NOVARTIS

Global Clinical Development - General Medicine

AIN457/Secukinumab

Clinical Trial Protocol CAIN457K2340 / NCT03259074

A randomized, partially-blinded, active-controlled multicenter study of secukinumab to demonstrate reduction of radiographic progression versus GP2017 (adalimumab biosimilar) at 104 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis

Document type:	Clinical Trial Protocol
EUDRACT number:	2017-000679-10
Version number:	v02 (Clean)
Clinical trial phase:	IIIb
Release date:	04-Feb-2021

Clinical Trial Protocol Template Version 3.1 (February 2016)

[redacted]

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List of abbreviations

[redacted]	[redacted]
AE	adverse event
ALT/SGPT	alanine aminotransferase/ serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Ankylosing SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
[redacted]	[redacted]
ASspiMRI-a	Ankylosing Spondylitis Spine Magnetic Resonance Imaging - activity
AST/SGOT	aspartate aminotransferase/ serum glutamic oxaloacetic transaminase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BMI	body mass index
BSL	baseline
CFR	US Code of Federal Regulations
CI	Confidence interval
CRF	case report/record form (paper or electronic)
CRO	contract research organization
CRP (hsCRP)	(high sensitivity) C-reactive protein
CSR	clinical study report
CTC	Common Terminology Criteria
DMARD	disease modifying anti-rheumatic drug
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
ELISA	enzyme-linked immuno sorbent assay
EMA	European Medical Agency
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GP2017	GP2017 (adalimumab biosimilar)
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
IFU	Instructions for Use

[redacted]

[redacted]	[redacted]
IL	interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	interactive response technology
i.v.	Intravenous(ly)
LDL	low density lipoprotein
LLN	lower limit of normal
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter of mercury
MRI	magnetic resonance imaging/image
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
[redacted]	[redacted]
[redacted]	[redacted]
PFS	pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PPD	purified protein derivative
PRN	pro re nata
PRO	patient reported outcome(s)
PsA	psoriatic arthritis
[redacted]	[redacted]
RBC	red blood cell
SAE	serious adverse event
s.c.	subcutaneous(ly)
SCR	screening
[redacted]	[redacted]
SI	sacroiliac
SmPC	Summary of Product Characteristics
SpA	spondyloarthritides
STIR	short tau inversion recovery
SUSAR	suspected unexpected serious adverse reactions
SV	screening visit
TD	study treatment discontinuation
TNF/TNFα	Tumor Necrosis Factor/ Tumor Necrosis Factor alpha
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
[redacted]	[redacted]

[redacted]

WoC	withdrawal of consent

[redacted]

Glossary of terms

Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Subject ID	A unique number assigned to each subject upon signing the informed consent
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. These data include subject identifier information, study information and biological samples
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 2

Amendment rationale

This protocol amendment is issued to align the blinding strategy between subjects, investigators, site and sponsor personnel.

As per the original study design:

- Subjects, investigators, site personnel, persons performing the assessments and monitors are unblinded to the study drug received. Secukinumab or GP2017 is supplied in an open label fashion (Section 5.4).
- Subjects, investigators, site personnel, persons performing the assessments, monitors and the Sponsor (with the exception of the bioanalyst) are blinded to secukinumab dose (150 mg, 300 mg). Designated Sponsor personnel involved in study conduct and the statistical analysis plan have been blinded to treatment group, GP2017 or secukinumab.

Due to the difference in blinding strategy between the site staff, monitors and the designated Sponsor personnel, accidental unblinding incidences with respect to study drug allocation of secukinumab vs GP2017 are occurring at an increasing rate, despite preventative measures. This is due to ongoing data review whereby information such as dosing frequency or therapy on study completion has to be regarded as potentially unblinding.

Therefore, in this amendment, the blinding strategy will be aligned between subjects, investigators, site personnel and the Sponsor. The designated Sponsor personnel will become unblinded to treatment group (GP2017 or secukinumab).

The dose of secukinumab (150 mg or 300 mg) will remain blinded, in a double blind fashion, for all (Section 5.4) in order to minimize the potential bias in the assessment and analysis of a potential dose-related response.

Patient flow through the study is not affected in any way by this amendment.

Primary and radiographic secondary endpoints will remain unaffected, as the images are scored by central imaging experts, who will remain fully blinded to study drug, secukinumab dose, and time point for efficacy.

There are no changes to informed consent forms or electronic database.

The ECG analysis in Section 9.5.3 was revised to reflect the protocol assessment table, which does not include post-baseline ECG collection.

Section 9.5.1 was modified to align with Amendment v.01 language.

Typographical errors were also corrected in Section 9.4.2.

At the time of this amendment, enrollment has been completed and all subjects have completed Week 52.

Amendment 1

Amendment rationale

This protocol amendment is primarily issued for the following reasons:

- New evidence observed from a long-term secukinumab ankylosing spondylitis Phase III study indicated a trend of dose-response between secukinumab 75 mg and 150 mg doses with intravenous loading on a Week 208 radiographic endpoint (Braun 2017). A similar observation with a more pronounced dose-response was observed in a secukinumab psoriatic arthritis Phase III study between secukinumab 150 mg and 300 mg doses with subcutaneous loading on a Week 24 radiographic endpoint (Mease 2018). Given this new evidence along with the need for clarity in defining estimands from the recently endorsed draft ICH E9 Addendum, the estimand attributes were rewritten, keeping the same strategy for addressing intercurrent events, but the testing was revised from a pooled secukinumab dose group versus GP2017 in the primary objective to compare the individual secukinumab doses versus GP2017. Thus, the primary objective was changed as follows: "To demonstrate the proportion of subjects on secukinumab (~~**combined**~~ 150 mg s.c. ~~**and**~~ **or** 300 mg s.c.) with no radiographic progression as measured by mSASSS at Week 104 is superior to subjects on GP2017 (adalimumab biosimilar 40 mg s.c.)." The statistical testing was altered to align with this change. However, the revision to the primary objective does not affect the sample size calculation of the study treatment arms.
- The Withdrawal of Consent (WoC) language (Section 5.6.3) has been revised according to the European Economic Area (EEA) General Data Protection Regulation (GDPR) required guidelines.
- In order to make the data collection process more fluent between the latest clinical database and the IRT, the Visit Name / Visit Number row in Table 6-1 "Assessment schedule" was removed.

At the time of this amendment, all subjects have been randomized into the study. Thus, no change to the study population is proposed by this amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underline for insertions.

The wording of the statistical testing strategy and power calculation as a result of the changes in the primary objective has been amended to reflect the rationale given above (Section 9).

[redacted]

The wording in the following sections, "Systemic corticosteroids" and Table 5-1 "Prohibited medication" (Section 5.5.7) has been amended to provide greater clarity.

Consistent with the interpretation from the original protocol, clarifying language regarding the collection of eligibility SI joint X-rays was added to Table 6-1 footnotes.

[redacted]

Additionally, this protocol amendment includes the correction of typographical and formatting errors and minor editorial changes for increased clarity of the text. Consequently, a small number of changes were implemented throughout the protocol.

None of the changes described in this amended protocol are made due to newly emerged safety considerations.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities as required.

[redacted]

Protocol summary

Protocol number	AIN457K2340
Title	A randomized, partially-blinded, active-controlled multicenter study of secukinumab to demonstrate reduction of radiographic progression versus GP2017 (adalimumab biosimilar) at 104 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis
Brief title	Study of the effect of secukinumab on radiographic progression in ankylosing spondylitis as compared to GP2017 (adalimumab biosimilar)
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate the impact on progression of structural damage in the spine as measured by the mSASSS in patients with AS. Data from this study will be used to support the submission of an AS label extension to include a claim on radiographic progression.
Primary Objective(s)	The primary objective of this study is to demonstrate the proportion of subjects on each secukinumab dose with no radiographic progression as measured by mSASSS at Week 104 is superior to subjects on GP2017 (adalimumab biosimilar).
Secondary Objectives	Objective 1: To demonstrate the change from baseline in mSASSS in subjects on each secukinumab dose is superior to GP2017 (adalimumab biosimilar) at Week 104. Objective 2: To demonstrate the proportion of subjects with a syndesmophyte at baseline with no new syndesmophytes at Week 104 on each secukinumab dose is superior to GP2017 (adalimumab biosimilar). Objective 3: To evaluate the Berlin sacroiliac (SI) joint edema score in subjects on each secukinumab dose at Week 104 versus GP2017 (adalimumab biosimilar) (in a subset of subjects at selected sites). Objective 4: To evaluate the ASspiMRI-a Berlin modification score in subjects on each secukinumab dose at Week 104 versus GP2017 (adalimumab biosimilar) (in a subset of subjects at selected sites). Objective 5: To evaluate ASAS 20 response, ASAS 40 response, ASAS partial remission and ASDAS inactive disease in subjects on secukinumab at Week 104. Objective 6: Overall safety and tolerability of secukinumab.
Study design	This is a multicenter, randomized, partially-blinded, active-controlled, parallel-group study.
Population	Male or female patients at least 18 years of age with AS fulfilling the Modified New York criteria for classification of ankylosing spondylitis, and with moderate to severely active disease despite previous or current NSAIDs/non-biologic DMARDs and with no prior history of biologic DMARDs (including anti-TNFα agent) therapy.

[redacted]

Key Inclusion criteria	Patients must have active AS, despite previous or current NSAIDs/ non-biologic DMARDs therapy, as measured by total BASDAI ≥ 4 on a scale of 0-10, spinal pain as measured by BASDAI question #2 ≥ 4 (0-10) and total back pain as measured by visual analog scale (VAS) ≥ 40 mm (0-100 mm). • Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed • Male or non-pregnant, non-lactating female patients at least 18 years of age • Diagnosis of moderate to severe AS with radiologic evidence (centrally read X-ray) fulfilling the Modified New York criteria for AS (Appendix 3) • Active AS assessed by total BASDAI ≥ 4 (0-10) at Baseline • Spinal pain as measured by BASDAI question #2 ≥ 4 (0-10) at Baseline • Total back pain as measured by VAS ≥ 40 mm (0-100 mm) at Baseline • hsCRP ≥ 5 mg/L OR presence of at least 1 syndesmophyte on centrally read spinal X-ray • Patients should have been on NSAIDs at the highest tolerated dose for at least 8 weeks prior to randomization with an inadequate response or failure to respond, or less than 8 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications • Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy are required to be on a stable dose for at least 2 weeks before randomization • Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization • Patients on MTX must be on stable folic acid supplementation before randomization • Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization • Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization
Key Exclusion criteria	• Patients with total ankylosis of the spine • Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician • Previous exposure to secukinumab, adalimumab or any other biological immunomodulating agent, including those targeting IL-17, IL-17 receptor or TNFα • Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine, oxycodone) • Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer

	• Any intramuscular corticosteroid injection within 2 weeks before randomization • Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19) • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in EU). • Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab or adalimumab therapy, including inflammatory bowel disease or uveitis • Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy • Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/100 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care • History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. • History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L) • Screening total WBC count < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL (85 g/L) • History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive central laboratory tuberculosis screening test as indicated in the assessment schedule in Table 6-1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated • Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization • History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been

[redacted]

	treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
Study treatment	AIN457 secukinumab GP2017 (adalimumab biosimilar)
Efficacy assessments	• X-ray of the cervical and thoraco-lumbar spine assessed by modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) • MRI of the spine and SI joints assessed by ASspiMRI-a Berlin modification score and Berlin SI joint edema score • Assessment of SpondyloArthritis International Society criteria (ASAS) • Patient's global assessment of disease activity (VAS) • Patient's assessment of back pain intensity (VAS) • Bath Ankylosing Spondylitis Functional Index (BASFI) • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • hsCRP • ASDAS response categories
Key safety assessments	• Evaluation of adverse events/ serious adverse events • Tuberculosis central laboratory test or local PPD skin test • Chest X-ray or MRI • Physical examination • Vital signs • Height and weight • Laboratory evaluations [redacted] • Pregnancy and assessment of fertility • Local tolerability (injection site reactions) • Tolerability of study treatment
Other assessments	[redacted]
Data analysis	The primary endpoint in the study is no radiographic progression (change from baseline ≤ 0.5) at Week 104. The statistical hypothesis tests secukinumab 150 mg s.c. or 300 mg s.c. versus GP2017 40 mg as the primary endpoint at Week 104 using the full analysis set.
Key words	ankylosing spondylitis, secukinumab, GP2017, adalimumab biosimilar, mSASSS, ASAS 20

[redacted]

1 Introduction

1.1 Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides (SpA). It is mainly characterized by involvement of the axial skeleton and sacroiliac (SI) joints, but also affects peripheral joints, entheses and extra-articular organs. A significant proportion of patients may present with associated extra-articular manifestations such as uveitis, psoriasis, inflammatory bowel disease (IBD), cardiovascular and pulmonary abnormalities. Generalized osteoporosis, as well as regional osteopenia are common in AS patients and predispose them to non-traumatic fractures in spite of young age and gender (male). The presence of the HLA-B27 human leukocyte antigen is strongly associated with AS: 90–95% of patients with AS who have European ancestry carry this marker. AS affects up to 1.1% of the population, is associated with significant morbidity and disability, and thus constitutes a major socio-economic burden.

First-line medication of mild AS consists of non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAID-refractory AS is hampered by the lack of efficacy of virtually all standard disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX). Tumor necrosis factor (TNF) blocking agents were successfully added to the armamentarium to treat AS (Braun 2002) and subsequently demonstrated prolonged efficacy up to eight years of follow-up (Baraliakos 2011). However, upon discontinuation of TNF blockers the disease relapses quickly (Baraliakos 2005), indicating that the inflammatory process may have only been inhibited but not completely abolished.

Secukinumab, a human monoclonal antibody that inhibits the effector function of IL-17A, has been previously shown to be better than placebo in improving the signs and symptoms of AS. In the Phase III MEASURE 1 and MEASURE 2 studies of 590 patients with AS, secukinumab significantly improved key clinical domains of disease versus placebo, including signs and symptoms, physical functioning, and quality of life (Baeten 2015).

Secukinumab as well as a number of anti-TNFs including adalimumab are approved for treatment of patients with active AS (Cosentyx® and Humira® package inserts and SmPCs). Results on signs and symptoms with both secukinumab and adalimumab have demonstrated good response along with rapid reduction of SI-joint and spinal inflammation as evidenced by MRI.

One of the key features of AS contributing to long term disability is the process of structural remodeling in the axial skeleton and the SI-joints. This process as evidenced by SI and spinal radiography typically begins with subchondral sclerosis in the SI-joints along with squaring and marginal sclerosis of the vertebral bodies. Over time SI joint erosions occur and vertebral body syndesmophytes form, ultimately leading to spinal fusion (Sieper 2009). The process is slow, progresses over 10 – 15 years and includes both osteoproliferative as well as absorptive processes.

Studies evaluating the effects of the anti-TNF agents adalimumab, etanercept and infliximab on radiographic damage in patients with AS did not demonstrate inhibition of radiographic progression after approximately 2 years of therapy compared to a historical cohort. The comparisons to the historical cohorts that had been treated with NSAIDs only have shown a

mean modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) progression of 0.8-0.9 over 2 years, regardless of anti-TNF or NSAID treatment (van der Heijde 2008a, van der Heijde 2008b, van der Heijde 2009).

Two-year spinal X-ray data from the secukinumab pivotal study MEASURE 1 suggest that IL-17A inhibition may have the potential to decrease spinal structural progression as evidenced by a mean mSASSS change after 2 years of therapy of ~ 0.3. This speaks to the potential of secukinumab to influence the long-term structural progression in the spine of patients with AS (Braun 2016).

However, a need exists for comparative studies to assess how different mechanisms of action can reverse or slow down structural progression. This will be the first study comparing an anti-IL17A treatment with an anti-TNF agent in AS. This study will provide critical scientific evidence that will improve evidence-based decision making in the treatment of patients with AS and play an important role in filling the current data gap between clinical research and day-to-day clinical practice on the therapeutic utility of biologic therapy in patients with active AS.

As of 25-Jun-2016, over 13,000 healthy subjects and patients have been enrolled into clinical studies with secukinumab, of whom approximately 9,600 have received at least one dose of secukinumab. Overall, secukinumab studies have investigated various indications (Rheumatoid Arthritis (RA), AS, Psoriatic Arthritis (PsA), psoriasis, multiple sclerosis, uveitis, Crohn's disease, dry eye syndrome, polymyalgia rheumatica) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. As of Jan-2016, secukinumab has been approved for the treatment of AS in the European Union, the US and multiple other countries. Full safety results from completed studies for AS, PsA and psoriasis show that secukinumab generally is safe and well tolerated. Please refer to the Investigator's Brochure (IB) for a more detailed review of the risk:benefit profile of secukinumab which supports the clinical development for the treatment of AS patients with secukinumab.

1.2 Purpose

The purpose of this study is to demonstrate the impact on progression of structural damage in the spine as measured by the mSASSS in patients with AS. Data from this study will be used to support the submission of an AS label extension to include a claim on radiographic progression.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate the proportion of subjects on secukinumab (150 mg s.c. or 300 mg s.c.) with no radiographic progression as measured by mSASSS at Week 104 is superior to subjects on GP2017 (adalimumab biosimilar 40 mg s.c.).

2.2 Secondary objectives

1. To demonstrate the change from baseline in mSASSS in subjects on secukinumab (150 mg s.c. or 300 mg s.c.) is superior to GP2017 (adalimumab biosimilar 40 mg s.c.) at Week 104.

[redacted]

2. To demonstrate the proportion of subjects with a syndesmophyte at baseline with no new syndesmophytes at Week 104 on secukinumab (150 mg s.c. or 300 mg s.c.) is superior to GP2017 (adalimumab biosimilar 40 mg s.c.).
3. To evaluate the Berlin SI joint edema score in subjects on secukinumab (150 mg s.c. or 300 mg s.c.) at Week 104 versus GP2017 (adalimumab biosimilar 40 mg s.c.) (in a subset of subjects at selected sites).
4. To evaluate the ASspiMRI-a Berlin modification score in subjects on secukinumab (150 mg s.c. or 300 mg s.c.) at Week 104 versus GP2017 (adalimumab biosimilar 40 mg s.c.) (in a subset of subjects at selected sites).
5. To evaluate ASAS 20 response, ASAS 40 response, ASAS partial remission and ASDAS inactive disease in subjects on secukinumab 150 mg s.c. compared to secukinumab 300 mg s.c. at Week 104.
6. Overall safety and tolerability of secukinumab.

3 Investigational plan

3.1 Study design

This multicenter study uses a randomized, partially-blinded, active-controlled, parallel-group design in subjects with AS. A screening period (SCR) of up to 10 weeks before randomization will be used to assess eligibility followed by 104 weeks of treatment. Two follow-up visits at Weeks 112 and 120 will occur thereafter.

At baseline (BSL), approximately 837 subjects whose eligibility is confirmed will be randomized to one of three treatment groups (1:1:1).

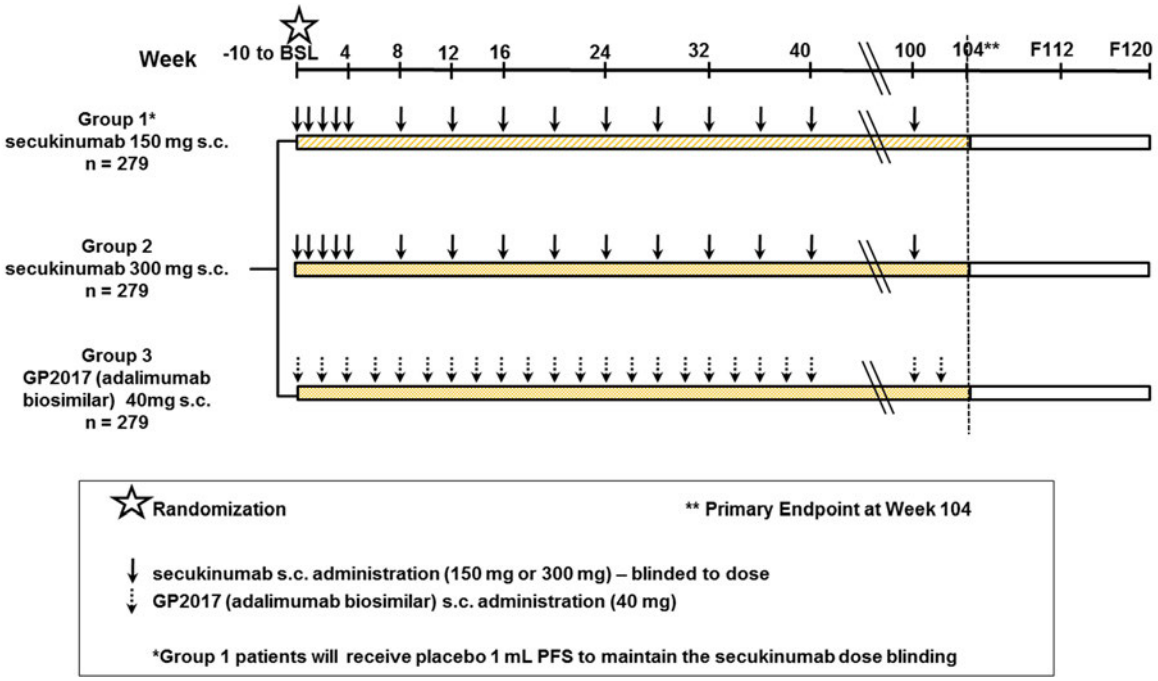
- Group 1: secukinumab 150 mg [1 x 1.0 mL s.c. plus placebo (1 x 1.0 mL s.c.)] at BSL, Weeks 1, 2 and 3, followed by administration every four weeks starting at Week 4
- Group 2: secukinumab 300 mg (2 x 1.0 mL s.c.) at BSL, Weeks 1, 2 and 3, followed by administration every four weeks starting at Week 4
- Group 3: GP2017 (adalimumab biosimilar) 40 mg (1 x 0.8 mL s.c.) at BSL followed by administration every two weeks

Although study treatment (secukinumab vs GP2017) will be provided in an open-label fashion to the subjects, secukinumab study treatment will be blinded to the dose. Subjects in groups 1 and 2 will know that they are on secukinumab, but will be blinded to which treatment arm and will not know whether they are receiving secukinumab 150 mg or 300 mg. Subjects in the GP2017 treatment group will know that they are receiving GP2017 (adalimumab biosimilar) 40 mg. Sponsor blinding is described in Section 5.4.

Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue treatment with prohibited medications (as described in Section 5.5.8) occurs, subjects may remain in the study but must discontinue study treatment. All subjects may remain in the study and should continue study-related assessments up to completion, regardless of whether they continue study treatment or not. Subjects who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue study treatment only or any further participation in the study at any time.

Two follow-up visits are to be completed after last administration of study treatment for all subjects, regardless of whether they complete the entire study as planned or discontinue prematurely.

Figure 3-1 Study design



3.2 Rationale for study design

The subject population will be described in more detail in the Section 4 below.

The randomized, partially-blinded, active-controlled, parallel-group design used in this study is based on the primary focus of this study, which is to demonstrate the ability of secukinumab to slow structural spinal progression over time relative to current standard of care for AS. The primary objective is based on mSASSS scoring of spinal X-rays obtained at baseline and Week 104, which will be conducted in a fully blinded fashion in this study with a partially-blinded design. Spinal structural progression in AS is known to be a slow process. Thus, the length of the study is required to be 2 years in order to detect radiographic changes and fully demonstrate the potential impact of therapy.

Evaluations of mSASSS scoring for the primary objective will be conducted by three independent readers who will be blinded to the subject name, subject initials, exam date, order of image acquisition, investigator site identifiers, study treatment group, and all other efficacy and safety assessments. As previously noted, a partially-blinded design will not bias the analysis of the primary or secondary radiographic endpoints, which are not subject or physician reported outcomes.

Adalimumab is a commonly used anti-TNF agent in AS and confers similar efficacy to secukinumab in terms of signs and symptoms (van der Heijde 2006). Radiographic progression data for AS subjects on adalimumab for up to 2 years are published and provide statistical

assumptions for the powering of the primary endpoint (van der Heijde 2009). Thus, adalimumab is well suited as the active comparator in this study.

While the GP2017 (adalimumab biosimilar) treatment group will be supplied with unblinded study medication, the secukinumab treatment groups will be blinded to the dose of secukinumab through the use of a blinded placebo injection in the 150 mg s.c. group. The blinding of the secukinumab treatments (150 mg or 300 mg) will allow for an evaluation of a potential dose-response of the 150 mg and 300 mg secukinumab doses on both efficacy and safety outcomes.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The secukinumab dosing regimens in this study are based upon the currently approved dose for AS, which is 150 mg s.c. every 4 weeks (with or without a loading dosage of 150 mg at Weeks 0, 1, 2, 3, and 4; country dependent), as well as the 300 mg s.c. dose, which is approved for PsA.

Notably, 300 mg s.c. administered monthly is an approved dose for secukinumab in both psoriasis and in PsA, and the safety profile for 300 mg s.c. every 4 weeks is comparable to 150 mg s.c. every 4 weeks (Langley 2014, Mease 2015). The higher dose of secukinumab confers an additional benefit in other disease conditions (e.g., psoriasis and PsA). This study will evaluate whether a higher dose of secukinumab will have an effect on subjects with AS with respect to structural spinal progression. While it will be known if the subject is receiving secukinumab or GP2017, the dose of secukinumab will be blinded. This will allow an assessment of the effect of 150 mg and 300 mg in an unbiased manner, as no study has yet assessed both 150 mg or 300 mg s.c. in AS.

Based on the rationale above, this study will evaluate both secukinumab 150 mg and 300 mg s.c. doses for the treatment of adults with active AS compared with GP2017 (adalimumab biosimilar) s.c. injection. As a biosimilar to adalimumab, the dosing of GP2017 reflects that of Humira®. Adalimumab is approved for the treatment of AS at a recommended dose of 40 mg administered s.c. every other week, which matches the treatment regimen that subjects randomized to the GP2017 treatment group will receive.

In summary, the secukinumab doses in this study are based on the approved AS dose and a well-characterized safety profile for both proposed secukinumab doses across the PsA, psoriasis and AS indications; the dose for the GP2017 active control is based on an approved dose demonstrating optimal efficacy and safety in subjects with AS.

Formulation to be used

This study will use secukinumab 150 mg/ 1 mL and placebo liquid in single-use pre-filled syringes (PFS). An investigational adalimumab biosimilar (GP2017) in the dose approved for AS (40 mg/ 0.8 mL) in a single-use PFS will be used.

3.4 Rationale for choice of comparator

An active comparator group is necessary to evaluate the structural benefit of secukinumab as compared to an approved standard of care therapy in AS. The randomized parallel-group controlled design is the most appropriate method to compare the two therapies and is consistent

[redacted]

with the study of other biologics in the treatment of AS, as outlined in EMA guidelines (EMA 2003).

In order to compare the structural effect of secukinumab 150 mg and 300 mg to the only other class of biologics (anti-TNF agents) approved for the treatment of AS, adalimumab was chosen as a commonly accepted reference therapy that is considered standard of care. GP2017 (40 mg s.c.), an investigational adalimumab biosimilar, will be utilized for the active comparator treatment arm. GP2017 is being developed as a proposed biosimilar to Humira® and includes adalimumab as the active ingredient. Due to the physicochemical and functional similarity between GP2017 and Humira® (EU-authorized and US-licensed), the expectation is that the clinical efficacy and safety profile of GP2017 will be similar to that of Humira®, whose favorable risk-benefit ratio has been established in a wide range of clinical trials and by a substantial amount of post-marketing experience (refer to the latest edition of GP2017 Investigator's Brochure).

This study does not include a placebo arm. Efficacy in terms of signs and symptoms is well-established for both secukinumab and adalimumab for subjects with active AS. Moreover, a placebo cohort would not be deemed ethically justifiable for this 2-year study, as AS is known to be a chronic progressive disease with structural damage.

[redacted]

3.6 Risks and benefits

Secukinumab has shown efficacy in several inflammatory diseases, including AS, PsA, and psoriasis. The large safety dataset of secukinumab across indications involving over 9,600 subjects did not show unexpected safety issues relative to the known mode of action. Secukinumab is safe and well-tolerated and has demonstrated a similar safety profile to etanercept and ustekinumab in two head-to-head comparison studies over one-year in psoriasis (Langley 2014, Thaçi 2015). The most frequently reported adverse events (AEs) are non-serious mild to moderate infections, mainly upper respiratory tract infections. In addition, there was an increase in localized mucosal or cutaneous candidiasis with secukinumab compared with placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment and did not require discontinuation of secukinumab. There was also a small increase in neutropenia cases with secukinumab compared with placebo. Most cases were mild to moderate, transient and reversible and without a temporal relationship to infections. Common Terminology Criteria (CTC) AE grade 3 neutropenia (< 1.0-0.5 x 10^9/L) was uncommonly observed with secukinumab. Hypersensitivity reactions include urticaria and rare events of anaphylactic reaction to secukinumab have also been observed in clinical studies.

With adalimumab, the most common AEs (incidence > 10%) across indications are infections (e.g., upper respiratory, sinusitis), injection site reactions, headache and rash (Humira® package insert, Humira® SmPC). The most common serious adverse events (SAEs) were serious infections including hepatitis B virus reactivation, neurologic or hematological reactions,

[redacted]

autoimmune disorders and malignancies. In clinical trials of Humira®, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) were observed in approximately 1% of subjects. The contraindications, precautions and warnings, as summarized in the Humira® SmPC apply also for the use of GP2017 (adalimumab biosimilar).

The immunogenicity potential, i.e. of eliciting anti-drug antibodies (ADA), is higher for adalimumab (up to 26%) than for secukinumab (< 1%). However, the presence of ADAs does not appear to be associated with development of adverse reactions for either secukinumab or adalimumab, although the development of ADAs has been associated with secondary treatment failure to adalimumab, but not to secukinumab (Cosentyx® package insert, Humira® package insert, Humira® SmPC).

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from its mechanism of action is anticipated to be similar or improved compared to the other approved inflammatory cytokine-targeting therapies. The expected safety profile for GP2017, as a biosimilar adalimumab, will also be expected to be similar to the reference safety profile of Humira® (Humira® package insert, Cosentyx® package insert). The risk to subjects in this study will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and extensive guidance for the investigators provided by Novartis and in the current version of the IBs for secukinumab and GP2017. Based on the overall risk-benefit assessment, along with the fact that secukinumab and adalimumab are approved treatments for subjects with active AS, the current study evaluating secukinumab with investigational adalimumab biosimilar as the comparator is justified.

4 Population

The study population will consist of male and female patients (≥ 18 years old at the time of consent) with AS fulfilling the Modified New York criteria for classification of ankylosing spondylitis (described in Appendix 3), and with moderate to severely active disease despite previous or current NSAIDs/ non-biologic DMARDs and with no prior history of biologic DMARDs (including anti-TNFα agent) therapy.

Patients must have a history of active AS, as measured by the following three assessments:

- total BASDAI ≥ 4 on a scale of 0-10
- spinal pain as measured by BASDAI question #2 ≥ 4 (0-10)
- total back pain as measured by visual analog scale (VAS) ≥ 40 mm (0-100 mm)

The study aims to randomize approximately 837 patients at approximately 200 centers worldwide. Since a 25% screening failure rate is expected, approximately 1,116 patients will be screened. Enrollment will stop as soon as the target number of randomized subjects is reached.

Patients may be re-screened only once, and no study-related re-screening procedure should be performed prior to written re-consent by the patient. Mis-randomization occurs when a patient who does not meet all eligibility criteria nevertheless receives a randomization number incorrectly; mis-randomized patients will not be re-screened.

[redacted]

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of moderate to severe AS with radiologic evidence (centrally read X-ray) fulfilling the Modified New York criteria for AS (Appendix 3)
4. Active AS assessed by total BASDAI ≥ 4 (0-10) **at Baseline**
5. Spinal pain as measured by BASDAI question #2 ≥ 4 (0-10) **at Baseline**
6. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) **at Baseline**
7. hsCRP ≥ 5 mg/L **OR** presence of at least 1 syndesmophyte on centrally read spinal X-ray
   - Subjects are permitted to have one hsCRP re-test during the screening period.
   - Spinal X-rays obtained to confirm presence of syndesmophytes will be performed after hsCRP results are confirmed by the central lab to be < 5 mg/L and must be confirmed by the central imaging vendor prior to inclusion in the study.
8. Patients should have been on NSAIDs at the highest tolerated dose for at least 8 weeks prior to randomization with an inadequate response or failure to respond, or less than 8 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications
9. Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy are required to be on a stable dose for at least 2 weeks before randomization
10. Patients taking MTX (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization
11. Patients on MTX must be on stable folic acid supplementation before randomization
12. Patients who are on a DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization
13. Patients taking systemic corticosteroids have to be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Patients with total ankylosis of the spine
2. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician
3. Previous exposure to secukinumab, adalimumab or any other biological immunomodulating agent, including those targeting IL-17, IL-17 receptor or TNFα
4. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine, oxycodone)

[redacted]

5. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer
6. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
7. Any intramuscular corticosteroid injection within 2 weeks before randomization
8. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g., 20 weeks for secukinumab, 5 months for adalimumab in EU). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

    In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of

[redacted]

the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

11. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab or adalimumab therapy, including inflammatory bowel disease or uveitis
12. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
13. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/100 mmHg), congestive heart failure (New York Heart Association status of class III or IV), uncontrolled diabetes, or very poor functional status unable to perform self-care
14. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
15. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L)
16. Screening total WBC count < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL (85 g/L)
17. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
18. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive central laboratory tuberculosis screening test as indicated in the assessment schedule in Table 6-1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
19. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization
20. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
21. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the study

[redacted]

22. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
23. Inability or unwillingness to receive injections with PFS
24. Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
25. Donation or loss of 400 mL or more of blood within 8 weeks before randomization
26. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization
27. Patients who know they will be unable to complete 2 year study treatment period
28. Plans for administration of live vaccines during the study period or 6 weeks prior to randomization

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study drugs:

Investigational treatment:

- Secukinumab 150 mg, liquid formulation in 1 mL PFS

Reference treatment:

- Placebo, liquid formulation in 1 mL PFS
- GP2017 (adalimumab investigational biosimilar) 40 mg, liquid formulation in 0.8 mL PFS

If the subject opts for self-administration and/or home administration (at protocol specified time points, see Table 6-1 and Table 6-2), subjects or caregivers will be instructed by site staff on how to self-administer the s.c. injection using the PFS containing the liquid formulation of each study drug. Subjects receiving secukinumab will follow the Secukinumab Instructions for Use (IFU) document, and subjects receiving GP2017 will follow the GP2017 (adalimumab biosimilar) IFU document. The subject may elect to self-administer the PFS at home when they are not visiting the site for any other study related procedures. Site staff will administer the injection to subjects who are not able or feel insecure to self-administer the PFS injection.

The secukinumab 150 mg PFSs and placebo 1 mL PFSs will be provided in a double-blind fashion and have identical appearance.

GP2017 (adalimumab biosimilar) 40 mg PFSs will be provided as unblinded supplies. They have a different appearance from secukinumab 150 mg / placebo 1 mL.

The study medication will be labeled as follows:

- Double-blind secukinumab and placebo PFS will be labeled as AIN457 150mg / 1 mL / Placebo

[redacted]

- Open-label GP2017 (adalimumab biosimilar) PFS will be labeled as adalimumab 40 mg / 0.8 mL

For detailed instructions on storage of the study drugs, please refer to Section 5.5.3.

5.1.2 Additional treatment

No additional treatment beyond investigational and reference treatments are included in this study.

5.2 Treatment arms

Subjects will be randomly assigned at the baseline visit to one of the following three treatment groups in a 1:1:1 ratio, with approximately 279 randomized subjects planned for each group.

- Group 1: secukinumab 150 mg
- Group 2: secukinumab 300 mg
- Group 3: GP2017 (adalimumab biosimilar) 40 mg

Subjects in both of the secukinumab dose groups will receive study treatment at BSL, Weeks 1, 2, 3 and 4 followed by treatment every 4 weeks through Week 100. Subjects in the GP2017 group will receive study treatment at BSL and every two weeks through Week 102. Subjects can self-administer all secukinumab / placebo and GP2017 doses as described in Section 3.1 at the study site or at home, according to the assessment schedule in Table 6-1 and Table 6-2.

5.3 Treatment assignment and randomization

At baseline all eligible subjects will be randomized via an Interactive Response Technology (IRT) system to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the subject. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and that the randomization of secukinumab doses is concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

This is a randomized, partially-blinded study of secukinumab versus an active comparator (GP2017 adalimumab biosimilar), in which the secukinumab groups are blinded to dose for the full 2-year study duration.

The partial-blinding will include:

- Subjects, investigators, site personnel, persons performing the assessments and the monitors will be aware of whether the subject is receiving secukinumab or GP2017 (adalimumab biosimilar)
- Subjects, investigators, site personnel, persons performing the assessments, monitors and the Sponsor will remain blinded to the dose group of secukinumab (150 mg versus 300 mg)
- Designated Sponsor personnel will remain blinded to the complete treatment group assignments to minimize bias to potential changes to the protocol and analysis (detailed in the Blinding Charter) until all subjects who remain in the study have completed 52 weeks.

Randomization data and treatment group information will be kept strictly confidential from the central imaging readers conducting the X-ray and MRI read assessments.

Subjects, investigator staff, persons performing the assessments, and Sponsor will remain blinded to the identity of the secukinumab dose from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study except the bioanalysts (2) the identity of the secukinumab dosage will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration and appearance.

Unblinding of secukinumab dose will only occur in the case of subject emergencies (see Section 5.6) and at the conclusion of the study.

[redacted]

The primary endpoint analysis may be performed after all subjects complete the assessments associated with the primary endpoint visit (Week 104) in order to support regulatory filing. Treatment group assignments will be unblinded after the Week 104 database lock. The final analysis will be conducted after all subjects complete the study at Week F120.

5.5 Treating the subject

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number available in the electronic data capture (EDC) system. The investigator or his/her staff will

[redacted]

contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data.

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the appropriate screening period CRF.

Subjects may be re-screened once and will receive a new Subject Number after they have been re-consented. Subjects who are mis-randomized cannot be re-screened.

5.5.2 Dispensing the study drug

Each study site will be supplied with secukinumab study drug in packaging of identical appearance. The GP2017 (adalimumab biosimilar) PFS will appear slightly different.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 3 treatment arms. Investigator staff will identify the study drug package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique Subject Number.

During the BSL visit or any of the scheduled on-site visits, if the subject opts for home administration (at protocol specified time points, see Table 6-1 and Table 6-2) the investigator or delegated site staff will dispense, via the IRT, an appropriate number of investigational treatment packages for the home self-administrations. The investigator staff will detach the outer part of the label and affix it to the source documentation (Drug Label Form). Detailed instructions on the self-administration of the study treatment will be described in the IFU provided to each subject and made available to the site staff and investigator. These instructions should be reviewed in detail by the subject and the site personnel.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to Novartis.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of the drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be

asked to return all unused study treatment and packaging at the next site visit or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site. Destruction of unused drug should be done according to local requirements and after the approval by the Novartis Clinical Team.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatments (secukinumab 150 mg, secukinumab 300 mg, GP2017 40 mg and matching placebo to secukinumab) are provided in PFSs for subcutaneous use. Administration of study treatment must occur after the study assessments for the visit have been completed. The PFS with the ready-to-use study treatment solution will be provided by the site staff to the subject. Detailed instructions on the self-administration of the study treatment will be described in the IFUs for secukinumab and GP2017 and provided to each subject.

At the BSL visit, or at any on-site visits during the treatment period, if the subject opts for self-administration and/or home administration (at protocol specified time points, see Table 6-1 and Table 6-2), subjects or caregivers will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Subjects will be asked to raise any questions and then to proceed with self-injection. However, if the subject is not comfortable self-injecting the study treatment, then the site staff or caregiver may administer it for the subject.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

[redacted]

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Home administration

During the BSL visit, the subject will have the opportunity to decide to self-administer the study treatment at home during the optional visits in which there are no scheduled site assessments (beginning with Week 1). Optional site visits are included in the assessment table of the study (Table 6-1 and Table 6-2), between visits in which study-related assessments are to be conducted. Subjects will be allowed to self-administer the study treatment by PFS at home or to visit the site during the optional visits to self-administer study treatment under the supervision of the site staff. If the subject opts for home administration of study treatment and is unable or unwilling to self-administer the treatment via PFS, a caregiver may administer the study treatment. Caregivers should be trained on the IFU prior to administering the study treatment

[redacted]

to the subject. It should be recorded on the appropriate CRF(s) whether the subject self-administered the study treatment at home or at the site and if a caregiver administered the treatment.

Prior to self-administration at home, subjects should contact the investigator/site staff in case they are experiencing any AE/SAEs, or have any concerns.

All dates and times of self-administrations by the subject during the study must be recorded on the appropriate CRF. Immediately before dispensing the package to the subject, site staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Study treatment interruption is also not permitted with the following exceptions:

- Study treatment interruption is only permitted if, in the opinion of the investigator, a subject is deemed to be at a significant safety risk unless administration of investigational treatment is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.
- The effect of secukinumab or adalimumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. The elimination of adalimumab may take up to four months (Humira® SmPC); in case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for four months for a subject taking GP2017. The study treatment should be interrupted for 12 weeks for a subject taking secukinumab.

Study treatment interruption or permanent discontinuation of study treatment will not affect the ability for the subject to remain in the study.

Any study treatment interruption must be recorded on the corresponding CRF.

5.5.6 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the study or worsening/exacerbation of their disease.

Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if treatment with prohibited biologics (as described in Section 5.5.8) is started, subjects may remain in the study but must discontinue study treatment. Efficacy and safety will be assessed at each on-site study visit, and subjects who are deemed by the investigator not to be benefiting from study treatment, or for any reason on the subject's own accord, will be free to discontinue study participation at any time. Changes in NSAIDs, non-biologic DMARDs and corticosteroid concomitant therapy are permitted as per investigator's and subject's clinical judgment. Please see Section 5.5.7, Section 5.5.8 and Section 5.6.2 for details.

Use of rescue medication must be recorded on the corresponding CRF.

[redacted]

5.5.7 Concomitant medication

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the appropriate CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis/CRO medical monitor before randomizing a subject or allowing a new medication to be started.

Guidelines for the use of specific medications are provided below:

Methotrexate

Subjects taking MTX (≤ 25 mg/week) must be on a stable dose for at least 4 weeks before randomization.

Folic acid

Subjects on MTX must be taking folic acid supplementation before randomization and during the study to minimize the likelihood of MTX associated toxicity.

Sulfasalazine

Subjects taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before randomization.

Systemic corticosteroids

Treatment with systemic corticosteroids (e.g., oral, intramuscular, i.v., s.c.) is permitted if the dose is stable within the 2 weeks preceding randomization through Week 104, up to a maximum daily dosage of 10 mg prednisone equivalent.

Higher-dose, time-limited corticosteroid courses (bursts) may be permitted for exacerbations of medical conditions unrelated to AS (e.g., asthma, chronic obstructive pulmonary disease (COPD), contact dermatitis) after randomization.

Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding CRF.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization. After randomization, no more than 1 joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period. Injection of intra-articular steroids is not permitted within 8 weeks prior to Weeks 16, 52 and 104.

[redacted]

Non-steroidal anti-inflammatory drugs (NSAIDs) (including COX-1 or COX-2 inhibitors) and acetaminophen/paracetamol

Subjects regularly using NSAIDs, low strength opioids, or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion in the study.

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN within the 2 weeks before randomization can continue to do so in the study; however, they have to refrain from any intake during the 24 hours before a visit with disease activity assessment.

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding CRF.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of the washout period through Week 104, unless otherwise specified below.

Live vaccines should not be given until 12 weeks after last study treatment administration of secukinumab. The elimination of adalimumab may take up to four months (Humira® SmPC); live vaccines should not be given until 16 weeks after last study treatment administration of GP2017.

Table 5-1 Prohibited medication

Medication	Washout period (before randomization)	Action (after randomization, through Week 104)
Any immunomodulating biologic drugs, including but not limited to TNFα inhibitors, denosumab, secukinumab, or other biologic drug directly targeting IL-17 or IL-17 receptor	No prior exposure	Discontinue study treatment
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents	No prior exposure	Discontinue study treatment
Any investigational treatment or participation in any interventional study	4 weeks or 5 half-lives (whichever is longer)	Discontinue study treatment
Live vaccinations	6 weeks	Through Week 120, interrupt study treatment 12 weeks for secukinumab and 16 weeks for GP2017
Stable use of systemic corticosteroids > 10 mg prednisone equivalent	2 weeks	Protocol deviation
Intra-articular corticosteroids	4 weeks	Dose adjustments permitted after randomization
Unstable dose of conventional synthetic DMARDs (e.g. MTX, sulfasalazine)	4 weeks	Dose adjustments permitted after randomization; no more than 1 DMARD concomitantly
Non-biologic targeted synthetic DMARDs (e.g. JAK inhibitors) (van der Heijde 2016)	4 weeks	Protocol deviation

[redacted]

Medication	Washout period (before randomization)	Action (after randomization, through Week 104)
Unstable dose of NSAIDs (COX1 or COX2 inhibitors), paracetamol/acetaminophen or low strength opioids	2 weeks	Dose adjustments permitted after randomization
Analgesics (other than NSAIDs, paracetamol/acetaminophen or low strength opioids)	4 weeks	Protocol deviation

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis/CRO monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study drug must be discontinued after emergency unblinding. Refer to Section 5.6.2 for Discontinuation of study treatment.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the corresponding CRF.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the subject's study completion (Week F120) and/or discontinuation.

[redacted]

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months for a subject previously on secukinumab and 4 months for a subject previously on GP2017 before initiating the treatment is recommended; elimination of adalimumab may take up to 4 months (Humira® SmPC).

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

Subjects may voluntarily discontinue study treatment (refuse study treatment but continue with study participation) or completely discontinue from the study (no further study participation) for any reason, at any time.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would negatively impact the risk/benefit of study participation.

Study treatment must be discontinued under the following circumstances:

- Subject wish
- Withdrawal of consent
- Pregnancy (see Section 6.5.9 and Section 7.6)
- Any situation in which study participation might result in a safety risk to the subject
- Emergence of the following adverse events:
  - Any severe or serious adverse event that in the judgement of the investigator, taking into account the subject's overall status prevent the subject from continuing study treatment
  - Life-threatening infection
  - Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevent the subject from continuing study treatment (A general guidance on clinically notable laboratory values is provided in Appendix 1.)
- Use of any prohibited treatment as per recommendations in Table 5-1

The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the appropriate CRF.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

Discontinuation of study treatment does not require the subject to be discontinued from the study and all ongoing visit assessments. Refer to Section 6 for the visit schedule and assessments.

If study drug discontinuation occurs because of treatment unblinding, please refer to Section 5.5.9.

[redacted]

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow any further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit (Week F120) has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

[redacted]

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and indicate with an "X" when the visits are performed.

Subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits will not lead to automatic discontinuation.

Screening will be flexible in duration based on the time required to be evaluated for eligibility. Sufficient time is allowed for potential medication washout, in addition to all other assessments indicated in Table 6-1. Upon confirmation that all inclusion and exclusion criteria have been met, the subject may be randomized. The full 10-week screening window is not required.

Screening will consist of two consecutive visits. During Screening Visit 1 (SV1), initial assessments will be performed as outlined in Table 6-1, including the collection of hsCRP central laboratory test and SI joint X-rays. It is recommended that the subject should not proceed to Screening Visit 2 (SV2) until confirmation of sacroiliitis per the Modified NY AS Criteria grading from the centrally read SI joint X-rays (Appendix 3). One retest of the hsCRP lab result may be performed during the screening period.

While the full screening window available is up to 10 weeks, SV2 should occur within the 4 weeks prior to randomization.

Subjects who prematurely discontinue the study treatment (secukinumab or GP2017) are encouraged to remain in the study to continue the study-related assessments until the completion of the study at Week F120. Every effort should be made to request the subjects to complete the final X-ray evaluations as part of the Week 104 visit assessments. Please refer to Section 5.6.2 for reasons for study treatment discontinuation.

Subjects who prematurely discontinue completely from the study for any reason should return for the final visit to conduct the Week 104 assessments (4 weeks after the last study treatment administration of secukinumab or 2 weeks after the last study treatment administration of GP2017), as well as return for the follow-up visits (Week F112 and F120). Every effort should be made to request discontinued subjects to complete the final X-ray and MRI evaluations as part of the Week 104 visit assessments, unless the last X-ray and/or MRI was taken within 12 weeks prior to discontinuation.

At the final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

If the subject refuses to return for these assessments or is unable to do so, every effort should be made to contact him/her or a knowledgeable informant by telephone to determine the reason. Attempts to contact the subject should be recorded in the source documentation.

[redacted]

Table 6-1 Assessment schedule – Part 1: Screening to Week 52

Period	Screening		Treatment																													
Week	SV1 -10 to -4	SV2 -4 to BSL	BSL	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Optional site visit				X	X	X		X	X	X		X		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	
Obtain informed consent	X																														
Inclusion/ Exclusion criteria[1]	X	X	X																												
Relevant medical history/ current medical condition	X	X	X																												
Prior medication	X	X	X																												
High sensitivity C-reactive protein (hsCRP)	X		X																												
X-ray of SI joints[2]	X[4]																														
X-ray (cervical + thoraco-lumbar) for mSASSS[2]	X[3, 4]		X[3, 4]																												
Local PPD skin test[5] or Central laboratory test for tuberculosis screening	X																														
AS disease assessment[6]		X																													
Demography		X																													
Cardiovascular medical history		X																													
Serum pregnancy test		X																													
Chest X-ray or MRI[7]		S																													
Hepatitis B, C or HIV serology (only in countries where required)**		S																													
Smoking history			X																												
Physical Exam		S	S				S				S		S				S								S						S

[redacted]

Period	Screening		Treatment																										
Week	SV1 -10 to -4	SV2 -4 to BSL	BSL	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Height		X																												
Weight		X	X										X																	X
Vital signs		X	X				X				X		X				X								X					X
ECG			X																											
HLA-B27			X																											
[redacted]																														
Lipids[9]			X																											X
Hematology, blood chemistry		X	X				X				X		X				X								X					X
Urine pregnancy test			X				X				X		X				X								X					X
[redacted]																														
Randomization via IRT			X																											
Administration of AIN457 150 mg or 300 mg s.c. study treatment			X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X	X
Administration of GP2017 40 mg s.c. study treatment			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI[10] (spine and SI joints)			X	[redacted]																										
BASDAI			X																											
BASFI			X																											
Patient's global assessment of disease activity (PADA VAS)			X																											
Patient's assessment of back pain intensity (PAP VAS)			X																											
[redacted]																														

[redacted]

Period	Screening		Treatment																											
Week	SV1 -10 to -4	SV2 -4 to BSL	BSL	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52
[redacted]																														
Concomitant medication/ non-drug therapy	X	X	Updated as necessary																											
[redacted]																														
Adverse events/ SAEs[11]	Updated as necessary																													

S To be recorded in source document but not in CRF

Greyed visits are visits with at-home dosing, optional for on-site dosing

The BSL visit and randomization is Day 1

1 Eligibility and relevant medical history assessments are conducted at SV1, SV2 and BSL.

2 SI joint and spinal X-ray image acquisition **must** follow the vendor's Image Acquisition Guidelines. An SI joint X-ray taken within 3 months prior to SV1 may be utilized. The SI joint X-ray will be centrally read for eligibility.

3 Spinal X-rays (cervical + thoraco-lumbar) to be collected during the screening period to confirm eligibility for subjects with CRP < 5 mg/L. Subjects with CRP ≥ 5 mg/L and confirmed study eligibility should obtain the spinal X-rays at BSL.

4 Re-screening subjects may utilize previous X-rays if taken within the past 3 months according to the imaging criteria.

5 The PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before randomization.

6 AS disease assessment includes: AS disease background, Modified New York criteria for AS and targeted medical history events related to AS.

7 A chest X-ray or MRI is required if it was not performed and evaluated within 3 months prior to screening. The X-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The X-ray may be replaced by an MRI assessment.

[redacted]

9 Sample must be obtained fasting.

10 MRI only performed in a sub-population of subjects at selected sites. All subjects at the selected MRI site should be considered for the MRI assessment.

11 AEs / SAEs occurring after the subject has signed the informed consent must be captured on the appropriate CRF.

For all subjects who discontinue from the study, the investigator should ensure that the subject completes the end of treatment visit (Week 104 visit assessments) 4 weeks after last study treatment of secukinumab or 2 weeks after last study treatment of GP2017, and also returns for the final follow-up visits, F112 and F120. Every attempt should be made to obtain the scheduled X-ray and MRI images at the final visit, unless the last X-ray and/or MRI were taken within 12 weeks before discontinuation.

** Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed at local site during screening period, only if required per local medical practice or local regulations prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the CRF.

[redacted]

Table 6-2 Assessment schedule – Part 2: Week 54 to Week 104 and Follow-up visits F112 and F120

Period	Treatment																								Follow-up	
Week	54	56	58	60	62	64	66	68	70	72	74	76	78	80	82	84	86	88	90	92	94	96	98	100	102	104*	F112	F120
Optional site visit	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X			
Physical Exam						S						S								S						S	S	S
Weight						X						X								X						X	X	X
Vital signs						X						X								X						X	X	X
High sensitivity C-Reactive protein (hsCRP)	[redacted]																									X		
Lipids[1]																										X	X	X
Hematology, blood chemistry						X						X								X						X	X	X
Urine pregnancy test						X						X								X						X	X	X
[redacted]																												
Administration of AIN457 150 mg or 300 mg s.c. study treatment		X		X		X		X		X		X		X		X		X		X		X		X				
Administration of GP2017 40 mg s.c. study treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
X-ray of SI joints																										X		
X-ray (cervical + thoraco-lumbar) for mSASSS																										X		
MRI[2] (spine and SI joints)																										X		
BASDAI	[redacted]																									X		
BASFI																										X		
Patient's global assessment of disease activity (PADA VAS)																										X		
Patient's assessment of back pain intensity (PAP VAS)																										X		

[redacted]

Period	Treatment																									Follow-up	
Week	54	56	58	60	62	64	66	68	70	72	74	76	78	80	82	84	86	88	90	92	94	96	98	100	102	104*	F112	F120
[redacted]																												
Concomitant medication/ non-drug therapy	Update as necessary																											
[redacted]																												
Adverse events/ SAEs[3]	Update as necessary																											
Treatment Period Completion form																										X		
Follow-up Period Completion form																												X

S To be recorded in source document but not in CRF or database

Greyed visits are visits with at-home dosing, optional for on-site dosing

1 Sample must be obtained fasting.

2 MRI only performed in a sub-population of subjects at selected sites. All subjects at the selected MRI site should be considered for the MRI assessment.

3 AEs / SAEs occurring after the subject has signed the informed consent must be captured on the appropriate CRF.

* For all subjects who discontinue from the study, the investigator should ensure that the subject completes the end of treatment visit (Week 104 visit assessments) 4 weeks after last study treatment of secukinumab or 2 weeks after last study treatment of GP2017, and also returns for the final follow-up visits, F112 and F120. Every attempt should be made to obtain the scheduled X-ray and MRI images at the final visit, unless the last X-ray and/or MRI were taken within 12 weeks before discontinuation.

[redacted]

6.1 Information to be collected on screening failures

Subjects who discontinue from the study prior to randomization are considered screen failures.

If a subject discontinues before entering the partially-blinded treatment period at baseline, the IRT system must be notified within 2 days and the reason for not being randomized will be entered on the appropriate screening phase CRF. In addition, only the CRFs related to the following assessments should be completed: demography, informed consent, re-screening and inclusion/exclusion. The CRF for adverse events (AEs) should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

All subjects who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs **occurring after informed consent is signed** recorded on the CRF capturing AEs, and SAEs if applicable, i.e. when SAE criteria are met.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgement, the test abnormality occurred prior to the informed consent signature.

6.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects and to be recorded in the CRF include:

- Age, sex, race, ethnicity
- Relevant AS and general medical history/current medical condition data until the start of investigational treatment: targeted medical history events related to AS, such as the history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis), number of previous DMARDs used, date of diagnosis of AS, previous AS therapies, functional status class according to the New York criteria, cardiovascular medical history and smoking history

Where possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the CRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

All dates and times of study treatment administration will be recorded on the appropriate CRF.

Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the appropriate CRF.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 5.5.5. Compliance will be assessed by a field monitor using information provided by the subject and the authorized site personnel. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

[redacted]

6.4 Efficacy

- X-ray of the cervical, thoracic and lumbar spine assessed by modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)
- X-ray of the SI joints
- MRI of spine and SI joints (in a subset of subjects at selected sites)
- Assessment of SpondyloArthritis International Society criteria (ASAS)
- Patient's global assessment of disease activity (VAS)
- Patient's assessment of back pain intensity (VAS)
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- hsCRP
- ASDAS-CRP and ASDAS response categories

All efficacy assessments should be performed prior to administration of study treatment. Details relating to the administration of all PROs are provided in Appendix 6.

6.4.1 X-ray

X-rays will be obtained as defined in the schedule of assessments (Table 6-1 and Table 6-2) and according to the imaging acquisition guidelines provided by the central imaging lab. Prior to the first imaging assessment for the study, the center should be trained and qualified by the central imaging lab. The X-ray requirements include lateral views of the cervical and thoraco-lumbar spine for mSASSS scoring (bottom 1/3 of C2 through top 1/3 of T1, inclusive) and anterio-posterior view of the pelvis including visibility of both SI joints. These images should be transferred to the central imaging lab following acquisition. Some X-rays may need to be repeated if deemed unacceptable by central review. In case of insufficient quality, the site will be advised and trained on any quality issues prior to the repeat X-ray, to keep any repeat X-rays to a minimum. The central imaging lab will conduct independent review for all spine and SI X-rays in this study.

6.4.1.1 No radiographic progression in mSASSS

No radiographic progression in mSASSS is defined as a change from baseline in mSASSS at Week 104 of ≤ 0.5. While the primary analyses will be based on this definition, additional analyses using ≤ 0 and < 2 will be performed.

6.4.1.2 Syndesmophyte

A syndesmophyte will be defined as a score of ≥ 2 for any individual vertebral edge within evaluable vertebral units. A new syndesmophyte is defined as an individual vertebral edge with a score of 0 or 1 at baseline that changes to a score of 2 or 3 at Week 104.

6.4.2 MRI

MRI will be performed at selected sites in a subgroup of approximately 30% of all randomized subjects. MRI will be performed to assess SI and spinal inflammation using a scoring system for quantification of AS-related pathologies, to investigate whether these changes are affected

[redacted]

by treatment with secukinumab or GP2017. The images will be obtained as defined in the schedule of assessments (Table 6-1 and Table 6-2) and according to the imaging acquisition guidelines provided by the central imaging lab. The MRI for each subject will include T1 and STIR sequences of the sagittal spine (cervical, thoracic and lumbar) and oblique coronal of the pelvis including both SI joints. These MRI images should be transferred as anonymized electronic files to the central imaging lab following acquisition. The central imaging lab will conduct independent review for all spine and SI MRI imaging in this study.

6.4.3 Assessment of SpondyloArthritis International Society criteria (ASAS)

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

ASAS domains:

- Patient's global assessment of disease activity measured on a VAS scale
- Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
- Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
- 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

6.4.3.1 ASAS Response Criteria 20% (ASAS 20)

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

6.4.3.2 ASAS Response Criteria 40% (ASAS 40)

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 domains and no worsening at all in the remaining domain.

6.4.3.3 ASAS partial remission criteria

The ASAS partial remission criteria are defined as a value not above 2 units in each of the four domains on a scale of 10.

6.4.3.4 Patient's global assessment of disease activity (VAS)

The patient's global assessment of disease activity will be performed using a 100 mm visual analog scale (VAS) ranging from not severe to very severe, after the question "*How active was your disease on average during the last week?*".

6.4.3.5 Patient's assessment of back pain intensity (VAS)

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "*Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?*" and "*Based*

[redacted]

on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?".

6.4.3.6 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

6.4.3.7 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem, captured as a continuous VAS), 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 severity
6. Morning stiffness duration

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness is taken. The mean of questions 5 and 6 is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical studies evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 seconds and 2 minutes to complete.

6.4.4 High sensitivity C-reactive protein (hsCRP)

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

6.4.5 ASDAS-CRP and ASDAS response categories

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in AS.

The ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) will be utilized to assess the disease activity status. Parameters used for the ASDAS include spinal pain (BASDAI question 2), the patient's global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/L (Sieper 2009, Lukas 2009).

[redacted]

Disease activity states are inactive disease, moderate disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and moderate disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cutoffs for improvement scores were a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement" (Machado 2011).

6.4.6 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across all ankylosing spondylitis studies.

This study involves exposure to radiation from X-rays of part of the thoracic, the cervical and lumbar spine and the SI joints. The radiation exposure from these procedures is not necessary for medical care but is intended for research purposes only.

The amount of cumulative *annual* radiation in this study is about 3.4 mSv for the combined X-ray procedures and is based on effective doses for various diagnostic radiological procedures reported in literature (Mettler 2008). This exposure is comparable to the natural radiation an average person receives in one year. The radiation dose between 3 mSv and 50 mSv is considered 'minimal' (Stabin 2009). Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired.

6.5 Safety

- Tuberculosis screening
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
- [redacted]
- Chest X-ray or MRI
- Electrocardiogram
- Pregnancy and assessment of fertility
- Local tolerability (injection site reactions)
- Tolerability of investigational treatment

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g., evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

6.5.1 Tuberculosis screening

Either a central laboratory test **or** a locally performed skin test must be performed at the screening visit to screen the subject population for latent tuberculosis infection. The results must be known prior to randomization to determine the subject's eligibility for the study.

[redacted]

Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that

- the subject has no evidence of active tuberculosis
- if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

Central laboratory test for Tuberculosis screening

The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

Local skin test for Tuberculosis screening

A PPD skin test is to be performed at screening and read before randomization to determine the subject's eligibility for the study. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the subjects must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the subject has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration $\geq$ 5 mm (or according to local practice/guidelines) is interpreted as a positive result.

6.5.2 Physical examination

The physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the relevant medical history CRF. Significant findings made during a physical exam after signing the ICF which meet the definition of an AE must be recorded on the appropriate CRF capturing AEs and if SAE criteria are met, also as a SAE.

6.5.3 Vital signs

This will include blood pressure and pulse rate measurements after 5 minutes rest in a sitting position.

If possible, vital sign assessments should be performed by the same study site staff member using the same validated device throughout the study.

[redacted]

6.5.4 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing), both without shoes will be measured.

If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. Clinically notable laboratory findings are defined in Appendix 1. All subjects with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.5.1 Hematology

Hemoglobin, platelet, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.

6.5.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

6.5.5.3 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol and triglycerides must be measured from a fasting blood sample.

[redacted]

[redacted]

6.5.7 Chest X-ray or MRI

A chest X-ray or MRI at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular, tuberculosis. The results must be known prior to randomization to determine the subject's eligibility for the study. These assessments will be documented in source records only and will not be entered into the CRF.

6.5.8 Electrocardiogram (ECG)

In this study, local ECG will be used. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. A single 12 lead ECG is collected. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The original ECGs (on non-heat-sensitive paper or a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site.

The ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

Clinically relevant abnormalities for the baseline ECG should be recorded on the relevant section of the CRFs capturing medical history/current medical conditions.

6.5.9 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the screening visit, and local urine pregnancy tests as indicated in Table 6-1 and Table 6-2. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

Secukinumab and GP2017 should not be given to pregnant women; therefore effective method of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 4.2).

6.5.10 Local tolerability (injection site reactions)

The local tolerability at the site of s.c. injection of the study treatment will be assessed in case of any local reaction, until this has disappeared.

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the appropriate CRF capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction.

[redacted]

6.5.11 Tolerability of investigational treatments

Tolerability will be assessed by adverse events, laboratory values, injection site reaction [redacted].

6.5.12 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in AS.

The safety assessments selected are standard and adequate for this indication/subject population.

6.6 Other assessments

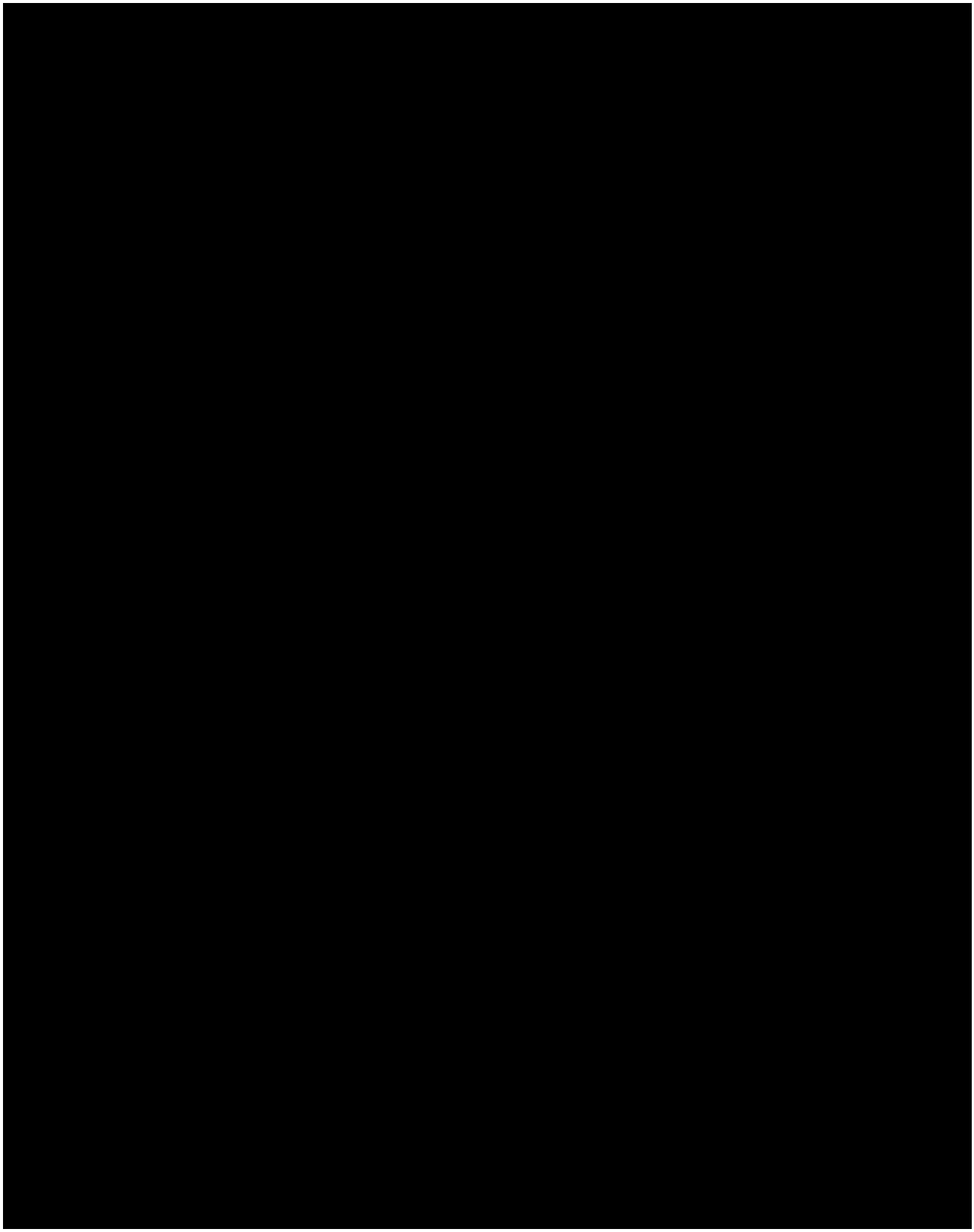
[redacted]

- HLA-B27

[redacted]

[redacted]

[redacted]



[redacted]

6.6.3 HLA-B27

A blood sample to analyze Human Leukocyte Antigen-B27 (HLA-B27) will be obtained from all subjects at baseline.

Details on the collection, handling and shipment of the sample to the central laboratory will be provided to investigators in the laboratory manual.

[redacted]

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to any study treatment (no/yes)
- its duration (start and end dates), or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.

[redacted]

- action taken regarding study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochures (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)

[redacted]

- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition

- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 20 weeks following the last administration of study treatment or until the end of study visit (whichever is later) must be reported to Novartis safety/CRO within 24 hours of learning of its occurrence. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up information to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

[redacted]

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see Appendix 1.

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate dose medication CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in study medication CRF (Yes/No)	Document in AE CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis/CRO within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capturing tools with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to the study medication specifications. Key study personnel must be available to assist the field monitor during these

visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs using fully validated, secure web-enabled software that conforms to US CRF 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The investigator must certify that the data entered into the electronic Case Report Forms (CRFs) are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

The investigator is responsible for assuring that the data entered by the site personnel into the CRFs are complete, accurate and that entry and updates are performed in a timely manner.

8.3 Database management and quality control

Novartis personnel will review the data entered by investigator site staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis/ CRO.

Subjects will fill in their PRO data on a site-based tablet. The system will be supplied by a vendor, who will also manage the database for PRO. The PRO data will be sent electronically to Novartis personnel/ CRO.

Imaging radiographs (except for chest X-rays) will be processed centrally by a vendor. After the reading of images by central readers, the results will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the subject will be tracked using an Interactive Response Technology (IRT) system. The system will be supplied by Novartis, who will also manage the database. Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

9 Data analysis

The analysis will be conducted on all subject data at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will generally include the number of subjects (N), minimum, lower quartile, mean, standard deviation median, upper quartile, and maximum. For categorical or binary variables, the number and percent of subjects in each category will be presented. P-values presented will be two-sided unless otherwise specified.

Data analyses will be presented by treatment regimen. Efficacy and safety data will be presented by the following three treatment groups.

- Secukinumab 150 mg
- Secukinumab 300 mg
- GP2017 40 mg

9.1 Analysis sets

The following analysis sets will be used in this study:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be evaluated according to the treatment assigned to at randomization.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. Subjects will be evaluated according to treatment received.

9.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

The following common background and demographic variables will be summarized:

- Gender, age, race, ethnicity, weight, height, and BMI.

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

- Patient's global assessment of disease activity and other ASAS components, hsCRP, use (yes/no) and separate dose of MTX (mg/week), sulfasalazine (g/day) and systemic corticosteroids (mg/day) at randomization, time since first diagnosis of AS (years), modified New York criteria for AS, mSASSS, number of syndesmophytes, HLA-B27, total back pain (VAS), nocturnal back pain (VAS), total BASDAI score and spinal pain (BASDAI question #2).

[redacted]

Medical history

A history of AS with focus on previous extra-articular involvement and past therapies for AS will be obtained. Any other significant prior or active medical condition at the time of signing informed consent will be recorded and coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

To establish a baseline level of cardiovascular risk, the number and percentage of subjects with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each subject has will also be summarized by treatment group. If it is unknown whether or not a subject currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that subject.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with injections received will be presented by treatment group.

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

Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

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

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 subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

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

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 the date of the last study visit will be a concomitant surgeries and procedures, including those which were started pre-baseline and continued into the period where study treatment is administered.

The number and percentage of subjects receiving prior and concomitant ankylosing spondylitis therapy will be presented by randomized treatment group as well as the reasons for stopping

[redacted]

their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to ankylosing spondylitis therapies previously. NSAID use will be summarized.

9.4 Analysis of the primary variable(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.4.1 and Section 9.5.1.

9.4.1 Variable(s)

The primary efficacy objective is to demonstrate that the proportion of subjects on secukinumab (150 mg or 300 mg) with no radiographic progression is superior to GP2017 40 mg at Week 104. The analysis of the primary objective will be based on the following estimand:

- Population – defined through appropriate inclusion/exclusion criteria to reflect the targeted AS population
- Variable – binary response variable indicating no radiographic progression, defined as a change from baseline in mSASSS at Week 104 of ≤ 0.5.
- Intercurrent event – regardless of adherence to randomized treatment
- Population-level summary – difference in proportions of responders between the secukinumab and GP2017 arms

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for no radiographic progression being tested is that there is no difference in the proportion of subjects with no radiographic progression at Week 104 in the secukinumab regimens versus GP2017 40 mg regimen.

Let p_j denote the proportion of subjects with no radiographic progression at Week 104 for treatment regimens j, j=0, 1 or 2 where

- 0 corresponds to GP2017 40 mg regimen,
- 1 corresponds to secukinumab 150 mg
- 2 corresponds to secukinumab 300 mg

In statistical terms, H_j: $p_j = p_0$, HA_j: $p_j \neq p_0$,

H_1: secukinumab 150 mg is not different to GP2017 regimen with respect to proportion of subjects with no radiographic progression at Week 104

H_2: secukinumab 300 mg is not different to GP2017 regimen with respect to proportion of subjects with no radiographic progression at Week 104

The primary analysis will be conducted via logistic regression with treatment as factor and includes baseline mSASSS as covariate. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model. Analysis will be done on the FAS.

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

Missing Week 104 data for a given subject will be imputed using an imputation model based on the observed data of subjects in the same randomized arm who also discontinued the study treatment but for whom Week 104 X-ray data is available ('retrieved dropout approach') and based on the observed data of the given subject (Baseline and Week 52).

The potential sparsity of the retrieved data may preclude fitting the proposed imputation model to impute the subjects with missing X-ray data at Week 104. In this case, an alternative approach may be used if necessary, which will be detailed in the statistical analysis plan.

9.4.4 Sensitivity analyses

Sensitivity analyses and supplementary analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust.

Sensitivity analyses may be conducted to determine the impact of missing data handling on the primary estimand by changing the covariate in the imputation model (e.g. using different ways of adjusting for baseline mSASSS, adding additional clinically relevant covariates).

Additional supplementary analyses may be conducted to examine different estimands which are also deemed clinically relevant.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables and the method for adjusting for multiplicity are described below. Handling of missing data for secondary variables included in the testing strategy will be the same as for the primary variable. All analysis will be done on the FAS.

Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at Week 104

Change from baseline in mSASSS will be evaluated using ANCOVA model with treatment as a factor and baseline mSASSS as a covariate.

Estimand definition:

- Population – defined through appropriate inclusion/exclusion criteria to reflect the targeted AS population
- Variable – mSASSS change from baseline at Week 104
- Intercurrent event – regardless of adherence to randomized treatment
- Population-level summary – difference in means between treatment

New syndesmophytes at Week 104

The proportion of subjects with no new syndesmophyte will be evaluated using a logistic regression model with treatment group as a factor and baseline mSASSS as a covariate. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model.

Estimand definition:

[redacted]

- Population – defined through subjects with syndesmophyte at baseline, within the targeted AS population defined by inclusion/exclusion criteria
- Variable – binary response variable indicating absence of new syndesmophyte at Week 104. Absence of new syndesmophyte is defined as having individual vertebral score < 2 for all interpretable locations which had no syndesmophyte at baseline
- Intercurrent event – regardless of adherence to randomized treatment
- Population-level summary – difference in proportion of absence of new syndesmophyte between the secukinumab and GP2017 arms

MRI of spine and SI joints

MRI analysis will be based on a subgroup of subjects who have MRI performed on spine and SI joints at selected sites.

The change from baseline to Week 104 in ASspiMRI-a Berlin modification score and Berlin SI joint edema score will be evaluated using a non-parametric ANCOVA model with treatment as factor and baseline score as covariate. Pairwise comparison will be performed for secukinumab (150 mg s.c. or 300 mg s.c.) versus GP2017. These will be assessed and analyzed outside the testing strategy.

If values are missing for baseline or post-baseline visit, the subject will be excluded from the analysis.

Summary statistics of observed data by visit and change from baseline will be provided for each treatment regimen. Summary statistics include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

ASAS 20, ASAS 40, ASAS partial remission and ASDAS inactive disease at Week 104

Response at Week 104 to ASAS 20, ASAS 40, ASAS partial remission and ASDAS inactive disease will be evaluated using a logistic regression model with treatment group as a factor and baseline score (if appropriate) as a covariate. These will be assessed and analyzed outside the testing strategy.

Testing strategy

The following hypotheses will be included in the testing strategy, which controls the family-wise two sided type-I-error at 5% level. The two primary hypotheses (H1 and H2) form the first family, which will be tested first at 5% level using the Hochberg (1988) procedure. The second family consists of the secondary hypotheses (H3 through H6), which will be tested only if both primary hypotheses have been rejected, and will be tested at 5% level using the graphical approach for sequentially rejective procedures (Bretz 2009) as illustrated in Figure 9-1:

Primary hypotheses:

H1: secukinumab 150 mg is not different to GP2017 40 mg with respect to proportion of subjects with no radiographic progression at Week 104

H2: secukinumab 300 mg is not different to GP2017 40 mg with respect to proportion of subjects with no radiographic progression at Week 104

[redacted]

Secondary hypotheses:

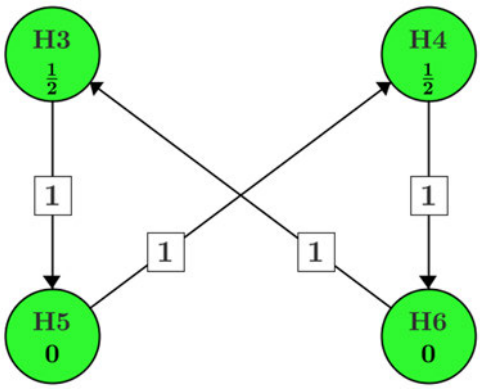
H3: secukinumab 150 mg is not different to GP2017 40 mg with respect to change from baseline in modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at Week 104

H4: secukinumab 300 mg is not different to GP2017 40 mg with respect to change from baseline in modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at Week 104

H5: secukinumab 150 mg is not different to GP2017 40 mg with respect to proportion of subjects with a syndesmophyte at baseline with no new syndesmophytes at Week 104

H6: secukinumab 300 mg is not different to GP2017 40 mg with respect to proportion of subjects with a syndesmophyte at baseline with no new syndesmophytes at Week 104

Figure 9-1 Testing strategy for the second family after both H1 and H2 have been rejected



The family-wise error rate will be controlled strongly at α=5% two-sided level with the proposed hierarchical testing strategy. In the first family, the Hochberg procedure will reject H1 and H2, if both of them are significant at level α simultaneously. Otherwise, it will reject H1 if it is significant at level α/2, or reject H2 if it is significant at level α/2. Because H1 and H2 represent two doses of secukinumab versus GP2017, the correlation between the two test statistics will be positive. In this case, the type I error is controlled for the Simes test (Sarkar and Chang 1997) and, thus, the family-wise error rate is controlled strongly for the Hochberg procedure.

Once both primary hypotheses within the first family are rejected then the α will be passed to the second family starting with each of the hypotheses H3 and H4 tested simultaneously at α /2. Then based on the rejection of one or both (of H3 and H4), the next endpoint will be tested hierarchically for each dose (through H5 and/or H6), respectively. This procedure will continue (pending rejection of the null hypotheses) until H5 and/or H6 are/is rejected respectively, then the respective α/2 can be passed on to the other secukinumab regimen's hierarchy of hypotheses in the second family (i.e. H3 or H4), if they are not already rejected at α/2. Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

[redacted]

[redacted]

[redacted]

9.5.3 Safety variables

Adverse events

Treatment-emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

As appropriate, the incidence of AEs will be presented per 100 subject years of exposure.

[redacted]

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

[redacted]

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline.

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a subject'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. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

[redacted]

Vital signs

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

ECG

Listings of ECG parameters at baseline will be provided.

[redacted]

[redacted]

[redacted]

[redacted]

9.7 Sample size calculation

An overall type I error (2-sided) 5% will be used to control type I error. A total of 279 subjects per each group is deemed appropriate to achieve adequate power for the primary and secondary endpoints for this study.

Based on the modeling of Secukinumab data from an unpublished non-interventional study that did a blinded re-read of radiographic X-ray images from a Secukinumab phase III study (Braun

[redacted]

2016) and from a historical cohort where subjects took NSAIDs, a no progression rate of 66% for Secukinumab-treated subjects and 51% for NSAIDs-treated subjects at Week 104 were calculated. Published data for anti-TNFs compared to a cohort of subjects who took NSAID showed no difference in change from baseline in mSASSS at Week 104 (van der Heijde 2009). Therefore, the 51% no progression rate calculated from the subjects who took NSAIDs will be used for GP2017. Assuming 80% of subjects will complete the 2-year study treatment period and provide both baseline and Week 104 evaluable radiographic films with 66% no progression rate at Week 104 and assuming for subjects who discontinue study treatment with 51% no progression rate at Week 104, a new no progression rate of 63% for Secukinumab was calculated using the definition of the estimand. Therefore, no progression rate of 63% for secukinumab and 51% for GP2017 were used as assumptions to calculate the sample size using a two-group Chi-square test of equal proportion (nQuery Advisor 7.0). This calculated approximately 73% power at α=0.025 for each secukinumab dose, and the power to reject at least one of these hypotheses using the Hochberg procedure is 88% at an overall type I error of 5%.

Analysis of an unpublished Phase III study showed a change from baseline in mSASSS at Week 104 with a mean of 0.52 and standard deviation of 2.5 for Secukinumab subjects. With a sample size of 279 subjects in each treatment group, a treatment difference of 0.58 (i.e. assuming GP2017 have a mean of 1.1 and the same standard deviation) yields approximately 68% power at $\alpha = 0.025$.

Analysis of an unpublished Phase III study showed the 68% of the randomized subjects have syndesmophyte at baseline and for this subset the proportion of subjects with no new syndesmophyte at Week 104 is 70% for Secukinumab. With a sample size of 190 subjects in each treatment group (about 68% of the planned randomized 279 subjects), a treatment difference of 15% (i.e. assuming GP2017 response rate of 55%) yields approximately 78% power at $\alpha = 0.025$.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

[redacted]

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the subject.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study, and for a minimum 16 weeks or longer if local label requires it (e.g., 20 weeks for Secukinumab, 5 months for GP2017 in EU) after the last dose. If there is any question that the subject will not reliably comply, they must not be entered in the study.

The study includes an optional PG ICF which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option to the subject. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in the PG assessments will in no way affect the subject's ability to participate in the main research study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a study, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the study protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and

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responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstance, including incidental collection, is an investigator allowed to collect additional data or conduct any additional procedure for any purpose involving any investigational drugs under the protocol, other than for the purpose of the study. If despite this interdiction, any additional data, information, or observations would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Clinically notable values will be forwarded to Novartis/CRO at the same time that they are sent to investigators. Any action based on these laboratory values should be discussed with Novartis/CRO personnel.

Table 13-1 Safety Analyses: Expanded Limits and Notable Criteria

	Final Harmonization	
Laboratory Variable	**Notable Criteria**	
	Standard Units	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	> 3 x ULN	> 3 x ULN
SGPT (ALT)	> 3 x ULN	> 3 x ULN
Bilirubin	> 2 x ULN	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN	> 2.5 x ULN
RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES		
Creatinine (serum)	> 2 x ULN	> 2 x ULN
HEMATOLOGY VARIABLES		
Hemoglobin	20 g/L decrease from baseline	
Platelet Count	< 100 x 10E9/L	
White blood cell count	< 0.8 x LLN	
Neutrophils	< 0.9 x LLN	

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13.3 Appendix 3: Modified New York criteria

Clinical criteria:

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.

[redacted]

- Limitation of motion of the lumbar spine in the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological criterion:

- Sacroiliitis grade ≥ 2 bilaterally or grade 3–4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion.

13.4 Appendix 4: Assessment of SpondyloArthritis International Society criteria (ASAS)

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

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
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

13.4.1 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 10 cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

13.4.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?
2. How would you describe the overall level of AS **neck, back or hip pain** you have had?
3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?
4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**
6. How long does your morning stiffness last from the time you wake up?

[redacted]

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The mean of questions 5 and 6 is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical studies evaluating new drug therapies directed at Ankylosing Spondylitis. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete).

13.5 Appendix 5: modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)

A total of 24 sites are scored on the lateral cervical and lumbar spine: the anterior corners of the vertebrae from lower border of C2 to upper border Th1 (inclusive) and from lower border of Th12 to upper border of S1 (inclusive). Each corner can be scored from 0 to 3, resulting in a range from 0 to 72 for the total mSASSS (Sieper 2009).

mSASSS scoring:

- 0 = normal
- 1 = sclerosis, squaring or erosion
- 2 = syndesmophyte
- 3 = bony bridge

13.6 Appendix 6: Guidelines for administering the questionnaires for patient reported outcomes

Before study start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the study and identify any items where a patient's response might highlight issues of potential concern.

For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a patient responds 'most or all of the time', then the study coordinator should inform the study investigator.

Before completion

1. Subjects should be provided with the correct questionnaire at the appropriate visits and in the appropriate language
2. Subjects should have adequate space and time to complete the forms
3. Questionnaire should be administered before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response
2. Only one response for each question
3. Also see "Addressing Problems and Concerns"

[redacted]

After completion

1. Check for completeness and not for content*
2. Check for multiple responses that were made in error

*However, any response which may directly impact or reflect the patient's medical condition (e.g., noting of depression) should be communicated by the study coordinator to the investigator).

Addressing problems and concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The patient does not want to complete the questionnaire(s)

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of patients. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline and thank the patient.

The patient is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The patient wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the patient provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for patient self-report. Patients should be discouraged from asking a family member or friend for help in completing a questionnaire.

The patient does not want to finish completing the questionnaire(s)

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the patient.

The patient is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed

[redacted]

forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (e.g., noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

While completing the questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim.* If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what *they* think the questions mean.

General information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

The investigator must complete the patient/visit information on the electronic device and ensure that the center number, patient's number and initials are identical to the Case Record Form. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.