NOVARTIS

Clinical Development

AIN457/Secukinumab

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An open-label, phase III, study of subcutaneous secukinumab to assess efficacy, safety and tolerability at up to 52 weeks in Japanese patients with active Ankylosing Spondylitis

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
6-Feb-2018	Before Week 52 DBL	New version for week 52 and 60 analysis	This is a statistical analysis plan (SAP) for week 52 and 60 analysis. This SAP was developed based on SAP amendment 3 for week 24 analysis.	

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List of abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
[redacted]	[redacted]
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
ASQoL	Ankylosing Spondylitis Quality of Life
ATC	anatomical therapeutic chemical classification system
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMD	bone mineral density
BME	bone marrow edema
BSL	baseline
CD	crohn disease
COX	cyclo-oxigenase
CPO	country pharma organization
CRO	contract research organization
CRP (hsCRP)	(high sensitivity) C-reactive protein
CSR	Clinical Study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMARD	disease modifying anti-rheumatic drug
DXA	dual energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA/EMEA	European Medicines Agency
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
GCP	good clinical practice
GGT	gamma glutamyl transpeptidase
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IBD	inflammatory bowel disease
IEC/EC	Independent Ethics Committee
IFN	interferon
IFU	instructions for use
IG	immunogenicity
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous(ly)
kg	kilogram
LDL	low density lipoprotein
LLN	lower limit normal
LLOQ	lower limit of quantification
[redacted]	[redacted]
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram
MRI	magnetic resonance imaging
MTX	methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
OC/RDC	Oracle clinical/remote data capture
OPG	osteoprotegerin
PCS	Physical Component Summary
PD	phamacodynamics
PFS	pre-filled syringe
PG	pharmacogenetics
PK	pharmacokinetics
PoC	proof- of- concept
PPD	purified protein derivative
PRN	pro re nata
PRO	patient reported outcome
PsA	psoriatic arthritis
QoL	quality of life
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-B ligand
RAP	Reporting and Analysis Process
RBC	red blood cell
RU	Resource Utilization
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCR	screening
s.c.	subcutaneous(ly)
SD	standard deviationSMQ
SOC	System Organ Class
SpA	spondyloarthritis
SUSAR	suspected unexpected serious adverse reaction
t.i.d.	*ter in die*, three times a day
TBL	total bilirubin

TFLs	Tables, Figures, Listings
TNF/TNFα	tumor necrosis factor
TNFα-IR	TNFα inhibitor inadequate responder
ULN	upper limit normal
VAS	Visual Analog Scale
VEs	vertebral edges
WBC	white blood cell
WHO	World Health Organization
WoCBP	women of child-bearing potential
[redacted]	[redacted]

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the data analysis section 9 of the clinical study protocol. The statistical methodology is described below and any deviation from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

The analysis results of this SAP will be presented in the clinical study report (CSR) and first interpretable results (FIR) output.

Study reference documents and versions available at the time of finalization of this SAP are listed in Table 1-1.

Table 1-1 Study reference documents and versions available at the time of finalization of this Statistical Analysis Plan (SAP)

Name of study reference documents	Version
Study protocol	v00(26-Nov-2015)
Standard TFLs	eRAP tool v2.0 and eRAP GenMed Lib_v1.2_31Mar2015G or later
eCRS (Case retrieval sheets)	The definition in the eCRS will be updated continuously. The latest one at the interim and final analyses will be used and the version of the eCRS used for the analyses will be described in a footnote in tables.

1.1 Study design

This multicenter study uses an open-label, single arm design. A screening (SCR) period running 4-10 weeks before baseline (BSL) will be used to assess eligibility followed by 52 weeks of treatment. The treatment periods consist of Treatment period 1 (BSL to week 24) and Treatment period 2 (week 24 to week 52). Week 52 follows a post-treatment follow-up until Week 60. A follow-up visit is to be done 12 weeks after last study treatment administration for all patients, regardless of whether they complete the entire study as planned or discontinue prematurely.

Secukinumab 150 mg s.c. once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4.

In total, approximately 30 patients whose eligibility is confirmed will enter the treatment period. At each study treatment visit patients will receive secukinumab 150 mg s.c. up to Week 48.

Rescue medication will not be allowed until Week 16. However, patients who are deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

The primary efficacy variable is the proportion of patients who achieve the Ankylosing SpondyloArthritis International Society Response Criteria (ASAS 20) at Week 16.

An interim analysis on the efficacy and safety data was performed after all patients have completed Treatment Period 1 (Week 24 visit), and will be performed after all patients have completed Treatment Period 2 (Week 52 visit). Additional analyses may be performed to support Health Authority interactions, as necessary.

1.2 Study objectives and endpoints

The primary objective is to assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline in Japanese patients with active AS based on the proportion of patients achieving an ASAS(Assessment of SpondyloArthritis International Society criteria) 20 response.

The secondary objectives are as follows:

1. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving an ASAS 40 response.
2. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving Bath Ankylosing Spondylitis Disease Activity (BASDAI) 50 response.
3. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)
4. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients meeting the ASAS 5/6 response criteria
5. To assess the efficacy of secukinumab 150 mg s.c at Week 16 relative to baseline based on the change from baseline in total BASDAI
6. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline in SF-36 PCS
7. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline in ASQoL
8. To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving an ASAS partial remission
9. To assess the pharmacokinetics of secukinumab in Japanese patients
10. To assess the development of immunogenicity against secukinumab
11. To assess overall safety and tolerability of secukinumab by vital signs, clinical laboratory values and adverse events (AEs) monitoring

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis. SAS (version 9.4 or later) in GPSII will be used for all analyses in this SAP.

Summary statistics for continuous variables will include the number of patients (N), mean, standard deviation, minimum, median, maximum (lower quartile, upper quartile, if appropriate). Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. The 95% confidence interval will be provided for efficacy variables as appropriate.

The cut-off date of the interim analysis at the applicable Week (e.g., Week 52) will be defined as the date of the last patient visit at the Week. All available data up to the cut-off date will be used in the interim analysis. The analysis results for efficacy variables by week will be presented only up to the applicable week(e.g., in case the Week 52 interim analysis, efficacy results at Week 60 will NOT be presented), while all available results from safety variables will be presented.

2.1.1 General definitions

Study treatment is defined as Secukinumab 150mg in the rest of this document.

In general, a baseline value refers to he last measurement made prior to administration of the first dose of study treatment. Baseline assessments scheduled for and captured on day 1 will be considered baseline measurements regardless of the time of assessment.

The first day of administration of study treatment (first dose) is defined as Study Day 1 or Day 1. All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose]+1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1). The descriptor ”Day 0“ will not be used.

2.1.2 Analysis visit windows

Analysis 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 will be created to cover the complete range of days within the study. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

The analysis visit windows depend on the visit schedule for the assessments and are shown in Table 2-1.

The analysis visit will be used for listing of visit and period.

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. The conventions in Table 2-2 will be used to determine the appropriate measurement to be summarized in the event of multiple measurements within a visit window.

Table 2-1 Analysis visit windows

Analysis Visit	Week	Scheduled Day	Visit window (Day)								
			Variables assessed everyVisit	weight, ECG	Vital signs, LAB	PK	[redacted] ASQoL, SF-36	[redacted] Immunogenicity	[redacted]	Lipids	Cardiovascular panel
Baseline	BSL	1	to 1	to 1	to 1	to 1	to 1	to 1		to 1	to 1
Week 1	1	8	2-11		2-11						
Week 2	2	15	12-18		12-18						
Week 3	3	22	19-25		19-25						
Week 4	4	29	26-43		26-43	2-71	2-43				
Week 8	8	57	44-71		44-71		44-71			2-85	
Week 12	12	85	72-99		72-99		72-99				
Week 16	16	113	100-127	2-239	100-127	72-141	100-141	2-141		86-239	2-141
Week 20	20	141	128-155		128-155						
Week 24	24	169	156-183		156-183	142-267	142-267	142-267			142-267
Week 28	28	197	184-211		184-239						
Week 32	32	225	212-239								
Week 36	36	253	240-267								
Week 40	40	281	268-295		240-323						
Week 44	44	309	296-323								
Week 48	48	337	324-351								
Week 52	52	365	352-393	240-393	324-393	268-393	268-393	268-393		240-393	268-393
Week 60	60	421	394-449	CRF visit	CRF visit	394-449	394-449	394-449		-	-

Variables assessed every visit: Patient's global assessment of disease activity (VAS), Patient's assessment of back pain intensity (VAS), BASFI, BASDAI, Spinal mobility (BASMI Linear + chest expansion), [redacted], hsCRP

Note that safety assessments in Week F60 in the post treatment follow-up period will NOT be mapped to Week 1 – Week 52 of Analysis Visits

Table 2-2 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment. Baseline assessments scheduled for and captured on day 1 will be considered baseline measurements regardless of the time of assessment. In case several measurements are taken on day 1 after the first dose of study treatment, the first one will be used.
Post-baseline efficacy	All data	The measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

2.2 Analysis sets

The following analysis sets will be used in this study:

Full analysis set (FAS): The FAS will be comprised of all patients who entered into the treatment periods.

Safety set: The safety set includes all patients who took at least one dose of study treatment during the treatment periods.

Note that patients not exposed to study drug at any visit (DVSPID = TRT01) will be excluded from the Safety set.

2.2.1 Subgroup of interest

Table 2-3 displays the subgroup of interest and endpoints evaluated based on the subgroups.

Table 2-3 Subgroup of interest and endpoints evaluated

Subgroup of interest	Endpoints
• Previous use of TNF-alpha inhibitors	• Primary and all secondary endpoints • Crude incidence of AE, SAE by SOC and PT
• hsCRP value (≤ 10 mg/L, >10mg/L) at baseline	• Primary and all secondary endpoints
• hsCRP value (≤ 5 mg/L, > 5 mg/L) at baseline	• Primary and selected secondary endpoint (ie, ASAS20 and ASAS 40)
• Age (< 65 yr, ≥ 65 yr) • Gender • Weight (< 70 kg, 70 – 90 kg, > 90 kg)	• Primary and selected secondary endpoint (ie, ASAS20 and ASAS 40) • Crude incidence of AE, SAE by SOC and PT

Note that the threshold value for subgroup analysis of hsCRP (≤ 10 mg/L, >10mg/L), age, and weight is same as the one in CTD Clinical Overview of Secukinumab in Ankylosing Spondylitis in EU and US.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients who entered the screening period will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of patients in the safety set who completed treatment periods, and Post-treatment follow-up, and who discontinued the study prematurely (including the reason for discontinuation) will be presented.

For each protocol deviation (PD), the number and percentage of patients for whom the PD applies will be tabulated for entire period (i.e., all PDs will be presented.) in the safety set.

2.3.2 Demographics and other baseline characteristics

The following common background and demographic variables will be summarized:

Continuous variables:

- Age at the time of informed consent
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

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

Categorical variables:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity
- Smoking status at baseline

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

Patient's global assessment of disease activity and other ASAS components, hsCRP, [redacted], TNF alpha inhibitor inadequate responder, number and previous use (yes/no) of TNF-alpha inhibitor, use (yes/no) and separate dose of methotrexate (mg/week), sulfasalazine (g/day) and systemic corticosteroids (mg/day) at baseline, time since first diagnosis of AS (years), time since onset of inflammatory back pain (years), HLA-B27, [redacted], BASDAI (Total and #2), BASMI (linear), BASMI components (all seven in original units).

Calculation method for dose of systemic corticosteroids is described in 2.4.2.

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

2.3.3 Medical history

Any condition entered on the Relevant medical history / current medical conditions CRF will

be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summaries for cardiovascular

medical history and ankylosing spondylitis medical history will also be provided on the safety set.

Smoking history will be summarized on the safety set.

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

2.4.1 Study treatment / compliance

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

In general, duration of exposure is defined as the time from first dose of study treatment to the end of treatment period. The end of treatment period will be defined as the last dose plus 84 days or last visit (including Week F60 in the Post-treatment follow-up period), whichever occurs earlier, i.e., for patients who discontinued or have their last visit earlier than last dose plus 84 days, the end of study treatment exposure will be the date of the last study visit.

Duration of exposure (days)= (last visit date or last dose date + 84 days whichever comes earlier) − first dose date + 1

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

2.4.2 Prior and concomitant therapies

Prior and concomitant medications will be summarized in separate tables based on the safety set. Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of study treatment and within 84 days after last dose will be a concomitant medication, including those which were started pre-baseline and continued into the treatment periods.

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.

Prior surgeries and procedures are defined as surgeries and procedures done prior to first dose of study treatment. Any surgeries and procedures done between the day of first dose of study

treatment and within 84 days after last dose will be concomitant surgeries and procedures, including those which were started pre-baseline and continued into the period where study treatment is administered.

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

The number and percentage of patients receiving prior and concomitant ankylosing spondylitis therapy (disease-specific therapy) will be presented by category for medication preferred term on the safety set. The category is "Topical glucocorticoids", "Systemic glucocorticoids", "Nonsteroidal anti-inflammatory drugs", "Tumour necrosis factor alpha inhibitor", and "Other ankylosing spondylitis medication". Glucocoriticoids in the eCRF page will be devided into two; Topical one and Systemic one based on whether the Route (CMROUTE in SDTM) is Topical or not. The category for NSAIDs will be specified based on whether the data is from the NSAIDs CRF page or not.

At a minimum, methotrexate, sulfasalazine and systemic corticosteroid intake at baseline (Day 1) will be presented based on the amount taken per time unit, e.g. mg/day. Since different steroids have different strengths the following multiplication factors will be used to convert a dose in mg into a prednisone equivalent dose in mg:

Cortisone (0.20), hydrocortisone (0.25), prednisolone (1.0), triamcinolone (1.25), methylprednisolone (1.25), dexamethasone (6.67), betamethasone (8.33) (corticosteroid converter website).

The reported dose and frequency of intake will be converted into the desired units. If the frequency is missing or specified as 'per needed', 'unknown', 'once', 'other' or if the dose or dose unit is missing, then the medication will not be part of the presentation.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary efficacy variable is the proportion of patients who achieve an ASAS 20 at Week 16. The analysis of the efficacy variable will be based on the FAS.

The ASAS response measures consist of the following assessment domains (Sieper, 2009):

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale. For ASAS response analyses, the total back pain will be used.
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale

4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

5. Spinal mobility represented by the BASMI lateral spinal flexion assessment
6. C-reactive protein (acute phase reactant)

The ASAS Response Criteria (ASAS 20) is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain.

The ASAS20 response will be evaluated in subgroups based on previous use of TNF-alpha inhibitors,hsCRP value (≤10 mg/L, >10mg/L, and ≤ 5 mg/L, > 5 mg/L) at baseline, age (< 65 yr, ≥ 65 yr), gender, weight (< 70 kg, 70 – 90 kg, > 90 kg) at baseline.

2.5.2 Statistical hypothesis, model, and method of analysis

A frequency table with the number and percentage of patients achieving an ASAS 20 at Week 16 will be presented. Because of the small number of patients in this study, the efficacy results will be presented in a descriptive manner. Neither statistical model nor statistical hypothesis is defined.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS 20 up to Week 52 will be handled as follows:

1. Patients who drop out of the trial for any reason will be considered non-responders from the time they drop out
2. Patients who do not have the required data to compute response (e.g. ASAS components) at baseline and at the specific time point will be classified as non-responders.

2.5.4 Supportive analyses

For binary efficacy variables, the percentage will be calculated based on the number of patients with an assessment at the analysis visits in the FAS (observed case analysis).

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

Not applicable

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

ASAS 40 at Week 16

The ASAS 40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.

Total BASDAI and BASDAI 50 at Week 16

The BASDAI consists of a 0 through 10 scale (1 being no problem and 10 being the worst problem), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (Q5 and Q6 above) is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score (total BASDAI). Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 secs and 2 mins to complete.

At least 4 questions should be non-missing to calculate the BASDAI score. Otherwise, the BASDAI score will be regarded as missing (Haywood 2002). If both Q5 and Q6 are missing or one of Q1 to Q4 is missing the total sum should be divided by 4 instead of 5. If two of Q1 to Q4 is missing and both Q5 and Q6 are not missing the sum should be divided by 3.

The BASDAI50 is defined as a 50% improvement over the initial total BASDAI (Braun, 2003; Rudwaleit, 2004).

hsCRP at Week 16

This assessment will be performed in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

ASAS 5/6 at Week 16

The ASAS 5/6 improvement criteria is an improvement of ≥20% in at least five domains.

SF-36 PCS at Week 16

See Section 2.11 Patient-reported outcomes.

ASQoL at Week 16

See Section 2.11 Patient-reported outcomes.

ASAS partial remission at Week 16

The ASAS partial remission criteria is defined as a value not above 2 units in each of the domains 1 to 4 on a scale of 10.

Pharmacokinetics of secukinumab in Japanese patients

See Section 2.9 Pharmacokinetic endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

Given the small number of patients in this study, the efficacy results will be presented in a descriptive manner. Neither statistical model nor statistical hypothesis is defined.

ASAS 40 at Week 16

A frequency table with the number and percentage of patients achieving an ASAS 40 at Week 16 will be presented.

BASDAI 50 at Week 16

A frequency table with the number and percentage of patients achieving a BASDAI 50 at Week 16 will be presented.

hsCRP at Week 16

For the change in hsCRP at Week 16, since evidence from the literature would suggest that the data is not normally distributed (Huffman, 2006), summary statistics will be provided on the $\log_e$ ratio of the treatment value vs. baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) to normalize the distribution of hsCRP. Summary statistics for the observed values and the change from baseline at Week 16 will be presented.

ASAS 5/6 at Week 16

A frequency table with the number and percentage of patients achieving an ASAS 5/6 at Week 16 will be presented.

Total BASDAI at Week 16

Summary statistics for the observed values and the change from baseline at Week 16 will be presented.

SF-36 PCS at Week 16

See Section 2.11 Patient-reported outcomes.

ASQoL at Week 16

See Section 2.11 Patient-reported outcomes.

ASAS partial remission at Week 16

A frequency table with the number and percentage of patients achieving an ASAS partial remission at Week 16 will be presented.

Pharmacokinetics of secukinumab in Japanese patients

See Section 2.9 Pharmacokinetic endpoints.

2.7.3 Handling of missing values/censoring/discontinuations

These handlings for binary efficacy variables up to Week 52 will be the same as described in 2.5.3. For binary efficacy variables, the observed case analysis (the percentage calculated based on the number of patients with an assessment at the analysis visits in the FAS) is also performed as the supportive analysis.

Missing values for continuous efficacy variables will not be imputed. Summary statistics will be presented based on all data available at the analysis visits.

2.8 Safety analyses

Summaries will be performed for entire treatment period in the Safety set.

2.8.1 Adverse events (AEs)

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

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

The crude incidence of treatment emergent adverse events will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in 5.4.4. In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for entire treatment period described below.

- Primary SOC level for AE
- Primary SOC and PT level for SAE

- Level 1 for risks and SMQ

AEs will be summarized by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). AEs reported will be presented in descending frequency according to its incidence in all patients starting from the most common event. 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 patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be presented for AEs possibly related to study treatment, death, serious adverse events (SAEs), SAEs possibly related to study treatment, AEs leading to discontinuation and AEs leading to temporary dose interruption.

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.

In addition, crude incidence of AEs will be derived by 3 months intervals (only the first occurrence will be counted in case of multiple occurrences.)

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

MedDRA version used is the latest one at the analysis performed and will be specified in the subsequent SAP by clinical database lock as applicable.

Based upon the clinical information disclosure requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term in the safety set population.

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

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

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

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

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

2.8.1.1 Adverse events of special interest / grouping of AEs

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

The crude incidence and exposure-adjusted incidence rates (only for level 1) will be summarized. In addition, listings will be provided presenting which patients experienced which risk.

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

2.8.2 Deaths

A listing for deaths will be presented. The listing will include trial period when death occured, and whether the death is on treatment, post-treatment follow-up, or screening will be identified.

2.8.3 Laboratory data

The general guideline for laboratory summaries(including Vital sign and ECGs) are as below:

- 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: using CRF visits (including early discontinued patients), i.e., not applying visit window and cut-off day 84. Summary of follow up visit outputs will be provided. 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.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry, and urinalysis). In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

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 test 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 parameter, the maximum change (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed analogously.

In addition, shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within entire 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 parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-3: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

These summaries will be split into hematology and chemistry.

Table 2-4 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	
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 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
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 entire treatment period 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.

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

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

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

Table 2-5 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 laboratory criteria**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.

Notes:

1) In studies which enroll 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

2) In case an Adjudication Committee is in place it may be meaningful to summarize all abnormalities classed as e.g., *definitely/probably* (depending on the categories used) related to study treatment

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 patient with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

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

Box plots will be presented for selected laboratory parameters: WBC, neutrophils, and liver (ALP, AST, ALT, bilirubin) and lipid (cholesterol, HDL, LDL, triglycerides) parameters.

2.8.4 Other safety data

2.8.4.1 ECG

Summaries of ECG are presented for all "on-treatment" data (see section 2.8.3).

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

QTc will summarized by computing the number and percentage of patients with:

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

Summary statistics will be presented for ECG variables by visit.

In addition, shift tables comparing baseline ECG interpretation (normal, abnormal, not available, total) with the worst on study interpretation (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-patient listing of all quantitative ECG parameters.

2.8.4.2 Vital signs

Summaries of vital signs are presented for all "on-treatment" data (see section 2.8.3).

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. 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

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

Table 2-6 Criteria fornotable 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

Data of patients with newly occurring notable vital signs abnormalities will be listed in an additional listing.

2.8.4.3 Immunogenicity

A patient listing of immunogenicity (anti-AIN457 antibodies) will be presented.

2.9 Pharmacokinetic endpoints

All patients with concentration data will be included in the pharmacokinetic data analysis.

Pharmacokinetic variables

Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit. In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for derivingthe geometric mean and CV (%) is as following:

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

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed. All data will be listed.

Statistical methods for pharmacokinetic analyses

Pharmacokinetic data of the study treatment will be analyzed with a population pharmacokinetic mixed effects model. The analysis will be based on a pooled data set, including pharmacokinetic samples from previous studies. The modeling approach will be further detailed in a modeling plan. Results will be reported separately.

2.10 PD and PK/PD analyses

An indirect response model, driven by study treatment concentration, will be used to characterize the time course of efficacy response. Further details of the modeling approach will be specified in a modeling plan. Results will be reported separately.

2.11 Patient-reported outcomes

The following patient-reported outcomes will be summerized. In general, the derived scores will be calculated when all variables for calculating the scores are non-missing otherwise specified.

For binary efficacy variables, analyses with the non-rensponder imputation described in 2.5.3 and with observed case will be performed.

SF-36

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. The SF-

36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients. SF-36 scoring will be done by an independent vendor.

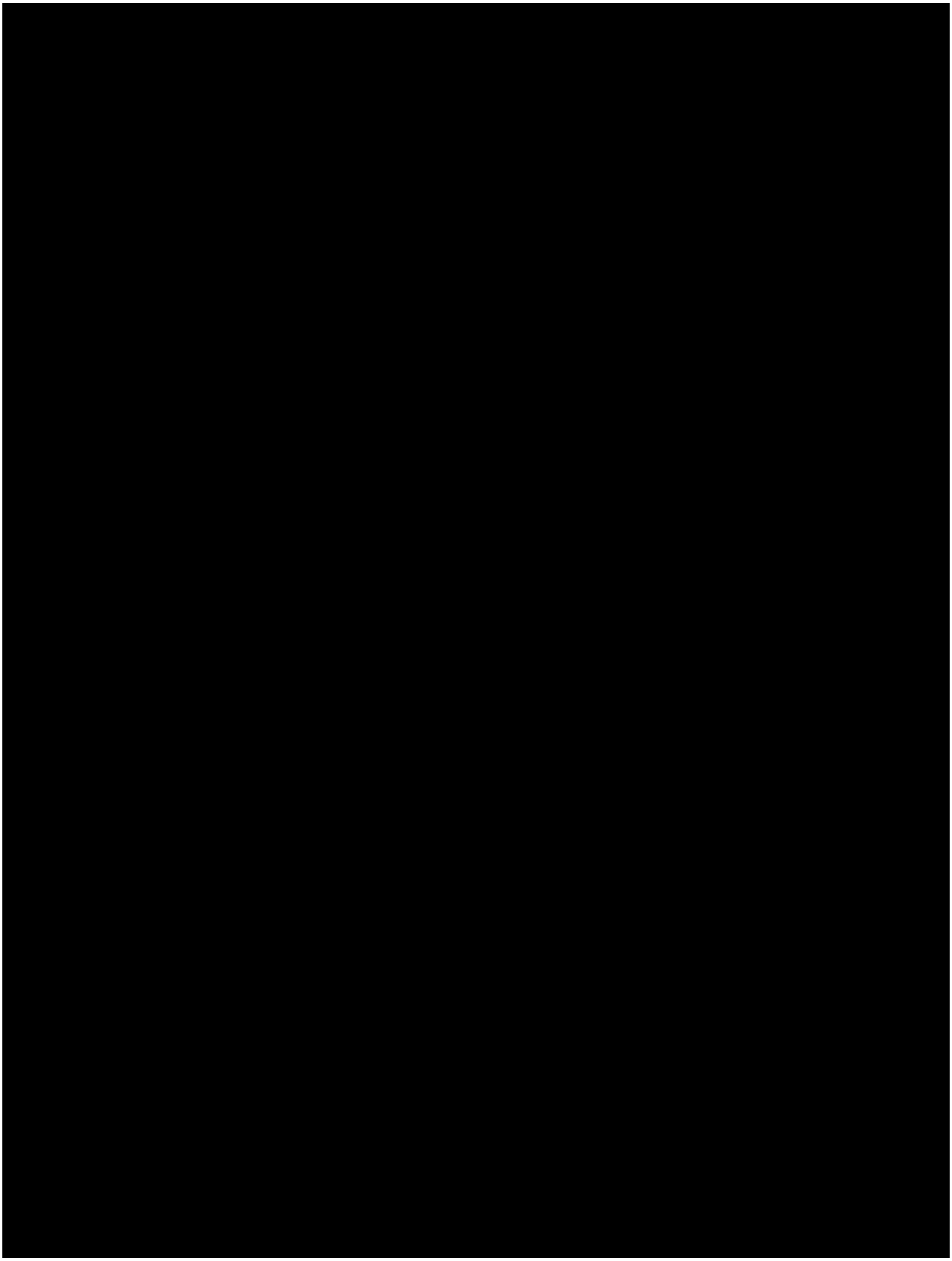
The following variables will be evaluated:

- SF-36 domain scores (based on a scale of 0-100).
- SF-36 PCS and MCS scores (norm-based scores).
- SF-36 PCS and MCS responder (improvement of ≥ 2.5 points, Lubeck 2004)

ASQoL

The ASQoL is a self-administered questionnaire designed to assess health-related quality of life in adult patients with Ankylosing Spondylitis. The ASQoL contains 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity). As such, lower score indicate better quality of life. Items include an assessment of mobility/energy, self-care and mood/emotion. The recall period is "at the moment," and the measure requires approximately 6 minutes to complete.

At least 15 answered questions are required to be able to calculate ASQoL using mean imputation, 18*(sum of answered)/(number answered) (Doward, 2003)



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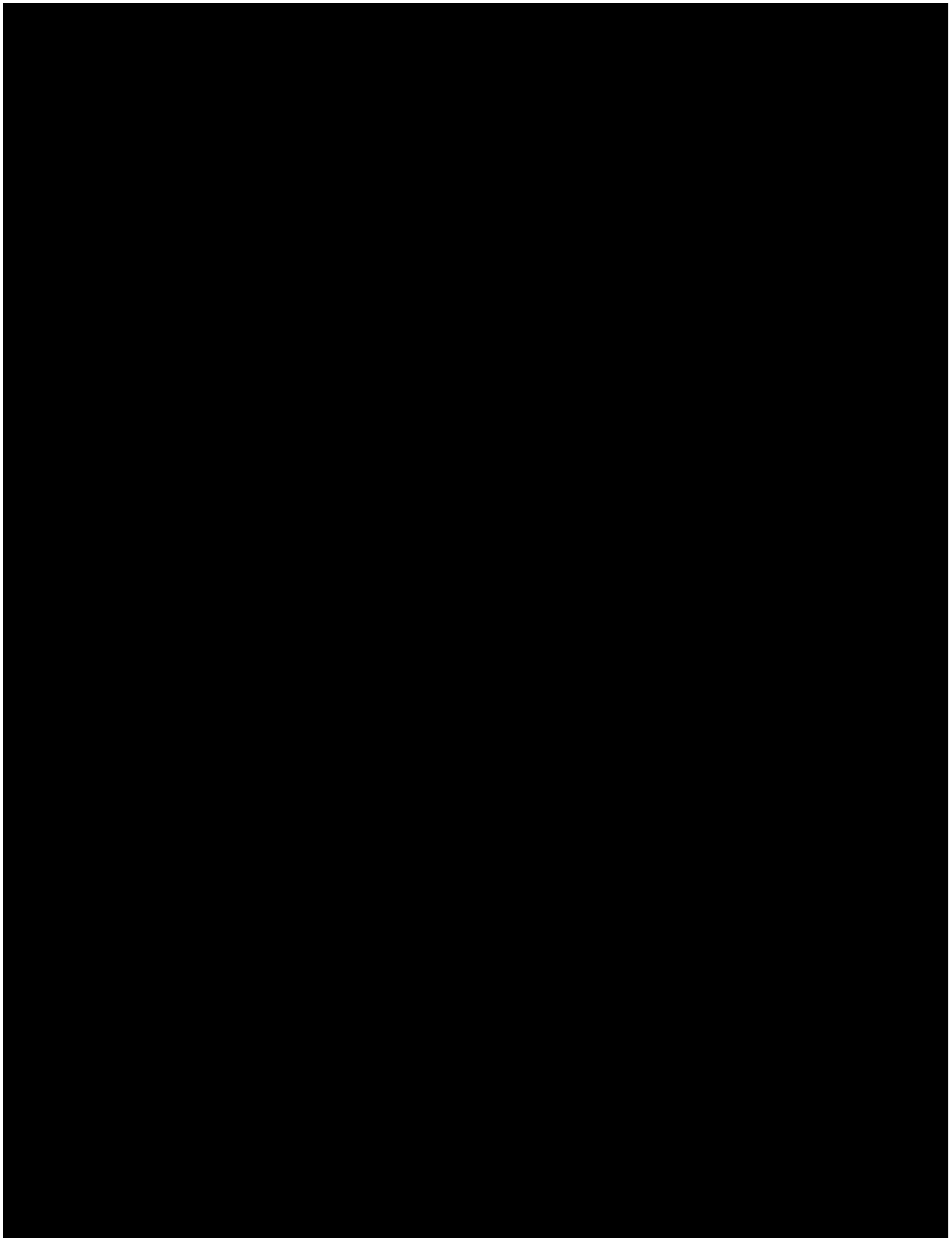
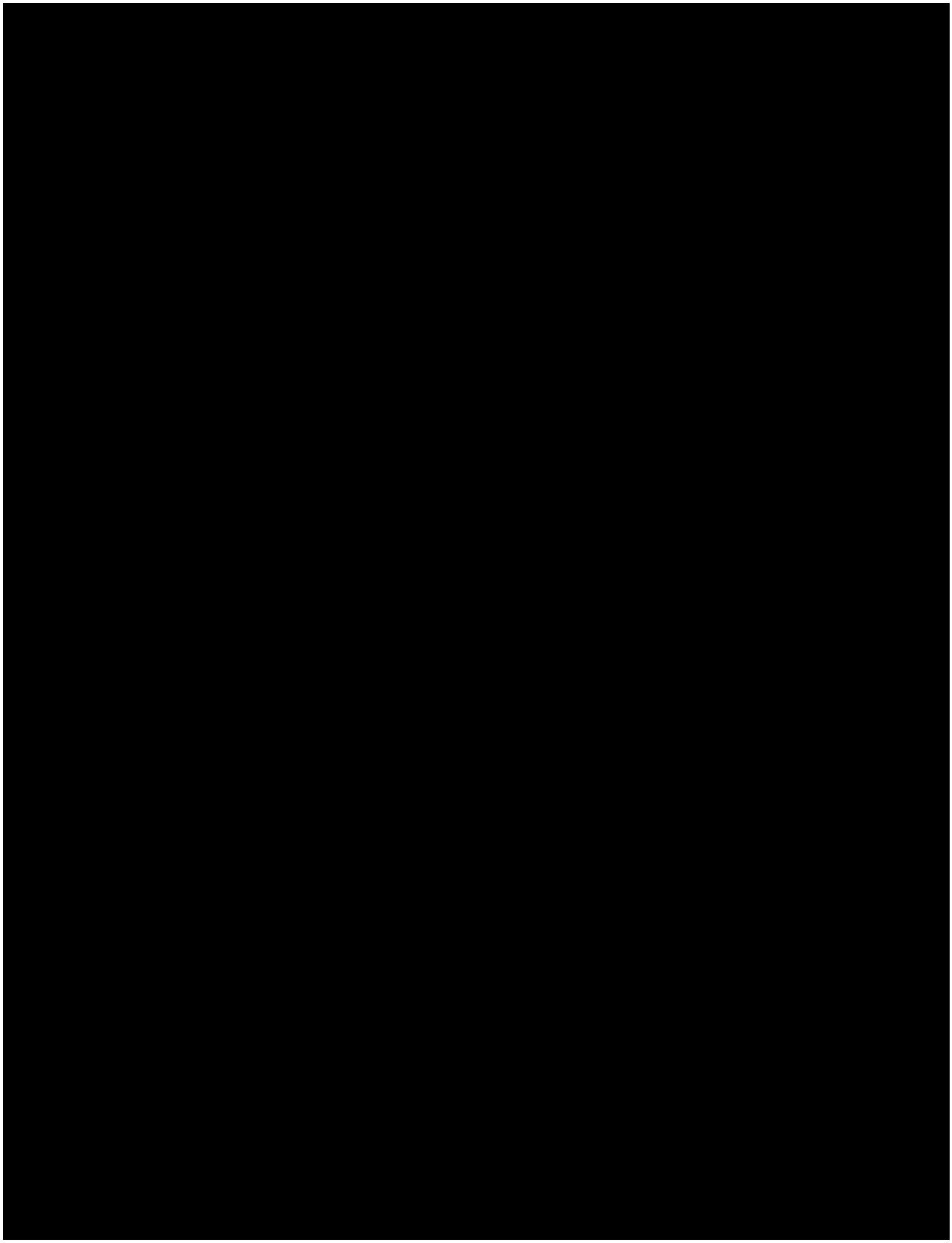
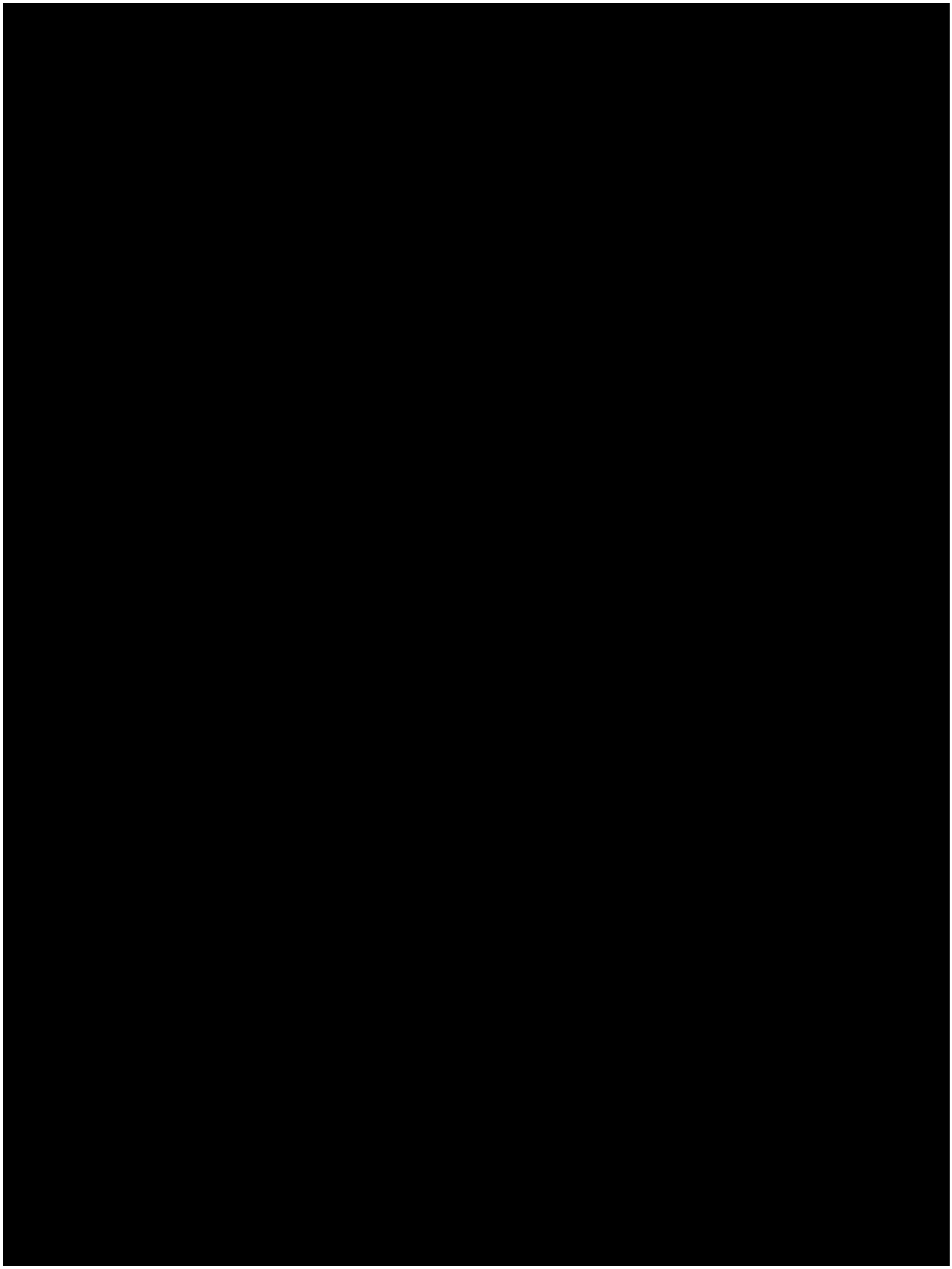
2.12 Biomarkers

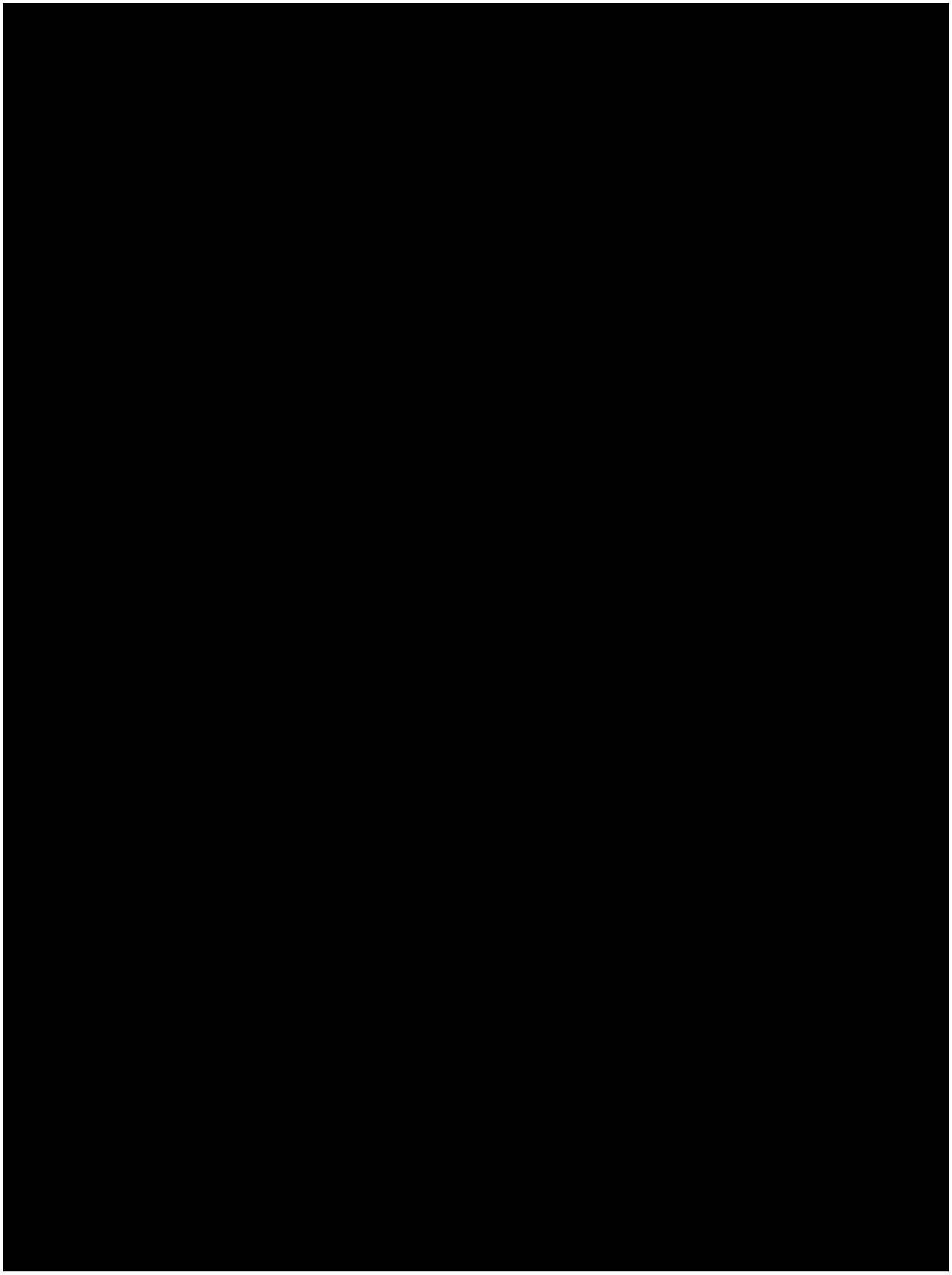
Not applicable.

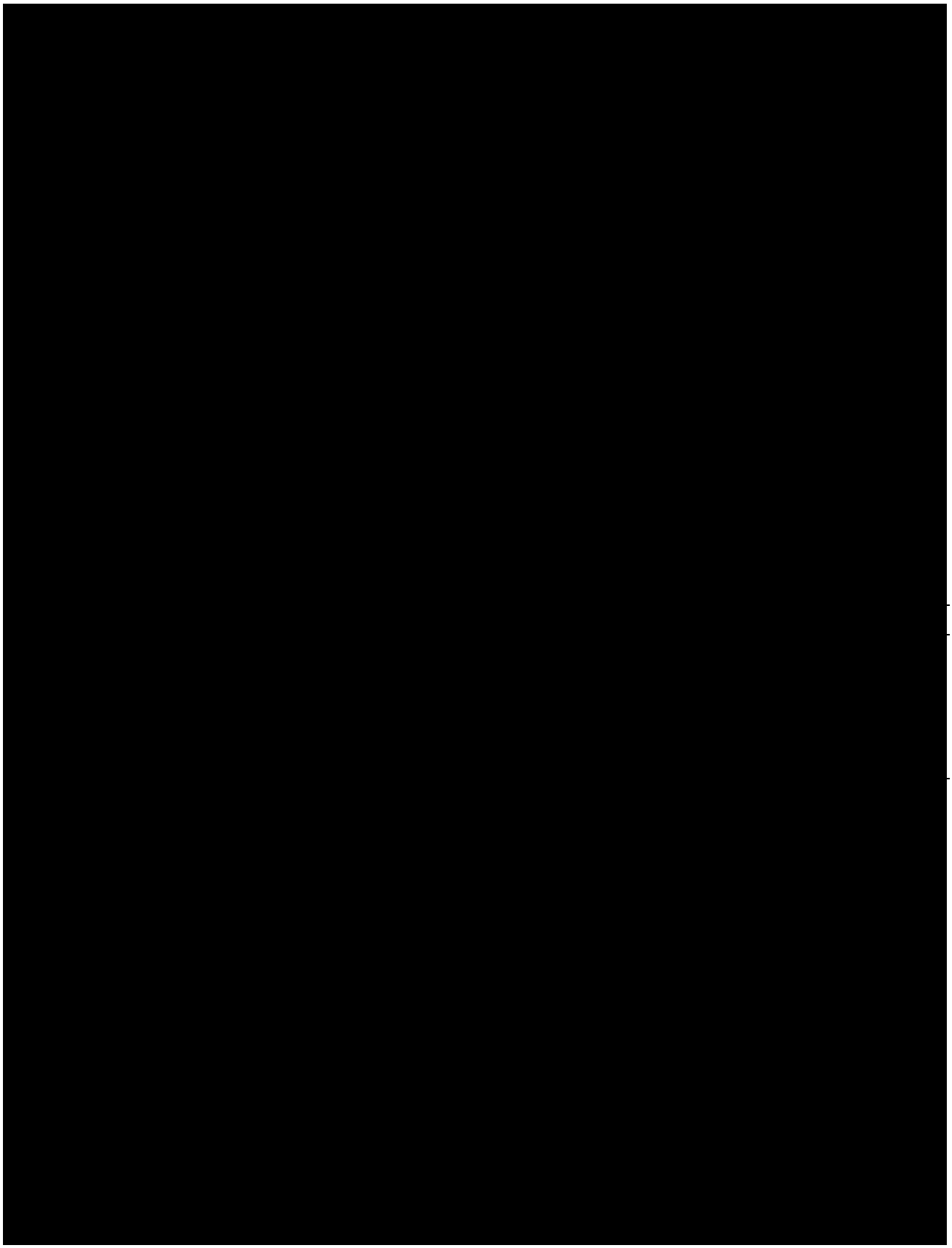
[redacted]











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2.14 Interim analysis

An interim analysis on the efficacy and safety data has been performed after all patients have completed the Treatment Period 1 (Week 24 visit), and will be performed after all patients have completed the Treatment Period 2 (Week 52 visit), in order to support regulatory filing. Additional analyses may be performed to support Health Authority interactions, as necessary.

3 Sample size calculation

With a very low prevalence of AS in Japan (0.0065%), it is expected that approximately 30 patients will be enrolled in this study based on the feasibility assessment. With 30 patients and assuming an ASAS20 response rate of 60% at week 16 (F2310), the estimated lower limit of 95% confidence interval for the ASAS20 response rate in Japanese population treated with secukinumab 150 mg s.c. will be approximately 42.5%, which is well above the upper limit of the 95% confidence interval for the response rate of control group derived in F2310 (ASAS20 response: 28.4%, Confidential Interval: 18.1-38.7).

4 Change to protocol specified analyses

There is no change.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

In case of missing date of study treatment, the date of the visit in which the missing date occurs will be imputed.

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.

Note, it may happen that the imputed AE start is after AE end date.

Table 5-1 Convention for imputation rule for AE start date

	Day	Month	Year
Partial adverse event start date	Not used	MON	YYYY
Treatment start date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Table 5-2 Imputation algorithm for AE start date

	MON missing	MON < TRTM	MON = TRTM	MON > TRTM
YYYY missing	NA			
YYYY < TRTY	01JULYYYY	15MONYYYY		
YYYY = TRTY	TRTSDT + 1	15MONYYYY	TRTSDT + 1	01MONYYYY
YYYY > TRTY	01JANYYYY	01MONYYYY		

AE end date will not be imputed.

5.1.3 Concomitant medication date imputation

The following table explains the notation used in the logic matrix for the partial start date of the concomitant medication (CMD). Please note that missing start dates will not be imputed.

Note, it may happen that the imputed CMD start date is after CMD end date.

Table 5-3 Convention for imputation rule for concomitant medication start date

	Day	Month	Year
Partial concomitant medication (CMD) Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Table 5-4 Imputation algorithm for concomitant medication start date

	MON missing	MON < TRTM	MON = TRTM	MON > TRTM
YYYY missing	NA			
YYYY < TRTY	01JULYYYY	15MONYYYY		
YYYY = TRTY	*	15MONYYYY	*	01MONYYYY
YYYY > TRTY	01JANYYYY	01MONYYYY		

* if CRF pages specify the date is prior to TRTSDT, then TRTSDT -1: otherwise TRTSDT + 1.

Concomitant medication end date will not be imputed.

5.2 AEs coding/grading

Please see section 2.8.1.

5.3 Laboratory parameters derivations

Normal ranges for differential count of leukocytes (absolute value) will be as follows:

Table 5-5 Normal ranges for differential counts of leukocytes

Laboratory test name	(Low, High) (Unit)
Basophils (absolute)	(0.0, 0.2) (x 10E3/uL)
Eosinophils (absolute)	(0.0, 0.7) (x 10E3/uL)
Lymphocytes (absolute)	(1.0, 4.0) (x 10E3/uL)
Monocytes (absolute)	(0.1, 0.9) (x 10E3/uL)
Neutrophils (absolute)	(1.6, 7.4) (x 10E3/uL)

5.4 Statistical models

5.4.1 Primary analysis

Summary statistics for binary and categorical data

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

With as $(1 - \alpha/2)$-quantile of the standard normal distribution (SAS: z = PROBIT$(1 - \alpha/2)$, n as total number of patients (i.e. number of patients in the denominator), and p as estimated crude incidence (number of patients 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 then L = p and if U < p then U = p.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary analysis

See Section 5.4.1 Primary analysis.

5.4.4 Safety analysis

Crude incidence and related risk estimates

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

For n patients, 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 patients 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) as Section 5.4.1.

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

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

It will be assumed that for each of n patients 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 treatment period or last dose plus 84 days whichever occur earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as $\lambda = D/T$, where $T = \sum_{j=1}^{n} t_j$ and D is the number of patients 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.

5.5 Rule of exclusion criteria of analysis sets

No exclusion criteria will be defined.

6 Reference

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