NOVARTIS

Clinical Development

AIN457/Secukinumab/Cosentyx®

CAIN457ADE11C / NCT03765788

A randomized, parallel-group, double-blind, placebo controlled, multicenter phase 2 trial to investigate the safety and efficacy of secukinumab (AIN457) in patients with giant cell arteritis (TitAIN)

Statistical Analysis Plan (SAP) Amendment 1

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Document History

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
26-Mar-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
15-Jul-2021	Prior to DB lock	Minor editorial changes	Amendment 1	
		Updated age categories to align with Clinical Disclosure Office reporting requirements; Added summary of the two subgroups of interest.		Section 2.3.2 Demographics and other baseline characteristics
		Clarified that the addition of 84 days is only applicable to study treatment.		Section 2.4.1 Study treatment / compliance
		Clarified that a patient is non-adherent if the patient takes prednisolone treatment for GCA for < 80% of the 26-week prednisolone taper regimen period.		Section 2.5.1 Primary endpoint
		Clarified that prednisolone refers to prednisolone for GCA. Clarified that the prednisolone done will be regarded as 0 mg/day if there are no prednisolone for GCA records and the patient is still in the study.		Section 2.7.2 Statistical hypothesis, model, and method of analysis
		Clarified that as blood pressure will be assessed for both arms, the average of the available blood pressure assessments will be summarized/listed.		Section 2.8.4.1 Vital signs

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Updated text to refer to 5 rather than 3 categories.		Section 5.4.1 EQ-5D
		Added a table to show the precoded item values.		Section 5.4.3 SF-36

Table of contents

List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
AIS	Aggregate Improvement Score
ATC	Anatomical Therapeutic Classification
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CDBL	Clinical Database Lock
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSR	Clinical Study Report
CTT	Clinical Trial Team
CV	Coefficient of Variation
CWS	Cumulative Worsening Score
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Sheet
EQ-5D	EuroQol-5D
ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Score
FAS	Full Analysis Set
GCA	Giant Cell Arteritis
[redacted]	[redacted]
IA	Interim Analysis
IA1	First Interim Analysis
IA2	Second Interim Analysis
IA3	Third Interim Analysis
LOQ	Limit of quantitation
MAP	Master Analysis Plan
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
MTX	Methotrexate
OR	Odds ratio
PCS	Physical Component Summary
PD	Pharmacodynamics
PFS	Prefilled syringe
[redacted]	[redacted]
PGA	Patient’s Global Assessment
PhGA	Physician’s Global Assessment
[redacted]	[redacted]

PMR	Polymyalgia rheumatica
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RAS	Randomized Analysis Set
RD	Risk difference
RR	Risk ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SD	Standard Deviation
SF-36	Short Form 36
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
VAS	Visual Analog Scale
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis for the clinical study report (CSR) for CAIN457ADE11C according to Section 9 of the study protocol (version no. 3 including Amendment 3) along with any additional analyses, specifications or deviations from this protocol planned before unmasking of the data. Determination of the sample size is specified in Section 3.

This document is written in the future tense. The CSR results will be used to provide information to support a phase III program of secukinumab in patients with giant cell arteritis (GCA).

The following documents were used to support the creation of this SAP:

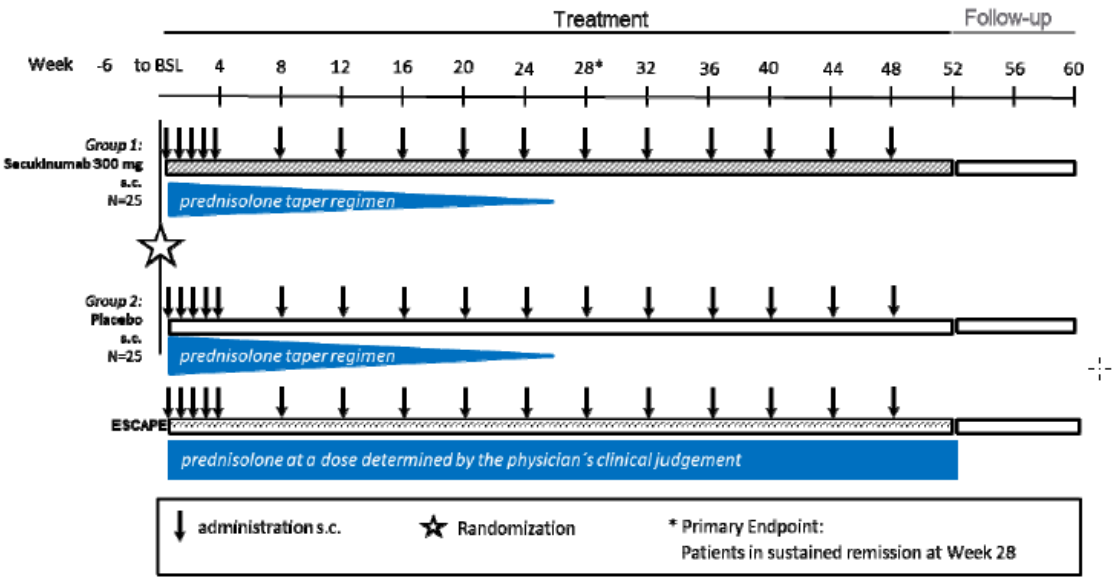
- Study protocol (version no. 3 including Amendment 3)
- Case report forms (CRFs) (version 9)
- AIN457 efficacy master analysis plan (MAP) M3 Amendment 5
- AIN457 safety master analysis plan (MAP) M3 Amendment 5

1.1 Study design

This is a randomized, parallel-group, double-blind, placebo-controlled, multicenter, phase II study designed to evaluate the efficacy of secukinumab compared to placebo in combination with a 26-week prednisolone taper regimen in terms of sustained remission in patients with newly diagnosed or relapsing GCA who are naïve to biological therapy.

The study will consist of 6-week (maximum duration) screening period, a 52-week treatment period and an 8-week safety follow-up period (Figure 1-1).

Figure 1-1 Study design



Patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere to the prednisolone taper regimen will enter "escape". Upon entering "escape", patients will receive prednisolone at a dose determined by the physician's clinical judgment and continue to receive secukinumab or placebo in a blinded manner. Patients in "escape" should continue to attend all subsequent scheduled visit assessments.

As outlined in the protocol, most flares occurred within the first 6 months in the GiACTA trial (Stone et al 2017). Therefore, the time point for the primary analysis of this study is at Week 28, to evaluate the effect of secukinumab in patients who are on study treatment or placebo for 24 weeks.

At the randomization visit (Baseline) all eligible patients will be given a randomization number that assigns them to one of the following 2 arms in a 1:1 ratio:

- Group 1: secukinumab 300 mg s.c. + 26-week prednisolone taper regimen
- Group 2: placebo s.c. + 26-week prednisolone taper regimen

The patient randomization list was produced by or under the responsibility of Novartis Biometry using a validated system ensuring assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme was reviewed and approved by a member or delegate of the Novartis Biometry Randomization Group. It is planned to randomize at least 25 patients per treatment group.

Patients will receive secukinumab/placebo at Baseline, Week 1, 2, 3, 4, then every 4 weeks thereafter through to Week 48 (last dose) at the study center. Assessments will be performed in accordance to the study schedule. Patients in both groups will follow the protocol-defined prednisolone taper regimen.

In total, three interim analyses (IAs) will be conducted unless deemed unwarranted by the study team:

- First interim analysis (IA1): after approximately 50% of patients reach Week 28
- Second interim analysis (IA2): after approximately 50% of patients reach Week 52
- Third interim analysis (IA3): 100% of patients reach Week 28

The analyses for each of the aforementioned IAs are detailed in separate SAPs.

1.2 Study objectives and endpoints

The following table (Table 1-1) is an overview of the study objectives and endpoints.

Table 1-1 Study objectives and endpoints

	Objective	Endpoint
Primary	• To evaluate the efficacy of secukinumab compared to placebo, in combination with a 26-week prednisolone taper regimen, based on the proportion of patients with GCA who have sustained remission.	• Proportion of GCA patients in sustained remission at Week 28

	Objective	Endpoint

Secondary	• To evaluate the efficacy of secukinumab in combination with a 26-week prednisolone taper regimen versus placebo in patients with GCA, measured by the following:
	  • Remission rate at Week 12
	  • Time to first flare after remission
		• Remission rate at Week 12
		• Time to first GCA flare after Baseline (up to Week 52)

	• Cumulative corticosteroid dose up to Week 28 and up to Week 52	• Total cumulative prednisolone dose over 28 weeks and 52 weeks
	• Proportion of patients with GCA who have sustained remission	• Proportion of GCA patients in sustained remission at Week 52
	• Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19, 28, 52	• Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19, 28 and 52
	• Changes from baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52 for each of the following:	• Changes from Baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52 for each of the following:
	• Physician's Global Assessment (PhGA), Visual Analog Scale (VAS)	• PhGA, VAS

	• Patient-reported outcomes (PROs)
	  • Patient's Global Assessment (PGA), VAS
	  • Functional Assessment of Chronic Illness Therapy Fatigue Score (FACIT-Fatigue)
	  • Short Form 36 (SF-36)
	  • EuroQoL-5D (EQ-5D)
		• PROs
		  • PGA, VAS
		  • FACIT-Fatigue
		  • SF-36
		  • EQ-5D

	• Laboratory parameters (Baseline vs. Week 28 and 52):
	  • C-reactive protein (CRP)
	  • Erythrocyte sedimentation rate (ESR)
		• Change from Baseline in CRP and ESR at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52

	• To evaluate the safety/ tolerability and immunogenicity of secukinumab in patients with newly diagnosed or relapsing GCA	• Safety and tolerability assessments over time: incidence and severity of adverse events (AEs) and serious AEs (SAEs)

[redacted]

2 Statistical methods

2.1 Data analysis general information

This study will be conducted under the sponsorship of Novartis. The analysis will be performed by Novartis NBS CONEXTS or a designated contract research organization (CRO) (if applicable).

All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version), unless otherwise noted.

The independent statistical and statistical programming team will perform the unblinded statistical analyses. These analyses are detailed in the respective data monitoring committee (DMC) and IA SAPs.

Data will be summarized with respect to demographic and other baseline characteristics along with safety observations.

Descriptive statistics (the number of non-missing observations [n], mean, median, standard deviation [SD], minimum, and maximum values) will be presented for continuous variables.

For categorical variables, the number and percentage of each category within a variable will be calculated for non-missing data. If a count of zero is obtained for categorical data, only the zero count will be displayed. If no treatment group satisfies a category, then the category will be

displayed, unless stated otherwise. A row (category) denoted 'Missing' will be included in count tabulations if a non-zero count of missing values is present. In addition, the corresponding percentage for this row will be displayed.

All data will be listed by center and subject number, unless otherwise stated.

It is planned that the data from all centers that participate in this study will be used so that an adequate number of patients will be available for analysis.

2.1.1 General definitions

2.1.1.1 Treatment

Study treatment

At Baseline, patients will be assigned to one of the following two arms in a 1:1 ratio:

- Group 1: secukinumab 300 mg subcutaneous (s.c.) + 26-week prednisolone taper regimen
- Group 2: placebo s.c. + 26-week prednisolone taper regimen

The study treatment is secukinumab 300 mg supplied in prefilled syringes (PFS) each containing 150 mg of secukinumab, or placebo supplied in PFS to match secukinumab dose.

Co-administered treatment

The co-administered treatment refers to prednisolone tablets for tapered oral administration (taper regimen from a dose of 25 mg to 60 mg at Baseline to 0 mg at Week 28). Prednisolone will be supplied as 1 mg, 5 mg, 10 mg, 20 mg tablets.

Note: Prednisolone may continue to be taken after the 26-week prednisolone taper regimen.

2.1.1.2 Date of first administration of treatment

Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment was administered and recorded on the "Dosage Administration Record-Investigational Product" electronic CRF (eCRF).

Date of first administration of co-administered treatment

The date of first administration of co-administered prednisolone treatment is defined as the first date when a non-missing dose of co-administered prednisolone treatment was administered and recorded on the "Dosage Administration Record-Prednisolone" eCRF.

Note: A patient may have a "0" dose as part of the prednisolone dosing taper regimen.

2.1.1.3 Date of last administration of treatment

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment was administered and recorded on the "Dosage Administration Record-Investigational Product" eCRF.

Date of last administration of co-administered treatment

The date of last administration of co-administered prednisolone treatment is defined as the last date when a non-missing dose of co-administered prednisolone treatment was administered and recorded on the "Dosage Administration Record-Prednisolone" eCRF.

Note: A patient may have a "0" dose as part of the prednisolone dosing taper regimen.

2.1.1.4 Safety observation period

The safety observation period (days) for treated patients begins at the first administration of study treatment within this study (refer to Figure 1-1). It finishes at:

- the date of the Month X visit for patients that attend it (for patients who have not discontinued study treatment or study prior to the Month X visit)
- the latest day in the window for the Month X visit for patients who have not discontinued (study treatment or study) prior to the Month X visit but do not attend that visit
- the date of the last visit (including the study discontinuation visit) for patients who have discontinued study treatment prior to the Month X visit

where Month X is the last scheduled visit in the study.

Safety observation period (days) is defined as:

- (date of last administration of study treatment - date of first administration of study treatment) + 85 (i.e. 84 days after last administration of study treatment)

2.1.1.5 Study day

The study day for a baseline or post-baseline scheduled or unscheduled visit is defined as:

- Study day = (Date of visit) - (Baseline date) + 1

For visits prior to baseline, the study day is defined as:

- Study day = (Date of visit) - (Baseline date)

2.1.1.6 Baseline date

Baseline date is referred to as Day 1 of the study. It is defined as the date of first administration of study treatment in this study for treated patients. If a patient is randomized but not treated then the baseline date is defined as the date of randomization.

2.1.1.7 Baseline and post-baseline definitions

The baseline value for efficacy and safety variables is the last available, non-missing, (scheduled or unscheduled) value collected prior to first administration of study treatment.

Some baseline assessments may be recorded on the day of the Baseline visit (Visit 3/Week 0). However the time of each of these assessments may not be recorded in the eCRF. In this case, only the assessments which, according to the protocol, should have been conducted pre-dose on Day 1 will be assumed to have been done prior to administration of study treatment on Day 1 when deriving baseline values recorded on the day of the Baseline visit (Visit 3/Week 0).

All data collected after the Baseline date are defined as post-baseline.

2.1.1.8 Coefficient of variation

The coefficient of variation (CV) will be calculated as:

- (SD/mean)*100

2.1.1.9 Geometric coefficient of variation

The geometric CV will be calculated as:

- sqrt(exp(variance of log-transformed data)-1)*100

2.1.1.10 Geometric mean

The geometric mean will be calculated as:

- exp((sum of log transformed data) / number of non-missing data points after log transformation)

2.1.1.11 Change from baseline and relative change from baseline definitions

Change from baseline and relative change from baseline will only be summarized for patients with both baseline and post-baseline data for the relevant visit and will be calculated using the following formulae:

- Change from baseline = Post-baseline value − baseline value
- Relative change from baseline (%) = 100 × ([Post-baseline value − baseline value]⁄ baseline value)

2.1.1.12 Visit windowing

The study day for each visit will be derived; this day will then be used to determine the analysis visit based on the visit windows outlined in Table 2-1. In addition the study day associated with each week will also be derived as a supportive analysis (see Table 2-2).

If more than one analysis visit occurs at a visit, only one will be selected for summary tables but all visits will be listed.

For categorical variables, the closest to the target study day is chosen (if two assessments have the same distance, than the earlier one will be chosen).

For continuous variables, the worst record is selected. It is noted that in the analyses performed, worst case is always well defined (e.g., for urine protein values “+” and “++”, the worst case is defined as “++”).

The analysis visit will be used for listing of visit and period. If a visit falls after the last visit window (i.e. after Day 435) it is not assigned an analysis visit and will be listed under the label "After last scheduled visit" (i.e. "After Week 60").

Table 2-1 Visit windows

Timepoint	Analysis visit	Target Study day	Visit window (study days)
	Baseline	1	-42 to 1
4	Week 1	8	2 to 11
5	Week 2	15	12 to 18
6	Week 3	22	19 to 25
7	Week 4	29	26 to 43
8	Week 8	57	44 to 71
9	Week 12	85	72 to 99
10	Week 16	113	100 to 127
11	Week 20	141	128 to 155
12	Week 24	169	156 to 183
13	Week 28	197	184 to 211
14	Week 32	225	212 to 239
15	Week 36	253	240 to 267
16	Week 40	281	268 to 295
17	Week 44	309	296 to 323
18	Week 48	337	324 to 351
19	Week 52	365	352 to 379
20	Week 56	393	380 to 407
21	Week 60	421	408 to 435

Table 2-2 Weekly period for co-administered prednisolone treatment

Timepoint	Week	Week definition
3	Week 0	Study day 1 to Study day 7
4	Week 1	Study day 8 to Study day 14
5	Week 2	Study day 15 to Study day 21
6	Week 3	Study day 22 to Study day 28
7	Week 4	Study day 29 to Study day 35
8	Week 5	Study day 36 to Study day 42
9	Week 6	Study day 43 to Study day 49
10	Week 7	Study day 50 to Study day 56
11	Week 8	Study day 57 to Study day 63
12	Week 9	Study day 64 to Study day 70
13	Week 10	Study day 71 to Study day 77
14	Week 11	Study day 78 to Study day 84
15	Week 12	Study day 85 to Study day 91
16	Week 13	Study day 92 to Study day 98
17	Week 14	Study day 99 to Study day 105

Timepoint	Week	Week definition
18	Week 15	Study day 106 to Study day 112
19	Week 16	Study day 113 to Study day 119
20	Week 17	Study day 120 to Study day 126
21	Week 18	Study day 127 to Study day 133
22	Week 19	Study day 134 to Study day 140
23	Week 20	Study day 141 to Study day 147
24	Week 21	Study day 148 to Study day 154
25	Week 22	Study day 155 to Study day 161
26	Week 23	Study day 162 to Study day 168
27	Week 24	Study day 169 to Study day 175
28	Week 25	Study day 176 to Study day 182
29	Week 26	Study day 183 to Study day 189
30	Week 27	Study day 190 to Study day 196
31	Week 28	Study day 197 to Study day 203
32	Week 29	Study day 204 to Study day 210
33	Week 30	Study day 211 to Study day 217
34	Week 31	Study day 218 to Study day 224
35	Week 32	Study day 225 to Study day 231
36	Week 33	Study day 232 to Study day 238
37	Week 34	Study day 239 to Study day 245
38	Week 35	Study day 246 to Study day 252
39	Week 36	Study day 253 to Study day 259
40	Week 37	Study day 260 to Study day 266
41	Week 38	Study day 267 to Study day 273
42	Week 39	Study day 274 to Study day 280
43	Week 40	Study day 281 to Study day 287
44	Week 41	Study day 288 to Study day 294
45	Week 42	Study day 295 to Study day 301
46	Week 43	Study day 302 to Study day 308
47	Week 44	Study day 309 to Study day 315
48	Week 45	Study day 316 to Study day 322
49	Week 46	Study day 323 to Study day 329
50	Week 47	Study day 330 to Study day 336
51	Week 48	Study day 337 to Study day 343
52	Week 49	Study day 344 to Study day 350
53	Week 50	Study day 351 to Study day 357
54	Week 51	Study day 358 to Study day 364
55	Week 52	Study day 365 to Study day 371
56	Week 53	Study day 372 to Study day 379
57	Week 54	Study day 380 to Study day 386
58	Week 55	Study day 387 to Study day 393
59	Week 56	Study day 394 to Study day 400

Timepoint	Week	Week definition
60	Week 57	Study day 401 to Study day 407
61	Week 58	Study day 408 to Study day 414
62	Week 59	Study day 415 to Study day 421
63	Week 60	Study day 422 to Study day 429

Note: Co-administered treatment refers to prednisolone taken for GCA. There should be a 26-week prednisolone taper regimen however a patient may take additional prednisolone over the 52-week treatment period.

2.2 Analysis sets

The following analysis sets will be used for the patients of interest:

- The Randomized Analysis Set (RAS) consists of all randomized patients. Unless otherwise specified, mis-randomized patients will be excluded from the RAS. (Misrandomized patients are defined as cases where patients were mistakenly randomized by the investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind treatment was not administered to the patient. If patients were re-screened and successfully randomized they will be included in the RAS according to the treatment assigned in the last randomization.)
- The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization and who received at least one dose of randomized study treatment (secukinumab or placebo). According to the intent to treat principle, patients will be analyzed according to the treatment assigned to them at randomization.
- The Safety Set includes all patients who received at least one dose of study treatment (secukinumab or placebo). Patients will be analyzed according to the study treatment received, where treatment received is defined as the treatment the patient received on the first day of study treatment.

The number of patients within each of the analysis sets used in this study will be summarized by treatment group and overall (i.e. all patients).

2.2.1 Subgroup of interest

The subgroups of interest for this study are:

- GCA diagnosis
  - New onset GCA (defined as GCA diagnosis date within 6 weeks of Baseline visit date or there is a protocol deviation, in relation to inclusion criteria 5, regardless of protocol deviation discrepancy status)
  - Relapsing disease GCA (defined as GCA diagnosis date > 6 weeks from Baseline visit date)
- Baseline co-administered prednisolone treatment
  - ≥ 40 mg/day
  - < 40 mg/day

2.3 Patient disposition, demographics and other baseline characteristics

Patient disposition, background and demographic characteristics will be reported for the RAS, unless otherwise specified.

No inferential tests for differences in background and demographic characteristics will be performed.

2.3.1 Patient disposition

Patient disposition will be summarized using:

- Study treatment disposition
- Study disposition

Note: Patients may stop study treatment but continue to stay in the study hence there will be a differentiation between study treatment and study disposition. Patients will be analyzed according to the treatment assigned at the last randomization (see Section 2.2 for further details).

The number and percentage of patients who completed study treatment, those who discontinued study treatment prematurely, along with the primary reason for study treatment discontinuation, will be presented for each treatment group and overall (i.e. all patients) for the RAS.

A similar summary table will be presented for study disposition, i.e. the treatment disposition phase.

All patient disposition data will be listed by treatment group, center, and subject number for the RAS.

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, the number and percentage of patients enrolled in each site will be provided.

2.3.2 Demographics and other baseline characteristics

Demographics and other baseline characteristics data will be summarized for each treatment group and overall (i.e. all patients) for the FAS. Patients will be analyzed according to the treatment assigned at the last randomization (see Section 2.2 for further details).

Descriptive statistics will be presented for the following continuous demographic and other baseline characteristics variables:

- Age (years)
- Height (cm)
  - Note: This will be presented for each treatment group and overall and in addition for each sex category in each treatment group and overall.
- Weight (kg)
  - Note: This will be presented for each treatment group and overall and in addition for each sex category in each treatment group and overall.
- Body mass index (BMI) (kg/m^2)
  - Defined as: (body weight in kg) / (height in meters)^2

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

Note: This will be presented for each treatment group and overall and in addition for each sex category in each treatment group and overall.

- Time since diagnosis of GCA (years)
  - Defined as: (date of Visit 1 - date of diagnosis of GCA) / 365.25

    For handling of missing or incomplete GCA diagnosis dates, refer to Section 5.1.4.
- Time since first GCA symptom (years)
  - Defined as: (date of Visit 1 - date of first GCA symptom) / 365.25

    For handling of missing or incomplete first GCA symptom dates, refer to Section 5.1.4.
- GCA diagnosis (New onset GCA, Relapsing disease GCA)
- Baseline co-administered prednisolone treatment (≥ 40, < 40 mg/day)

The number and percentage of patients in each category of the following categorical variables overall will be presented:

- Weight group (< 70, ≥ 70 to < 90, ≥ 90 kg)
- Current smoking status (Current, Former, Never)
- Race (White, Black or African American, Asian)
- Sex (Male, Female)

All important demographics and other baseline characteristics data will be listed by treatment group, center, and subject number for the RAS.

In addtion, for the legal requirements of clinicaltrials.gov and EudraCT, the following age categories will also be presented:

- 18 to < 65 years
  - Note: Inclusion criteria 3 indicates that patients must be at least 50 years of age to be included in this study. Therefore for this study the subgroup category 18 to < 65 years is equivalent to 50 to < 65 years.
- 65 to < 85 years
- ≥ 85 years

2.3.2.1 Medical history

Relevant medical histories and current medical conditions at the time of informed consent will be summarized for each treatment group and overall (i.e. all patients) for the FAS.

Note: If there are COVID-19 infected patients in this study, descriptive summaries of medical history will be provided first by all patients of interest, then by COVID-19 infected patients and non-COVID-19 infected patients.

The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical histories will be coded using the most recent (i.e. latest version as per clinical database lock [CDBL]) Medical Dictionary for Regulatory Activities (MedDRA). The primary SOCs

will be presented in alphabetical order and the PTs will be presented by decreasing proportion in the overall group.

2.3.2.2 Cardiovascular medical history

Cardiovascular medical history will be presented by treatment group and overall (i.e. all patients) for the Safety Set.

Note: If there are COVID-19 infected patients in this study, descriptive summaries of medical history will be provided first by all patients of interest, then by COVID-19 infected patients and non-COVID-19 infected patients.

The number and percentage of patients with an occurrence of the following events will be provided:

- Type 1 diabetes
- Type 2 diabetes
- Hypertension
- Dyslipidemia/Hyperlipidemia
- Prior transient ischemic attack
- Prior hemorrhagic stroke
- Prior ischemic stroke
- Prior stroke: unknown type
- Myocardial infarction
- Atrial fibrillation
- Supraventricular tachycardia
- Deep vein thrombosis
- Pulmonary embolism
- Peripheral arterial disease
- Stable coronary artery disease
- Gout

In addition, the number and percentage of patients with an ongoing event at Baseline will be provided in a summary table by treatment group and overall (i.e. all patients) for the Safety Set.

2.3.2.3 GCA medical history

GCA medical history will be presented by treatment group and overall (i.e. all patients) for the Safety Set.

Note: If there are COVID-19 infected patients in this study, descriptive summaries of medical history will be provided first by all patients of interest, then by COVID-19 infected patients and non-COVID-19 infected patients.

The number and percentage of patients with an occurrence of the following events will be provided:

- Diplopia

- Blurring of vision
- Transient partial visual loss (Amaurosis fugax) - Left eye
- Transient partial visual loss (Amaurosis fugax) - Right eye
- Visual field defect - Left eye
- Visual field defect - Right eye
- Loss of vision - Left Eye
- Loss of vision - Right Eye
- Relative afferent pupillary defect
- Headache
- Scalp tenderness
- Claudication of jaw muscles
- Temporal artery abnormality
- Fever
- Night sweat
- Weight loss
- Large vessel involvement
- Polymyalgia rheumatica

In addition, the number and percentage of patients with an ongoing event at Baseline will be provided in a summary table by treatment group and overall (i.e. all patients) for the Safety Set. Only the following GCA medical history events can be classified as ongoing or not at Baseline:

- Diplopia
- Blurring of vision
- Transient partial visual loss (Amaurosis fugax) - Left eye
- Transient partial visual loss (Amaurosis fugax) - Right eye
- Relative afferent pupillary defect

2.3.3 Protocol deviations

The number and percentages of patients with each important protocol deviation type will be tabulated by treatment group and overall (i.e. all patients) for the FAS. The results will be grouped using the broad categories defined in the current Standard Operating Procedure (SOP) which are:

- Patient did not satisfy entry criteria
- Patient received the wrong treatment or incorrect dose
- Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Patient took an excluded concomitant medication
- Others

All important protocol deviations will be listed by treatment group, center, and subject number for the FAS.

Note: There is no per protocol analysis set in this study. Therefore no protocol deviation will lead to exclusion from any of the analysis sets.

In addition, pandemic related protocol deviations will be summarized by category and relationship. All COVID-19 related protocol deviations will also be listed for the FAS.

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

Summaries will be presented for the Safety Set. Patients will be analyzed according to treatment received (see Section 2.2 for further details).

2.4.1 Study treatment / compliance

The number and percentage of study treatment injections will be summarized by treatment group by means of contingency tables.

In case it cannot be identified from the data collected or assumed from the planned treatment whether an injection contained placebo or secukinumab, it will be assumed that the syringe contained secukinumab.

The duration of exposure to study treatment will be summarized by treatment group. Duration of exposure to study treatment will be defined as the time from first dose of study treatment to the end of the treatment period. The end of treatment period will be defined as the last dose of the study treatment plus 84 days or last visit whichever occurs earlier. i.e., for patients who discontinued or have their last visit earlier than last dose of study treatment plus 84 days, the end of study treatment exposure will be the date of the last study visit in the corresponding treatment period.

Duration of exposure (weeks) = (min(end of treatment period date, last dose of study treatment date + 84 days) - first dose of study treatment date + 1)/7

The number of patients with exposure of the following time thresholds will be displayed:

- any exposure
- ≥ 1 week
- ≥ 2 weeks
- ≥ 3 weeks
- ≥ 4 weeks
- ≥ 8 weeks
- ≥ 12 weeks
- ≥ 16 weeks
- ≥ 20 weeks
- ≥ 24 weeks
- ≥ 28 weeks
- ≥ 32 weeks
- ≥ 36 weeks
- ≥ 40 weeks

- ≥ 44 weeks
- ≥ 48 weeks

Descriptive statistics will also be provided for the study treatment group for the following:

- Actual cumulative dose
  Defined as: the sum of all doses of study treatment during the treatment disposition phase
- Dose intensity
  Defined as: the ratio of actual cumulative dose of study treatment received and actual duration of exposure of study treatment (weeks)

Note: Each study treatment injection is equivalent to 150 mg. Patients assigned to study treatment should take 2 injections (150 mg) weekly from Week 0 to Week 4 and then every 4 weeks until Week 48.

The duration of exposure to the co-administered prednisolone treatment will also be summarized by treatment group using the same logic and rules as the study treatment (with the exception that the addition of 84 days is only applicable to study treatment). In addition descriptive statistics of the average daily dose (mg/day) of co-administered prednisolone treatment overall during the study and at each week (refer to Table 2-2 for weekly visit windowing) during the 26-week prednisolone taper regimen will be presented for each treatment group.

Furthermore descriptive statistics of the co-administered prednisolone treatment at the time of first flare post-baseline will also be provided.

Co-administered prednisolone treatment data will be listed by treatment group, center, and subject number for the Safety Set. In addition, a co-administered prednisolone treatment data listing will also be provided for the subset of patients who did not adhere to the prednisolone taper regimen.

2.4.2 Prior, concomitant and post therapies

Medications will be identified by Anatomical Therapeutic Chemical (ATC) class and PT according to the World Health Organization (WHO) Drug Reference List dictionary (version 18.9 or a more recent version).

Note: If there are COVID-19 infected patients in this study, descriptive summaries of prior and concomitant medications will be provided first by all patients of interest, then by COVID-19 infected patients and non-COVID-19 infected patients.

Summaries will be presented separately for prior and concomitant medications. Tables will show the number and percentage of patients receiving at least one dose of the therapy.

Note: Methotrexate (MTX) will not be included in the aforementioned summaries for prior and concomitant medications. Separate summaries will be created for prior and concomitant use of MTX.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment

and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Prior or concomitant medication will be identified based on recorded or imputed start dates of medication taken in this study. The rules for imputing incomplete start dates are described in Section 5.1.3. All prior and concomitant medication data will be listed by treatment group, center, and subject number.

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

2.4.3 Signs and symptoms of GCA

The number and percentage of patients who experienced flare due to GCA will be summarized by visit for each treatment group and overall (i.e. all patients). The summary table will also include the number and percentage of patients with each of the following individual signs and symptoms of GCA:

- Fever (Yes, No)
- Symptoms of polymyalgia rheumatica (PMR) (Yes, No)
- Localized headache, temporal artery or scalp tenderness (Yes, No)
- Acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy(A-AION) (Yes, No)
- Transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes) (Yes, No)
- Jaw or mouth pain (Yes, No)
- New or worsened extremity claudication (Yes, No)
- Other features judged by both the clinician-investigator to be consistent with a GCA or PMR flare (Yes, No)

Note: More than 1 sign and symptom of GCA may be selected.

2.5 Analysis of the primary objective

Patients will be analyzed according to the treatment assigned at the last randomization (see Section 2.2 for further details).

2.5.1 Primary endpoint

The primary endpoint is the proportion of GCA patients who are in sustained remission until Week 28.

The analysis of the primary variable will be based on the following estimand:

- Analysis set: FAS (for the patients of interest as outlined in Section 2.1)
- Variable of interest: Proportion of GCA patients who are in sustained remission until Week 28
  - Sustained remission: Patients without flare until Week 28 and in adherence to the protocol prednisolone taper regimen.

- Note: Flare is determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA.
- Adhere to prednisolone taper: Patients do not adhere to the prednisolone taper regimen if during the 26-week prednisolone taper regimen any of the following occur:
  - Patient does not take prednisolone medication for GCA for ≥ 6 consecutive days.
  - Patient takes prednisolone treatment for GCA for < 80% of the 26-week prednisolone taper regimen period.
  - Patient has received additional prednisolone for GCA to that stated in the taper regimen.

    Note: This criteria (receiving additional prednisolone) does not apply to those patients in the "escape arm".

    This means a patient is classified as receiving an additional prednisolone for GCA to that stated in the taper regimen if in the timeframe:
    - [Week 0-Week 11] the patient's weekly dose is 20% over the stated dosage of prednisolone, or
    - [Week 12-Week 26] the patient's weekly dose is 30% over the stated dosage of prednisolone.
  - Patient received an additional corticosteroid to that stated in the taper regimen. Note: This will be based on the respective PD associated with this criteria.

  Note: The final decision on whether the patient is non-adherent to the prednisolone taper will be confirmed by the blinded medical team on a by-patient basis in a Blind Data Review Meeting (BDRM) prior to CDBL. This decision will be documented in the associated BDRM minutes.
- Intervention effect: Effect between secukinumab versus placebo at Week 28 regardless of adherence to randomized treatment.
- Measure of intervention effect: Odds ratio (OR).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint variable of interest is binary, hence a binomial distribution will be assumed for the observed data from this study. It is of interest to estimate a one-dimensional scalar parameter (the primary endpoint estimand Θ) using Bayesian inference.

To perform this inference, a prior distribution for Θ must first be specified. The response rate of the comparable placebo arm of the GIACTA study (Stone et al 2017) will be used as the prior distribution for the placebo response rate for the primary endpoint in this study. The parameters of this Beta distribution are 10 and 43, i.e. Beta (10, 43). The prior distribution for the response rate on secukinumab will be a Beta distribution with parameters 0.5 and 0.5, i.e. Beta (0.5, 0.5). This prior distribution was chosen because it has low weight to reflect the lack of current knowledge on the response rate on secukinumab in GCA.

The process of Bayesian inference involves passing from a prior distribution, $p(\Theta)$, to a posterior distribution, $p(\Theta|y)$ where y refers to the data of interest from this study. Due to the conjugate nature of the Beta distributions, the posterior distributions of the primary endpoint

estimand Θ will also be Beta distributions. As the Beta distribution has a closed form nature, descriptive statistics of the posterior distribution are also available in closed form.

Using the prior distribution information and the study data, the Beta posterior distribution for each treatment group will be derived.

$$\Theta|y \sim Beta\,(y + a, n - y + b)$$

Note: y = study data (i.e. proportion of GCA patients who are in sustained remission until Week 28) for the treatment of interest; n = number of randomized patients for the treatment of interest; a, b = the shape parameters from the prior Beta distribution [Beta(a,b)] associated with the treatment of interest.

One hundred thousand random draws from the Beta posterior distributions will then be taken based on the seed 190207. An estimate of the 95% posterior interval (i.e. the 95% credibility interval), using the the 2.5 and 97.5 percentiles as well as the median (50 percentile) will be obtained. The median and 95% credibility interval of the OR, risk difference (RD) and risk ratio (RR) will be presented.

Note: Odds ratio is the ratio of odds of the primary endpoint in secukinumab to the odds of the event in placebo. The odds of an event refers to the number of events / the number of non-events. Risk difference is the difference in proportions of the patients with the primary endpoint in secukinumab vs placebo. Risk ratio (also known as relative risk) is the ratio of risk of the primary endpoint in secukinumab to the risk of the primary endpoint in placebo.

For this study, similar response rates to the GIACTA study (Stone et al 2017) for the primary endpoint are expected, i.e. 56% secukinumab response rate and 18% placebo response rate. If the secukinumab response rate was < 40% this may indicate that further trials in this indication would not be worthwhile. Therefore assuming the 18% placebo response rate is fixed, the treatment response rates would translate into a RD of:

- 38% (expected effect, based on 56%-18%)
- 22% (minimal effect, based on 40%-18%)

This study would suggest to proceed with the development of secukinumab in this indication, if the following GO-criterium are satisfied:

- the posterior probability of a relevant effect (RD > 0.22) is at least 50% (also written as prob(RD > 0.22 | y) ≥ 50%)

and

- the posterior probability of any effect (RD > 0) is at least 90% (also written as prob(RD > 0 | y) ≥ 90%)

The posterior probabilities for a relevant effect and for any effect will be determined to give guidance in deciding whether to proceed in the development of secukinumab in this indication.

The posterior probability of the OR and the RR of the comparison of secukinumab versus placebo being greater than 1 will also be provided. Note: An OR or RR greater than 1 indicates a favourable outcome for secukinumab vs placebo in regard to the primary endpoint.

Furthermore, the proportion of patients in sustained remission until Week 28 (Yes, No) will be summarized descriptively by treatment group. This analysis does not take into account the prior information, it is only based on information from this study.

In addition, all primary endpoint data will be listed by treatment group, center, and subject number for the FAS.

2.5.3 Handling of missing values/censoring/discontinuations

Patients will be classified as non-responders if they fulful any of the following:

- Do not achieve remission within 12 weeks of Baseline
  - Note: Remission refers to the absence of flare.
- Are in the "escape arm"
  - Note: This refers to the patient entering escape between Baseline and Week 28.
- Prematurely discontinue study treatment prior to Week 28
  - Note: Absence of flare is checked prior to study treatment administration.
- Do not have information to evaluate sustained remission response until Week 28

Patients receiving less than the full amount of prednisolone for GCA as required by the taper, e.g. due to missing tablets, will not be classified as non-responders with the exception of those who are classified as non-adherent to the prednisolone taper regimen (refer to Section 2.5.1 for definition of adherence to the prednisolone taper regimen). Note: The final decision on whether the patient is non-adherent to the prednisolone taper will be confirmed by the blinded medical team on a by-patient basis in a BDRM prior to CDBL. This decision will be documented in the associated BDRM minutes.

2.5.4 Supportive analyses

In order to assess the robustness of the primary endpoint, the following analyses are planned:

- Using a non-informative prior, i.e. uniform prior Beta (0.5, 0.5), for both treatment groups
- A logistic regression model with treatment in the model. ORs along with the respective 2-sided 80% confidence interval (CI) will be derived for the treatment comparison.

Furthermore, the primary analysis will be repeated based on only signs and symptoms of GCA in order to mitigate against the possibility of biasing.

In addition, the reasons why a patient is determined to be a responder or non-responder to the primary endpoint will be summarized.

Subgroup analyses (see Section 2.2.1 for further details) will only be performed if at least 5 patients are present in each subgroup. Some grouping of classes will be considered if there are too few patients in some subgroups.

[redacted]

2.6 Analysis of the key secondary objective

There are no key secondary objectives in this study.

2.7 Analysis of secondary efficacy objectives

Patients will be analyzed according to the treatment assigned at the last randomization (see Section 2.2 for further details) for the FAS.

The analyses of the secondary efficacy objectives will not take into account the prior information, it is based only on information from this study.

2.7.1 Secondary endpoints

The following secondary endpoints will be analyzed:

- Proportion of GCA patients who adhere to the prednisolone taper regimen and are in sustained remission at Week 52
- Remission rate at Week 12
- Time to first GCA flare after Baseline (up to and including Week 52)
- Total cumulative prednisolone dose from start of co-administered treatment to Week 28, 52
- Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19, 28, 52
- Change from Baseline in PhGA VAS at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in PGA VAS at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in FACIT-Fatigue at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in SF-36 at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in EQ-5D at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in CRP (mg/L) at Week 4, 8, 12, 16, 20, 24, 28, 36, 40, 44, 48, 52
- Change from Baseline in ESR (mm/hr) at Week 4, 8, 12, 16, 20, 24, 28, 36, 40, 44, 48, 52

2.7.2 Statistical hypothesis, model, and method of analysis

The proportion of patients in sustained remission until Week 52 (Yes, No) will be summarized descriptively for each treatment group. Note: Sustained remission at Week 52 refers to patients without flare until Week 52 and in adherence to the protocol prednisolone taper regimen. Flare is determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA. In addition, the reasons why a patient is determined to be a responder or non-responder to patients in sustained remission until Week 52 will be summarized.

The proportion of patients in remission (Yes, No) at each time point will be summarized descriptively for each treatment group. Note: Remission refers to the absence of flare. This summary table will only summarize remission information up to 4 weeks post last administration of study treatment.

The time to first GCA flare after remission (up to and including Week 52) will be summarized using Kaplan Meier curves. Descriptive statistics will also be provided for time to first GCA flare after remission in days (up to and including Week 52). This will also include information on follow-up. Follow-up is defined as:

- (Date of event or censoring – Baseline date) + 1 (regardless of censoring)

Total cumulative prednisolone dose from the first dose of co-administered prednisolone treatment to Weeks 26, Week 28, and 52 will be summarized over time by treatment group. Note: Prednisolone dose refers to prednisolone dose taken for GCA.

The number and percentage of patients on prednisolone dose ≤ 5mg/day at Week 19, 28 and 52 will be summarized by treatment group. Note:

- Prednisolone dose refers to prednisolone dose taken for GCA.
- Prednisolone dose refers to the average co-administered prednisolone treatment in the week of interest.
- Prednisolone dose for GCA will be based on the information collected on the "Dosage Administration Record-Prednisolone" eCRF. However as the prednisolone taper regimen is planned to be 26-weeks in duration, the Investigator is not required to enter daily prednisolone records on the "Dosage Administration Record-Prednisolone" eCRF post Week 26 unless the patient has taken additional prednisolone for GCA. Therefore if the patient is still in the study at the post Week 26 week of interest and has no prednisolone information in the "Dosage Administration Record-Prednisolone" eCRF for that week of interest the patient will be regarded as having 0 mg/day at that week of interest.

Descriptive summary statistics for the change as well as relative change from baseline of PhGA VAS to each study visit of interest will be presented for each treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

The analysis of the PRO secondary endpoints is detailed in Section 2.10.

Descriptive summary statistics for the change from baseline of CRP and ESR to each study visit of interest will be presented for each treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values. Further details are provided in Section 2.8.3. This analysis will also be presented for the following subgroups:

- Sustained remission until Week 28 (Yes, No)
- Sustained remission until Week 52 (Yes, No)

2.7.3 Handling of missing values/censoring/discontinuations

For sustained remission until Week 52, patients will be classified as non-responders if they fulful any of the following:

- Do not achieve remission within 12 weeks of Baseline
  - Note: Remission refers to the absence of flare.
- Are in the "escape arm"
  - Note: This refers to the patient entering escape between Baseline and Week 52.
- Prematurely discontinue study treatment prior to Week 52
  - Note: Absence of flare is checked prior to study treatment administration.
- Do not have information to evaluate sustained remission response until Week 52

Patients receiving less than the full amount of prednisolone for GCA as required by the taper, e.g. due to missing tablets, will not be classified as non-responders with the exception of those who are classified as non-adherent to the prednisolone taper regimen (refer to Section 2.5.1 for definition of adherence to the prednisolone taper regimen). Note: The final decision on whether

the patient is non-adherent to the prednisolone taper will be confirmed by the blinded medical team on a by-patient basis in a BDRM prior to CDBL. This decision will be documented in the associated BDRM minutes.

For remission rate at Week 12, patients will be classified as non-responders if they fulfil any of the following:

- Prematurely discontinue study treatment
- Enter "escape" therapy

Note: Patients will be classified as non-responders for the above two scenarios from the point of withdrawal/escape onwards. Patients with a missing remission status at Week 12 will be classified as non-responders.

For time to first GCA flare after remission (up to and including Week 52), patients who:

- Prematurely discontinue study treatment prior to Week 52 will be censored at the time of premature discontinuation
- Complete treatment and do not have a flare will be censored at their last visit in the treatment phase

2.8 Safety analyses

Patients will be analyzed according to treatment received (see Section 2.2 for further details) for the Safety Set.

2.8.1 Adverse events

Adverse events will be coded by primary SOC and PT according to the MedDRA version 23.0 or later and will be presented for the whole study period. Only treatment emergent AEs (TEAEs) will be summarized.

Treatment emergent AEs are defined as events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity after dosing based on preferred term and within last dose + 84 days. For handling of missing or incomplete start and end dates, refer to Section 5.1.2.

Treatment emergent AEs will be summarized for each treatment group by presenting the crude incidence of patients having any TEAE and having a TEAE by primary SOC and by PT. Patients who experienced multiple AEs for a PT will be counted once for that PT, similarly for patients with multiple AEs per primary SOC. For summaries of TEAEs by severity, if a patient reports more than one AE with the same PT, only the AE with the maximum severity will be counted. Similarly, if a patient reports more than one AE within the same primary SOC, the event with the maximum severity will be counted for the SOC level. If the severity of a particular AE is missing, this severity will be treated as missing in summaries and listed accordingly.

The following TEAE information will be summarized separately by contingency tables:

- Adverse events, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC and PT
- Adverse events, suspected to be related to study treatment, by primary SOC and PT

- Adverse events, suspected to be related to co-administered prednisolone treatment, by primary SOC and PT
- Serious AEs, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC and PT
- Serious AEs, suspected to be related to study treatment, by primary SOC and PT
- Serious AEs, suspected to be related to co-administered prednisolone treatment, by primary SOC and PT
- Adverse events, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC, PT and maximum severity (mild, moderate, severe)
- Adverse events leading to study treatment discontinuation, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC and PT
- Adverse events leading to study treatment discontinuation, suspected to be related to study treatment, by primary SOC and PT
- Adverse events leading to study treatment discontinuation, suspected to be related to co-administered prednisolone treatment, by primary SOC and PT
- Adverse events requiring study dose adjustment/interruption, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC and PT
- Adverse events requiring additional therapy, regardless of relationship to study or co-administered prednisolone treatment, by primary SOC and PT

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, 2 required tables on TEAEs which are not SAEs with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by primary SOC and PT.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same primary 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.

2.8.1.1 Adverse events of special interest / grouping of AEs

Specific groupings of AEs of special interest (AESI) will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with secukinumab or AEs which are similar in nature (although not identical). Note that certain AEs may be reported within multiple groupings. These AESIs are updated on a regular basis at the secukinumab program level. The most recent version of the AESI search criteria form as described in the electronic Case Retrieval Sheet (eCRS) will be used for the reporting activity.

AESIs will be summarized regardless of study drug relationship, for each treatment group by grouping and PT.

2.8.2 Deaths

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

2.8.3 Laboratory data

Only "on-treatment" laboratory data (i.e. all assessments in the the safety observation as defined in Section 2.1.1.4) will be summarized.

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

Descriptive summary statistics for the change from baseline to each study visit of interest 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. In addition, shift tables using the low/normal/high/ (low and high) classification will be used to compare Baseline to the worst on-treatment value.

For urinalysis, frequency tables will be presented.

All laboratory data will be listed by center, subject number, and visit/time and if ranges are available, abnormalities will be flagged.

2.8.4 Other safety data

2.8.4.1 Vital signs

Only "on-treatment" vital signs data (i.e. all assessments in the the safety observation as defined in Section 2.1.1.4) will be summarized.

Descriptive summary statistics for the change from baseline to each study visit of interest will be presented. These descriptive summaries will be presented by vital sign parameter and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values. Note: As blood pressure will be assessed for both arms, the average of the available blood pressure assessments will be summarized/listed.

All vital signs data will be listed by center, subject number, and visit/time and if ranges are available, abnormalities will be flagged.

2.8.4.2 Immunogenicity

The number and percentage of patients without immunogenicity and with positive immunogenicity will be provided. The number and percentage of patients with neutralizing antibodies will be presented as well.

All immunogenicity results (anti-AIN457 antibodies) will be listed by treatment group, center, subject number, and study visit.

2.8.4.3 QuantiFERON TB-Plus test

All QuantiFERON TB-Plus test results will be listed by treatment group, center, subject number, and study visit.

[redacted]

2.10 Patient-reported outcomes

The following secondary PRO endpoints will be analyzed according to treatment received (see Section 2.2 for further details) for the FAS:

- Change from Baseline in PGA VAS at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in FACIT-Fatigue at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in SF-36 at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline in EQ-5D at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52

Descriptive summary statistics for the change as well as relative change from baseline of PGA VAS to each study visit of interest will be presented for each treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

Descriptive summary statistics for the change as well as relative change from baseline of FACIT-Fatigue to each study visit of interest will be presented for each treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

For SF-36, the following variables will be evaluated:

- SF-36 domain scores

- SF-36 domain score responders
  - Type I responders (improvement of ≥ 5 points in ≥ 6 domains)
  - Type II responders (improvement of ≥ 10 points in ≥ 3 domains)
- SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (norm-based scores)
- SF-36 PCS and MCS score responders
  - Type I responders (improvement of ≥ 2.5 points)
  - Type II responders (improvement of ≥ 5 points)

Descriptive summary statistics for the change as well as relative change from baseline of SF-36 domain and summary scores to each study visit of interest will be presented for each treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values. The proportion of responders at each time point will be summarized descriptively for each treatment group.

The EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with 5 categories and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of patients in each of the 5 categories for each question will be presented by study visit and treatment group. Descriptive summary statistics will be provided for the change from baseline of health state assessment (known as EQ-5D-5L VAS) and EQ-5D-5L utility index (see Section 5.4.1 for further details) by study visit and treatment group.

2.11 Biomarkers

Not applicable.

[redacted]

[redacted]

2.13 Interim analysis

In total, 3 IAs will be conducted:

- IA1 – after approx. 50% of patients reach Week 28
- IA2 – after approx. 50% of patients reach Week 52
- IA3 - 100% of patients reach Week 28

The analyses for each of the aforementioned IAs are detailed in separate SAPs.

Prior to the protocol amendment version no. 2 including Amendment 2, the analyses of the primary endpoint and all other data at Week 28 were intended to be the final analysis of this study. As the blinded treatment period was extended until Week 52, this formerly final analysis will be conducted as IA3.

All IAs, in particular IA2 on Week 52 data will be informative to the planning of a Phase 3 program of secukinumab in GCA. There will be no multiplicity adjustment.

An independent unblinded study team will perform all interim analyses. Details will be specified in the Interim Analyses Charter.

3 Sample size calculation

Based on the observed response rates in the GIACTA study (Stone et al 2017), there were 56 out of 100 patients on tocilizumab every other week (56%) in combination with 26-week prednisolone taper regimen and 9 out of 51 patients treated with placebo (18%) in combination with 52-week prednisolone taper regimen. The expected observed responders in a sample size of 25 patients per treatment group is then 25*(56/100) = 14 and 25*(9/51) = 4. The posterior distribution of the expected difference in proportions was investigated for the sample size of 25 patients per treatment group.

Using an uninformative prior Beta (1, 1) for the secukinumab group and an informative prior for the expected observed responders in the placebo group of Beta (10, 43), 10000 Monte Carlo simulations of each posterior density was then computed and the posterior distribution of the difference then described using the 2.5, 50 (median) and 97.5 percentiles (Table 3-1).

Other plausible outcomes have been investigated if the observed response rates are different from expected (refer to Table 3-1).

Table 3-1 Sensitivity to changes in assumptions in observed response rates

Observed response rate		Posterior quantiles for p1 – p2			Posterior Prob(p1 > p2)
Secukinumab (p1)	Placebo (p2)	2.5%	Median	97.5%	
0.56	0.16	0.19	0.38	0.56	0.99
0.56	0.20	0.16	0.36	0.55	0.99
0.56	0.24	0.15	0.35	0.55	0.99

Observed response rate		Posterior quantiles for p1 – p2			Posterior Prob(p1 > p2)
Secukinumab (p1)	Placebo (p2)	2.5%	Median	97.5%	
0.56	0.28	0.13	0.34	0.54	0.99
0.52	0.16	0.14	0.34	0.53	0.99
0.48	0.16	0.11	0.31	0.51	0.99

4 Change to protocol specified analyses

[redacted]

The baseline prednisolone dose subgroup categories have been updated from > 40 mg/day and ≤ 40 mg/day to ≥ 40 mg/day and < 40 mg/day to align with the planned prednisolone taper regimen.

Sustained remission at a timepoint refers to patients being without flare until that timepoint and in adherence to the protocol prednisolone taper regimen. As adherence to the protocol prednisolone taper regimen is a component of the sustained remission definition already; any redundant mention of adherence to prednisolone taper regimen has been removed throughout this document.

Any reference to the time point after clinical remission has been updated to be after Baseline; this aligns more clearly with what was planned to be analyzed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

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

5.1.2 Adverse event date imputation

5.1.2.1 Adverse event end date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.2.2 Adverse event start date

Adverse events with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment within this study.

Partial AE start dates are imputed with reference to the first administration of study treatment within this study as outlined in the table below.

The date value is split into day, month, year sections and referenced in the imputation table as outlined below.

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Treatment Start	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates AE start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates AE start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, Treatment Start +1)
(C) Before Treatment Start	15MONYYYY

Relationship	
Before Treatment start	Partial date indicates AE start date prior to Treatment Start Date in this study
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

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

- If the AE end date is complete and the (imputed) AE end date < Treatment Start Date then AE start reference date = min (study informed consent date, earliest visit date).
- Else AE start reference date = Treatment Start Date

To impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the study treatment start date year value, the AE started before study treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the study treatment start date year value, the AE started after study treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the study treatment start date month or greater than the study treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

5.1.3.1 Concomitant medication end date

To impute concomitant end date:

1. If the concomitant end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the concomitant end year value is missing or ongoing, the imputed concomitant end date is set to NULL.
2. Else, if the concomitant end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
3. If the concomitant end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).

If the imputed concomitant end date is less than the existing concomitant start date, use the concomitant start date as the imputed concomitant end date.

5.1.3.2 Concomitant medication start date

Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the first administration of study treatment within this study in accordance with the rules outlined below.

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

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(C) Uncertain	(A) = 15MONYYYY Before Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY 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 in this study
After Treatment start	Partial date indicates CMD start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date in this study
Imputation calculation	

Relationship	
NC/Blank Uncertain	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, Treatment Start Date +1)
(C) Uncertain	IF CMDTYP IN (1, 3) THEN Treatment Start Date -1 ELSE IF CMDTYP IN (. 2) THEN Treatment Start Date +1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

To compute concomitant start date:

1. If the concomitant start date year value is missing, the imputed concomitant start date is set to one day prior to study treatment start date.
2. If the concomitant start date year value is less than the study treatment start date year value, the concomitant medication started before study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the mid-year point (01JULYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
3. If the concomitant start date year value is greater than the study treatment start date year value, the concomitant started after study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the year start point (01JANYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the month start point (01MONYYYY).
4. If the concomitant start date year value is equal to the study treatment start date year value:
   a. And the concomitant month is missing or the concomitant month is equal to the study treatment start date month, then the imputed concomitant start date is set to one day prior to study treatment start date.
   b. Else if the concomitant month is less than the study treatment start date month, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
   c. Else if the concomitant month is greater than the study treatment start date month, the imputed concomitant concomitant start date is set to the month start point (01MONYYYY).

If complete (imputed) concomitant end date is available and the imputed concomitant start date is greater than the (imputed) concomitant end date, then imputed concomitant start date should be set to the (imputed) concomitant end date.

5.1.4 Other imputations

5.1.4.1 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If diagnosis year < study treatment start date year and diagnosis month is missing, the imputed diagnosis date is set to the mid-year point (01JULYYYY)
- Else if diagnosis month is not missing, the imputed diagnosis date is set to the mid-month point (15MONYYYY)
- If diagnosis year = study treatment start date year and (diagnosis month is missing OR diagnosis month is equal to study treatment start month), the imputed diagnosis date is set to one day before study treatment start date

5.2 Adverse events coding/grading

Reporting of AEs will be based on MedDRA version 23.0 or higher. For the analysis purpose, the latest version of MedDRA available at CDBL will be used for reporting activity.

5.3 Laboratory parameters derivations

All laboratory parameters were analyzed at a central laboratory with the exception of the following which were analyzed locally:

- ESR
- Urinalysis
- Urine pregnancy test

If the statistics and statistical programming team receive any laboratory data in conventional rather than SI units, these will be converted to SI units using the global conversion library in GPS.

5.3.1 Imputation rules

If laboratory values are provided as "<X" (i.e. below limit of detection) or ">X", prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential:

- xxx count = (WBC count) * (xxx %value / 100)

5.4 Questionnaires

5.4.1 EQ-5D

This questionnaire is used to assess the health status in adults. The measure is divided into 2 distinct sections.

The first section includes one item addressing each of 5 dimensions:

- mobility
- self-care
- usual activity
- pain/discomfort
- anxiety/depression

Patients rate each of these items from "no problems", "slight problems", "moderate problems", "severe problems", or "extreme problems". A composite health index is then defined by combining the levels for each dimension.

The second section measures self-rated (global) health status utilizing a vertically oriented VAS where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today".

Computing EQ-5D-5L utility index values

The following derivation is based on the SPSS value set - Germany - EQ-5D-5L using the German (GER) Ludwig value set version 1.1 (last updated 17FEB2020).

```
*****************************************************************
*SPSS syntax code for the computation of index*
*values with the GER TTO value set*
*****************************************************************;

IF (mobility=1) disut_mo=0.
IF (mobility=2) disut_mo=0.026.
IF (mobility=3) disut_mo=0.042.
IF (mobility=4) disut_mo=0.139.
IF (mobility=5) disut_mo=0.224.

IF (selfcare=1) disut_sc=0.
IF (selfcare=2) disut_sc=0.050.
IF (selfcare=3) disut_sc=0.056.
IF (selfcare=4) disut_sc=0.169.
IF (selfcare=5) disut_sc=0.260.

IF (activity=1) disut_sc=0.
IF (activity=2) disut_sc=0.036.
IF (activity=3) disut_sc=0.049.
IF (activity=4) disut_sc=0.129.
IF (activity=5) disut_sc=0.209.

IF (pain=1) disut_sc=0.
IF (pain=2) disut_sc=0.057.
IF (pain=3) disut_sc=0.109.
IF (pain=4) disut_sc=0.404.
IF (pain=5) disut_sc=0.612.


IF (anxiety=1) disut_sc=0.
IF (anxiety=2) disut_sc=0.030.
IF (anxiety=3) disut_sc=0.082.
IF (anxiety=4) disut_sc=0.244.
IF (anxiety=5) disut_sc=0.356.

Compute disut_total= disut_mo +disut_sc +disut_ua +disut_pd +disut_ad.

Compute EQindex = 1-disut_total.
execute.
```

5.4.2 FACIT-Fatigue

The questionnaire is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.

Patients respond to each item on a 5-point Likert-type scale:

- 0 = not at all
- 1 = a little bit
- 2 = somewhat
- 3 = quite a bit
- 4 = very much

based on their experience of fatigue during the past 2 weeks.

The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction. It should be noted that numbering the questions from 1 to 13, it is evident that questions 7 and 8 are worded in the positive direction (4 indicates a desirable response) and all other questions are worded in the negative directions (4 indicates an undesirable response). Thus, it is necessary to reverse the responses for all but questions 7 and 8 (i.e. original response of 0 gets mapped to 4, 1=3, 2=2, 3=1, and 4=0) for scoring purposes. When there are missing item scores, the subscale score was computed by summing the non-missing item scores, multiplying by 13 (the total number of items in the scale) and dividing by the number of non-missing items (i.e. normalizing the results). The latter rule applied only when at least half of the items (seven or more) are non-missing.

FACIT-Fatigue subscale scores range from 0 to 52, where higher scores represent less fatigue.

5.4.3 SF-36

The Standard SF-36 v2 survey is used to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight scales that can be scored individually (Maruish 2011). Note: Self-Evaluated Transition is not regarded as a scale.

Table 5-1 SF-36 domains

Domain	Total no. of items	Item
Physical Functioning	10	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role-Physical	4	4a, 4b, 4c, 4d
Bodily Pain	2	7, 8
General Health	5	1, 11a, 11b, 11c, 11d
Vitality	4	9a, 9e, 9g, 9i
Social Functioning	2	6, 10
Role-Emotional	3	5a, 5b, 5c
Mental Health	5	9b, 9c, 9d, 9f, 9h
Self-Evaluated Transition	1	2

Each item will have a precoded item value as outlined in the table below.

Table 5-2 Precoded item values

Domain	Item	Response Choice	Precoded value
Physical Functioning	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	Yes, limited a lot	1
		Yes, limited a little	2
		No, not limited at all	3
Role-Physical	4a, 4b, 4c, 4d	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
Bodily Pain	7	None	1
		Very mild	2
		Mild	3
		Moderate	4
		Severe	5
		Very severe	6
	8 (if both Items 7 and 8 are answered)	Not at all (and Item 7 Precoded value=1)	1
		Not at all (and Item 7 Precoded value=2 through 6)	1
		A little bit (and Item 7 Precoded value=1 through 6)	2
		Moderately (and Item 7 Precoded value=1 through 6)	3
		Quite a bit (and Item 7 Precoded value=1 through 6)	4
		Extremely (and Item 7 Precoded value=1 through 6)	5
	8 (if Item 7 is not answered)	Not at all	1
		A little bit	2
		Moderately	3
		Quite a bit	4
		Extremely	5
General Health	1	Excellent	1
		Very good	2
		Good	3
		Fair	4
		Poor	5

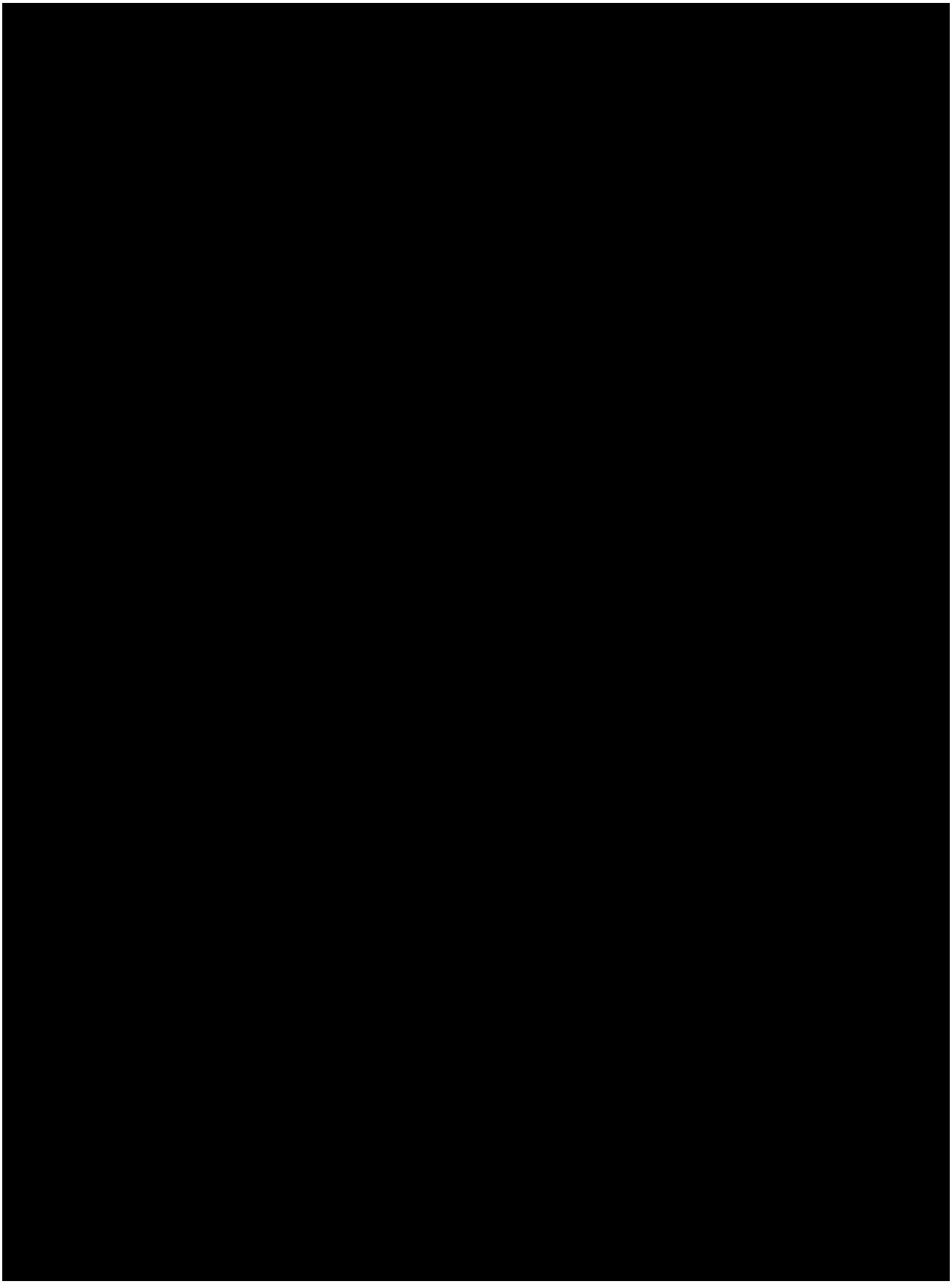
Domain	Item	Response Choice	Precoded value
	11a, 11c	Definitely True	1
		Mostly True	2
		Don't Know	3
		Mostly False	4
		Definitely False	5
	11b, 11d	Definitely True	1
		Mostly True	2
		Don't Know	3
		Mostly False	4
		Definitely False	5
Vitality	9a, 9e	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
	9g, 9i	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
Social Functioning	6	Not at all	1
		Slightly	2
		Moderately	3
		Quite a bit	4
		Extremely	5
	10	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
Role-Emotional	5a, 5b, 5c	All of the time	1
		Most of the time	2
		Some of the time	3

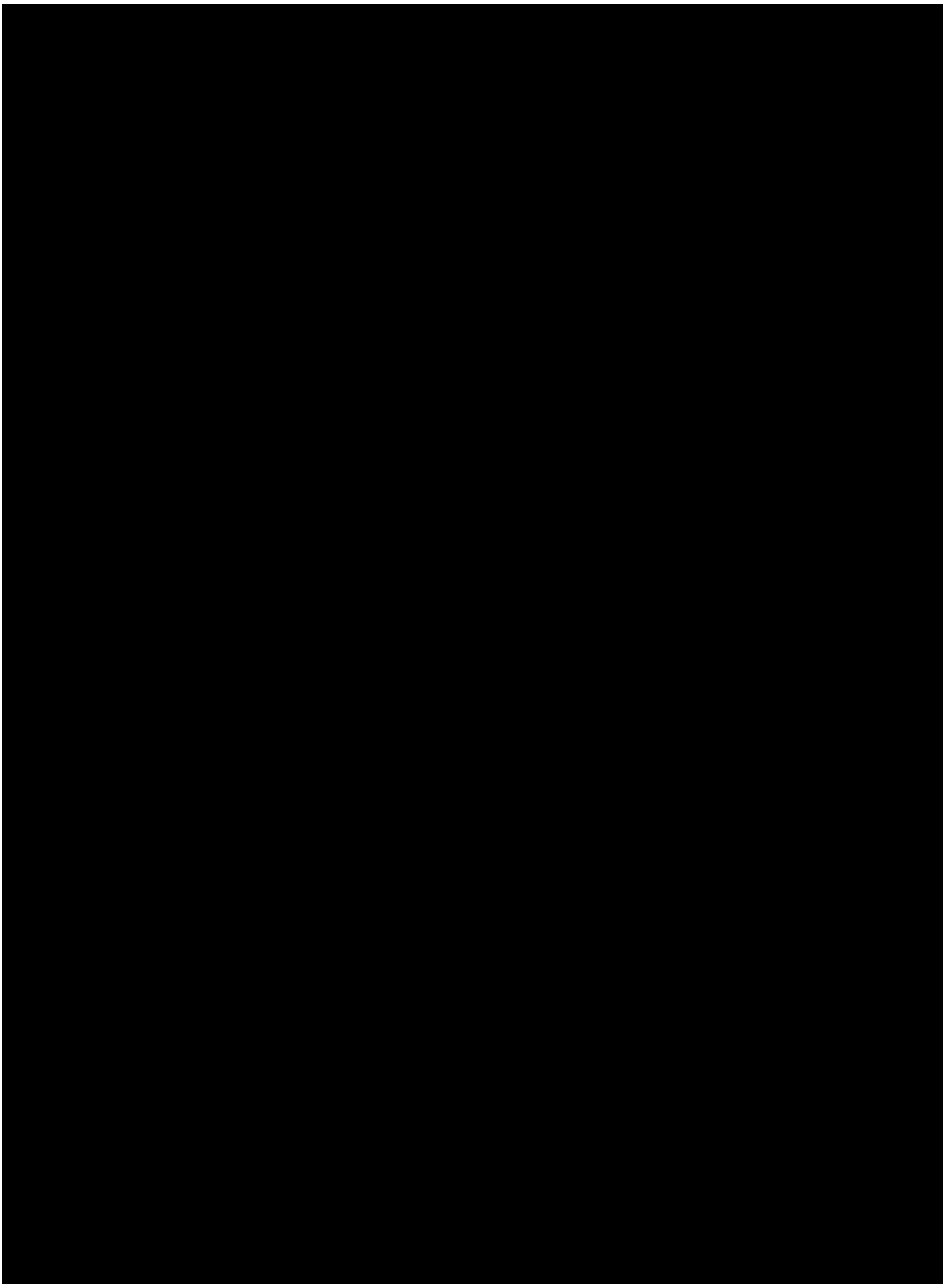
Domain	Item	Response Choice	Precoded value
		A little of the time	4
		None of the time	5
Mental Health	9b, 9c, 9f	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
	9d, 9h	All of the time	1
		Most of the time	2
		Some of the time	3
		A little of the time	4
		None of the time	5
Self-Evaluated Transition	2	Much better now than one year ago	1
		Somewhat better now than one year ago	2
		About the same as one year ago	3
		Somewhat worse now than one year ago	4
		Much worse now than one year ago	5

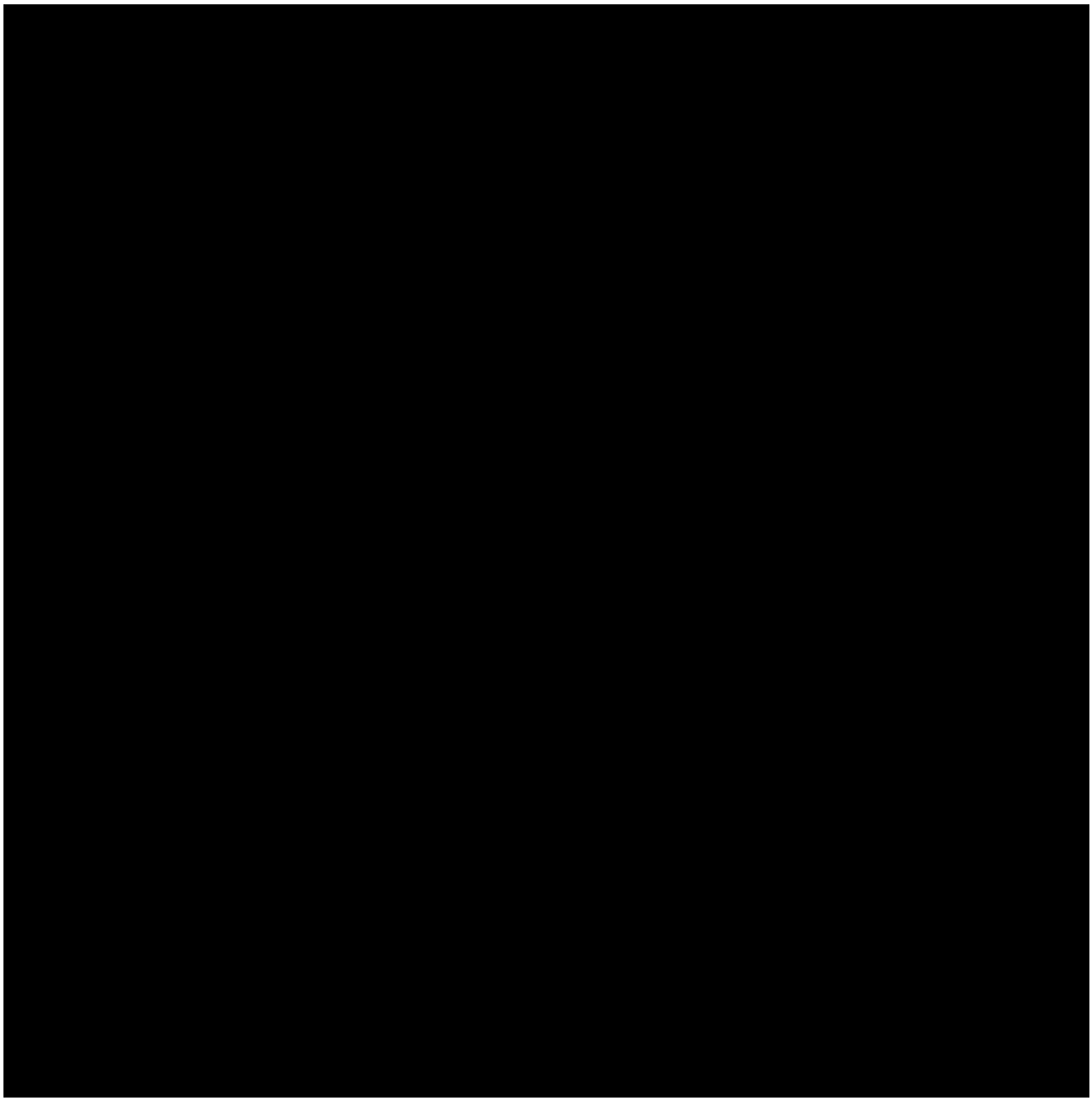
The source SF-36 data will be provided to the third party vendor Quality Metric via a secure data exchange. The vendor will complete the required derivations and provide a dataset to the Novartis study team containing:

- the scale scores transformed to 0 to 100 scores for each domain
- norm-based scores for each domain

  Note: These are the scores normed to the US population to have a mean of 50 and standard deviation of 10
- component summary scores (PCS, MCS)







5.5 Statistical models

Primary analysis

SAS Code for Bayesian Analysis

The Bayesian analysis will be performed using SAS.

Note that for this illustrative example:

- the data are stored in the file data_set
- response1 = number of patients in the secukinumab treatment group who fulfil the primary endpoint

- number1 = number of patients in the secukinumab treatment group in the population of interest
- a1, b1 = the shape parameters from the prior Beta distribution [Beta(a,b)] associated with the secukinumab treatment group
- response2 = number of patients in the placebo treatment group who fulfil the primary endpoint
- number2 = number of patients in the placebo treatment group in the population of interest
- a2, b2 = the shape parameters from the prior Beta distribution [Beta(a,b)] associated with the placebo treatment group

```
data <data_set>;
*** set the seed;
call streaminit(190207);
  *** one hundred thousand draws from the Beta posterior distributions;
  do draw=1 to 100000;
    ***secukinumb treatment group;
    post_resp1=RAND('BETA',<a1>+<response1>,<number1>+<b1><response1>);
    ***placebo treatment group;
    post_resp2=RAND('BETA',<a2>+<response2>,<number2>+<b2>-<response2>);
    ***risk difference;
    rd=post_resp1 - post_resp2;
    ***risk ratio;
    rr=post_resp1/post_resp2;
    ***odds ratio;
    or=(post_resp1/(1 - post_resp1))/(post_resp2/(1 - post_resp2));
    output;
  end;
run;

***obtain percentiles of interest to determine median and 95%
credibility interval;
proc univariate data=<data_set>;
  var post_resp1 post_resp2 rd rr or;
  output out=percentiles1 pctlpts=2.5 25 50 75 97.5 pctlpre=post1_
post2_rd_ rr_ or_;
run;

***determine probabilities of interest;
proc sql;
  create table prob1 as
  select mean(or gt 1) as probnor1,
         mean(rd gt 0.22) as probnrd1,
         mean(rd gt 0.38) as probnrd2,
         mean(rd gt 0) as probnrd3,
         mean(rr gt 1) as probnrr1
  from <data_set>;
quit;
```

Secondary analysis

SAS Code for Kaplan-Meier Plot

The time to event analysis will be performed using the SAS procedure PROC LIFETEST.

Note that for this illustrative example:

- the data are stored in the file data_set
- timevar = survival time
- censorvar = censoring variable (Note: 1 indicates a censored time)
- stratavar = stratification variable

```
ODS GRAPHICS ON;
PROC LIFETEST DATA=<data_set> PLOTS=survival (failure test at
risk(outside(0.15))=0 to 360 by 30);
TIME <timevar> * <censorvar> (1);
STRATA <stratavar>;
RUN;
```

The option OUTSIDE(0.15) reserves 15% of the vertical graph window for the at-risk table. It can be adjusted.

SAS Codes for Kaplan-Meier Table

The summary statistics for time to event analysis will be performed using SAS procedure PROC LIFETEST.

Note that for this illustrative example:

- the data are stored in the file data_set
- timevar = survival time
- censorvar = censoring variable (Note: 1 indicates a censored time)
- stratavar = stratification variable

```
PROC LIFETEST DATA = <data_set> method=km
                                conftype=linear;
TIME <timevar> * <censorvar> (1);
STRATA <stratavar>;
RUN;
```

SAS code for logistic regression

For the appropriate treatment difference, the treatment cohorts should be sorted or coded appropriately before using this model.

The analysis will be performed using SAS procedure PROC GENMOD as below. Note that for this illustrative example:

- the data are stored in the file data_set
- treatmentvar = treatment cohort variable
- responsevar = dependent variable
- catvar = categorical variable of interest

- contvar = continuous variable of interest

```
PROC GENMOD DATA = <data_set>;
CLASS <treatmentvar> <catvar>
TABLES <responsevar> = <treatmentvar> <catvar> <contvar> / DIST=BINOMIAL
LINK=LOGIT;
LSMEANS <treatmentvar> / PDIFF CL;
RUN;
```

5.6 Rule of exclusion criteria of analysis sets

Table 5-4 Protocol deviation categories used

PD Category	PD Code
Eligibility	INCL or EXCL
Discontinuation of treatment/ study	WITH
Prohibited Concomitant Medication	COMD
Study drug (incorrect dose, wrong treatment)	TRT
Other	OTH

The full list of protocol deviations are defined in the edit check specifications which is located in the document management system in the following folder:

- 'CREDI Projects/A/AIN457A/CREDI Studies/AIN457ADE11C/Administrative Files (study level)/Validation and Planning documents'

Table 5-5 Patient classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
RAS	OTH03	No informed consent; Not randomized
FAS	OTH03	No informed consent; Not randomized; No study drug taken during the study
Safety Set	OTH03	No informed consent; No study drug taken during the study

6 References

CAIN457 Project Master Analysis Plan (MAP)

- [CREDI Projects/A/AIN457A/Administrative files/CIS (Clinical Information Sciences)/Biostatistics – AIN457 safety MAP M3 Amendment 5]
- [CREDI Projects/A/AIN457A/Administrative files/CIS (Clinical Information Sciences)/Biostatistics – AIN457A efficacy MAP M3 Amendment 5]

CAIN457ADE11C Protocol

- [CREDI Projects/A/AIN457A/CREDI Studies/AIN457ADE11C/CSP (Clinical Study Protocol) – CAIN457ADE11C_Protocol_V02_Final_13052019_clean.pdf]

[Novartis (2020) COVID-19 (Coronavirus) Guidance Start and End Dates by Region for Sensitivity Analyses; Version 3.0 28-Oct-2020.]

[redacted]

Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated.

Stone J, Tuckwell K, Dimonaco S, et al (2017) Trial of Tocilizumab in Giant-Cell Arteritis. The New England Journal of Medicine. N Engl J Med;377:317-328.