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A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of secukinumab 300 mg and 150 mg in adult patients with active psoriatic arthritis after 16 weeks of treatment compared to placebo and to assess the safety, tolerability and efficacy up to 52 weeks

Statistical Analysis Plan (SAP)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ATC	Anatomical Therapeutic Classification
BL	Baseline
BMI	Body mass index
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DAS	Disease Activity Score
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA/EMEA	European Medicines (Evaluation) Agency
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI©	Health Assessment Questionnaire – Disability Index
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IGA mod 2011	Investigator's Global Assessment modified 2011
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	[redacted]
LFT	Liver function test
LOCF	Last-observation-carried-forward
MDA	Minimal Disease Activity
[redacted]	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs

[redacted]	[redacted]
mmHg	Millimeter mercury
MMRM	mixed-effects model repeated measures
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
OS	Overall Survival
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PD	Protocol deviation
PFS	Progression-Free Survival
PK/PD	Pharmacokinetics/ Pharmacodynamic
PRO	Patient-reported Outcomes
PsA	Psoriatic arthritis
[redacted]	[redacted]
[redacted]	[redacted]
PSOC	Primary System Organ Class
PT	Preferred Term
QoL	Quality of Life
RF	Rheumatoid factor
SAP	Statistical Analysis Plan
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SCR	Screening
SF-12	Medical Outcome Short Form (12) Health Survey
SJC	Swollen Joint Count
SMQ	Standardized MedDRA Query
SpA	Spondyloarthritis
[redacted]	[redacted]
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TJC	Tender Joint Count
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
[redacted]	[redacted]

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses which will be used in the phase 4 clinical trial AIN457FUS01.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analysis plans in this document refer to the related statistical analysis sections in clinical study reports.

Data will be analyzed by Novartis Product Life-Cycle Services and/or a designated Contract Research Organization using statistical software SAS® Version 9.4 according to Section 9 (Data Analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR. The statistical methodology is described below and the deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section 16.1.9 of CSR.

Please refer to the following document:

- Clinical Protocol CAIN457FUS01

1.1 Study design

This study uses a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. Approximately 250 adult patients (in 2:2:1 ratio; 100 secukinumab 300 mg, 100 secukinumab 150 mg and 50 placebo) with active psoriatic arthritis (PsA) and with a target skin lesion with PASI score of 1 or greater will be randomized from approximately 65 investigative sites in the United States.

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration of up to 8 weeks before randomization, followed by a treatment period up to Week 52.

Patients that do not require a washout, can proceed on to the baseline visit once all inclusion/exclusion criteria are being met.

At baseline (BL), patients whose eligibility is confirmed will be randomized to one of three treatment groups and will enter the Placebo-Controlled Treatment Period.

Treatment Period 1

The Treatment Period 1 is defined as starting from Randomization through Week 16 (prior to the Week 16 dose). At the start of the Placebo-Controlled Treatment Period, patients will be randomized via IRT in a 2:2:1 ratio to one of three treatment groups (secukinumab 300 mg s.c., secukinumab 150 mg s.c. or placebo s.c.).

- **Group 1- Secukinumab 300 mg**: secukinumab 300 mg (two s.c. injections of the 150 mg dose) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.
- **Group 2- Secukinumab 150 mg**: secukinumab 150 mg (one s.c. injection of the 150 mg dose and one s.c. secukinumab injection of placebo) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

- **Group 3- Placebo**: placebo (two s.c. injection of 150 mg secukinumab placebo per dose) once per week for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks.

Treatment Period 2

- Patients receiving secukinumab 300 mg (**Group 1**) will continue to receive same dose up to Week 52.
- At Weeks 16, 28 and 40 patients on secukinumab 150 mg (**Group 2**) will be classified as responders (≥ 20% improvement from BL in both tender and swollen joint counts) or non-responders.
  - At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at weeks 28 or 40.
  - Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg every 4 weeks and will continue this dose up to Week 48.
- Patients on placebo (**Group 3**) regardless of their responder status will start receiving secukinumab 300 mg every 4 weeks from Week 16 up to Week 48.

Those patients whose tender and swollen joint counts both reduce by ≥ 20% from baseline will be classified as 'responders' and those patients who do not meet the responder criteria will be classified as 'nonresponders'.

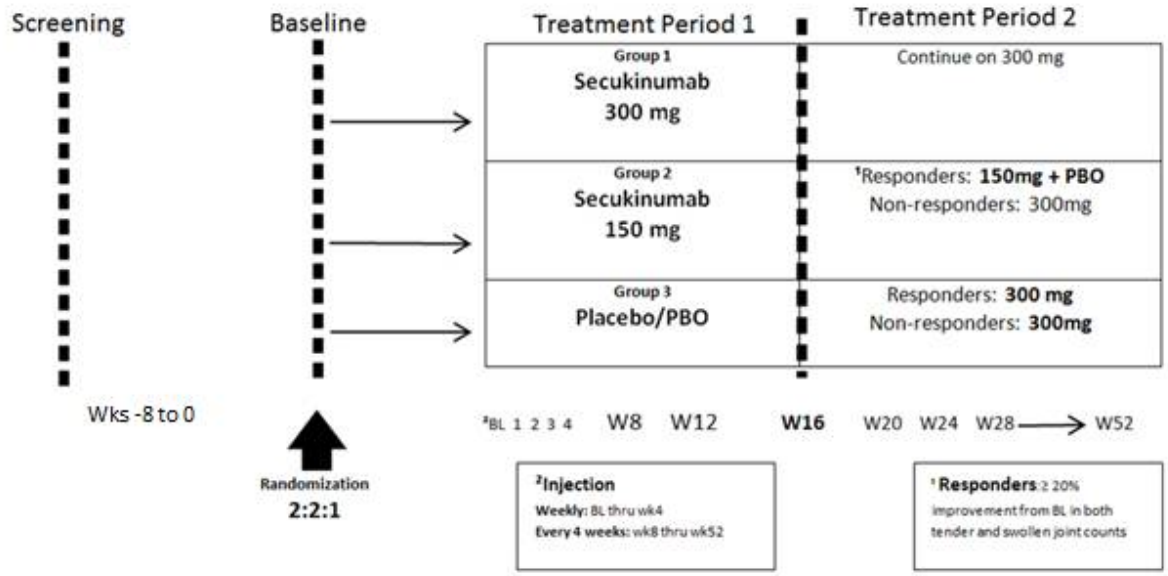
Patients, investigators/site staff, persons performing assessments, and Novartis study personnel will remain blinded to individual treatment assignment from the time of randomization until the final database lock.

Rescue medication will not be allowed during the day of the clinical visit and before completion of Week 16 assessments. Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, patients will be discontinued from the study if rescued with prohibited biologics and should obtain end of study assessments at the earliest possible date, provided consent to do so has not been withdrawn.

No stratification at randomization will be performed.

The following figure describes the study design.

Figure 1.1: Study Design



Primary analysis time point

The primary analysis will be performed at Week 16.

Interim analyses

As planned, database lock will be performed at the end of Treatment Period 1 (Week 16), after all patients have completed the Week 16 visit. Data analyses will follow after first database lock.

1.2 Study objectives and endpoints

Table 1.2-1: Objectives and endpoints

Objective	Endpoint
Primary objective	
To demonstrate that the efficacy of secukinumab 300 mg at Week 16 is superior to placebo in adult patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.	ACR20 response (yes, no)
Secondary objectives	

To evaluate the efficacy of secukinumab 150 mg compared to placebo at Week 16 in patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.	ACR20 response (yes, no)
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients withdactylitis in the subset of patients who have dactylitis at baseline.	Dactylitis (yes, no)
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients with enthesitis in the subset of patients who have enthesitis at baseline.	Enthesitis (yes, no)
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 in subset of patients with active PsA and number of tender and swollen joints less than 10 at baseline based on the proportion of patients achieving ACR20, ACR50, and ACR70 responses.	ACR20, ACR50, and ACR70 responses
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving ACR50 and ACR70 responses.	ACR50 and ACR70 responses
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving Minimal Disease Activity (5 of the following 7 criteria: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or IGA mod 2011 ≤1,, patient assessment of pain (0-100 Visual Analog Scale (VAS)) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1)	Minimal Disease Activity (yes, no) (5 of the following 7 criteria: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or IGA mod 2011 ≤1, patient assessment of pain (0-100 Visual Analog Scale (VAS)) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1)
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the proportion of patients achieving a PASI75, PASI90, and PASI100 responses	PASI75, PASI90, PASI100 responses (yes, no)

To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in DAS28-CRP.	Change from baseline in DAS28-CRP
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS).	Change from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS)
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in SF12.	Change from baseline in SF12
To evaluate the efficacy of secukinumab 300 mg and 150 mg compared to placebo at Week 16 based on the change from baseline in HAQDI.	Change from baseline in HAQ-DI
To evaluate the overall safety and tolerability of secukinumab 300 mg and 150 mg compared with placebo as assessed by vital signs, clinical laboratory values, and adverse events (AE) monitoring.	Overall safety, as measured by frequency and severity of adverse events (AE) monitoring and changes in clinical laboratory values and vital signs from baseline

[redacted]

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis Product Life-Cycle Services and/or a designated Contract Research Organization.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

As the primary analysis time point is Week 16, there will be a database lock after all patients have completed the Week 16 visit and data are clean and complete. At that time, only the statistician and programmer(s) from Novartis and/or a designated CRO will be unblinded in order to perform the analysis. Results from the analyses of all data through Week 16 will be shared internally. For publication purposes, summary results from the Week 16 primary analysis time point may be shared with the health care community; however, individual subject-level data will remain blinded until the end of the trial. A final database lock will occur when all patients have completed the study.

Summary statistics for continuous variables will include mean, standard deviation, standard error of mean, median, 25th and 75th percentiles, interquartile range, minimum, and maximum at each time point. Summary statistics for discrete variables will be presented in the number and percent of patients in each category. Summary statistics will also be presented graphically wherever applicable. If not otherwise specified, p-values and confidence interval (CI) will be presented as two-sided and the default level of significance will be set to 0.05 (two-sided). For all continuous variables (efficacy and safety), change from baseline and percentage change from baseline by visit will also be presented.

Data analyses will be presented by treatment group. Efficacy and safety data for the placebo-controlled period (or the entire Treatment Period as appropriate) will be presented by the following 3 treatment groups. Patients may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period).

Eligible patients will be randomized to secukinumab 300 mg (Group 1), secukinumab 150 mg (Group 2) or placebo (Group 3) for the first 16 weeks (until Week 16 treatment). Note that the treatment groups above for a patient may differ depending on the time period of the analysis and whether one assesses the patient for efficacy or safety.

The analysis will be conducted on all patients' data at Week 16 and at the time the trial ends (Week 52).

For Treatment Period 2, all data analyses will be presented by Weeks 16, 28 and 40, based on the number of patients who switched to secukinumab 300 mg and number of patients who continued in secukinumab 150 mg at the respective visits.

All the assessments from scheduled visits will be included for summaries and analyses, whereas the listing will include available data.

Comparative efficacy data

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo) will focus on the time period when both active drug and the placebo are given in a manner suitable for making comparisons (i.e., first 16 weeks of treatment). Comparative efficacy will be performed based on the FAS using the randomized treatment. After week 16 till week 52, the efficacy variables will be summarized descriptively or otherwise specified using inferential analysis, on the FAS.

2.1.1 General definitions

Study treatment

- **Investigational Treatment:**

  Secukinumab **150 mg** provided in 1.0 mL in PFS for s.c. injection.

  Secukinumab **placebo** provided in 1.0 mL in PFS for s.c. injection.

Dates and time windows

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, **study treatment end date** is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the core study.

Study day

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g., visit, lab samples, AEs). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for "time since event" data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1. Time from events prior to the start of study drug, e.g., time since diagnosis, is calculated as the difference between the start date of study drug and the date of prior event.

Note that, the first dose day is Day 1, and the day before the first dose day is counted as Day -1 (not Day 0).

Baseline and post-baseline definitions

In general, a baseline value refers to the last measurement made prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

Treatment Period: There are 2 Treatment Periods for this study defined as:

Treatment Period 1 is defined as the 16-week, placebo-controlled, double-blind Treatment Period starting from baseline till Week 16.

Treatment Period 2 is a 36-week, double-blind active Treatment Period starting from Week 16 till Week 52.

Lost to follow up: The patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw

On-treatment period: The period where the patients are exposed to the study treatment. For this study the treatment phase consists of 52 weeks.

2.1.2 Visits 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. For example, if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject

may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Of note, subjects are allowed to have gaps in visits.

Table 2-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183
Week 28	28	197	Day 184-211
Week 32	32	225	Day 212-239
Week 36	36	253	Day 240-267
Week 40	40	281	Day 268-295
Week 44	44	309	Day 296-323
Week 48	48	337	Day 324-351
Week 52	52	365	Day 352-379

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments. For efficacy, visit windows refer to date of randomization.

2.1.3 Multiple assessments within visit windows

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

For baseline assessment definition, see section 2.1.1. For post-baseline visit windows, the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined.
- in case qualitative variables are based on quantitative variables, e.g., PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

[redacted]

2.2 Analysis sets

The following analysis sets will be used for the statistical reporting and analyses:

Randomized Set: The Randomized Set includes all randomized patients.

Safety Set: The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received.

Full Analysis Set (FAS): The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set.

Psoriasis Subset: The Psoriasis Subset comprises patients in whom at least 3% of body surface area was affected by psoriatic skin involvement at baseline.

Dactylitis Subset: The Dactylitis Subset comprises patients who have LDI >= 1 at baseline.

[redacted]

Up-titrated Subset: Up-titration Subset includes all completed patients who were up-titrated from 150 mg to 300 mg in Treatment Period 2, based on the response.

For efficacy analyses, following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

2.2.1 Subgroup of interest

Planned subgroups of interest are the subsets defined in Section 2.2.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics and the number and percentage of patients in each category will be presented for categorical variables for each treatment group of all patients, and also by the subgroup of patients with dactylitis at baseline, and the subgroup of patients with enthesitis at baseline. The summaries will be reported for both the Randomized Set and the Full Analysis Set (FAS).

2.3.1 Patient disposition

The number and percentage of patients screened will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of patients in the Randomized Set and FAS who are enrolled, and who completed the treatment periods and who discontinued the study prematurely (including the reason for discontinuation) will be presented at the end of each Treatment Period (Week 16 and Week 52), if appropriate, for each treatment group and all patients.

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

2.3.2 Patient demographic and other baseline characteristics

The following demographic and baseline variables, if collected, will be summarized:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2
- RAPID3

Categorical variables:

- Age categories (≥18 - <40, ≥40 - <65, ≥65 - <75, 75 years and older)
- Sex
- Race
- Ethnicity
- Child-bearing status (for females only)

Baseline disease characteristics will also be summarized for the following variables:

- The time (years) since first PsA diagnosis, PsA disease duration (if different from time since diagnosis)
- History and, duration of psoriasis, including time (years) since first diagnosis of psoriasis

- Smoking status at baseline
- Alcohol status at baseline
- Tuberculosis (TB) status

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions eCRF will Be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary.

- Summary will be provided for cardiovascular medical history.
- Previous PsA/psoriasis treatments of each therapy will also be summarized.
- Chest X-ray (screening) results will also be listed.

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

2.4.1 Study treatment / compliance

Study Treatment

The summaries by treatment group will be performed cumulatively by the actual treatment received (as follows) for every visit until Week 16.

Treatment groups in Treatment Period 1:

- Secukinumab 300 mg
- Secukinumab 150 mg
- Placebo

For entire treatment period, the summaries by treatment group will be performed cumulatively by the actual treatment received (as follows) for every visits till Week 52, including the patients who switched at Weeks 16, 28, 40.

Treatment groups for entire treatment period analysis:

For efficacy variables:

- Secukinumab 300 mg
- Secukinumab 150 mg - 150 mg (R)
- Secukinumab 150 mg - 300 mg (NR)
- Any Secukinumab 150 mg
- Placebo - Secukinumab 300 mg

For safety variables

- Any Secukinumab 150 mg
- Any Secukinumab 300 mg
- Any Secukinumab

The analysis of study treatment data will be based on the Safety Set. The number of active and placebo injections will be summarized by treatment group up to Week 52.

Duration of exposure

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of subjects with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Duration of exposure of study Treatment Period 1 will be defined as the time from first dose of study treatment till the end of Treatment Period 1 (Week 16).

Duration of exposure of switched treatment group (for patients switching from placebo to secukinumab 300 mg, or secukinumab 150 mg to 300 mg) in Treatment Period 2 will be defined as the time from treatment switch to end of Treatment Period 2 (Week 52).

The duration of exposure of initial treatment group in Treatment Period 2 will be defined as the time from first dose (Week 16) till the end of Treatment Period 2 (for secukinumab 300 mg group) or until the switch (for secukinumab 150 mg group).

For patients who discontinue, this will be the patient's last visit in the corresponding treatment period.

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

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

The analyses of duration of exposure described above will be done for the entire study treatment periods.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the days of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered. Safety Set will be used for the analysis.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

Prespecified concomitant medications (Methotrexate (MTX), Folic acid, Systemic corticosteroids, Non-steroidal anti-inflammatory drugs (NSAIDs) (including selective COX-2 inhibitors), low strength opioids and acetaminophen) will be summarized by categories, route of administration and preferred term.

In addition, prior and concomitant medication data will be listed.

Rescue medication

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

Rescue medication must not be used before completion of Week 16 assessments.

Changes in NSAIDs concomitant therapy is permitted after Week 16 assessments per investigator's clinical judgment.

Rescue medication will be summarized similarly to concomitant medication.

2.5 Analysis of the primary objective

The primary objective is to demonstrate that the efficacy of secukinumab 300 mg at Week 16 is superior to placebo in patients with active PsA based on the proportion of patients achieving an American College of Rheumatology 20 (ACR20) response.

A patient will be considered as improved according the ACR20 criteria if she/he has at least 20% improvement in the two following measures:

- Tender joint count,
- Swollen joint count.
- and at least 20% improvement in at least 3 of the following 5 measures:

a. Patient's assessment of pain,

b. Patient's Global Assessment of Disease Activity,

c. Physician's Global Assessment of Disease Activity,

d. Health Assessment Questionnaire (HAQ) score,

e. Acute phase reactant (high sensitivity C-reactive protein (hsCRP) or ESR) Primarily, CRP will be used to calculate ACR response. ESR will only be used in the event CRP is missing.

2.5.1 Primary endpoint

The primary efficacy variable is ACR20 response (yes, no). The primary analysis time point will be at Week 16.

The primary analysis of the primary efficacy variable will be based on the Full Analysis Set.

2.5.2 Statistical hypothesis, model, and method of analysis

Let π_j denote the probability of an ACR20 response at Week 16 for treatment group j, j = 0, 1, 2, where 0 corresponds to placebo, 1 corresponds to secukinumab 150 mg, and 2 corresponds to secukinumab 300 mg. Accordingly, $\pi_j/(1-\pi_j)$ is the odds for treatment group j, j = 0, 1, 2.

The following null hypotheses (H_{01} and H_{02}) will be tested against their corresponding alternative hypotheses (H_{A1} and H_{A2}):

$H_{01}: [\pi_1/(1-\pi_1)]/[\pi_0/(1-\pi_0)] \leq 1$ versus $H_{A1}: [\pi_1/(1-\pi_1)]/[\pi_0/(1-\pi_0)] > 1$

$H_{02}: [\pi_2/(1-\pi_2)]/[\pi_0/(1-\pi_0)] \leq 1$ versus $H_{A2}: [\pi_2/(1-\pi_2)]/[\pi_0/(1-\pi_0)] > 1$

The primary efficacy variable will be analyzed at Week 16 using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight (in kg) as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported. If the p-value for a dose of secukinumab versus placebo is < 0.05 and the corresponding odds ratio is greater than 1, statistical significance in favor of that dose of secukinumab is shown.

Methotrexate usage at baseline and body weight are assumed to have possible impact on the variable, so those will be included in the logistic regression model, even though the factors will not be used to stratify at randomization.

The primary variable will also be analyzed at each time point till Week 16 using the same model.

Number and percentages of ACR20 responders will be reported for each treatment group by visit in entire treatment period up to Week 52 using oberved data. Similar summary will be provided for ACR20 using non-responder imputation.

Number and percentages of ACR20 responders will be reported for each treatment group, concomitant methotrexate usage at baseline and by visit in entire treatment period up to Week 52. Similar summary will be provided for ACR20 using non-responder imputation.

2.5.3 Handling of missing values/censoring/discontinuations

Patients who discontinued prematurely for any reason will be considered non-responders from the time they discontinued. Patients who do not have the required data to compute ACR20 response (i.e., tender and swollen joint counts and at least three of the five ACR components) at baseline and at the specific time point will be classified as non-responders.

In an additional analysis, missing data for ACR20 response variable will be handled by multiple imputation. Multiple imputation 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 explanatory variables, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis, the ACR components will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis, the response status will be imputed based on the individual treatment arm information.

2.5.4 Supportive analyses

The primary efficacy variable will also be analyzed at each time point till Week 16 for the Full Analysis Set using the Cochran-Mantel-Haenszel (CMH) test to compare secukinumab 300 mg against placebo, adjusting for methotrexate usage at baseline (yes, no) (Stokes, Davis, and Koch, 2012).

If the treatment comparison p-value is < 0.05 and the proportion of patients who are ACR20 responders is higher in a secukinumab treatment group compared to the placebo treatment group, statistical significance in favor of that dose of secukinumab is shown. Two 95% confidence intervals for the difference between each dose of secukinumab versus placebo in the proportion of patients who are ACR20 responders will be calculated using the normal approximation to the binomial distribution.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table1.2-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

All the secondary efficacy evaluation will be performed on FAS.

The secondary efficacy variables are the following:

1. Dactylitis (yes, no)
2. Enthesitis (yes, no)
3. ACR50 response (yes, no)

4. ACR70 response (yes, no)
5. Minimal Disease Activity (yes, no)
6. PASI75 response (yes, no)
7. PASI90 response (yes, no)
8. PASI100 response (yes, no)
9. Change from baseline in DAS28-CRP
10. Change from baseline in PASDAS
11. Change from baseline in SF12
12. Change from baseline in HAQ-DI

2.7.2 Statistical hypothesis, model, and method of analysis

Dactylitis and enthesitis

Analyses of dactylitis and enthesitis will be performed at each time point up to Week 16. The data for the subgroup of patients who have dactylitis at baseline (similarly for enthesitis) will be used and the data will be analyzed using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence interval for the odds ratios, and p-values based on the fitted model will be reported.

[redacted]

Number and percentages of patients with presence of enthesitis will be reported for each treatment group and by visit in entire treatment period up to Week 52. Similar summary will be provided for patients with presence of enthesitis using non-responder imputation.

The above analyses will be done on Dactylitis Subset, [redacted]

ACR20, ACR50, and ACR70 responses

ACR20, ACR50, ACR70 responses at each time point up to Week 16, and in subsets of patients with active PsA and number of tender and swollen joints < 10 and ≥ 10 at baseline will be analyzed using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

Additionally, ACR50 and ACR70 responses will be analyzed as analogous to primary efficacy variable at each time point up to Week 16.

Number and percentages of ACR50 and ACR70 responders will be reported for each treatment group, concomitant methotrexate usage at baseline and by visit in entire treatment period up to Week 52. Similar summary will be provided for ACR50 and ACR70 using non-responder imputation.

Number and percentages of ACR50 and ACR70 responders in subsets of patients with active PsA and number of tender and swollen joints < 10 and ≥10 at baseline will be reported for each treatment group and by visit in entire treatment period up to Week 52. Similar summary will be provided for ACR50 and ACR70 using non-responder imputation.

Minimal Disease Activity

Minimal Disease Activity response at each time point up to Week 16 will be analyzed using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

Number and percentages of Minimal Disease Activity response will be reported for each treatment group and by visit in entire treatment period up to Week 52. Similar summary will be provided for Minimal Disease Activity response using non-responder imputation method.

Very Low Disease Activity

Very Low Disease Activity (yes, no) is achived when 7 out of the following 7 criteria are met: ≤1 tender joint, ≤1 swollen joint, PASI ≤1 or IGA mod 2011 ≤1, patient assessment of pain (0-100 Visual Analog Scale (VAS)) ≤15, patient global assessment of disease (VAS) ≤20, HAQ-DI ≤0.5, tender entheseal points ≤1.

Very Low Disease Activity response at each time point up to Week 16 will be analyzed using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

Number and percentages of Very Low Disease Activity response will be reported for each treatment group and by visit in entire treatment period up to Week 52 for the observed data. Similar summary will be provided for Very Low Disease Activity response using non-responder imputation method.

PASI75, PASI90, PASI100 responses

Response to PASI75, PASI90, PASI100 at each time point up to Week 16 will be analyzed using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

The above analyses will be done on Psoriasis Subset.

Number and percentages of PASI75, PASI90, and PASI100 responders will be reported for each treatment group and by visit in entire treatment period up to Week 52. Similar summary will be provided for PASI75, PASI90, and PASI100 responders using non-responder imputation method.

DAS28-CRP

The change from baseline in DAS28-CRP at each time point up to Week 16 will be analyzed by an analysis of covariance (ANCOVA) model with treatment (3 treatment groups), baseline, methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The least squares means (LS Means) of the three treatment groups, least squares mean differences between each dose of secukinumab and placebo, 95% confidence intervals for the difference between each dose of secukinumab and placebo, and p-values based on the fitted linear model will be reported.

Summary statistics for observed DAS28-CRP score and change from baseline in score will be reported for each treatment group and by visit in entire treatment period up to Week 52.

PASDAS

The change from baseline in PASDAS at each time point up to Week 16 will be analyzed by an analysis of covariance (ANCOVA) model with treatment (3 treatment groups), baseline, methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The least squares means (LS Means) of the three treatment groups, least squares mean differences between each dose of secukinumab and placebo, 95% confidence intervals for the difference between each dose of secukinumab and placebo, and p-values based on the fitted linear model will be reported.

Summary statistics for observed PASDAS score and change from baseline in score will be reported for each treatment group and by visit in entire treatment period up to Week 52.

SF12

Refer to Section 2.11.

HAQ-DI

Refer to Section 2.11.

Summary statistics will include relative and absolute frequencies for the binary variable (ACR20, ACR50, ACR70, dactylitis, enthesitis, Minimal Disease Activity, Very Low Disease Activity, PASI75, PASI90, PASI100) and the number of patients (N), mean, standard deviation,

median, 25th and 75th percentiles, interquartile range, minimum, and maximum for the continuous variables (DAS28-CRP, PASDAS, etc.,) for each treatment group and by visit. Graphical representation will also be performed if required.

2.7.3 Handling of missing values/censoring/discontinuations

Patients who discontinued prematurely for any reason will be considered non-responders from the time they discontinued. Patients who do not have the required data to compute ACR response (i.e., tender and swollen joint counts and at least three of the five ACR domains) at baseline and at the specific time point will be classified as non-responders. For all other binary variables, non-responder imputation will be applied.

Missing data for continuous variables will be imputed using the last-observation-carried-forward (LOCF) method.

2.7.4 Supportive analyses

Not applicable.

2.8 Safety analyses

All the safety analysis will be performed on Safety Set.

Summaries may performed separately for initial (Weeks 1-16) and entire Treatment Period till Week 52.

The analyses for treatment-emergent adverse events, serious adverse events and risks based on adverse events will be summarized. Safety analyses will be performed on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ from the treatment assigned at randomization only if a subject received the wrong treatment during the entire study.

For those patients who received not the treatment randomized, i.e. who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

2.8.1 Adverse events (AEs)

The crude incidence of treatment emergent adverse events (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be reported, using the statistical methods described in Section 5.4.5.

In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for Treatment Period 1 and Treatment Period 2 to adjust for differences in

exposure. The description of exposure calculation is mentioned in Section 2.4.1. The statistical methods for calculation of exposure-adjusted incidence rate and its 95% confidence interval are described in Section 5.4.4. A graphical display of the crude incidence rates and exposure-adjusted rates will be presented for all AEs and serious AEs by system organ class.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for

- adverse events suspected to be related to study drug by the investigator
- deaths
- serious adverse events
- adverse events leading to discontinuation
- adverse events leading to temporary dose interruption
- non-serious adverse events

Adverse events will also be reported separately by SMQ according to MedDRA, using a narrow search. The MedDRA version used for reporting the study will be described in a footnote.

A listing of non-treatment emergent adverse events will be done. These adverse events occurred before the first dose of the study treatment. The crude incidence rate will be provided without treatment information.

Algorithms for date imputations will be provided in Programming Specifications.

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

An overview of the safety analyses and which will be performed for each analysis period is

described in Table 2.1 below.

Table 2.8-1 Overview of analyses on some safety data

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ECG), lab criteria

Day 1 – Week 16	• Crude Incidence • Exposure time adjusted incidence *	• Crude Incidence	• Crude Incidence	• Crude Incidence	• Crude Incidence	• Crude Incidence
Entire Treatment (upto Week 52)	• Crude Incidence • Exposure time adjusted incidence *	• Crude Incidence	• Crude Incidence	• Exposure time adjusted incidence *	• Crude Incidence • Exposure time adjusted incidence *	• Crude Incidence

*Exposure-adjusted incidence rates will be done for the following:
• at the PSOC for AE and SAE
• at the PT level for common AEs, which is defined as at least 2% of the patients in the combined secukinumab groups during the initial Treatment Period or events that had an incidence rate of at least 5.0 cases per 100 subject-years in the combined secukinumab groups during the entire treatment period
• at Level 1 for Risks and SMQ analyses

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term).

2.8.2 Deaths

Separate summaries and listings will be provided for deaths for each treatment period.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry and urinalysis).

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory variable and treatment group. Change from baseline will only be summarized for patients with both baseline and

post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

For each variable, the maximum change (maximum decrease and maximum increase) from baseline within each study period will be analyzed analogously.

QuantiFERON TB-Gold test will also be analyzed by the central laboratory.

In addition, shift tables will be provided for all variables to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the reference laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. Also the shifts to the most extreme laboratory test value within a Treatment Period will be presented as well (including category "high and low"). These summaries will be presented by laboratory test and treatment group.

The following laboratory variables will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2.8-2: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

Table 2.8-2 CTCAE grades for laboratory variables to be analyzed

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	
Platelet count Decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell Decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count Decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count Decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 xULN	>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
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

*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 initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. Patients with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2.8-3 below:

Table 2.8-3 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2Xuln
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Hy's Law) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.

Notes:
In studies which enroll patients with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality Criteria

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

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

Separate summaries and listings will be provided for urine pregnancy results by visit for each treatment period.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

All available ECG related data will be listed.

2.8.4.2 Vital signs

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

change from baseline = post-baseline value – baseline value

The number and percentage of subjects with newly occurring notable vital signs will be presented. Clinically notable vital signs are provided in the table below

Table 2.8-4 Criteria for notable vital sign abnormalities

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

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

All HR-QoL variables will be evaluated based on FAS patients.

The secondary efficacy variables related to patient-reported outcomes are:

- Change from baseline in SF12
- Change from baseline in HAQ-DI

SF12

The change from baseline in SF12 at each time point till Week 16 will be analyzed by an analysis of covariance (ANCOVA) model with treatment (3 treatment groups), baseline SF12 score, methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The least squares means of the three treatment groups, least squares mean differences between each dose of secukinumab and placebo, 95% confidence intervals for the difference between each dose of secukinumab and placebo, and p-values based on the fitted linear model will be reported.

The SF-12v2 score will be computed in the following steps:

1. Enter the data
2. Recode out-of-range item values as missing
3. Reverse score and/or recalibrate scores for four items
4. Compute raw case scores
5. Transform raw scale scores to 0-100

Table: Scale Items Aggregated and Range of possible Scores

SF-12v2 scale	Sum Final item values	Lowest possible raw scores	Possible raw score range
Physical functioning (PF)	Items 2a+2b	2	4
Role Physical (RP)	Items 3a+3b	2	8
Bodily Pain (BP)	Item 5	1	4
General Health (GH)	Item 1	1	4
Vitality (VT)	Item 6b	1	4
Social Functioning (SF)	Item 7	1	4
Role Emotional (RE)	Items 4a+4b	2	8
Mental Health (MH)	Items 6a+6c	2	8

Transformed scale = ((Actual raw score-lowest possible raw score)/Possible raw score range)*100

HAQ-DI

The HAQ-DI was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQ-DI,assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty (1), much difficulty (2), and unable to do (3).

The purpose of the HAQ-DI in this study is to assess the functional ability of patients with PsA.

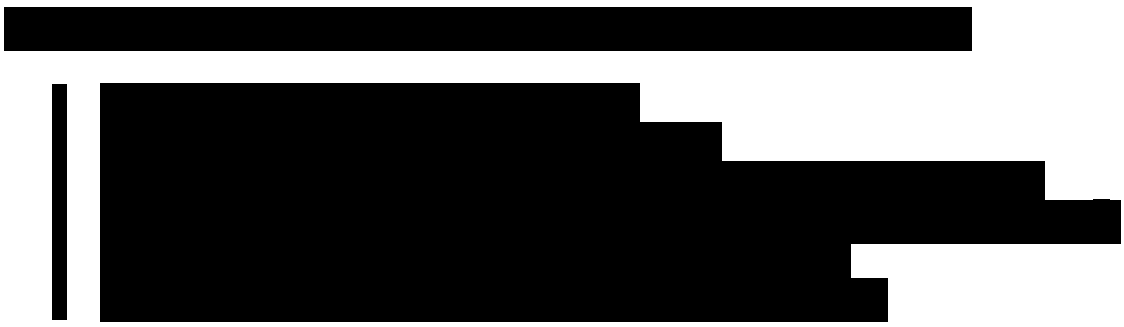
Analysis of HAQ-DI total score will be analogous to the analysis of SF12 for all time points up to Week 16.

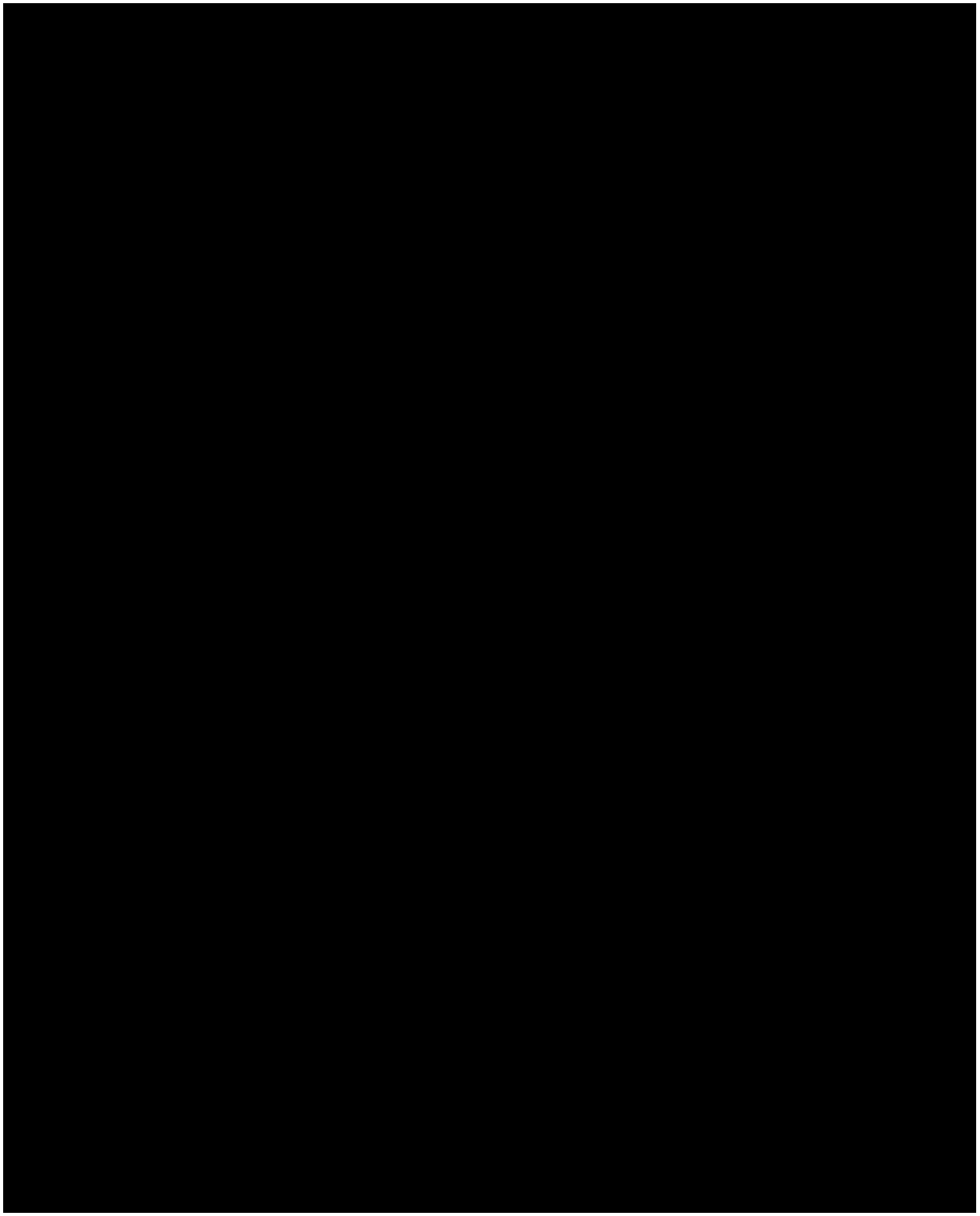
In addition, the following two binary variables will be analyzed:

- HAQ-DI response, where response = yes if HAQ-DI score <= 0.5).
- HAQ-DI MCID, where response = yes if HAQ-DI change from baseline <= -0.35).

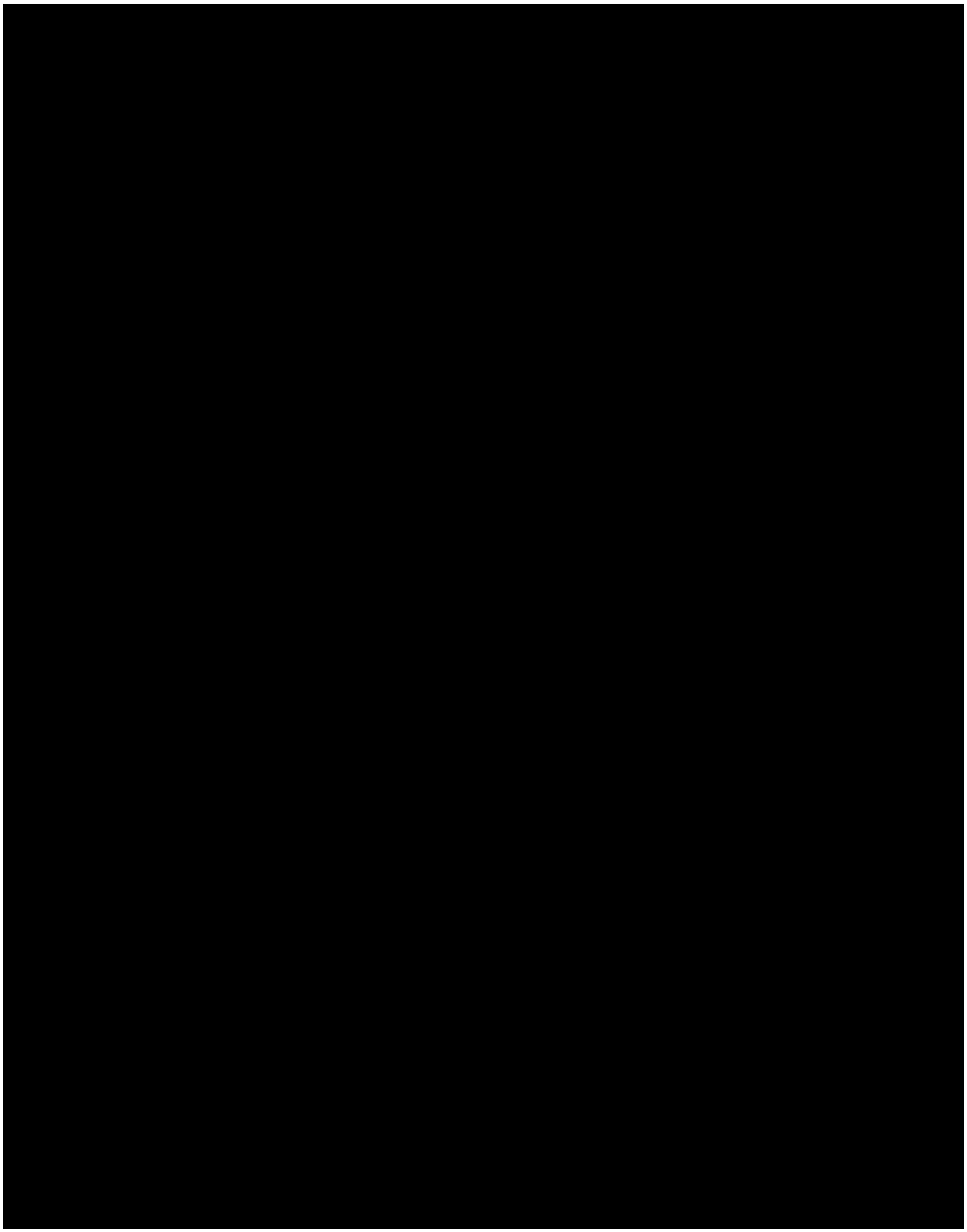
The above analysis will be done at each time point using a logistic regression model with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight as explanatory variables. The odds ratios for each dose of secukinumab versus placebo, 95% confidence intervals for the odds ratios, and p-values based on the fitted model will be reported.

In addition, number and percentages will be provided for HAQ-DI responders by treatment group at each visit for entire treatment period. Similar analysis will be performed using non-responder imputation.



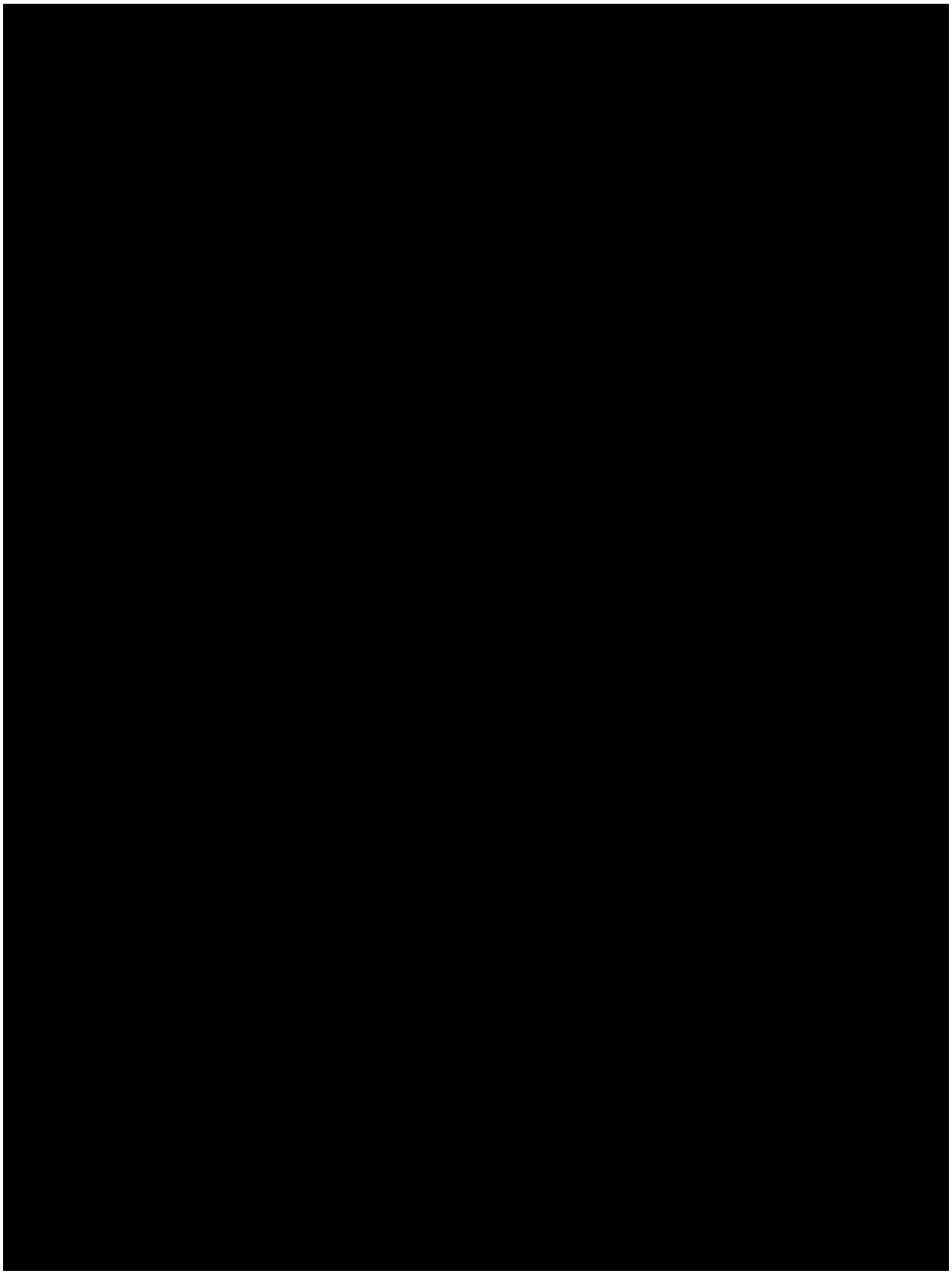


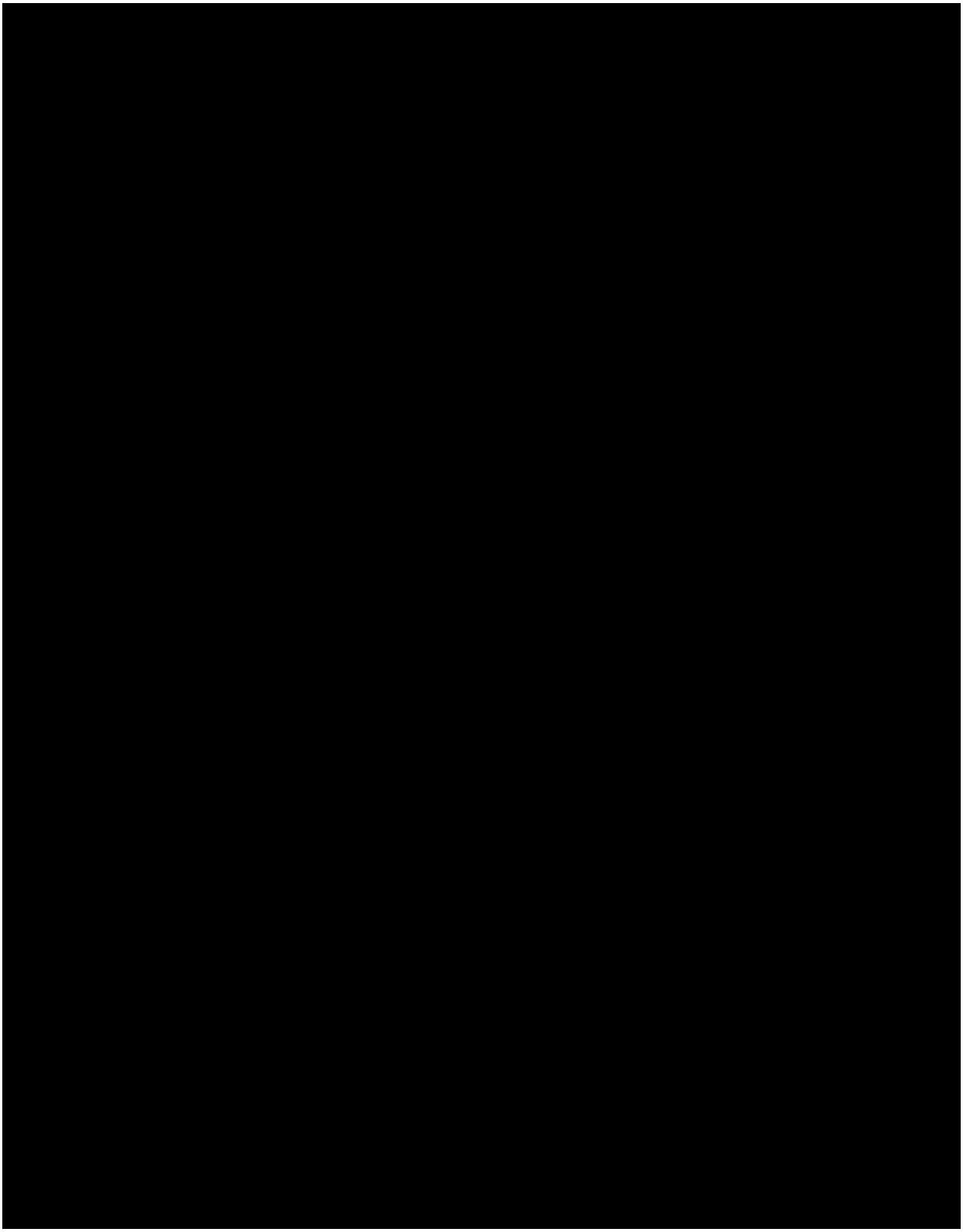
NOVARTIS

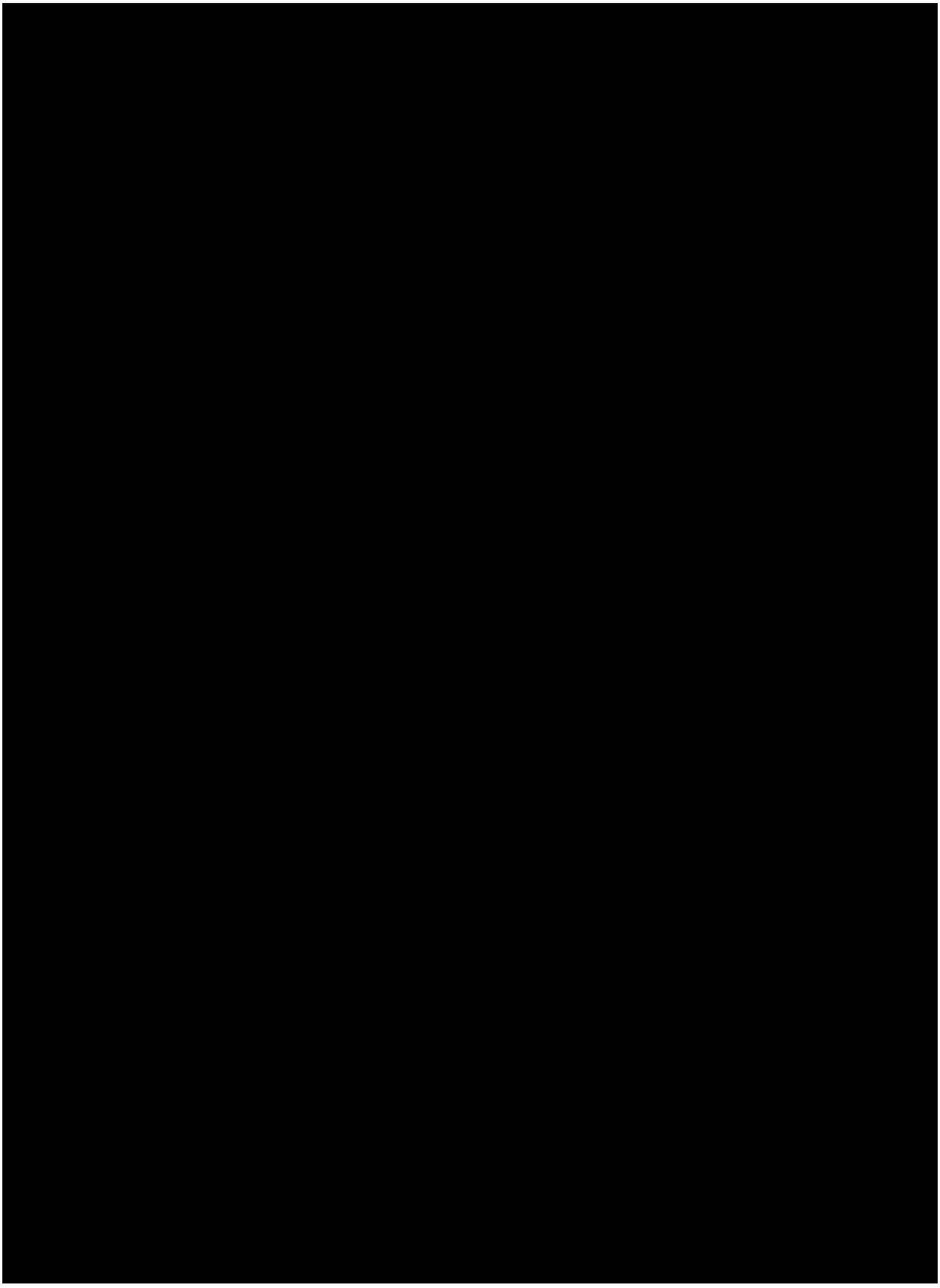


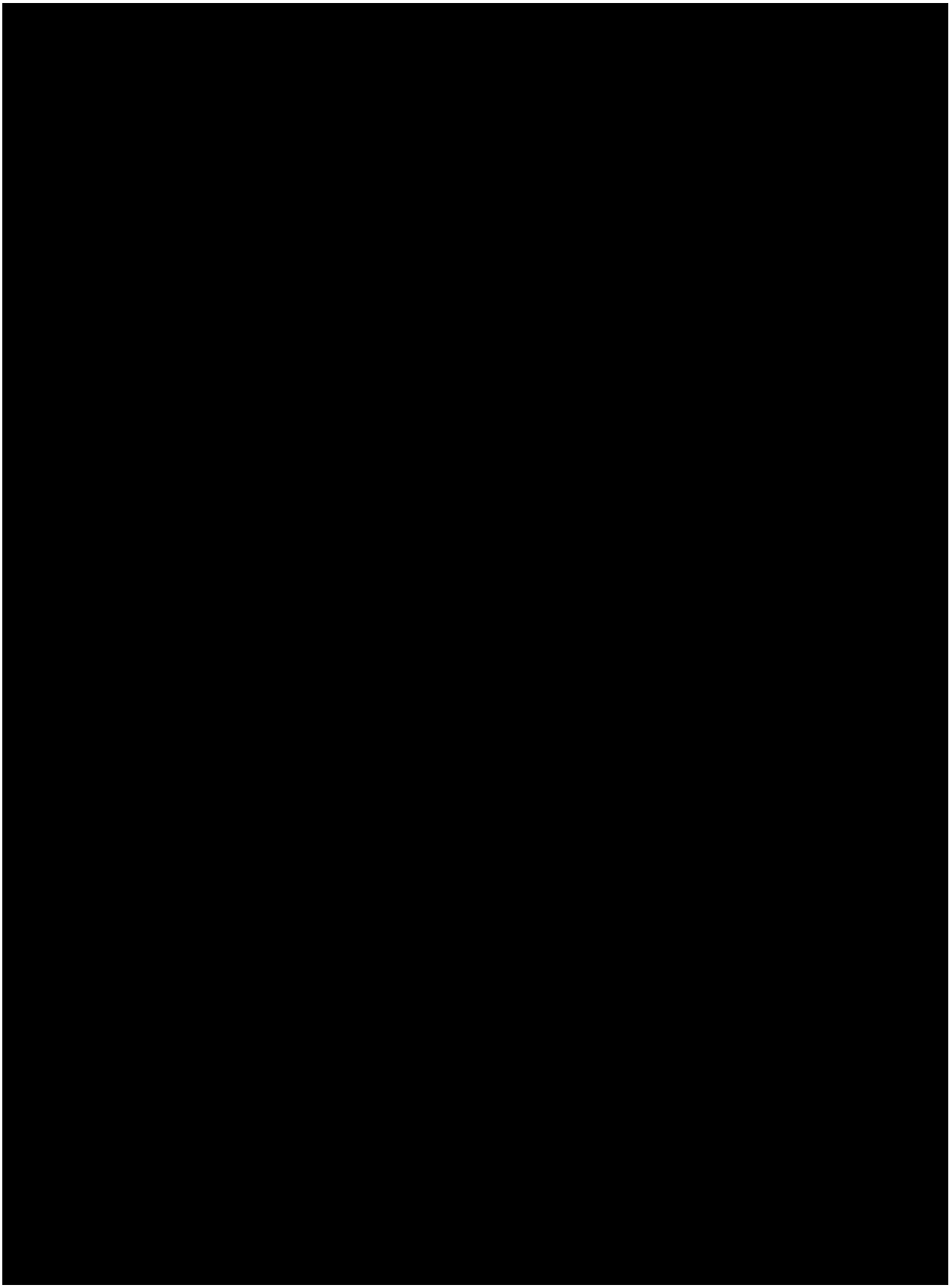
2.12 Biomarkers

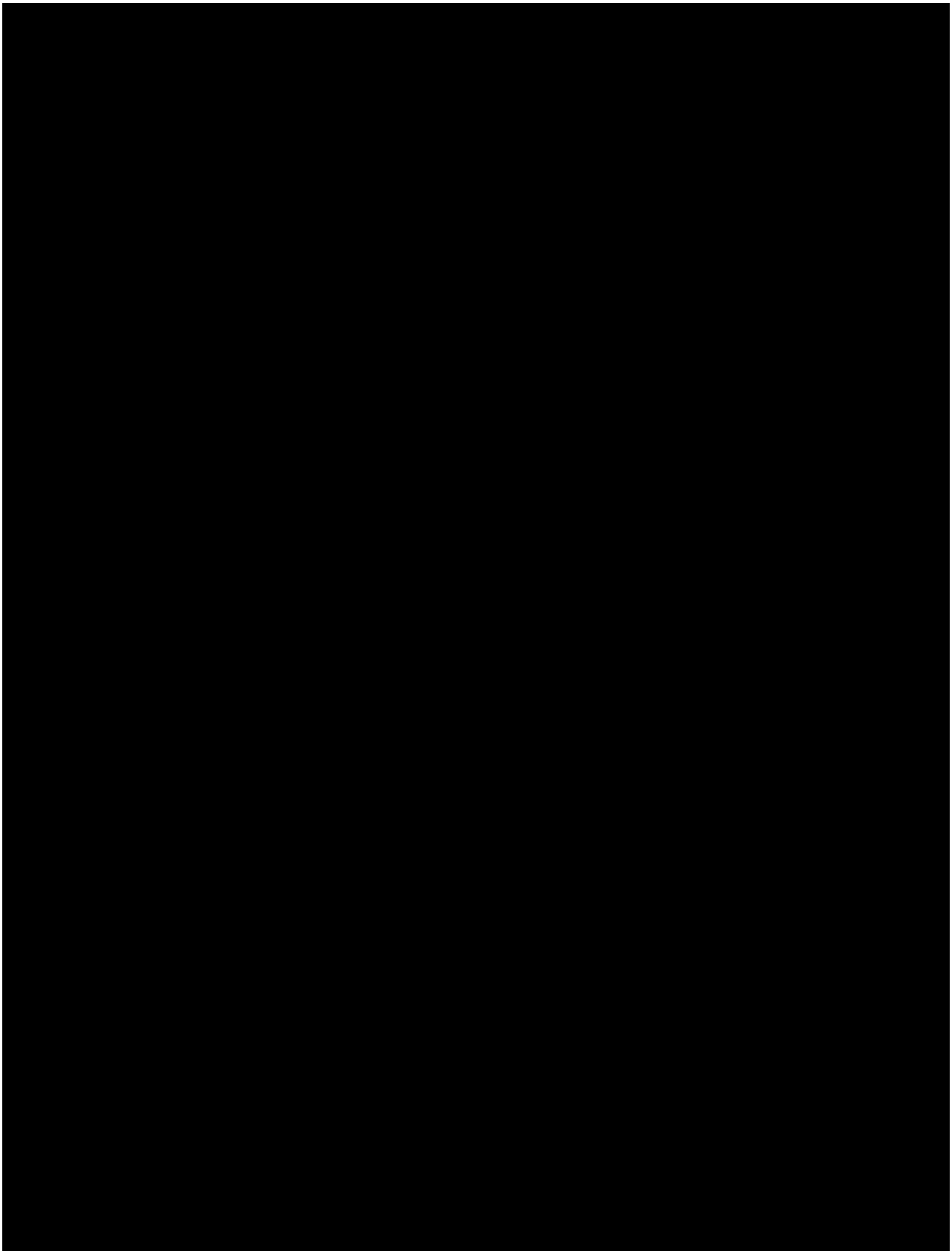
Not applicable.

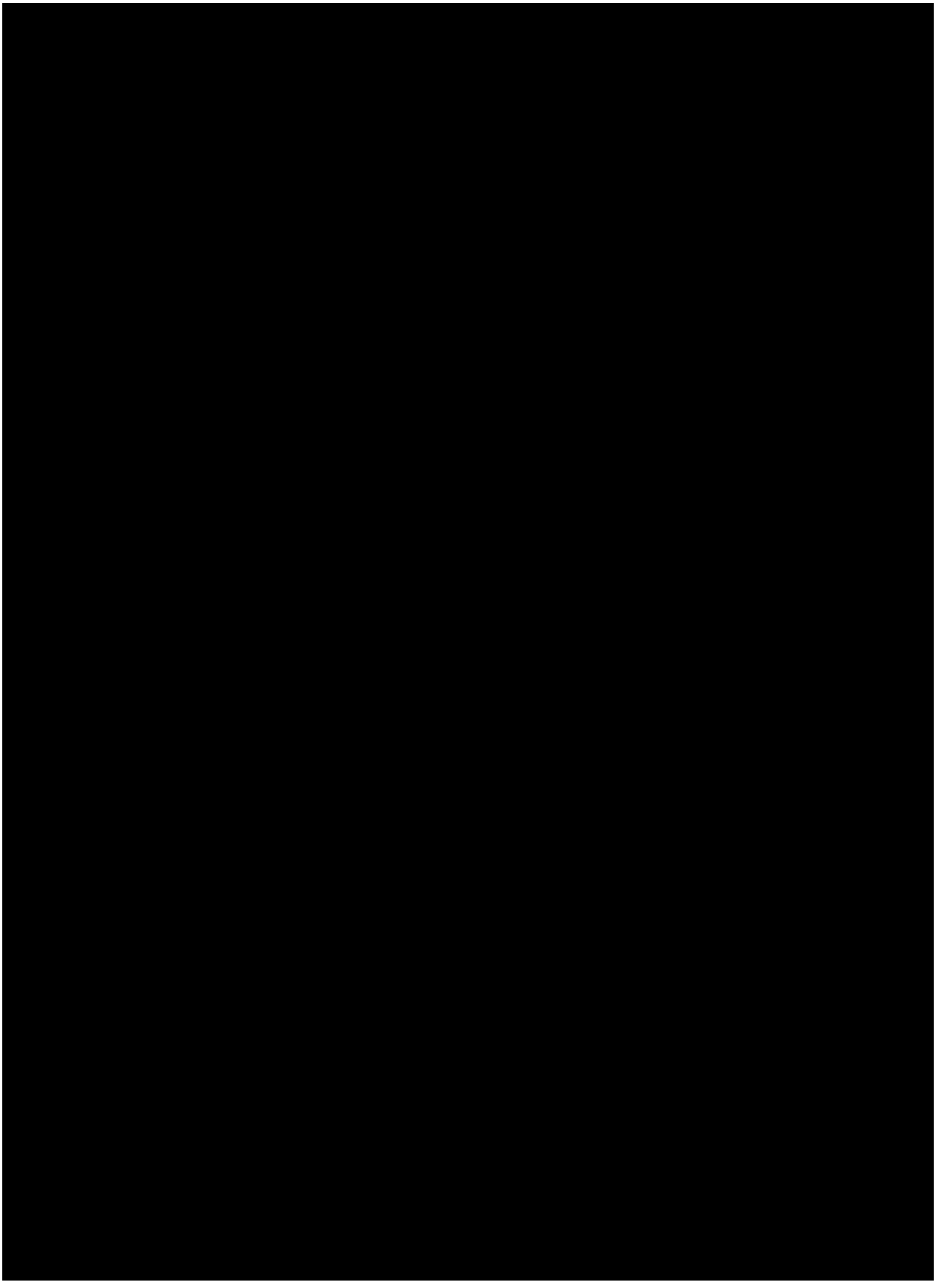


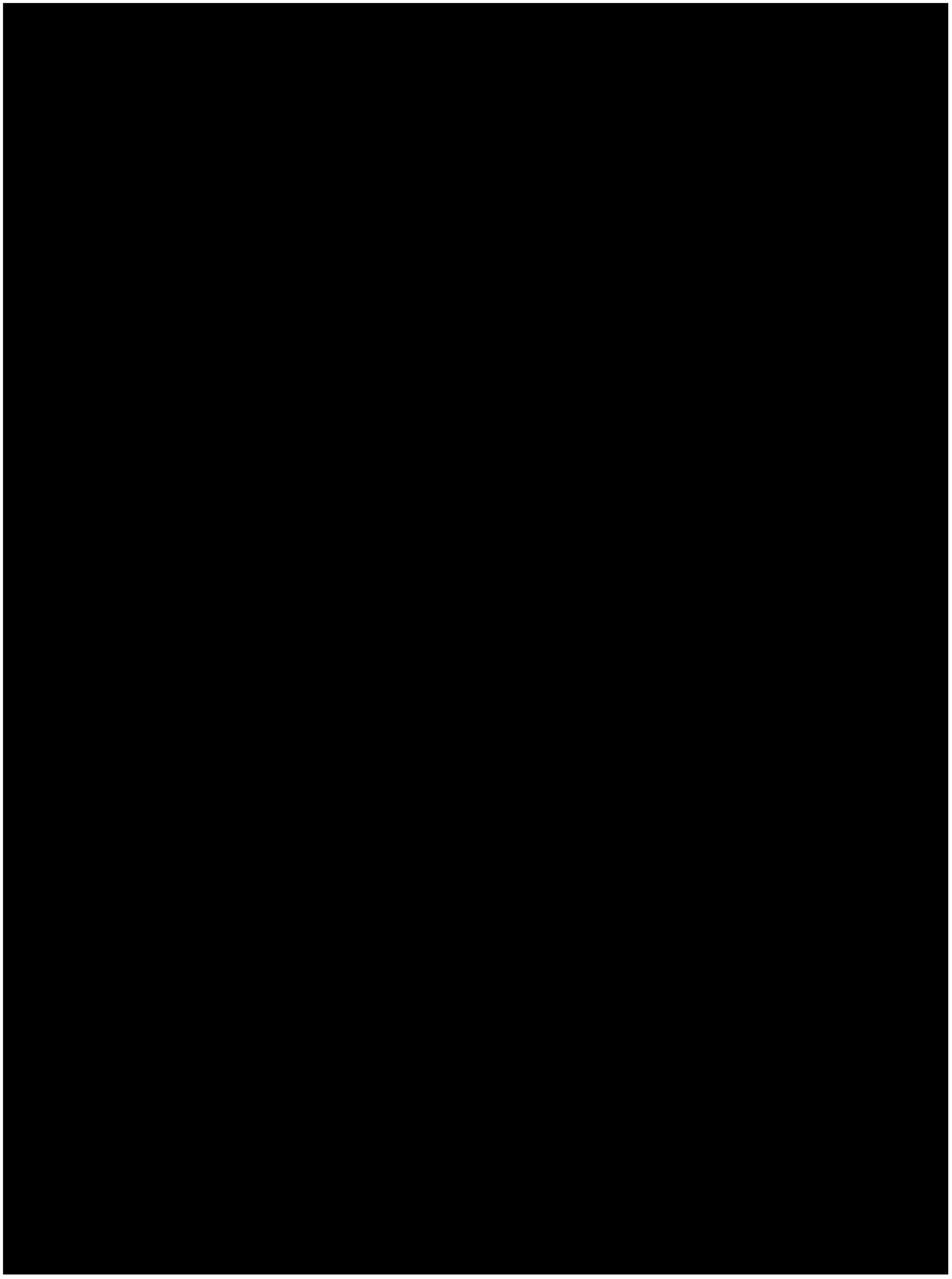


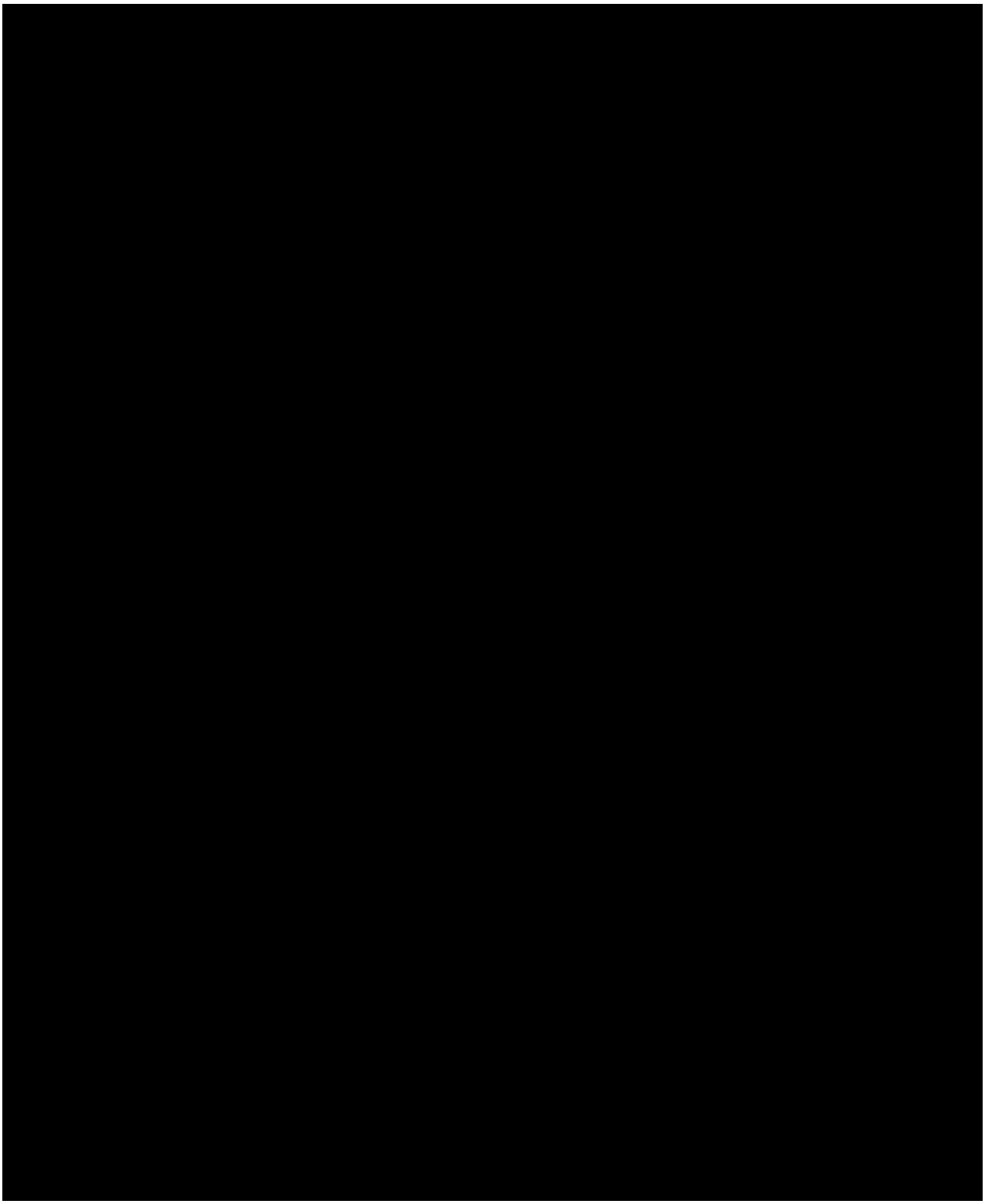


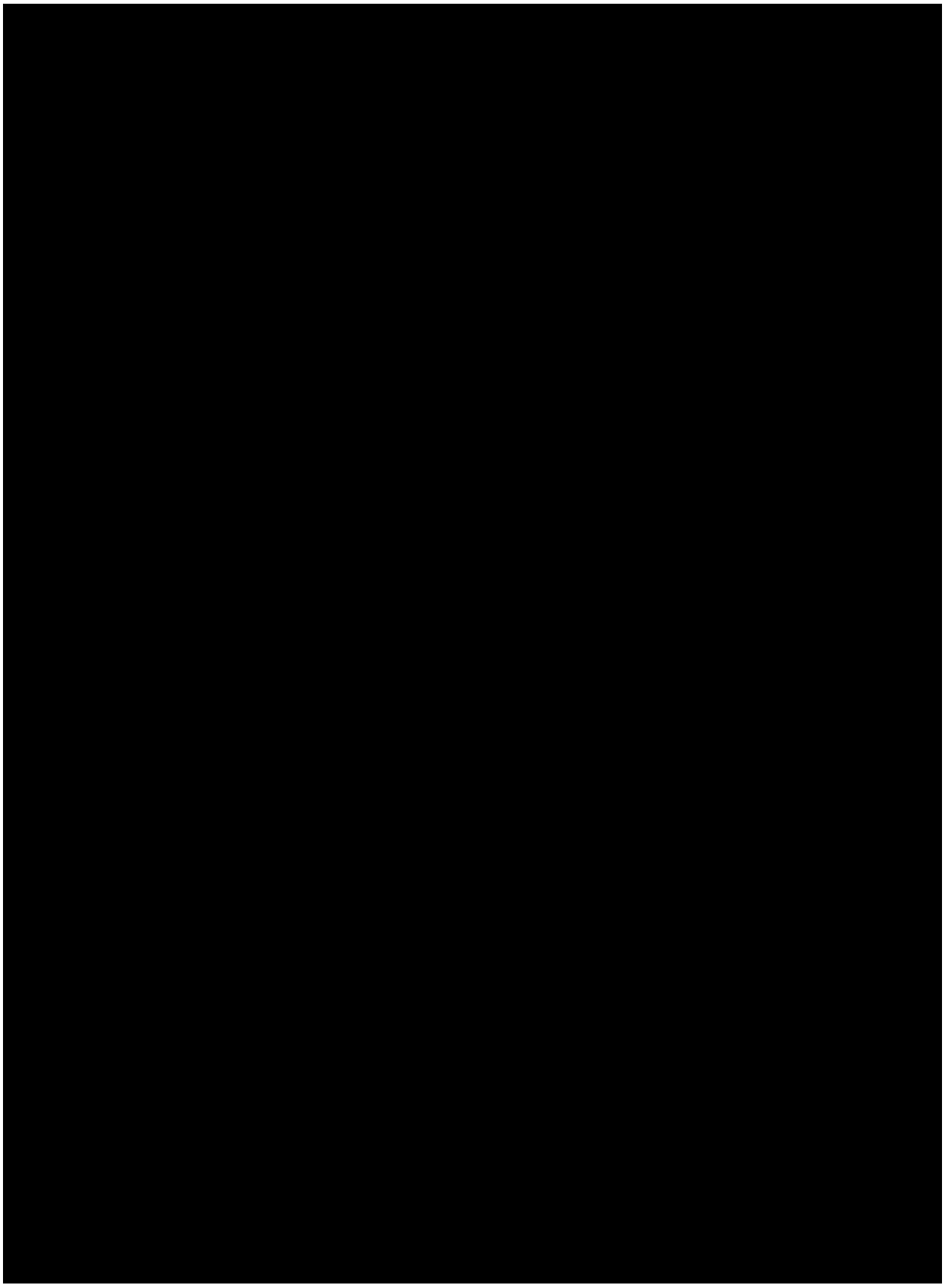












2.14 Interim analysis

The database of this study will be locked twice, first after the end of Treatment Period 1 (Week 16) and again after the end of Treatment Period 2 (Week 52). Data analyses will follow after database lock at Week 16. The main analysis for the primary objective will be done at Week 16. As Week 16 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

3 Sample size calculation

The sample size was calculated based on the primary efficacy variable (i.e., ACR20 response) for the primary comparison (i.e., secukinumab 300 mg versus placebo). ACR20 response rates of 50% for secukinumab 300 mg and 20% for placebo (corresponding to an Odds ratio of 4) at Week 16 were assumed, based on results from AIN457F2312 (FUTURE 2) study. Using a continuity-corrected chi-squared test, an allocation ratio of 2:1, a two-sided significance level of 0.05, and a power of 0.90, approximately 88 patients in secukinumab 300 mg group and 44 patients in placebo group will be needed.

Assuming a loss to follow-up rate of 10% and a 2:2:1 allocation ratio (secukinumab 300 mg: secukinumab 150 mg: placebo), the total number of randomized patients will be approximately 250 (100 on secukinumab 300 mg, 100 on secukinumab 150 mg, and 50 on placebo).

The sample size estimation was done using query Advisor 7.0.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

This section will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

Not applicable

5.1.2 AE date imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSIN	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSIN	**NC** Uncertain	**N C**	**N C**	**N C**
YYYY < TRTY	**(D)** Before Treatment Start	**(C)**	**(C)**	**(C)**
YYYY = TRTY	**(B)** Uncertain	**(C)** Before Treatment	**(A)** Uncertai	**(A)** After Treatment
YYYY > TRTY	**(E)** After Treatment Start	**(A)** After Treatment	**(A)** After Treatment	**(A)** After Treatment

The following table is the legend to the logic matrix.
If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial, AE end date > = Treatment start date or AE is ongoing, then AE start reference = treatment start date.

Relationship	Time imputation

Before AE start reference	Partial date indicates AE start date prior to AE start	
After AE start reference	Partial date indicates AE start date after AE start	
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start	
Imputation Calculation		
NC/Blank	No convention	
(A)	MAX(01MONYYYY, AE start reference+1 day)	
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	
Complete date	No date imputation	If time is captured for the study Case1: if AE start date is not equal to AE start reference then do the following:

Relationship	Time imputation
	If minutes missing then AESTMF = M and time is imputed to hh: 00 If minutes missing then AESTMF = H and time is imputed to 00:00 Case2: if AE start date = AE start reference then AESTMF = H and time is imputed to treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing

Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. if AE end date is not equal to Treatment end date, then do the following:

if minutes missing then time is imputed to hh: 00 if time missing then time is imputed to 00:00

Case 2: if AE end date = Treatment end date then time is imputed to treatment end time
If the AE end date is partial then end time is imputed to 00:00.

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.

5.1.3 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication. The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day		Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	**(C2)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start
YYYY = TRTY	**(C2)** Uncertain	**(A)** Before Treatment Start	**(C1)** Uncertain	**(B)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY

(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ' ' THEN TRTSDT+1
(D)	01JULYYYY
(E)	01JANYYYY

Concomitant Medication End Date Imputation

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31), if month is missing, (C2, D, E)

Imputed date = min (completion/discontinuation visit date, last day of the Month), if day is missing. (A, B, C1)

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.

5.1.3.1 Prior therapies date imputation

Same as above.

5.1.3.2 Post therapies date imputation

Same as above.

5.1.3.3 Other imputations

Same as above.

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

The primary analysis will be performed comparing treatments with respect to the primary

efficacy variable in a logistic regression model with treatment, methotrexate usage at baseline (yes, no), and body weight as explanatory variables.

```
Proc logistic data=aaa;
Class TRT MTX/ param=glm;
Model AVAL= TRT MTX weight;
Lsmeans TRT / diff cl exp;
Ods output diffs=lsm_diff;
Run;
```

Logistic regression will be applied to response variables at each visit.

In cases where logistic regression doesn't converge, Fisher's exact test will be applied for comparisons between AIN457 doses. In this case, no odds ratios or confidence intervals will be estimated, but p-values may be calculated.

```
Proc freq data=aaa;
Table TRT * AVAL / fisher;
Where TRT in ("AIN457 xx mg" "Placebo");
Run;
```

In cases where separation is a concern, e.g. 0% response in one treatment (sub) group, an exact logistic regression model will be applied.

```
Proc logistic data=aaa exactonly;
Class TRT MTX / param=glm;
Model AVAL = TRT MTX weight;
Exact TRT / estimate;
Ods output exactoddsratio=exactoddsratio;
Run;
```

For supportive analysis using Cochran-Mantel-Haenszel (CMH) test to compare treatment adjusting methotrexate usage at baseline, the following code will be used.

```
proc freq data=aaa;
  tables TRT*MTX / cmh;
run;
```

where AVAL= dependent variable
TRT= Treatment
MTX= Methotrexate usage at baseline
Weight= body weight

Multiple Imputation

A multiple imputation will be performed based on MAR with treatment (3 treatment groups), methotrexate usage at baseline (yes, no), and body weight (in kg) as explanatory variables of primary efficacy variable (ACR20 response) for visits up to the primary time point (Week 16) using Markov Chain Monte Carlo (MCMC) method with EM algorithm.

Impute the missing values 100 times (NIMPUTE) with a seed=457<studycode> as shown below:

```
proc mi data= min= max= out=imp minmaxiter=10000000 nimpute=100 seed=457;
        by trt;
        var weight_base mtxuse_base var1_week1-var1_week16;
        mcmc chain=multiple initial=em;
run;
```

Where var1 is the 1st component of ACR and this step will be repeated for every components of ACR, e.g., as follows:

```
proc mi data=imp min=<min of scale> max=<max of scale> out=imp2 minmaxiter=10000000
nimpute=100 seed=457;
        by trt _imputation_;
        var weight_base mxtuse_basevar2_week1-var2_week16;
        mcmc chain=multiple initial=em;
run;
```

The score and ACR response can now be calculated based on the complete data. The response rate will be calculated for each imputation and then combined using Rubin's rules.

In order to calculate the response rate for each imputation, PROC FREQ will be used as follows.

Calculate binomial proportion and standard error for each imputation.

```
proc freq data=<ACR20>;
  by trt visit _imputation_ ;
  tables <response> / binomial (level=2 cl=wilson correct) ;
  ods output BinomialProp=imp_bpr;
run;
```

Transpose the dataset for subsequent use with PROC MIANALYZE.

```
proc transpose data=imp_bpr out=imp_trs(drop=_name_) ;
  by trt visit _imputation_ ;
```

```
  var nvalue1; id name1; idlabel label1;
run;
```

Apply LOGIT transformation: y=log(p/(1-p)) and std. err. transformation: <new se> = se/(p*(1-p))

```
data logit;
  set imp_trs(rename=(_bin_=p e_bin=se));
  by trt visit _imputation_ ;
  lmean=log(p/(1-p));
  lse=se/(p*(1-p));
run;
```

The transformed binomial proportion estimates and standard errors are combined by applying Rubin's rules for multiple imputed data sets.

```
proc mianalyze data=logit;
  by trt visit ;
  modeleffects lmean;
  stderr lse;
  ods output ParameterEstimates=logitres;
run;
```

The combined data should be transformed back using the following formula: p=1/(1+exp(-y))

```
data miexpres;
  set logitres;
  by trt visit ;
  resti = 1/(1+exp(-estimate));
  rlow = 1/(1+exp(-lclmean));
  rupp = 1/(1+exp(-uclmean));
run;
```

Of note, sometimes all responses may be imputed to 0 or 1 at a given combination of response variable, treatment group and visit. Such cases should be considered separately. The combined final response rate would be the same as the original response but the 95% CI will be undefined.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary analysis

Categorical variables will be analyzed using the logistic model, using the code described above.

Continuous variables will be analyzed using an analysis of covariance (ANCOVA) model with treatment, baseline value, methotrexate usage at baseline (yes, no), and body weight as explanatory variables.

```
Proc mixed data=aaa order=internal;
Class TRT MTX;
Model change=TRT MTX BLV weight/ ddfm=kr;
Lsmeans TRT/ cl diff;
Contrast "sec300 vs plb" TRT 1 0 -1/ cl diff alpha=0.05;
Contrast "sec150 vs plb" TRT 0 1 -1/ cl diff alpha=0.05;
Run;
```

For supportive analysis using Cochran-Mantel-Haenszel (CMH) test to compare treatments adjusting for methotrexate usage at baseline, the same code will be used as described above.

5.4.4 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 event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. 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 = $\sum t_j$, (j=1,..., n) 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 θ T 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 and Anwer, 1993; Ulm, 1990):

Lower confidence limit:

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

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.

5.4.5 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:

$$L = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is:

$$U = 100 \times \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

In addition, if L > p x 100 then L = p x 100 and if U < p x 100 then U = p x 100.

5.4.6 Mixed-effects repeated measures model

Change from baseline in log (hsCRP) will be analyzed using mixed-effects model repeated measures (MMRM) with treatment (3 treatment groups), visit, baseline hsCRP, methotrexate usage at baseline (yes, no), and body weight (kg) as explanatory variables. An unstructured covariance structure will be assumed for this model.

SAS code for mixed model:

```
proc mixed data=aaa;
class TRT USUBJID AVISITN;
model CHG=TRT AVISITN WEIGHT BASE
/ s ddfm=kr;
```

```
lsmeans TRT*AVISITN / diff cl;
repeated AVISITN / type=un subject=USUBJID;
run;
```

In case the MMRM model does not converge the following sequential steps will be used:
1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.

2. change type=un to type=cs.

5.5 Rule of exclusion criteria of analysis sets

Table 5.5-1 Protocol deviations that cause subjects to be excluded

Protocol deviation ID	Deviation text description	Severity code	Excluded from analysis set
INCL01	Patients have not signed Informed Consent Form prior to initiation of any study related procedure.	1	Exclude from Full Analysis Set and Safety Set
INCL02A	Age criteria not met.	1	Include in everything
INCL02B	Non-pregnant, Non-lactating female patients.	1	Include in everything
INCL03A	Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline ≥ 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each).	1	Include in everything
INCL03B	Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline < 3 tender joints out of 78 and ≥ 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)	1	Include in everything

INCL03C	Diagnosis of PsA classified by CASPAR criteria and with symptoms for less than 6 months with moderate to severe PsA who must have had Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline ≥ 3 tender joints out of 78 and < 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)	1	Include in everything
INCL03D	Diagnosis of PsA classified by CASPAR criteria and with symptoms for less than 6 months with moderate to severe PsA who must have had Diagnosis of PsA classified by CASPAR criteria and with symptoms for at least 6 months with moderate to severe PsA who must have had at Baseline < 3 tender joints out of 78 and < 3 swollen joints out of 76 (dactylitis of a digit counts as one joint each)	1	Include in everything
INCL04	Subject's target psoriatic skin lesion with a PASI score should be 1 or greater will be included in the study	1	Include in everything
INCL05	RF and/or Anti-cyclic citrullinated peptide (anti-CCP) antibodies should be negative at screening.	1	Include in everything
INCL06	Patients regularly using NSAIDs, as part of their PsA therapy should be on stable dose for at least 2 weeks before randomization to allow inclusion. And, they should remain on a stable dose in the study up to Week 16.	1	Include in everything
INCL07A	Patients taking corticosteroids are on a stable dose of less than or equal to 10mg per day prednisone or equivalent for at least 2W before randomization and should remain on a stable dose up to week 16.	1	Include in everything
INCL07B	Patients taking corticosteroids are on a stable dose of less than or equal to 10mg per day prednisone or equivalent for at least 2W before randomization and should remain on a stable dose up to week 16.	1	Include in everything
INCL08	Patients taking MTX ($\leq$ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before	1	Include in everything

	randomization and must remain on a stable dose up to study completion		
INCL09	Patients on MTX must be on stable folic acid supplementation at randomization	1	Include in everything
INCL10	Patients who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine washout has been performed.	1	Include in everything
EXCL01	Subjects with Chest X-ray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician should not be included in the study.	1	Include in everything
EXCL02	Subjects with previous exposure to Secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor should not be included in the study	1	Include in everything
EXCL03	Subjects in use of any investigational drug and/or devices within 4 weeks before randomization, or a period of 5 half-lives of the investigational drug, whichever is longer should be excluded from the study	1	Include in everything
EXCL04	Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization OR Insufficient washout of prohibited psoriasis treatments: -Oral or topical retinoid are excluded 4 weeks prior to randomization -Photochemotherapy (e.g. PUVA) is excluded 4 weeks prior to randomization -Photoherapy (e.g. UVA or UVB) is excluded 2 weeks prior to randomization -Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency) is are excluded 2 weeks prior to randomization	1	Include in everything

EXCL05	Subjects with history of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes should not be included in the study.	1	Include in everything
EXCL06	Subjects with any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization should not be included in the study	1	Include in everything
EXCL07	Subjects with intra-articular injections therapy (e.g. corticosteroid) within 4 weeks before randomization should not be included in the study.	1	Include in everything
EXCL08	Patients who ever received biological immunomodulating agents those targeting TNF alpha, IL6 and IL12/ IL23 investigational or approved should not be included in the study	1	Include in everything
EXCL09	Patients with previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g.,alemtuzumab, anti-CD4, anti-CD5, anti-CD3, anti-CD19) should not be included in the study.	1	Include in everything
EXCL10	Subjects ,who are pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test should not be included in the study.	1	Include in everything
EXCL11	Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information. Effective contraception methods include: • Total abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception	1	Include in everything

	• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient • Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository • Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception • Placement of an intrauterine device or intrauterine system In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea as defined by Central Lab FSH and/or estradiol levels		
EXCL12	Subjects with active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of Secukinumab therapy, should not be included in the study.	1	Include in everything
EXCL13	Subjects with underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or	1	Include in everything

	gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy should not be included in the study.		
EXCL14	Subjects with significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, should be excluded from the study.	1	Include in everything
EXCL15	Subjects with the history of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin should not be included in the study.	1	Include in everything
EXCL16	Subjects with the history of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L) should not be included in the study.	1	Include in everything
EXCL17	Subjects with total WBC count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85 g/L) at screening should not be included in the study.	1	Include in everything
EXCL18	Subjects with active systemic infections during the last two weeks prior to randomization (exception: common cold) should be excluded from the study.	1	Include in everything
EXCL19A	Subjects with the history of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule	1	Include in everything

EXCL19B	No history of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule	1	Include in everything
EXCL20	Subject with Known infection with human immunodeficiency virus (HIV) or human immunodeficiency virus , hepatitis B or hepatitis C at screening or randomization should be excluded from the study.	1	Include in everything
EXCL21	Subjects with the history of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years should not be included in the study (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)	1	Include in everything
EXCL22	Subjects with current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial.	1	Include in everything
EXCL23	Subject's inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins) should not be included in the study.	1	Include in everything
EXCL24	Subject with any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol should not be included in the study	1	Include in everything
EXCL25	Subject donation or subject with loss of 400 mL or more of blood within 8 weeks before	1	Include in everything

	dosing (randomization) should not be included in the study		
EXCL26	Subjects with the history or evidence of ongoing alcohol or drug abuse, within the last six months before randomization should not be included in the study	1	Include in everything
EXCL27	Subjects who have plans for administration of live vaccines during the study period or 6 weeks prior to randomization should not be included in the study	1	Include in everything
TRT01	Incorrect study medication administered by subject	4	Include in everything
TRT02	Any incorrect route of administration of study drug used at any time during the study, per protocol	4	Include in everything
TRT03	Two records with same "Date of dose" (i.e., Injection A and B)	4	Include in everything
TRT04	At Weeks 16, 28 and 40 patients on secukinumab 150 mg (Group 2) who are responders will continue to receive secukinumab 150 mg (1.0 mL) plus placebo (1.0 mL) every 4 weeks until next evaluation of responder status at weeks 28 or 40.	4	Include in everything
TRT05	Patients who did not meet the responder criteria at Week 16, 28 or 40 will start receiving secukinumab 300 mg s.c.every 4 weeks and will continue this dose up to Week 52.	4	Include in everything
TRT06	Missed or partial doses of study medication administered by subject	4	Include in everything
COMD01	Use of prohibited medication at any time during the study after randomization until Week 16	5	Include in everything
COMD02	Use of prohibited medication with potential impact on key efficacy and/or safety evaluations at any time during the study after Week 16	5	Include in everything
COMD03	subject received a live virus vaccination during the study	5	Include in everything
OTH01	If Date of visit is recorded then the Physician's Global Assessment QSRSFLT at corresponding visits are not expected to be null.	998	Include in everything

OTH02	PASI score is blank when visit date is present and PASI total score is missing.	998	Include in everything
OTH03	If the sex of the subject is Female and the response to "Is subject of child bearing status" is recorded as "Able to bear children" on Demography CRF then the "Date of assessment" Urine pregnancy test CRF is not expected to null at Visits Baseline, Week 4, Week 12, Week 16, Week 32, Week 24, Week 40	998	Include in everything
OTH04	What was the result of the tuberculosis workup? = "Latent" then on prior conmed page, medication with reason 'tuberculosis' (% preferred term) is present with start date prior to <Date of assessment> on tuberculosis assessment page. If false, then Screening disposition page 2 with subject status as Screen Failure should appear.	998	Include in everything
OTH05	Screening and Baseline visits occurred on the same date so eligibility could not be confirmed at time of randomization	998	
OTH06	ICH-GCP non-compliance of study site in the study	998	
OTH07	Failure to perform key study procedures	998	

6 References

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

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