with non-response regardless of the reason for the missing data (e.g., premature study discontinuation, missed visit, or administrative issue).

2.8 Safety analyses

All safety evaluations will be performed on the SAF

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

- Adverse events: Only treatment emergent records are reported in the tables, and listings have the "treatment emergent" flag displayed.
- Other safety data (e.g. laboratory data, vital sign, ECG, Physical examination etc):
  - by visit summary statistics tables: only include "on-treatment" records in the tables, i.e., assessments within last dose plus 84 days cutoff. Listings have the "on-treatment" flag displayed. Follow up visits (eCRF visits) may be summarized separately if required.

For the Main Study, the safety of secukinumab compared with nb-UVB will be evaluated. For the Mechanistic Sub-study, similar safety evaluations will be performed by treatment and study phase.

Entire treatment/study period for Main study (A1a+A1b and B1a+B1b)

Entire treatment period = randomization to Week 52 (EOT); for safety analysis include FU period up to last dose + 84 days.

Entire study period = randomization to end of study (EOS); includes follow up period (Week 208)

2.8.1 Adverse events (AEs)

For all subjects enrolled in the study, AEs data will be summarized and analyzed together by treatment arms for the SAF.

Treatment emergent AEs are defined as (events started on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity on or after dosing based on preferred term , and within 84 days (inclusive) after the last dose of study treatment. Only primary paths within MedDRA will be considered for AE reporting.

Adverse events will be summarized by presenting, for each treatment arm, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity (mild/moderate/severe) and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries.

If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

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

Separate summaries will be provided for psoriatic arthritis, SAEs, other significant AEs leading to discontinuation from the study, and AEs leading to study treatment discontinuation.

The crude incidence of treatment emergent adverse events will be presented for the entire treatment period. The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.1.1. In addition, exposure adjusted summaries including 95% confidence intervals for the occurrence rate of AEs in 100 subject years will be provided by treatment (see Section 5.1 Crude incidence and related risk estimates) for the treatment period. Appropriate figure will be displayed. For exposure adjusted summary.

For SAEs occurred during entire study a listing will be prepared for all subjects randomized . For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared displaying all adverse events for that subject and flag AEs that occurred after the first treatment error. In Mechanistic study due to the limited number of subjects, a listing will be only provided for safety set.

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

Algorithms for AE date imputations will be provided in Section 5.32.

Any AE, SAE related to Covid-19 will be summarized and listed seperately.

Table 2-4 Adverse events of special interest / grouping of AEs

The following adverse events of special interest will be summarized based on safety set.

Special AE interest	MedDRA Code	MedDRA Term	MedDRA Level
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	90000883	Non-melanoma skin cancer (BCC and SCC) [STANDARD] (NMQ)	NMQ1
Infections and infestations	10041925	Staphylococcal infections	HLT
Hepatobiliary disorders	10085260	Hepatitis virus infections	HLT
Infections and infestations	20000231	Infective pneumonia (SMQ)	MQ1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	90000901	Malignant or unspecified tumours (SMQ excl BCC and SCC) [AIN457] (NMQ)	NMQ1
Infections and infestations	90000882	Oesophageal candidiasis [STANDARD] (NMQ)	NMQ1
Infections and infestations	10019972	Herpes viral infections	HLT
Infections and infestations	10007951	Central nervous system infections and inflammations	HLGT
Infections and infestations	10017528	Fungal infectious disorders	HLGT
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	90000646	Skin tumours malignant and unspecified [STANDARD] (NMQ)	NMQ1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20000091	Malignant or unspecified tumours (SMQ)	MQ2
Infections and infestations	90000542	Infections of skin structures [STANDARD] (NMQ)	NMQ1
Psychiatric disorders	20000037	Suicide/self-injury (SMQ)	MQ2
Infections and infestations	10028440	Mycobacterial infectious disorders	HLGT
Infections and infestations	10021881	Infections and infestations	SOC
Immune system disorders	20000214	Hypersensitivity (SMQ)	MQ1
Cardiac disorders	90000281	MACE (MI, Stroke, Cardiovascular death) [AIN457] (NMQ)	NMQ1
Infections and infestations	90000701	Opportunistic infections [FINGOLIMOD] (CMQ)	NMQ1

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

2.8.1.1 Deaths

Separate summary and listing will be provided for deaths.

2.8.2 Laboratory data

2.8.2.1 Hematology and clinical chemistry

Similar to AEs, the laboratory data will be summarized and presented by treatments for the SAF.

The summary of laboratory evaluations will include 2 groups of laboratory tests (hematology and clinical chemistry).

- All the summary of lab outputs (newly occurring notables, maximum changes, shift tables, by visit summary statistics) will consider the "on-treatment" data. i.e., all assessments within last dose plus 84 days.

  Follow up visit summary: Summary of follow up visit outputs may be provided if required. The listing will provide follow up visit records.

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

Descriptive summary statistics for the change from Baseline to each study visit will be presented by test group, laboratory test, and treatment arm. Change from Baseline will only be summarized for subjects with both Baseline and post-Baseline data. For each parameter, the maximum change from Baseline within each study phase will be analyzed analogously.

change from baseline = post baseline value – baseline value

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment arm. The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-5: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented for each parameter by treatment and analysis phase. These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

Table 2.5 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	< LLN - 100 g/L	< 100 - 80 g/L	< 80 g/L	Life-threatening consequences; urgent intervention
Platelet count	< LLN – 75.0 x10e9 /L	< 75.0 - 50.0 x10e9 /L	< 50.0 – 25.0 x10e9 /L	< 25.0 x 10e9 /L

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
decreased				
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*	> 1 - 1.5 x baseline; > ULN - 1.5 x ULN	> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	> 3.0 baseline; > 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
ALP increased	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Glucose increased (Hyperglycemia)	; > ULN - 8.9 mmol/L	> 8.9 - 13.9 mmol/L	> 13.9 - 27.8 mmol/L	> 27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	< 3.0 - 2.2 mmol/L	< 2.2 - 1.7 mmol/L	< 1.7 mmol/L
Cholesterol high	> ULN - 7.75 mmol/L	> 7.75 - 10.34 mmol/L	> 10.34 - 12.92 mmol/L	> 12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	> 3.42 - 5.7mmol/L	> 5.7 - 11.4 mmol/L	> 11.4 mmol/L

*Note: for “creatinine increased” the baseline criteria do not apply

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either first or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged. The number and percentage of subjects with clinically CTCAE grade newly occurring or worsening after baseline will be presented.The expanded laboratory ranges and the clinically notable abnormalities of key laboratory variables are given in Table 2-6. Number and percentages of subjects with notable lab values will be summarized by treatment as well as listed.

Table 2-6 Criteria for notable abnormalities

Liver function and related variables	
Total bilirubin	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN
Renal function and electrolyte variables	
Creatinine (serum)	> 1.5 x ULN
Potassium	> 6 mmol/L or < 3 mmol/L
Sodium	> 160 mmol/L or < 115 mmol/L
Urinalysis variable	
Protein urine dipstick	2+ (100 mg/dL)
Hematology values	
Hemoglobin	≥ 20 g/L decrease from 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

Individual subject data listings will be provided for subjects with newly occurring or worsening abnormal laboratory data.

Visit wise count and percentage and listing will be produced for urinalysis - local lab result parameters.

2.8.3 Other safety data

2.8.3.1 ECG data

Data collected in "12 Lead ECG Evaluation – Local" eCRF page will be listed.

2.8.3.2 Vital signs

Vital sign measurements will be analyzed using summary statistics for the change from Baseline along with their absolute values for each post-Baseline visit and presented by vital sign and treatment arm. Change from Baseline will only be summarized for subjects with both Baseline and post-Baseline values.

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

Only "on-treatment" vital signs will be summarized (i.e. assessments within last dose plus 84 days). All vital signs will be listed with "on-treatment" flag displayed.

The criteria for notable vital sign abnormalities are given in Table 2.8. The number and percentage of subjects with newly occurring notable vital signs will be presented. A listing of subjects with newly occurring notably abnormal vital signs will be provided.

Table 2-8 Criteria for notable vital sign abnormalities

Vital signs (unit)	Normal measure	Notable abnormality
Systolic blood pressure (mmHg)	90 to < 120 mmHg	>= 140 mmHg (hypertension) or < 90 mmHg (hypotension)
Diastolic blood pressure (mmHg)	60 to < 80 mmHg	>= 90 mmHg (hypertension) or < 60 mmHg (hypotension)
Pulse (bpm)	60 to 100(bpm)	> 100 bpm (tachycardia) or < 60 bpm (bradycardia)

Note: A blood pressure indicative of prehypertension (systolic blood pressure of 120 to < 140 mmHg and/or diastolic blood pressure of 80 to < 90 mmHg) will not be regarded as notable (Chobanian, Bakris, and Black 2003).

A listing of the newly-occurring notably abnormal vital signs will be provided. "Vital sign" eCRF page will be used to get this information.

2.9 Pharmacokinetic endpoints

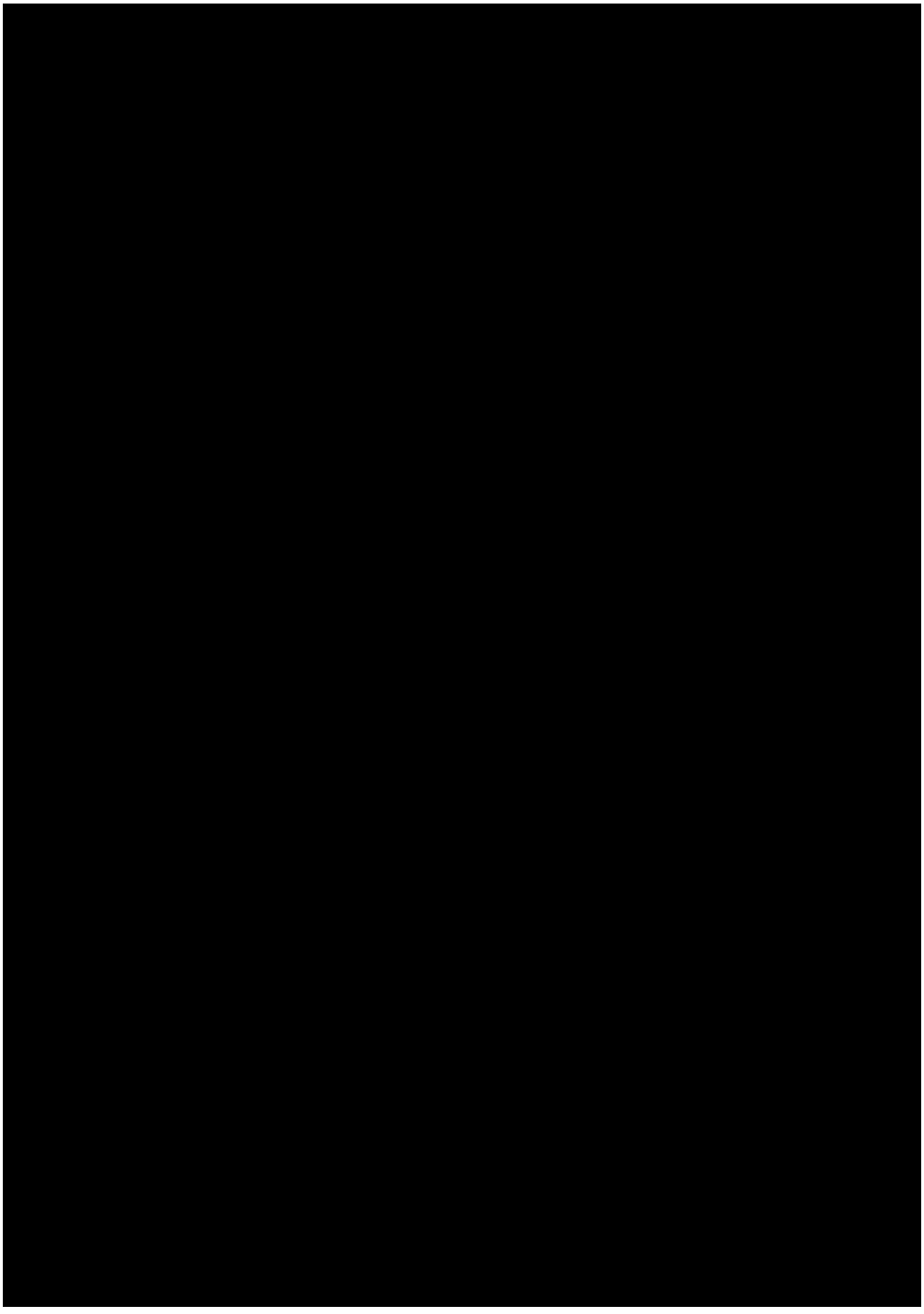
Not Applicable.

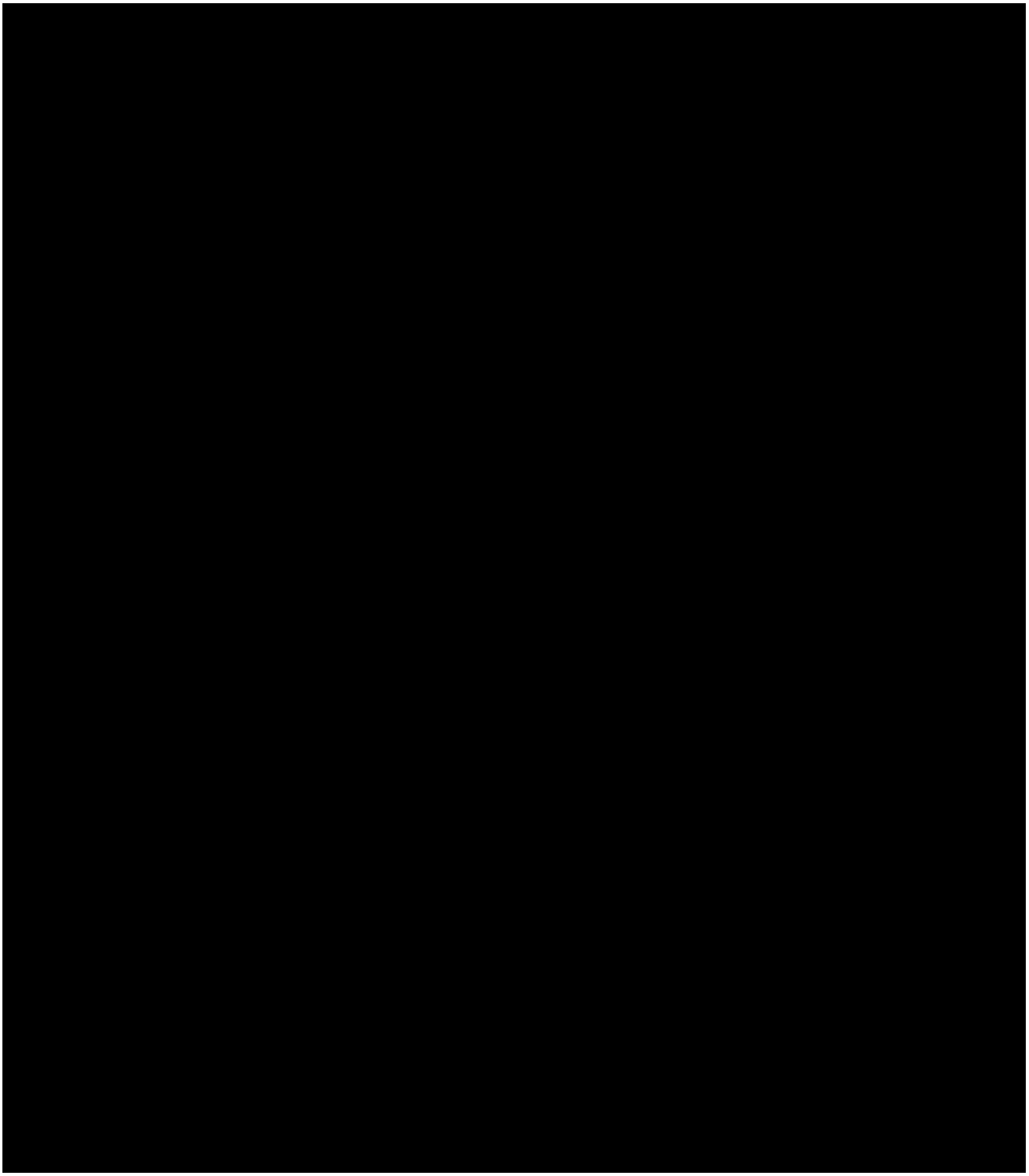
2.10 Skin Biopsy

Skin biopsies will be collected from subjects participating in the mechanistic sub-study as per the schedule defined in Table 1-2 in Study design section. SAF will be used for the analysis.

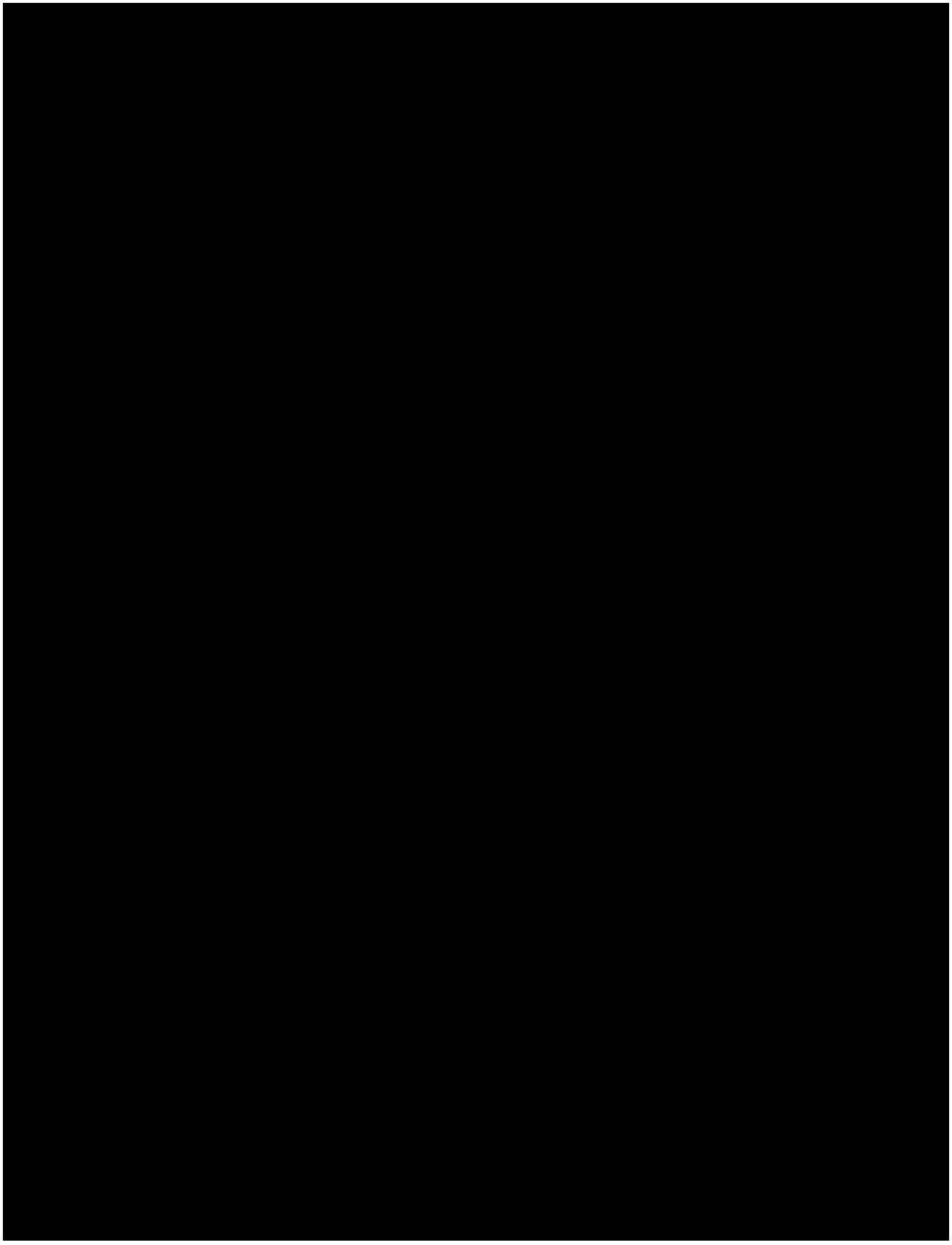
Punch biopsies from lesional or resolved skin (2 biopsies, 4 millimeters in diameter) and never-lesional skin (1 biopsy, 3 millimeters in diameter) will be taken according to the schedule shown in Table 2-2, and transported to Karolinska Institute, Stockholm, Sweden. Biopsy 1 from lesional or resolved skin (4 millimeters in diameter) sample will be used for gene expression analysis and Biopsy 2 from lesional or resolved skin (4 millimeters in diameter) and never-lesional skin (1 biopsy, 3 millimeters in diameter) will be used for histology analysis.

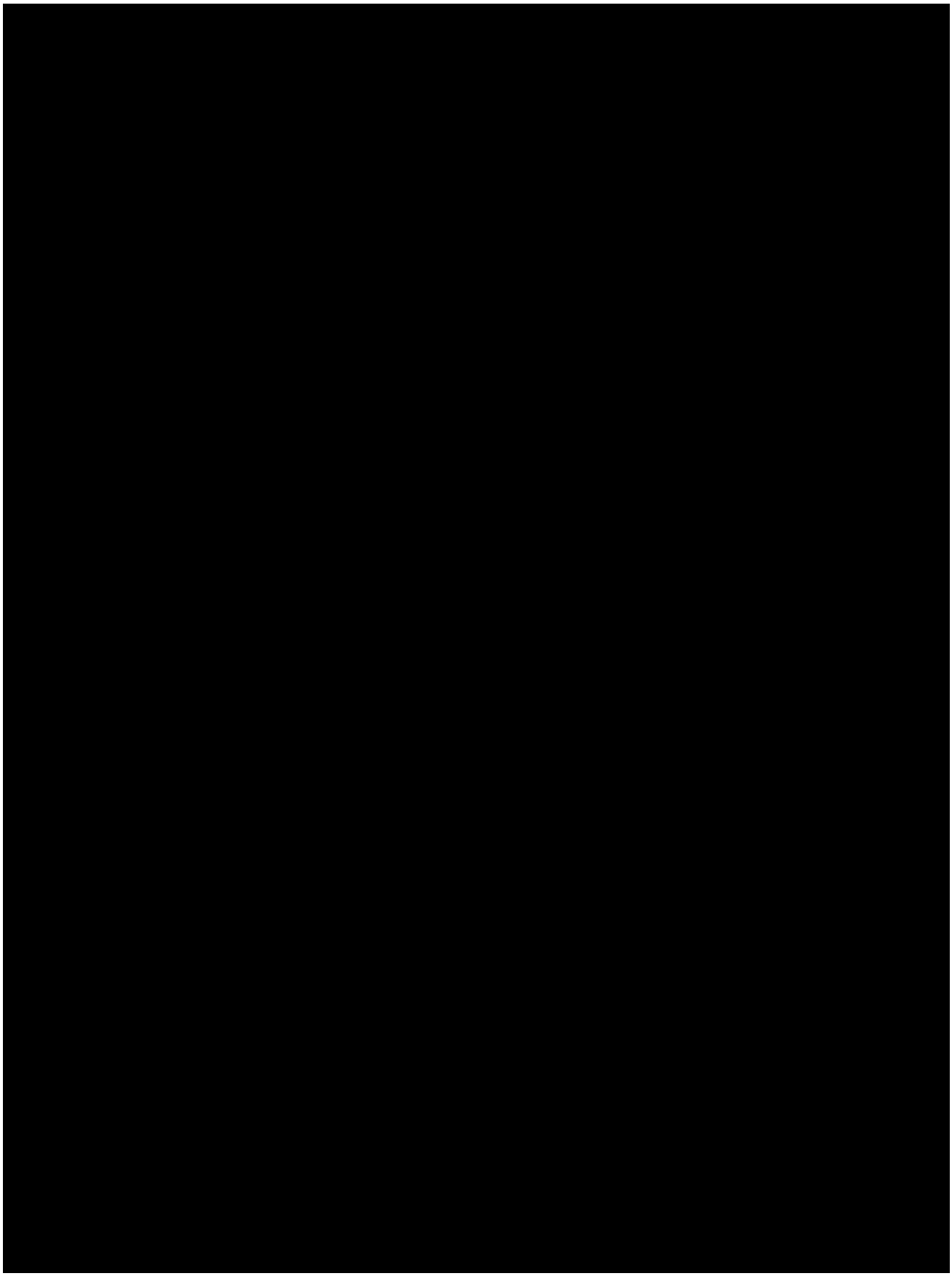
Skin biopsies will be taken from subjects in Arm A1b, Arm A2, Arm B1b, Arm C1, and Arm C2 to assess the total number of T_{rm} cells and subsets of these cells, especially those capable of producing IL-17A and IL-22 inflammatory mediators considered to be vital to maintain subclinical inflammation.

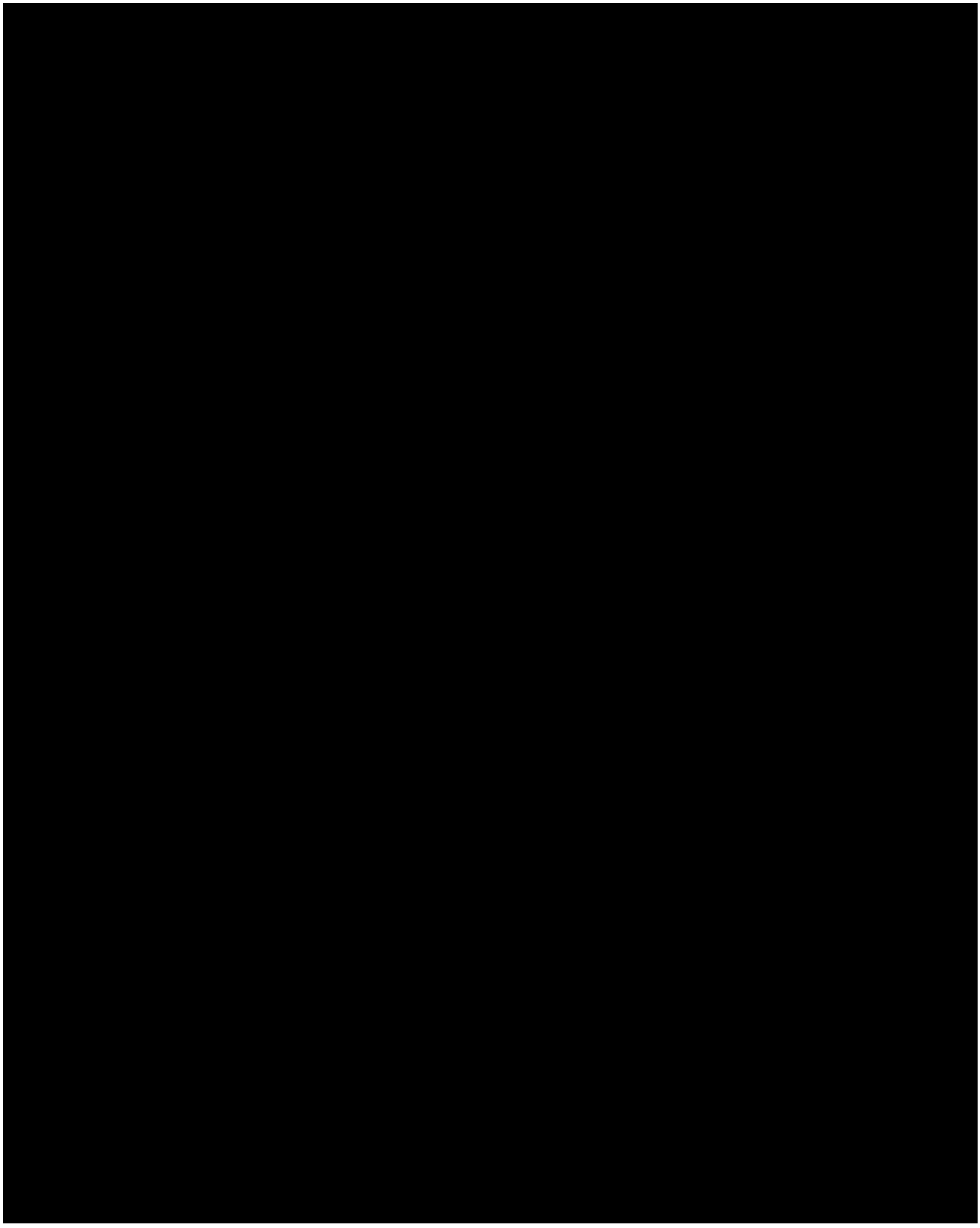


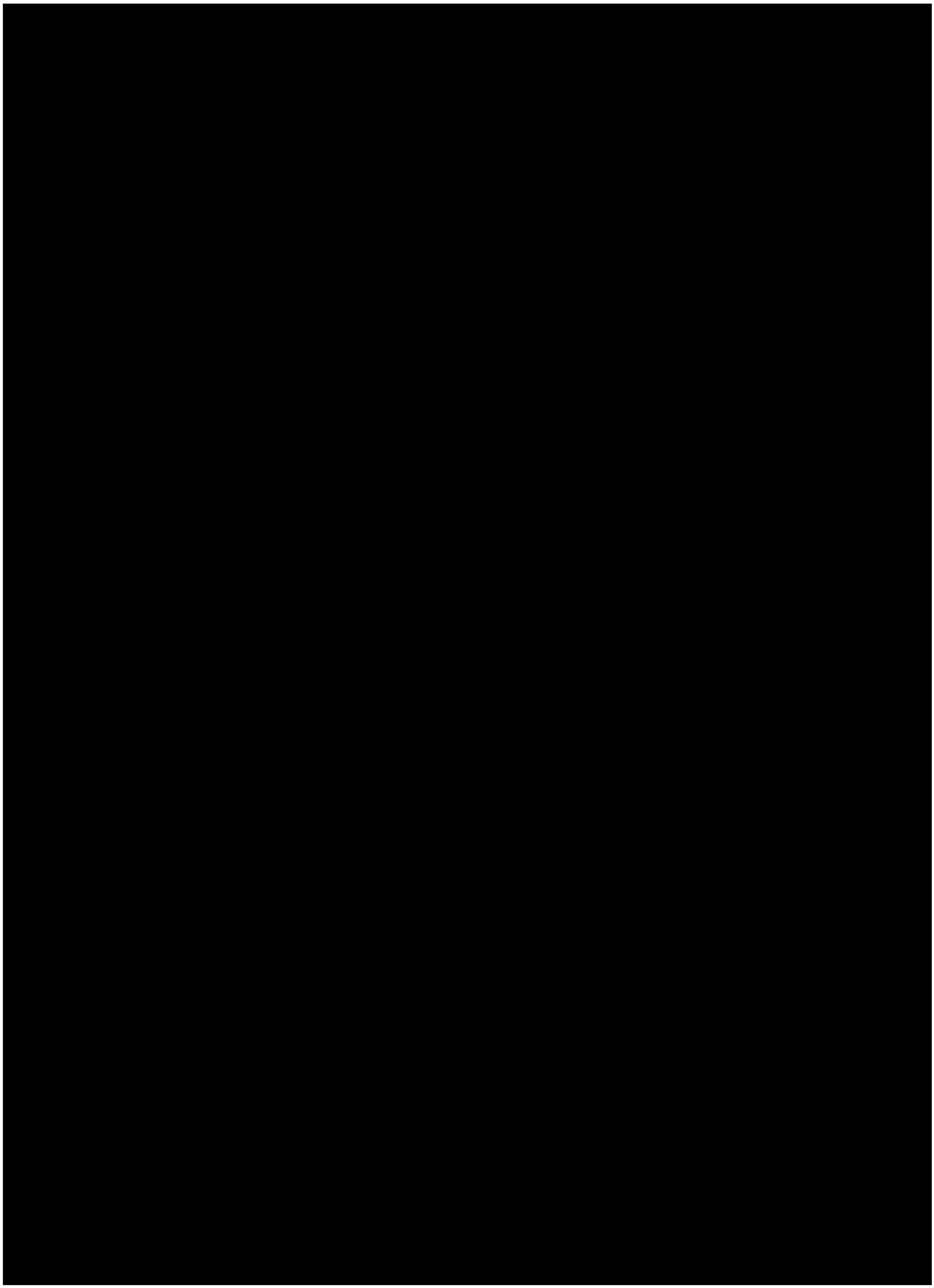


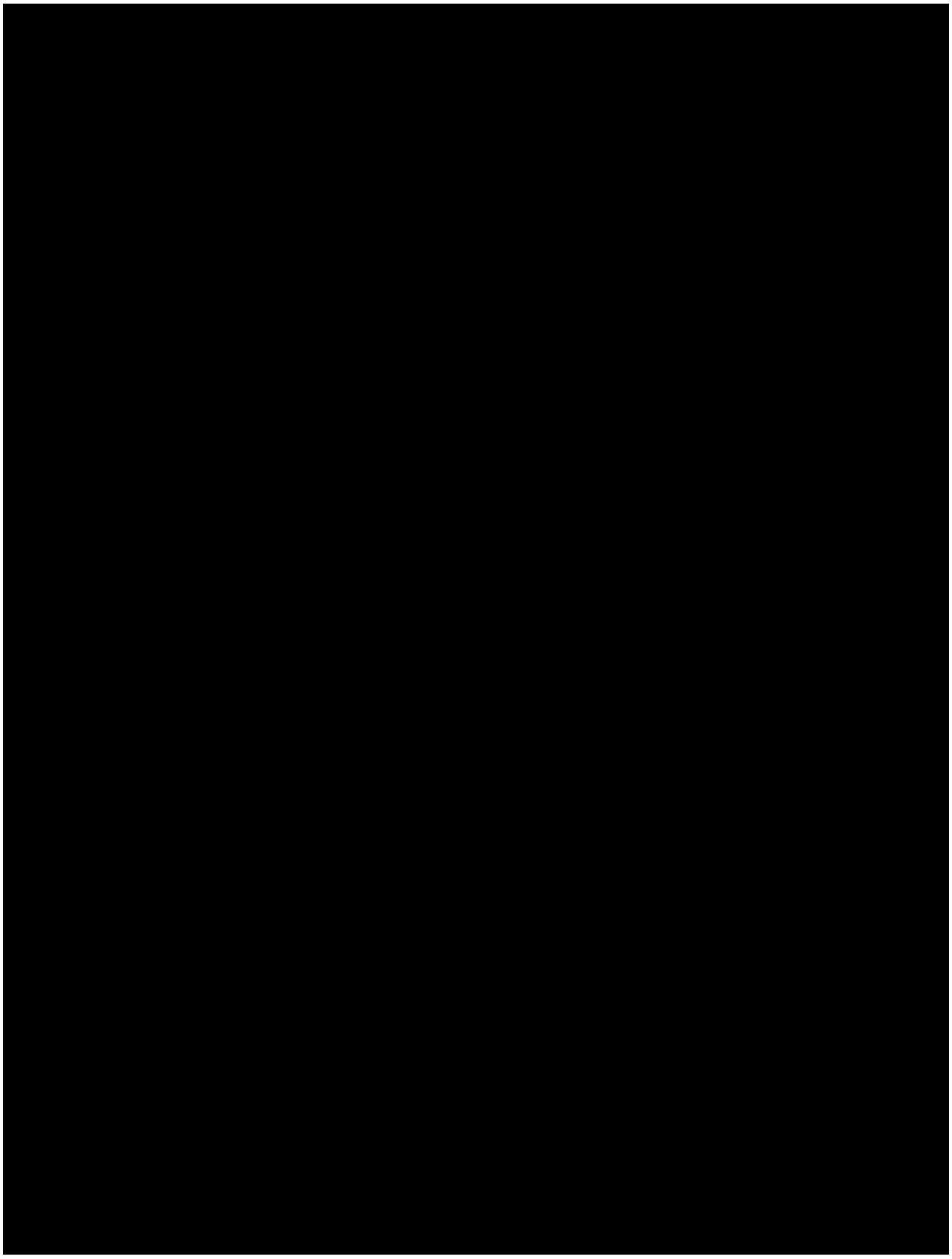
2.13 Other Exploratory analyses

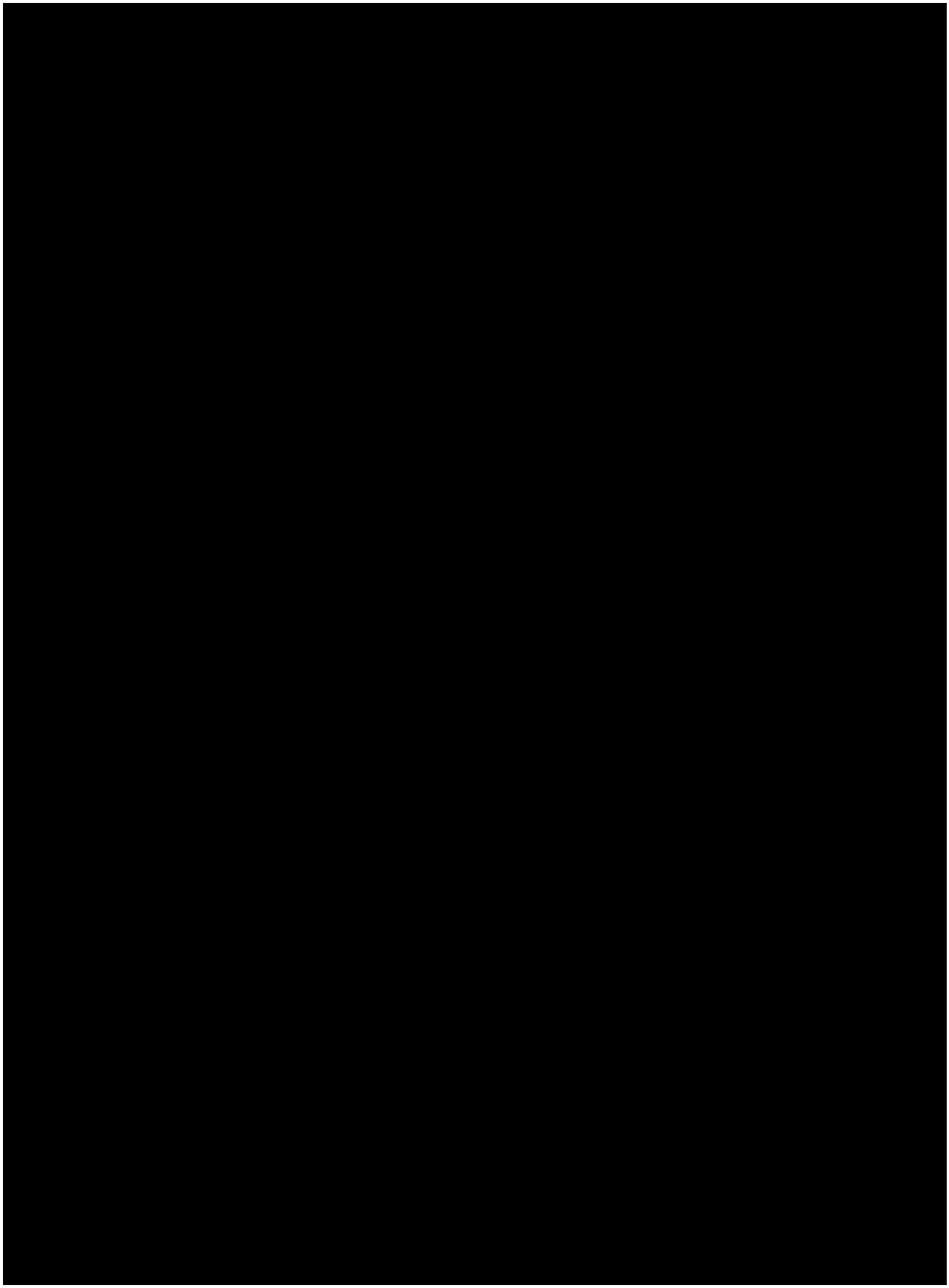


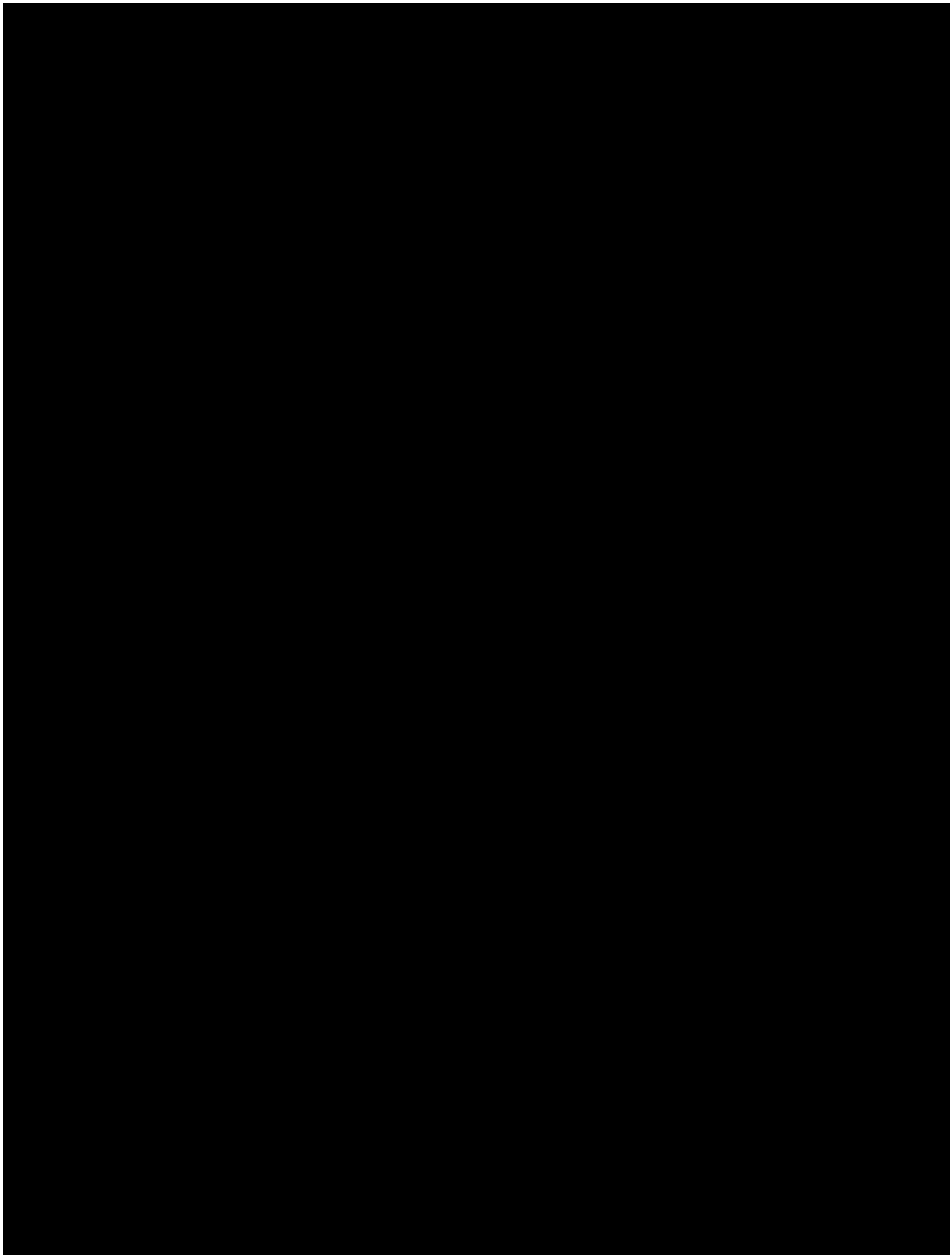












2.13.4 Investigators global assessment mod 2011 score and response over time

Treatment Arm A1 will be compared with Arm B1 based on IGA mod 2011 0/1 responses at Week 104 using a similar logistic regression model as described in Section 2.7.1.

Further, IGA mod 2011 0/1 responses at Week 104 will be analyzed by means of logistic regression model similar to the secondary analysis with treatment as a predictor variable and the significant variables among Baseline IGA mod 2011 score, age, and body mass index, and their interactions with treatment. Forward selection procedure based on the likelihood ratio test would be used to select the best subset of covariates. The estimated adjusted odds ratio will be displayed along with the associated 95% confidence interval.

In case of low responses achieved, the logistic regression model may not converge OR in case of non-sigificant difference between treatment groups any covariate may not get selected in logistic regression model with either of selection method . In such cases, we will use Wald's 1-sided test for comparison of treatment groups in IGA 0/1 score at Week 104.

IGA mod 2011 score will be summarized descriptively, using number and percentages by visits. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

For the treatment arms in the Mechanistic Sub-study, the above-stated analyses will also be repeated for both IGA score and IGA mod 2011 0/1 response over the 52 weeks of the Treatment Phase based on the observed data (i.e., until Week 52 for Arms A1b, B1b, and C1, and until

Week 104 for Arms A2 and C2) and Follow-up phase. Summary statistics for IGA mod 2011 0/1 response for treatment phase will also be performed with Non-responder imputation method upto Week 104. For follow-up phase analysis if required separate analysis is performed for change from Week 52 (For Arm A2; Week 104) to post-baseline visits in follow-up phase.

Handling of missing data

Missing IGA 0/1 response values will be imputed with non-response regardless of the reason for the missing data (e.g., premature study discontinuation, missed visit, or administrative issue).

Analysis will be based on the FAS and mFAS.

An analysis for imputed data (NRI approach) will be performed upto Week 104 and based on observed data will be performed upto Week 208.

2.14 Interim analysis and early termination

2.14.1 Interim analysis

An interim analysis for the Mechanistic Sub-study will be performed at Week 16. Subject data of treatment arm A1b, A2, B1b, C1, C2 will only be analyzed.
The Week 16 Interim analysis will be conducted after all subjects have either completed Week 16 or discontinued from of the study or lost to follow up prior to the Week 16. As this analysis at Week 16 will not involve any formal hypothesis testing, no adjustment for multiplicity will be required.

A similar interim analysis for the Mechanistic Sub-study will be performed after all subjects have either completed week 52 or discontinued from the study or lost to follow up prior to the week 52. Subject data of treatment arm A1b, A2, B1b, C1, C2 will only be analyzed.
The Similar interim analysis will be also performed for Week 104 after all subject have either completed Week 104 or discontinued or lost to follow up prior to week 104 .

Efficacy, safety and biopsy data up to Week 16 visit for all subjects will be summarized. AE and topical conrticosteroid listing will be presented on the entire treatment phase i.e. reports AE data collected until last subject Week 16 cut-off date.

Following treatment arm will be displayed until otherwise specified Week 16 interim analysis.

1. New onset subjects

Secukinumab(A1b+A2) and nb-UVB (B1b)

2. Chronic subjects

Secukinumab (C1+C2)

Following data points will be analyzed during Interim analysis:

Desicriptive statistics , frequency and percentages will be provided for continious and categorical datapoints respectively.
Following data points will be reported for Screening visit, Baseline visit upto Week 16 visit as applicable.

Demographic, BMI, prior medication, prior plaque-type psoriasis therapy will be displayed for Screening or Baseline Visit as applicable. In prior plaque-type psoriasis therapy, count and percentage for all therapy types and reason of discontinuation will be presented.

Treatment administration of Secukinumab and nb-UVB, Adverse events and serious adverse events will be presented till Week 16 visit.

From efficacy data point PASI score and IGA mod 2011 will be presented for Baseline and Week 16. PASI 75, 90, 100 and IGA mod 0/1 response will be presented for Week 16.

For the Main study Week 52 and Week 104 IA performed to meet the analysis requirement of analysis endpoints at Week 52 and Week 104. Clinical Study report was prepared for Week 52 primary efficacy analysis.

2.14.2 Early Termination

The study team has made a decision to terminate the study by the end of June 2023 instead of June 2024 (i.e., per protocol expected LPLV) due to the very low number of patients (11) remaining in the treatment-free long-term extension period of the study inability to draw additional meaningful scientific conclusions. The early termination will not have any impact on any of the secondary or primary endpoints, and is not due to any safety concerns.
The revised last patient visit (152 week) in the study is projected as 30 Jun 2023 and this date will be considered as the study termination date.

2.15 Additional analyses

Based on the results of Week 104 Main study analysis, it was decided that additional analyses were required without applying imputations and for the subjects who entered the follow-up period. These analyses were added during Week 104 Interim analysis only and were beyond the protocol specified analysis.
These additional analyses were performed only for some efficacy endpoints and based only on the observed data without applying imputation on the subjects who entered follow-up epoch. This additional analysis will consider the hypothesis testing criteria same as for respective endpoints of Main study (i.e. for Key secondary endpoint or exploratory endpoints).

2.15.1 Additional analysis objectives and endpoints

The objectives of this additional analysis are to compare secukinumab (Arm A1) versus nb-UVB (Arm B1) subjects in the follow-up efficacy analysis set with regards to the following items:

1. Proportion of all subjects who achieve at least PASI 90 at Week 104.
[redacted]
3. Proportion of subjects who achieve at least IGA mod 2011 0/1 response at Week 104.
[redacted]

2.15.2 Analysis sets

Two analysis sets will be defined for the additional analysis:

Follow-up Efficacy Analysis Set : Subjects in the mFAS who have at least one PASI assessment after Week 52 up to Week 104, and who have no major protocol deviations based on < PASI50 criteria i.e. Subjects with < PASI50 response at the end of treatment epoch at Week 52 lead to protocol deviations, will be excluded from this analysis set.

Follow-up Safety Analysis Set: Subjects in the mFAS who have at least one safety assessment after Week 52 up to Week 104.

2.15.3 Subject disposition

Subject disposition data will be summarized separately for the additional analysis. All tables, figures and listings mentioned in this section will be based on the Follow-up efficacy analysis set.

Subject disposition will be summarized for follow-up phase as described in Section 2.3.1 for the subjects in follow-up efficacy analysis set.

Primary reason for subject discontinued follow-up phase by week 208, Week 52- Week 104, Week 104-Week 152 and Week 152- Week 208 will be summarized by treatment group.

Median time to event (i.e. study discontinued) after Week 52 and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation (PROC LIFETEST option conftype=log-log). Completers will be treated as censored. An analysis will be followed as :

- Date of event minus date of Week 52 plus 1 day for subjects experiencing the event
  OR
- Date of censoring minus date of Week 52 plus 1 day for subjects not experiencing the event

Time from End of Treatment to Week 52:

Duration between Last dose of Treatment to the Analysis visit Week 52 will be analyzed as ; (Treatment end date -Date of Week 52 + 1) . Summary statistics n, mean, median, SD, Min, Max , Q1 and Q3 of duration of end of treatment to Week 52 is analyzed. Number and percentage of subjects will be displayed for the subjects with duration of > 4 weeks, > 8 weeks , > 12 weeks , > 16 weeks and so on. Analysis to be displayed up to the maximum duration between last dose of treatment to the Analysis visit Week 52 for every 4 weeks.

Subjects with missing visit week 52 date will be excluded from analysis of time to discontinuation and time from End of Treatment to Week 52.

2.15.4 Demographics and Baseline characteristics

For the additional analysis , summary statistics (n, mean, median, std, min and max) will be presented for continuous demographic and Baseline characteristic variables at baseline and Week 52 visit by treatment for all subjects in the follow-up efficacy analysis set

Similarly for categorical variables, the number and percentage of subjects in each category will be presented similar to Main study for baseline and Week 52 visit by each treatment arm for all subjects in the follow-up efficacy analysis set.

Age group, weight group and BMI group will be presented for both baseline and Week 52. All other demographic and baseline characteristic categorical variables will be presented only at baseline.

2.15.4.1 Demographics

Age , age categories (18-30, 31-50) , weight, weight group, BMI and BMI group variables will be summarized for both baseline and Week 52. Week 52 visit date will be used to calculate subject age at the time of visit at Week 52.

All other variables presented as in Section 2.3.2.1 will be summarized only at baseline.

2.15.4.2 Disease history and Baseline characteristics at Visit 1 and Week 52

Disease history and baseline characteristics collected at baseline (Visit 1) will be summarized by treatment for follow-up efficacy analysis set . All variables will be presented as in Section 2.3.2.2

In addition, the following disease characteristics categories will be presented at Week 52:

- PASI total score
- PASI categories (0, > 0-3, > 3-5, > 5)
- PASI response (50-75, >75-90, >90-100)
- [redacted]
- IGA mod 2011 score
- [redacted]

2.15.5 Analysis of PASI 90 response at Week 104

2.15.5.1 Comparison of Secukinumab vs nb-UVB for PASI90 response at Week 104 for follow up efficacy analysis set

In the comparison of Secukinumab vs nb-UVB for PASI90 response at Week 104 for Follow-up efficacy analysis set. selection of subjects for PASI90 response at Week 104 will be similar to the section 2.6.1 .

2.15.5.2 Statistical hypothesis, model, and method of analysis

For the additional analysis, the same hypothesis testing and method of analysis will be performed as secondary analysis Section 2.6.2 . An analysis will be performed only for observed data at week 104.

2.15.5.3 Handling of missing values/censoring/discontinuations

The addtional analysis will be performed only for the observed data at Week 104 , hence missing data will not be imputed.

[redacted]

[redacted]

[redacted]

[redacted]

2.15.9 Investigators global assessment mod 2011 score and response over time

Treatment Arm A1 will be compared with Arm B1 based on IGA mod 2011 0/1 responses at Week 104 using a similar logistic regression model as described in Section 2.7.1.
Analysis will be performed on FUP efficacy analysis set on observed data only.

IGA mod 2011 score will be summarized descriptively, using number and percentages by visits. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998). Graphical presentation will be performed for responders (%) at each scheduled visit from observed data using scatter plot.

IGA mod 2011 score will be summarized descriptively, using number and percentages by visits. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

[redacted]

3 Sample size calculation

The sample size calculation is performed for the primary endpoint (proportion of PASI 90 responders at Week 52) and the key secondary endpoint (proportion of all randomized subjects who achieve PASI 90 response at Week 104). The selected total sample size is 160 subjects, such that 80 subjects are randomized in each arm.

The sample size calculation based on the proportion of PASI 90 responders at Week 104 was performed using PASS 11.

The power calculations for the primary endpoint are based on the asymptotic Wald test to compare secukinumab 300 mg s.c. versus nb-UVB using the hierarchical method to adjust for multiplicity. Based on data (unpublished) and experiences from recent studies, it is assumed that the proportion of PASI 90 responders at Week 52 will be around 70% after early treatment with secukinumab 300 mg s.c. (Arm A1) and around 35% after 1 or 2 cycles of nb-UVB treatment (Arm B1). With assumed approximate 0% dropout rate in Arm A1, and 20% in Arm B1 until Week 52 due to lack of efficacy or AEs (considered non-responders), the response rate would change to 70% and 28%, respectively. Assuming an absolute difference of 42% in the proportion of subjects achieving PASI 90 at Week 52, the sample size of 80 subjects in each arm would provide 99.9% power at the 1-sided significance level of 0.025 using asymptotic Wald test for equality of proportions (using PASS 11).

For the Mechanistic Sub-study, additional 12 randomized subjects will be treated for 104 weeks with secukinumab 300 mg s.c. (Arm A2), along with 12 subjects each from Arm A1b and Arm B1b, and will serve as active groups. Further, 12 subjects identified with chronic plaque psoriasis will be allocated to secukinumab 300 mg s.c. for 52 weeks (Arm C1) and another 12 subjects with chronic plaque psoriasis will be treated during 104 weeks with secukinumab 300 mg s.c. (Arm C2), both serving as control groups for the Mechanistic Sub-study. As the Mechanistic Sub-study will not involve any formal testing of hypothesis, the sample size for it is obtained in an illustrative manner.

4 Change to protocol specified analyses

In Study design section , under follow up subsection “PASI90 score” is mentioned in the protocol however it is updated as “PASI90 response”.

Randomized set is added.

[redacted]

PASI 75 is added in the section 2.13.2.1 and 2.14.

[redacted]

A new population called Modified full analysis set (mFAS) is introduced. Randomized subjects who received treatment are considered in this population. Primary, key secondary and additional secondary endpoints will be analysed using mFAS along with FAS. [redacted]

Statistical analysis for Week 156 will be performed at the actual scheduled visit Week 152.

5 Appendix

5.1 Crude incidence and related risk estimates

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

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

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

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

Then the lower limit is

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

and the upper limit is

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

In addition, if L > p then L = p and if U < p then U = p.

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

5.1.2 Relative risk and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (nb-UVB) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the relative risk is estimated as p_1/p_0 with $p_1=x_1/n_1$ and $p_0=x_0/n_0$.

An asymptotic 100*(1-α)% confidence interval on the relative risk will be based on the back-transformed large sample confidence limits on the log-transformed relative risk estimate which are obtained by application of the delta-method and Slutzky's theorem (Lachin 2000). The SAS procedure PROC FREQ with option RELRISK in the TABLES statement will be used to provide the asymptotic 100*(1-α)% confidence interval on the relative risk. The estimate is not computed if either x_1 or x_0 equals 0. In this case, or if the crude incidences are low in both groups, the relative risk will be approximated by the odds ratio for which an exact confidence interval will be obtained as specified in Section 5.1.3. If the relative risk is not well

approximated by the odds ratio but asymptotic normality is questionable, STATXACT will be used.

5.1.3 Odds ratio and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g. placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$. A conditional exact 100*(1-α)% confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR.

5.2 Exposure adjusted incidence rate and related risk estimates

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

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

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

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

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

5.2.2 Exposure-adjusted event rate and 100*(1-α)% confidence interval

For each of n subjects t_j (j=1,...,n) specifies the exposure time. The number of occurrences of a treatment emergent event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of events (episodes). Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on

(Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

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

5.3 Imputation rules

5.3.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

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

5.3.2 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 as below

- 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).
- 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.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y

Else if month of the imputed date is not equal to MON then date flag = M

Else if day of the imputed date is not equal to day of original date then date_flag = D Else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H

Else if minutes of the imputed time is not equal to minutes of original time then time flag = M Else time flag = null.

5.3.3 Concomitant medication date imputation

Impute concomitant medication (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. **Concomitant Medication Date Flag**

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.3.3.1 Prior therapies date imputation

Same as section 5.3.3.

5.3.3.2 Post therapies date imputation

Same as section 5.3.3.

5.3.3.3 First diagnosis date imputation

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

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

b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).

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

a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).

b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.4 AEs coding/grading

.

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

5.5 Laboratory parameters derivations

Not Applicable.

5.6 Statistical models

5.6.1 Primary analysis

For the primary analysis (at Week 52), the following hypothesis testing will be performed:

$$H_{01}: p_{sec} = p_{nbUVB} \; versus \; H_{A1}: p_{sec} > p_{nbUVB}$$

where p_{sec} and p_{nbUVB} are the proportion of PASI 90 responders in the secukinumab 300 mg s.c. (Arm A1) and nb-UVB (Arm B) groups, respectively.

Model:

Forward selection method will be performed in order to select the subset of significant covariates from Baseline PASI score, age and BMI, and their interaction with treatment.

Logit(π_i) = β_1* treatment + β_2* Baseline PASI score + β_3* age + β_4* BMI + β_5* Baseline PASI score * treatment + β_6* age * treatment + β_7* BMI * treatment + error

where π_i is the probability that the ith subject is PASI 90 responder given that ith subject receives x_j treatment, where treatment x_j is AIN if j is 1 and nb-UVB if j is 2.

SAS code:

Using the PROC LOGISTIC the estimates of treatment differences and corresponding adjusted odds ratio and 95% CI. For Primary , Additional secondary objective. And in Other section as applicable.

```
proc logistic data= <PASI_IGA> descending covout outest=betas;
      class TRT/param=glm;
      model RESPONDER (event='1')= <Baseline XXX> <Treatment> <Age> <BMI>
                  / selection=forward

                    details
                    lackfit;
                  Lsmeans trt/diff cl exp ODDSRATIO;
ods output diffs=lsm_diff;
   run;
```

If there is any convergence issues, then

For Non convergence, Wald test:

```
PROC FREQ DATA=<Imputed dataset> ORDER=DATA;
   Weight <Count>;
```

```
    TABLES <treatment group>*<response variable>/riskdiff(equal var=Null Cl=wald) alpha=0.05;
RUN;
```

Multiple Imputation

The number of imputations will be set to 500, the seed for the random function will be set to 4572322. The input data set should have one record per subject with Baseline PASI score as well as all change from Baseline PASI score.

To generate the multiple imputed data sets proc MI can be used as follows (example):

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi> OUT=<impdata> SEED=457<studycode> NIMPUTE=500;
 VAR <Baseline BMI> <age>
       <Baseline PASI>
    <change from baseline  PASI week 16> - <change from baseline PASI week 52> PASI week primary endpoint>
     BY <treatment group>;
RUN;
ODS LISTING;
```

Programming notes:

- The SAS procedure MIANALYZE expects a variable called "_IMPUTATION_ which is generated by the MI procedure. It might be needed to set the SAS option "VALIDVARNAME=UPCASE" temporarily in the program before the MI call, this option should be reset after the MIANALYZE call to VALIDVARNAME=V6.
- In case there are none missing in one treatment group, the MI procedure does not impute any values. In this case the corresponding data need to be imputed manually outside PROC MI and added to the dataset <impdata>.

The imputed data are saved in data set <impdata>. The outcomes of interest, i.e. the PASI 90 response will be calculated, e.g. as follows:

```
DATA <impdata2>;
 SET <impdata>;
IF <change from Baseline PASI week primary endpoint>/<Baseline PASI <= -0.90 THEN <PASI 90 response> =1;
ELSE <PASI 90 response>=0;
```

The treatment differences for each imputed data set will then be evaluated by means of a logistic regression model with treatment as an explanatory variable and significant covariates among Baseline PASI score, age, and BMI, and interaction terms with treatment as covariates, as described in Section 2.5.2.

This analysis will be done by _IMPUTATION_ for each pairwise comparison to the nb -UVB group. The data set should be sorted such that the nb-UVB group comes last. The model should be estimating response probability = 1 by using DESECENDING option.

The MIANALYZE procedure expects the parameter estimate in the variables ESTIMATE, and the corresponding standard error in the variable STDERR. The standard error can be derived for the log(odds ratio). Based on the data set Common RelRisks, as described above, those can be programmed as

```
…
IF value NE . AND value>0 THEN ESTIMATE=LOG(value);
IF lowercl NE . AND value>0 THEN STDERR=LOG(lowercl/value)/-PROBIT(1-<alpha>/2);
Effect="LogOR";
...
```

The estimates and standard errors of the log(odds ratio) based on the 500 imputed data are then combined by applying Rubin's rules for multiple imputed data sets, see Little and Rubin (2002).

Programming notes:

- The variables ESTIMATE and STDERR in the input data set for the MIANALYZE procedure may not be missing. Records with missing values need to be deleted and the variable _IMPUTATION_ needs to be renumbered and regenerated since for each bygroup the procedure expects consecutive numbers starting at 1.
- The ESTIMATE and STDERR in terms of odds ratios from logistic regressions will be transformed to follow a normal distribution before MIANALYZE procedure. They will be transformed back to Odds Ratio to get the corrected ESTIMATE and corresponding CIs.

An example SAS procedure MIANALYZE will be applied as follows:

```
DATA <modified dataset_t>;
SET <modified dataset>;
stderr= stderror;
VARIABLE="estimate";
RUN ;

ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=<results> VarianceInfo=<varinfo> ModelInfo=<modelinfo>;
PROC MIANALYZE PARMS=<modified dataset>;
BY <by-variables>;
MODELEFFECTS ESTIMATE;
RUN;

ODS LISTING;
data <results_back>;
set <results>;
estimate=exp(ESTIMATE);
LCLMEAN=estimate*exp(-1.96*stderr);
UCLMEAN=estimate*exp(+1.96*stderr);
RUN ;
```

The ODS OUTPUT data set ParameterEstimates contains the estimate for the log(odds ratio), in ParameterEstimates.Estimates and the lower and upper confidence intervals (ParameterEstimates.LCLmean and ParameterEstimates.UCLmean). These three variables can be back-transformed and will be displayed together with the variable ParameterEstimates.PROBT. For the statistical appendix the ODS OUTPUT data sets Parameter Estimates, VarianceInfo and ModelInfo will be merged and displayed.

Result displayed:

Estimated adjusted odds ratio and the associated 95% confidence interval long with p-value.

In case if logistic regression does not converge, risk difference estimates will be provided. The SAS procedure PROC FREQ for risk difference estimates will be applied as follows:

5.6.1.1 Logistic regression (Supportive analysis)

```
PROC GENMOD <option>;
CLASS <stratum> <treatment>;
MODEL <response> = <explanatory variables> / link=logit dist=bin type3;
ESTIMATE "OR. AIN 300 mg VS. nb_UVB" <treatment> 1 -1/exp;
ODS OUTPUT Estimates=Estimates;
RUN;
```

5.6.1.2 Tipping point

The goal of the tipping point analysis is to identify assumptions about the missing data and presumed non-response under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of those assumptions can be discussed.

Defining all cases with missing data at a specific visit as uncertain cases (i.e. the subject could be either a responder or a non-responder) the following notations are made for a comparison of 2 treatment regimens:

R_i: Number of observed responders from subjects randomized to regimen i

NR_i: Number of observed non-responders from subjects randomized to regimen i

M_i: Number of uncertain response cases from subjects randomized to regimen i

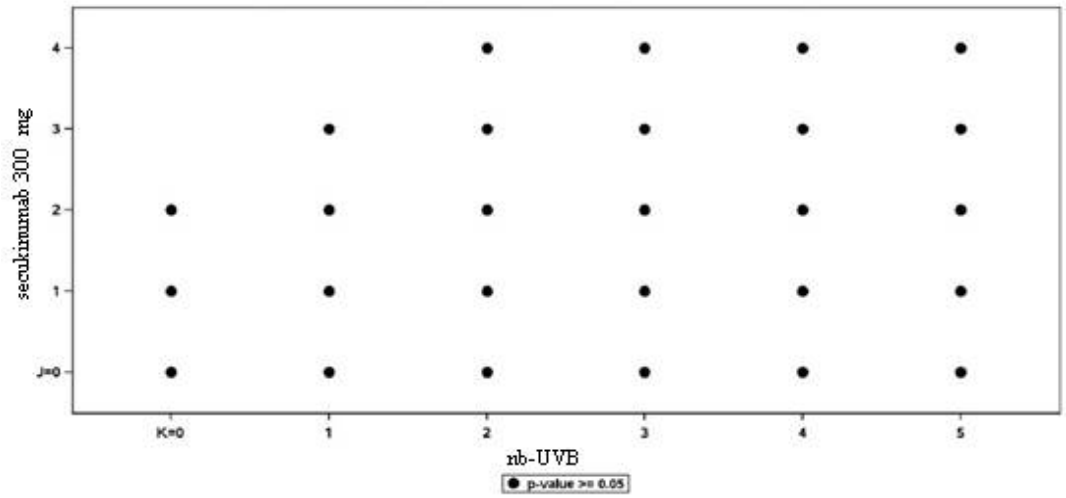
Where i=1, 2 denotes the 2 regimens to be compared.

A Chi-square test can now be performed comparing the 2 regimens for each possible combinations of uncertain response. Table 5-1 shows an outline of all the possibilities for the comparisons, where J_i takes values from 0 to M_i for regimen i.

Table 5-1 Counts in tipping point analysis

Response	Regimen 1 (N=N_1)	Regimen 2 (N=N_2)
Yes (responder)	$R_1 + J_1$	$R_2 + J_2$
No (non-responder)	$NR_1 + (M_1-J_1)$	$NR_2 + (M_2-J_2)$

Figure 5-1: Example of TPA for PASI 90 at Week 52 where dots represent insignificant p-values (>= 0.05)



J: Number of responders in uncertain cases from patients randomized to secukinumab 300 mg
K: Number of responders in uncertain cases from patients randomized to nb-UVB.

In an example shown in Figure 5-1 the treatment group (secukinumab 300 mg) has 4 missing values while the nb-UVB group has 5 missing values. The analysis results of all the possible combinations of responders between the 4 missing values and 9 missing values missing values from each groups are presented. Only the results of insignificant p values from the Chi square test are illustrated because they constitute a region in which significant treatment effect is overturned.

SAS code for Chi-square test of a specific assignment of uncertain cases:

ods output chisq=*chisquare*;

proc freq data=;

table *treatment**response* / chisq;

weight *n*;

run;

The input dataset should only include the 2 regimens to be compared. Number of subjects included in each of the four cells of Table 5-1 (e.g. $R_1 + J_1$) is denoted by *n*.

In order to also take strata and covariates into consideration a logistic regression model may also be performed for selected combinations of response distributions (e.g. worst case scenario where J_1=0 and J_2=M_2).

5.6.2 Key secondary analysis

Same as primary analysis but for Week 104 data by using exact logistic regression.

However, In case of low responses or comparision without covariates , Exact logistic regression model will be applied with exactonly options and treatment as fixed effect factor . Model will use link=logit function . Depending on covariates, Time to run the model can be decide with maxtime = option. Exact statement will be used to get estimate values and odds ratio . To get both , odds ratio and point estimate we will apply Estimate = Both option in Exact statement.

Proc logistic data = dataset descending EXACTONLY;

EXACTOPTIONS MAXTIME = 200 ONDISK;

By _imputation_;

Class TRT01PS / PARAM = ref;

Model avalc (event = ‘Y’) = TRT01PS / LINK = LOGIT;

Exact “Secukinumab vs nb-uvb” TRT01PS / ESTIMATE = Both joint;

ODS OUTPUT Exactoddsratio = odds;

ODS OUTPUT exactparmest = est;

Run;

5.6.4 Time to event

Estimation of the distribution of the survival times will be obtained using the Kaplan-Meier method which gives nonparametric estimates of the survivor function. A template of the SAS code to get survival estimates and corresponding standard error for each treatment group is given below:

ods output productlimitestimates=*pl_estimate*;

proc lifetest data= outsurv=*failure_estimate* atrisk stderr;

by *treatment*;

time *event***censor*(1);

run;

Where *event* contains time to the event of interest and *censor* variable contains either a 1 (event did not occur) or 0 (event occurred.) If the event of interest did not occur, *event* will be equal to the last timepoint where the subject was at risk. Survival times for each randomization stratum level can be obtained using the above code by adding the *strata* variable to the BY statement.

5.7 Rule of exclusion criteria of analysis sets

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

Table 5-2 Subject classification rules

Analysis set	Non-PD criteria that cause a subject to be excluded
Full Analysis Set (FAS)	Misrandomized subject
Safety set	Subjects who did not take any study treatment
Modified Analysis Set	Subjects who did not take any study treatment
Folllow-up efficacy set	Subject does not have PASI assessment after W52 to W104
Follow-up safet set	Subject does not have Safety assessment after W52 to W104

6 Reference

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26; 404‑413

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

Rubin DB (1987) Multiple imputation for non-response in surveys. New York: John Wiley & Sons.