

Development - General Medicine

AIN457/Secukinumab

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

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## List of abbreviations

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

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

MRI	magnetic resonance imaging
MTX	methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
PD	pharmacodynamics
PFS	pre-filled syringe
PG	pharmacogenetics
PK	pharmacokinetics
PoC	proof- of- concept
PPD	purified protein derivative
PRO	patient reported outcome
PsA	psoriatic arthritis
OC/RDC	Oracle clinical/remote data capture
OPG	osteoprotegerin
PCS	Physical Component Summary
PRN	pro re nata
QoL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
RANKL	receptor activator of nuclear factor kappa-B ligand
RU	Resource Utilization
SAE	serious adverse event
SCR	screening
s.c.	subcutaneous(ly)
SD	standard deviationSMQ
SpA	spondyloarthritis
SUSAR	suspected unexpected serious adverse reaction
t.i.d.	<i>ter in die</i> , three times a day
TBL	total bilirubin
TNF/TNF $\alpha$	tumor necrosis factor
TNF $\alpha$ -IR	TNF $\alpha$ inhibitor inadequate responder
ULN	upper limit normal
VAS	Visual Analog Scale

VEs                    vertebral edges  
WBC                    white blood cell  
WHO                    World Health Organization  
WoCBP                women of child-bearing potential  
[REDACTED]            [REDACTED]

## Glossary of terms

Assessment	<i>A procedure used to generate data required by the study</i>
DMARD	<i>Disease Modifying Anti-rheumatic Drug; In this study this term refers only to non-biologics.</i>
Enrollment	<i>Point/ time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)</i>
Epoch	<i>The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended. Study 'epoch' will be referred to study period in the protocol</i>
Rescue medication	<i>Any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/ exacerbation of their disease</i>
Inadequate response to TNF $\alpha$	<i>Active disease despite stable treatment with anti-TNF<math>\alpha</math> for at least 3 months at a stable dose or for at least one dose in the case of lack of tolerance</i>
Investigational drug	<i>The drug whose properties are being tested in the study; this definition is consistent with US CRF 21 Section 312.3 and is synonymous with 'investigational new drug' or 'investigational medicinal product'</i>
Investigational treatment	<i>All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new treatment." This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage</i>
Loading regimen	<i>A series of 4 weekly subcutaneous doses of secukinumab, given at baseline (BSL), Weeks 1, 2, and 3, prior to initiating subcutaneous maintenance dosing given every 4 weeks starting at Week 4</i>
Medication number	<i>A unique identifier on the label of each investigational / study drug package</i>
Premature subject withdrawal	<i>Point/time when the subject exits from the study prior to the planned completion of all study treatment administration and assessments; at this time all study treatment administration is discontinued</i>

Re-Screening	<i>A subject who qualified for all or most eligibility criteria but could not be entered within the screening epoch can be considered for re-screening only once</i>
Stop study participation	<i>Point/time at which the subject came in for a final evaluation visit or when study treatment was discontinued whichever is later</i>
Study drug/ treatment	<i>Any treatment administered to the subject as part of the required study procedures; includes investigational treatment and any control drugs</i>
Study/investigational treatment discontinuation	<i>Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal</i>
Subject number	<i>A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study</i>
Variable	<i>Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points</i>

## Protocol summary

Protocol number	CAIN457H1301
Title	An open-label, phase III, study of subcutaneous secukinumab to assess efficacy, safety and tolerability at up to 52 weeks in Japanese patients with active Ankylosing Spondylitis
Brief title	Study of efficacy and safety of secukinumab in Japanese patients with active Ankylosing Spondylitis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biologic
Study type	Interventional
Purpose and rationale	To assess the clinical efficacy, safety and tolerability of secukinumab subcutaneous injections up to 52 weeks in Japanese patients with active AS despite current or previous NSAID and/or anti-TNF $\alpha$ therapy. Efficacy and safety data will be used to support the registration of secukinumab in Japan for the treatment of active AS.
Primary Objective(s)	To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline in Japanese patients with active AS based on the proportion of patients achieving an ASAS(Assessment of SpondyloArthritis International Society criteria) 20 response.
Secondary Objectives	<ul style="list-style-type: none"><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving an ASAS 40 response.</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving Bath Ankylosing Spondylitis Disease Activity (BASDAI) 50 response.</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP)</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients meeting the ASAS 5/6 response criteria</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline in total BASDAI</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline in SF-36 PCS</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the change from baseline in ASQoL</li><li>• To assess the efficacy of secukinumab 150 mg s.c. at Week 16 relative to baseline based on the proportion of patients achieving an ASAS partial remission</li><li>• To assess the pharmacokinetics of secukinumab in Japanese</li></ul>

	<p>patients</p> <ul style="list-style-type: none"><li>• To assess the development of immunogenicity against secukinumab</li><li>• To assess overall safety and tolerability of secukinumab by vital signs, clinical laboratory values and adverse events (AEs) monitoring</li></ul>
Study design	This is a multicenter, open-label, single arm study.
Population	This study population consist of 30 male and female patients aged at minimum 18 at time of consent, with moderate to severe AS fulfilling the Modified New York criteria for ankylosing.
Inclusion criteria	<p>Patients eligible for inclusion in this study have to fulfill all of the following criteria:</p> <ul style="list-style-type: none"><li>• 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</li><li>• Male or non-pregnant, non-lactating female patients at least 18 years of age</li><li>• Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI <math>\geq 4</math> (0-10) and spinal pain as measured by VAS <math>\geq 4</math> cm (BASDAI question #2) <b>at Baseline</b></li><li>• Patients should have been on NSAIDs at the highest recommended dose for at least 3 months prior to baseline with an inadequate response or failure to respond, or less than 3 months if therapy had to be withdrawn due to intolerance, toxicity or contraindications</li><li>• 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 baseline</li><li>• Patients who have been on a TNF<math>\alpha</math> inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to baseline or have been intolerant to at least one administration of an anti-TNF<math>\alpha</math> agent</li><li>• Patients who have previously been on a TNF<math>\alpha</math> inhibitor will be allowed entry into study after appropriate wash-out period prior to baseline:<ul style="list-style-type: none"><li>• 8 weeks for Remicade<sup>®</sup> (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)</li><li>• 10 weeks for Humira<sup>®</sup> (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)</li></ul></li><li>• Patients taking systemic corticosteroids have to be on a stable dose of <math>\leq 10</math> mg/day prednisone or equivalent for at least 2 weeks before baseline</li></ul>
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.

	<ul style="list-style-type: none"><li>• Chest x-ray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician</li><li>• Patients with total ankylosis of the spine</li><li>• Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)</li><li>• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor</li><li>• Use of any investigational drug and/or devices within 4 weeks of baseline, or a period of 5 half-lives of the investigational drug, whichever is longer</li><li>• History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes</li><li>• Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before baseline</li><li>• Any intramuscular corticosteroid injection within 2 weeks before baseline</li><li>• Patients previously treated with any biological immunomodulating agents except for those targeting TNF<math>\alpha</math></li><li>• 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)</li><li>• 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 hCG laboratory test</li><li>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information.<ul style="list-style-type: none"><li>• Effective contraception methods include:</li><li>• 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</li><li>• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment</li><li>• Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient</li><li>• Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository</li><li>• Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate &lt; 1%), for example</li></ul></li></ul>
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	<p>hormone vaginal ring or transdermal hormone contraception</p> <ul style="list-style-type: none"><li>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 study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.</li><li>Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis</li><li>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</li><li>Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (<math>\geq 160/95</math> 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</li><li>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:<ul style="list-style-type: none"><li>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.</li><li>If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.</li><li>History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6 <math>\mu</math>mol/L)</li><li>Screening total WBC count <math>&lt; 3,000/\mu\text{l}</math>, or platelets <math>&lt; 100,000/\mu\text{l}</math> or neutrophils <math>&lt; 1,500/\mu\text{l}</math> or hemoglobin <math>&lt; 8.5</math> g/dl (85 g/L)</li><li>Active systemic infections during the last two weeks (exception: common cold) prior to baseline</li><li>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-</li></ul></li></ul>
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	<p>72 hours, and a positive result is defined as an induration of <math>\geq 5</math> mm or according to local practice/guidelines) or a positive T-SPOT test as indicated in the assessment schedule in <a href="#">Table 6-1</a>. 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</p> <ul style="list-style-type: none"><li>• Known infection with HIV, hepatitis B or hepatitis C at screening or baseline</li><li>• 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)</li><li>• Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial</li><li>• Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)</li><li>• 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</li><li>• Donation or loss of 400 mL or more of blood within 8 weeks before dosing</li><li>• History or evidence of ongoing alcohol or drug abuse, within the last six months before baseline</li><li>• Plans for administration of live vaccines during the study period or 6 weeks prior to baseline</li></ul>
Investigational and reference therapy	Secukinumab 150 mg s.c.
Efficacy assessments	<ul style="list-style-type: none"><li>• Assessment of SpondyloArthritis International Society criteria (ASAS)</li><li>• [REDACTED]</li><li>• Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• [REDACTED] and hsCRP</li><li>• [REDACTED]</li><li>• [REDACTED]</li></ul>
Safety assessments	<ul style="list-style-type: none"><li>• T-SPOT test or PPD skin test</li><li>• Chest x-ray or MRI</li><li>• Physical examination</li><li>• Vital signs</li></ul>

	<ul style="list-style-type: none"><li>• Height and weight</li><li>• Laboratory evaluations</li><li>• Hepatitis B, C and/ or HIV serology</li><li>• Immunogenicity</li><li>• Electrocardiogram</li><li>• Pregnancy and assessment of fertility</li><li>• Local tolerability (Injection site reactions)</li><li>• Tolerability of secukinumab</li></ul>
Other assessments	<ul style="list-style-type: none"><li>• Health-related Quality of Life</li><li>• [REDACTED]</li><li>• HLA-B27</li><li>• Pharmacokinetics</li></ul>
Data analysis	The primary efficacy variable is the proportion of patients who achieve an ASAS 20 at Week 16. The analysis of the efficacy variable will be based on the FAS. A frequency table with the number and percentage of patients achieving an ASAS 20 at Week 16 will be presented.
Key words	Ankylosing spondylitis, chronic inflammatory disease, Japanese, secukinumab, AIN457

## 1 Introduction

### 1.1 Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease which belongs to a group of conditions known as spondyloarthritides. It is mainly characterized by involvement of the axial skeletons and the sacroiliac joints, but also affects peripheral joints, entheses and extraarticular organs. A significant proportion of patients may present with associated extraarticular 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 antigen is strongly associated with AS: 90%-95% of patients with AS have European ancestry and carry this marker. Prevalence of AS is about 1.1% of the population in European countries, however in Japan, AS prevalence is about 0.0065% ([Hukuda et al. 2001](#)). AS is associated with significant disability, and thus constitutes a major burden to the patients.

The first-line drug treatment of mild AS consists of non-steroidal anti-inflammatory drugs (NSAIDs), although there is no evidence that this class of medication alters the disease course or prevents the progression of disability. Treatment with tumor necrosis factor (TNF) blocking agents were successfully added to the armamentarium to treat AS ([Braun et al. 2002](#)) and subsequently demonstrated prolonged efficacy up to eight years of follow-up ([Baraliakos et al. 2011](#)). However, upon discontinuation of TNF blockers the disease relapses quickly ([Baraliakos et al. 2005](#)), indicating that the inflammatory process may only be suppressed but not completely abolished. Results reported in the ASSERT study, the largest study ever conducted on Magnetic Resonance Imaging (MRI) evaluation of spinal lesions in AS, demonstrated a near complete resolution of inflammatory lesions at the 24 week time point with anti-TNF therapy ([Braun et al. 2006](#)). However, in other reports AS inflammatory bone lesions depicted by MRI did not completely disappear under TNF antagonist therapy over a six-month study period. The bone lesions persisted despite full clinical remission, which suggests that the inflammatory process was still remaining ([Zochling et al. 2007](#)). Similarly, residual bone marrow edema (BME) as determined by MRI may represent a persistent inflammatory process in rheumatoid arthritis (RA) patients ([Brown et al. 2006](#)) and psoriatic arthritis (PsA) patients ([Anandarajah et al. 2008](#)) despite clinical remission. Structural damage could be significant and usually irreversible, with both osteoproliferative and osteodestructive changes observed on imaging studies. Classic radiographic findings include syndesmophytes, with progression to total spinal fusion in some cases. Radiographs of the sacroiliac joint often show sclerosis, erosion, and eventually fusion.

Together, these observations indicate that other treatments are needed to treat patients who do not respond to TNF blockers and/or who have incomplete resolution of inflammatory changes as evidenced on MRI studies. Current treatment options for patients with intolerance or inadequate response to anti-TNF $\alpha$  agents treatment are limited due to slow onset of activity and safety concerns. Interleukin (IL)-17 antagonism by secukinumab represents a novel approach to interfere with the chronic inflammatory process by selectively targeting the

cytokine of the unique subset of helper Th17 cells, as well as other cells that play a role in inflammation.

Assuming a potential role of Th17 cells in the inflammatory infiltrate in AS, it can be speculated that locally disturbed homeostasis of osteoclastogenic and osteoblastogenic mechanisms characteristic of Spondyloarthritis (SpA) might be amenable to correction via IL-17 antagonism.

Animal data suggest that IL-17 blockade reduces receptor activator of nuclear factor kappa-B ligand (RANKL) dependent osteoclastogenesis upstream of TNF $\alpha$  ([Koenders et al. 2005](#)). Serum sRANKL levels and sRANKL/Osteoprotegerin (OPG) ratios are up-regulated in patients with AS and have relationship with bone mineral density (BMD) and radiological changes ([Kim et al. 2006](#)).

Notably secukinumab showed good efficacy in patients with AS based upon result of the Proof of Concept study (CAIN457A2209) and phase III studies (CAIN457F2305, CAIN457F2310). Study CAIN457A2209 suggested that secukinumab demonstrated high efficacy, achieving an ASAS 20 response at Week 6 in 59% of the patients on secukinumab versus 24% on placebo, and was well-tolerated ([Baeten et al. 2013](#)). At week 94, patients had sustained clinical responses as 87% of the inflammatory vertebral edges (VEs) at baseline resolved under treatment as seen in MRI assessments ([Baraliakos et al. 2015](#)). In CAIN457F2305 and CAIN457F2310, in a mixed population of both TNF-naive and TNF-IR patients, ASAS20 response at Week 16 was 60.8% for IV-150 mg vs 28.7% for placebo (CAIN457F2305) and 61.1% for 150 mg s.c. vs 27.0% for placebo (CAIN457F2310) respectively. ASAS40 response rates were around 40% on secukinumab 150 mg.

Based on these clinical study results, marketing applications have been submitted to the US, EU and more than 10 other countries for the use in patients with moderate to severe active AS. These applications are all under review by the Health Authorities. In Japan, biologics which have been approved for treatment of AS are two anti-TNF $\alpha$  agents, adalimumab and infliximab. There is no effective treatment for patients who have an inadequate response to anti-TNF $\alpha$ . In consideration of these circumstances, a development program of secukinumab for AS has also been projected in Japan.

This local Japan study is planned as a registration study to support the data of the global phase III program in AS and collect experience data of treatment for Japanese AS patients.

Secukinumab is approved in Japan for psoriasis and psoriatic arthritis at 300 mg s.c.

## 1.2 Purpose

The purpose of this phase III study is to assess the clinical efficacy, safety and tolerability of secukinumab subcutaneous injections up to 52 weeks in Japanese patients with active AS despite current or previous NSAID and/or anti-TNF $\alpha$  therapy. Efficacy and safety data will be used to support the registration of secukinumab in Japan for the treatment of active AS.

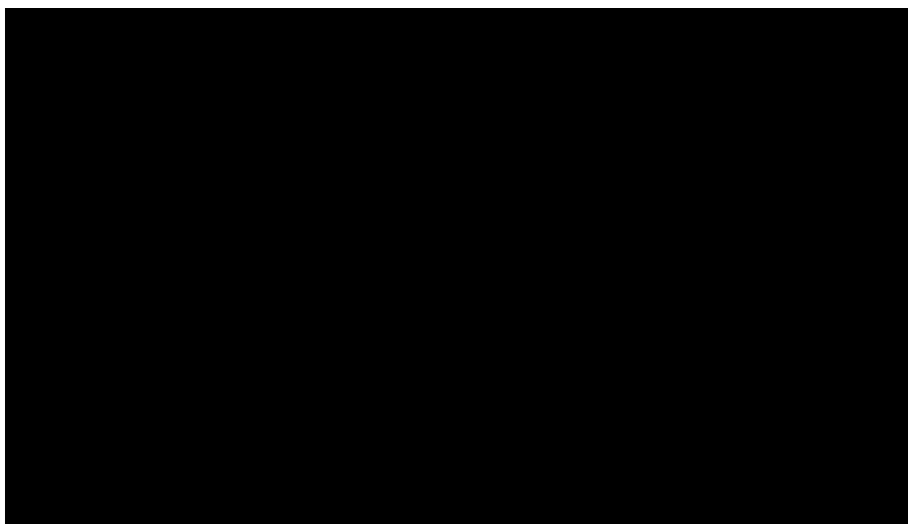
## **2 Study objectives**

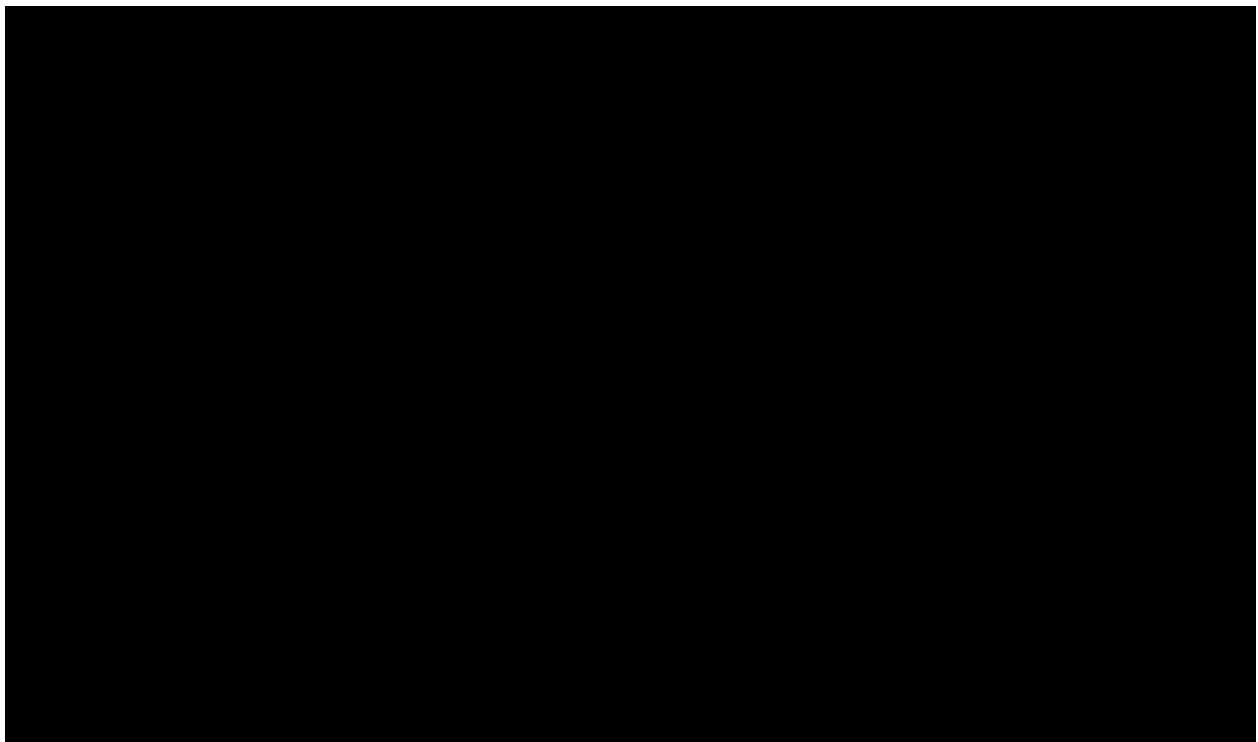
### **2.1 Primary objective(s)**

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

### **2.2 Secondary objectives**

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





## **3      Investigational plan**

### **3.1    Study design**

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

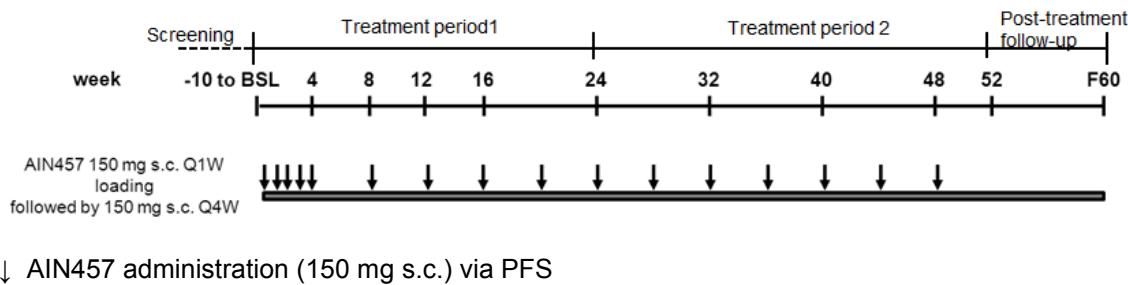
Secukinumab 150 mg s.c. will be administered once weekly at BSL, Weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4.

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

Rescue medication will not be allowed until Week 16. However, patients who are deemed not to be benefiting from the study treatment by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time ([Section 5.5.6](#)).

Subjects who complete the 1 year trial may be eligible to enter an extension study when it will be planned.



**Figure 3-1 Study design**

↓ AIN457 administration (150 mg s.c.) via PFS

### 3.2 Rationale of study design

As mentioned in [Section 1.1](#), clinical study results (CAIN457F2305, CAIN457F2310) demonstrated the efficacy and safety of the drug in patients with moderate to severe active AS. However, there is no experience for secukinumab in Japanese patients with AS. Because of the very low prevalence of AS in Japan (0.0065%), it is very difficult to implement a large placebo controlled confirmation study in Japan and an open label design was chosen. It is expected that approximately 30 patients will be enrolled in this study based on feasibility assessments.

No clinically relevant differences in secukinumab PK are observed between Japanese and non-Japanese healthy volunteers (CAIN457A1101). Based on population PK analyses, only body weight had a relevant impact in the model. The impact of other covariates including race on exposure is considered to be not clinically relevant. The difference in weight between the global AS population ( $78.1 \pm 14.2$  kg) and the Japanese AS population ( $65.6 \pm 14.1$  kg) ([Remicade i.v. 100 application dossiers for marketing authorizations \[Approved on 5-Feb-2010\]](#)) was similar to that between the global psoriasis population ( $88.6 \pm 23.6$  kg) and Japanese psoriasis population ( $74.4 \pm 16.6$  kg) ([Cosentyx s.c. 150 mg application dossiers for marketing authorizations \[Approved on 26-Dec-2014\]](#)). Based on this, it is assumed that secukinumab AS phase III results can be used as pivotal data for Japan.

A similar study design had been used in a previous clinical trial for the use of anti-TNF $\alpha$  inhibitors for AS patients in Japan ([Kobayashi et al. 2012](#)). The secukinumab Japan local study is planned for a registration in Japan to support data of the global phase III studies and collect experience data of treatment for Japanese AS patients. The study will include secukinumab only to collect as many data on the efficacy and safety as possible from a limited number of Japanese AS patients.

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

In 2 pivotal phase III trials (CAIN457F2305 with IV loading, CAIN457F2310 with SC loading), the efficacy of the secukinumab 150 mg sc regimen demonstrated consistent efficacy across multiple endpoints, with clinically meaningful improvements in AS measures of signs and symptoms, objective measures of inflammation, physical function, and patient-reported quality of life. In contrast, the 75 mg sc regimen did not achieve statistical significance for any of the pre-defined hierarchical endpoints in Study CAIN457F2310. The magnitude of treatment effect for the 150 mg s.c. loading and maintenance regimen in Study

CAIN457F2310 was the same as observed for the i.v. loading regimens in Study CAIN457F2305, but without the high peak exposures associated with iv loading in that study. This suggests little to no added benefit from increasing the dose (or exposure) above 150 mg s.c., at least in the initial treatment epoch (16 weeks). Based on these data, secukinumab was submitted to obtain the indication for AS in US and EU as following posology;

Secukinumab is recommended for adult patients with active AS. The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, and 3 followed by monthly dosing starting at Week 4.

Population PK models were built upon secukinumab concentration data from studies conducted in psoriasis, PsA and AS patient populations. Various covariates to explain inter-patient variability in exposure, such as body weight, age, gender, race (Non-Asian vs. Asian including Japanese), and baseline disease severity were evaluated in the model to assess any differences among subgroups that might affect secukinumab PK and ultimately its clinical efficacy. Only body weight has a relevant impact in the model, and the relationship between body weight and exposure is near-linear.

No clinically relevant differences in secukinumab PK are observed between the various autoimmune diseases studied (Psoriasis, RA, AS, PsA, crohn disease (CD), AS, non-infectious uveitis). PK is also similar when compared between healthy volunteers and psoriasis patients. Based on these data, dose and regimen are selected in this study as supported by the results from the global phase III studies.

### **3.4 Rationale for choice of comparator**

This study has no comparator and all patients will receive secukinumab 150 mg.

### **3.5 Purpose and timing of interim analyses/design adaptations**

A primary end point analysis will be performed after all patients have completed Treatment Period 1 (Week 24 visit) to support regulatory filing. Additional analyses may be performed to support Health Authority interactions, as necessary.

### **3.6 Risks and benefits**

The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance for the investigators provided in the Investigator's Brochure (IB).

As of June 2015, approximately 12000 patients have been enrolled in both completed and ongoing studies with secukinumab, with over 9600 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. across various indications (plaque psoriasis, RA, AS, PsA, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica).

The risk profile of secukinumab in AS is informed by the safety experience from arthritides and psoriasis trials. Based on the pooled analysis, infections, neutropenia and hypersensitivity are identified as safety risks with secukinumab. Detailed information on the safety profile of secukinumab can be found in the "Reference Safety Information" of the IB. In the phase III AS studies CAIN457F2305 and CAIN457F2310 in 590 patients, the most common side

effects were nasopharyngitis, diarrhea, headache, upper respiratory tract infection and dyslipidemia. However, these side effects were also seen in patients who received placebo. In the submission dossier for chronic plaque psoriasis and psoriatic arthritis, a comparable safety profile between Japanese and non-Japanese patients was observed.

From the standpoint of the overall risk benefit assessment, the current trial with secukinumab is justified.

## 4 Population

The study population will be comprised of the following patients who have passed screening assessments, comply with inclusion / exclusion criteria and have provided written consent:

Male and female patients aged at minimum 18 at time of consent, with moderate to severe AS fulfilling the Modified New York criteria for ankylosing spondylitis (described in [Appendix 3](#)) with prior documented radiological evidence (x-ray or radiologist's report).

Patients must have a history of active AS, a BASDAI  $\geq 4$  (0-10) and spinal pain as measured by visual analogue scale (VAS)  $\geq 4$  cm, on a scale of 0-10 cm (BASDAI question #2).

Patients included must have active disease despite current or previous NSAIDs or TNF $\alpha$  inhibitor therapy.

Patients can be re-screened only once. This is a Japan local study and it is expected that approximately 38 patients will be screened and 30 patients will be enrolled.

A screening failure rate of 20% is anticipated. Enrollment will stop as soon as the target number of patients is reached.

### 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to 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 prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI  $\geq 4$  (0-10) and spinal pain as measured by VAS  $\geq 4$  cm (BASDAI question #2) **at Baseline**
4. Patients should have been on NSAIDs at the highest recommended dose for at least 3 months prior to baseline with an inadequate response or failure to respond, or less than 3 months if therapy had to be withdrawn due to intolerance, toxicity or contraindications
5. 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 baseline
6. Patients who have been on a TNF $\alpha$  inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to baseline or have been intolerant to at least one administration of an anti-TNF $\alpha$  agent

7. Patients who have previously been on a TNF $\alpha$  inhibitor will be allowed entry into study after appropriate wash-out period prior to baseline:
  - a. 8 weeks for Remicade<sup>®</sup> (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
  - b. 10 weeks for Humira<sup>®</sup> (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
8. Patients taking systemic corticosteroids have to be on a stable dose of  $\leq$  10 mg/day prednisone or equivalent for at least 2 weeks before baseline

#### **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. Chest x-ray or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
2. Patients with total ankylosis of the spine
3. Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, morphine)
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks of baseline, or a period of 5 half-lives of the investigational drug, whichever is longer
6. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
7. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before baseline
8. Any intramuscular corticosteroid injection within 2 weeks before baseline
9. Patients previously treated with any biological immunomodulating agents except for those targeting TNF $\alpha$
10. 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)
11. 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 hCG laboratory test
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information.
  - Effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (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 study treatment.  
Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

13. Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis
14. 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
15. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension ( $\geq 160/95$  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
16. 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.
  - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
17. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dl (132.6  $\mu$ mol/L)
18. Screening total WBC count  $< 3,000/\mu\text{l}$ , or platelets  $< 100,000/\mu\text{l}$  or neutrophils  $< 1,500/\mu\text{l}$  or hemoglobin  $< 8.5$  g/dl (85 g/L)

19. Active systemic infections during the last two weeks (exception: common cold) prior to baseline
20. 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  $\geq 5$  mm or according to local practice/guidelines) or a positive T-SPOT 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
21. Known infection with HIV, hepatitis B or hepatitis C at screening or baseline
22. 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)
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
24. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
25. 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
26. Donation or loss of 400 mL or more of blood within 8 weeks before dosing
27. History or evidence of ongoing alcohol or drug abuse, within the last six months before baseline
28. Plans for administration of live vaccines during the study period or 6 weeks prior to baseline

## 5 Treatment

### 5.1 Protocol requested treatment

#### 5.1.1 Investigational treatment

Novartis/CRO will supply the following study treatments:

- Investigational Treatment:
  - Secukinumab 150 mg provided in a 1 mL PFS (one PFS for 150 mg dose)

Patients will be instructed by site staff on how to self-administer the s.c. injection using the PFS containing the liquid formulation of secukinumab, based on the Instructions for Use (IFU). The s.c. investigational drug will be administered by the patient into the appropriate injection site of the body under the supervision of the site staff.

Site staff will administer the injection to subjects who are not able or feel insecure to self-administer the PFS injection.

The study medication will be labeled as follows:

- Secukinumab PFS will be labeled as: AIN457 150 mg/1 ml

For detailed instructions on storage of the investigational treatments, please refer to [Section 5.5.4](#).

### **5.1.2 Additional study treatment**

No additional treatment beyond investigational treatment is requested for this trial.

### **5.2 Treatment arms**

This trial is an open label, one arm study. All patients will be treated with secukinumab 150 mg.

### **5.3 Treatment assignment, randomization**

At baseline, all eligible patients will receive secukinumab 150 mg s.c. in open-label fashion. Patients will receive all secukinumab doses as described in [Section 3.1](#) at the study site, according to the assessment schedule in [Table 6-1](#).

### **5.4 Treatment blinding**

Not applicable.

### **5.5 Treating the patient**

#### **5.5.1 Patient numbering**

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank CRF book available from the electronic data capture (EDC) system.

If an enrolled patient fails to be treated for any reason, the reason will be entered on the Screening Study Disposition CRF.

#### **5.5.2 Dispensing the investigational treatment**

Each study site will be supplied by Novartis with secukinumab 150 mg PFS.

#### **5.5.3 Handling of study treatment**

##### **5.5.3.1 Handling of investigational treatment**

Investigational 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 investigational treatment should 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 the respective Novartis CPO Quality Assurance.



Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug 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.

#### **5.5.3.2 Handling of other study treatment**

Not applicable.

#### **5.5.4 Instructions for prescribing and taking study treatment**

Study treatment (150 mg secukinumab) will be administered s.c. by 1 mL PFS throughout the study as 150 mg / 1 mL secukinumab.

Administration of study treatment will be allowed to occur via self-injection at the study site through Week 48. Administration of study treatment must occur after the study assessments for the visits that have been completed. The PFS with the ready-to-use study treatment solution will be provided by the site staff to the patient. Detailed instructions on the self-administration of the study treatment will be described in the IFU for secukinumab and provided to each patient.

If the patient is not comfortable self-injecting the study treatment, then the site can administer it for the patient.

At the BSL visit, patients will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise any questions and then to proceed with self-injection.

At the Week 1 visit, patients will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e., no prior retraining) for the remainder of the trial. However, if the patient is not comfortable self-injecting the study treatment, then the site staff may administer it for the patient. Any event related to self-injection should be reported appropriately.

Administration of investigational treatment should occur after sample collection for PK assessments at visits specified in [Table 6-1](#).

The investigator should promote compliance by instructing the patient to attend the study visits as scheduled and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled.

### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

Study treatment dose adjustments are not permitted. Study treatment interruption is although not permitted with the following exceptions: Study treatment interruption is only permitted if, in the opinion of the investigator, a patient 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 on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks. Any study treatment interruption must be recorded on the corresponding eCRF page.

### **5.5.6 Rescue medication**

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Rescue medication must not be used before completion of Week 16 assessments. Although no patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in [Section 5.5.8](#)) occurs, patients will be discontinued from the study. Efficacy will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based on safety and efficacy assessments (see [Section 5.5.9](#)) or for any reason on their own accord will be free to discontinue participation in the study at any time. Changes in NSAID concomitant therapy are permitted as per investigator's clinical judgment after all Week 16 assessments are completed. Please see [Section 5.5.7](#), [Section 5.5.8](#) and [Section 5.5.9](#) for further details.

Any use of rescue medication must be recorded in the Prior/Concomitant medications eCRF page.

### **5.5.7 Concomitant treatment**

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

Guidelines for the use of specific medications are provided below:

#### **Methotrexate**

Patients taking MTX ( $\leq 25$  mg/week) must be on a stable dose for at least 4 weeks before baseline and maintained stable until Week 52.

#### **Folic acid**

Patients on MTX must be taking folic acid supplementation before baseline and during the trial to minimize the likelihood of MTX associated toxicity.

### **Sulfasalazine**

Patients taking sulfasalazine ( $\leq 3$  g/day) must be on a stable dose for at least 4 weeks before baseline and maintained stable until Week 52.

### **Leflunomide wash-out with cholestyramine**

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might be considered. Cholestyramine could be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in patients who require a drug elimination procedure. If a patient receives the dose of 8 g t.i.d. for 11 days, he/she could be safely randomized 4 weeks after the beginning of the 11 days treatment epoch.

### **Systemic corticosteroids**

Treatment with systemic corticosteroids is permitted if the dose was stable within the 2 weeks preceding baseline, up to a maximum daily dosage of 10 mg prednisone equivalent. Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 16, although the corticosteroid dose should not be reduced rapidly.

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

Intra-articular corticosteroids are not permitted within the 4 weeks preceding baseline and up to Week 16. After Week 16, 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 Week 52.

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

Patients on regular use of NSAIDs or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before baseline to allow inclusion in the study.

NSAIDs, low strength opioids or paracetamol/acetaminophen PRN can be taken during the study; however, patients should refrain from any intake during at least the 24 hours before a visit with disease activity assessment.

After the Week 16 assessments are completed, a change in the NSAID intake regimen is permitted.

Any change of the NSAID/paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page

### **5.5.8 Prohibited Treatment**

Use of the treatments displayed in [Table 5-1](#) is NOT allowed after the start of the washout period unless otherwise specified below.

Live vaccines should not be given until 12 weeks after last study treatment administration.

**Table 5-1      Prohibited treatment**

Prohibited treatments	Washout period (before BSL)
Etanercept*	4 weeks
Infliximab*	8 weeks
Adalimumab, golimumab, certolizumab*	10 weeks
Unstable dose of MTX or sulfasalazine (until Week 52)	4 weeks
Other DMARD (except MTX or sulfasalazine)	4 weeks
Leflunomide	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (COX1 or COX2 inhibitors) (until Week 16)	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent** (until Week 16)	2 weeks
Intra-articular steroid injections (until Week 16)	4 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than paracetamol/acetaminophen or low strength opioids PRN	4 weeks
Live vaccinations	6 weeks

\* These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation (see [Section 5.5.9](#)).

\*\* See details about corticosteroid management in [Section 5.5.7](#).

### **5.5.9      Discontinuation of study treatment**

Patients may voluntarily discontinue study treatment for any reason at any time.

They may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from the study and record this information on the appropriate Study Phase Completion eCRF.

Patients who discontinue study should undergo an end of treatment visit (corresponds to the last visit for the patient's current period of treatment: e.g., Week 24, Week 52) at 4 weeks after last study treatment and then also return after an additional 8 weeks for a final follow-up visit, corresponding to Week F60 (12 weeks after last study treatment; see [Table 6-1](#)). The

final follow-up visit should be performed before any new treatment is initiated. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw from the study), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who are prematurely discontinued from the study will not be replaced.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - a. Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with prohibited co-medication
  - b. Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated *in situ* carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  - c. Life-threatening infection
  - d. Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in [Appendix 1](#)).
  - e. Pregnancy
  - f. Use of any biologic immunomodulating agent except secukinumab
  - g. Any protocol deviation that results in a significant risk to the patient's safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given patient if there is a lack of improvement or worsening of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the patient's well-being.

### **5.5.10 Withdrawal of consent**

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

### **5.5.11 Loss to follow-up**

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

### **5.5.12 Emergency breaking of assigned treatment code**

Not applicable.

### **5.5.13 Study completion and post-study treatment**

A patient will be considered to have completed the study if he/she received a maximum of 48 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Week F60.

Information on the patient's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Phase Completion eCRF page.

The investigator must provide follow-up medical care for all patients 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 treatment. In case of a biologic treatment, a waiting period of 12 weeks after the last study treatment before initiating the treatment is recommended.

### **5.5.14 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. 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 patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the early termination of the trial.

## **6 Visit schedule and assessments**

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day or as close to it as possible.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit. Documentation of attempts to contact the patient should be recorded in the source documentation

**Table 6-1 Assessment schedule**

Week	Screening <sup>1</sup>		Treatment period 1												Treatment period 2							Post-treatment follow-up
	SV1 -10 to -4	SV2 ≤ -4	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*	F60*		
Obtain informed consent	X																					
Inclusion/Exclusion criteria <sup>2</sup>	X	X	X																			
Relevant medical history/ current medical condition <sup>2</sup>	X	X	X																			
Prior medication	X	X	X																			
AS assessment and history of extra-axial involvement <sup>3</sup>	X																					
Demography	X																					
Cardiovascular medical history			X																			
Smoking history			X																			
Physical Exam <sup>4</sup>		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S		
Height		X																				
Weight		X	X										X		X**					X	X	
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PPD skin test <sup>5</sup> or T-SPOT test		X																				
Chest x-ray or MRI <sup>4, 6</sup>		S																				
Hematology, blood chemistry, urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test		X																				
Hepatitis B, C and/ or HIV serology*** <sup>4</sup>		S																				
Urine pregnancy test			X				X		X	X			X				X		X	X		
ECG			X							X			X**						X	X		
Administration of s.c. study treatment via PFS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PK assessments (at predose)			X					X			X		X		X				X	X		



Week	Screening <sup>1</sup>		Treatment period 1												Treatment period 2						Post-treatment follow-up
	SV1 -10 to -4	SV2 ≤ -4	BSL	1	2	3	4	8	12	16	20	24*	28	32	36	40	44	48	52*		
Treatment period 1 completion form													X								
Treatment period 2 completion form																				X	
Post-treatment follow-up completion form																				X	

<sup>1</sup> If the patient's washout period ≤ 4 weeks, Screening visit 1 (SV1) and Screening visit 2 (SV2) can be performed on the same day.

<sup>2</sup> Eligibility and relevant medical history assessments are conducted at SV1, SV2 and BSL. The data for all three visits should be recorded on the corresponding eCRFs available at SV1

<sup>3</sup> Extra-axial involvement as uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis

<sup>4</sup> These assessments are source documentation only and will not be entered into the eCRF.

<sup>5</sup> A PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before baseline.

<sup>6</sup> 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 patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The x-ray may be replaced by a MRI assessment.

<sup>7</sup> AEs/SAEs occurring after the patient has signed the informed consent must be captured on the appropriate eCRF page.

<sup>8</sup> Sample must be obtained in the fasting state.

\* For all patients who discontinue the study, the investigator should ensure that the patient completes an end of treatment visit (corresponds to the last visit for the patient's current treatment period) 4 weeks after last study treatment to complete assessments shown for Week 24 (Treatment period 1) or Week 52 (Treatment period 2) in [Table 6-1](#), and also returns after an additional 8 weeks for a final follow-up visit, F60 in [Table 6-1](#) (12 weeks after last study treatment). The final visit should be performed before any new treatment is initiated.

\*\*Assessment for weight, Lipid and ECG at week 24 should be done only for patients who discontinue during treatment period 1.

\*\*\* Hepatitis B and/or hepatitis C and/or HIV serology testing should be performed during screening epoch prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRF.

## **6.1 Information to be collected on screening failures**

Patients may discontinue from the study prior to entering the treatment epoch at baseline. These patients are considered screening failures.

If a patient discontinues before entering the treatment epoch at baseline, the reason for not being entered treatment epoch will be entered on the Screening Phase Disposition eCRF page. In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the Adverse event (AE) eCRF should be completed for any Serious Adverse Events (SAEs) that occurred during the screening epoch. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

All patients who have signed informed consent and are entered into the Treatment period 1 of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event eCRF and as SAE if applicable, i.e. when SAE criteria are met.

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

## **6.2 Patient demographics/other baseline characteristics**

Patient demographic and baseline characteristics data to be collected on all patients and to be recorded in the eCRF include:

- Year of birth, age, sex, race, ethnicity and source of patient referral
- Relevant AS and general medical history/current medical condition data until the start of study treatment, history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis), date of onset of inflammatory back pain, number of previous DMARDs used, date of diagnosis of AS, previous AS therapies, cardiovascular medical history and smoking history

Whenever possible, diagnoses and not symptoms will be recorded here.

## **6.3 Treatment exposure and compliance**

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Drugs administered prior to start of treatment and other drugs continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in [Section 5.5.5](#). Compliance will also be assessed by a Novartis/CRO monitor using information provided by the authorized site personnel.

## **6.4 Efficacy**

- Assessment of SpondyloArthritis International Society criteria (ASAS)

- [REDACTED]
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- [REDACTED]
- [REDACTED]
- [REDACTED] and hsCRP
- [REDACTED]
- [REDACTED]

#### **6.4.1 Assessment in SpondyloArthritis International Society Criteria (ASAS)**

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

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

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

##### **6.4.1.1 ASAS Response Criteria (ASAS 20)**

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

##### **6.4.1.2 ASAS Response Criteria (ASAS 40)**

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

##### **6.4.1.3 ASAS 5/6 improvement criteria**

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

##### **6.4.1.4 ASAS partial remission criteria**

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

#### **6.4.2 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 Patient's assessment of inflammatory back pain intensity (VAS)**

The patient's assessment of inflammatory back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain, after the questions "*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 on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?*". For ASAS calculation the total back pain will be used.

#### **6.4.4 Bath Ankylosing Spondylitis Functional Index (BASFI)**

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The ten questions were chosen with a major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 100 mm VAS is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

#### **6.4.5 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), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

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

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

##### **6.4.5.1 BASDAI 50**

The BASDAI 50 is defined as an improvement of at least 50% in the BASDAI compared to baseline.

#### **6.4.6 Bath Ankylosing Spondylitis Metrology Index (BASMI linear)**

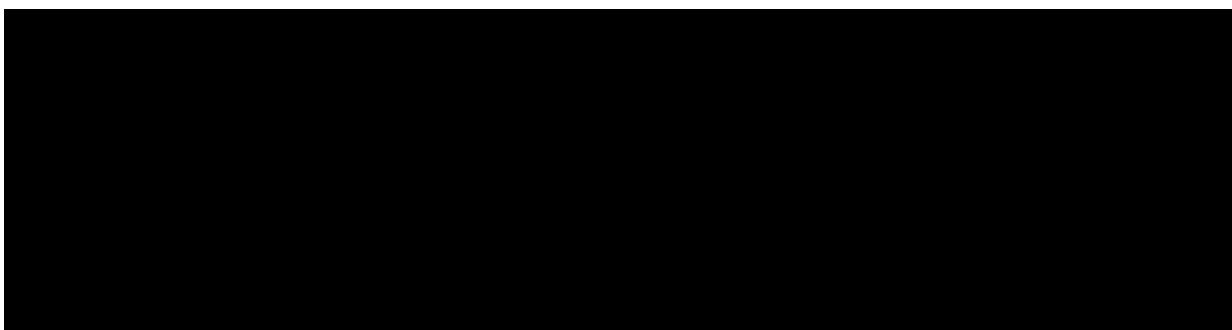
The BASMI is a validated instrument that uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters include:

1. Lateral spinal flexion
2. Tragus-to-wall distance
3. Lumbar flexion (modified Schober)
4. Maximal intermalleolar distance
5. Cervical rotation angle

Additionally, the following assessments should be taken:

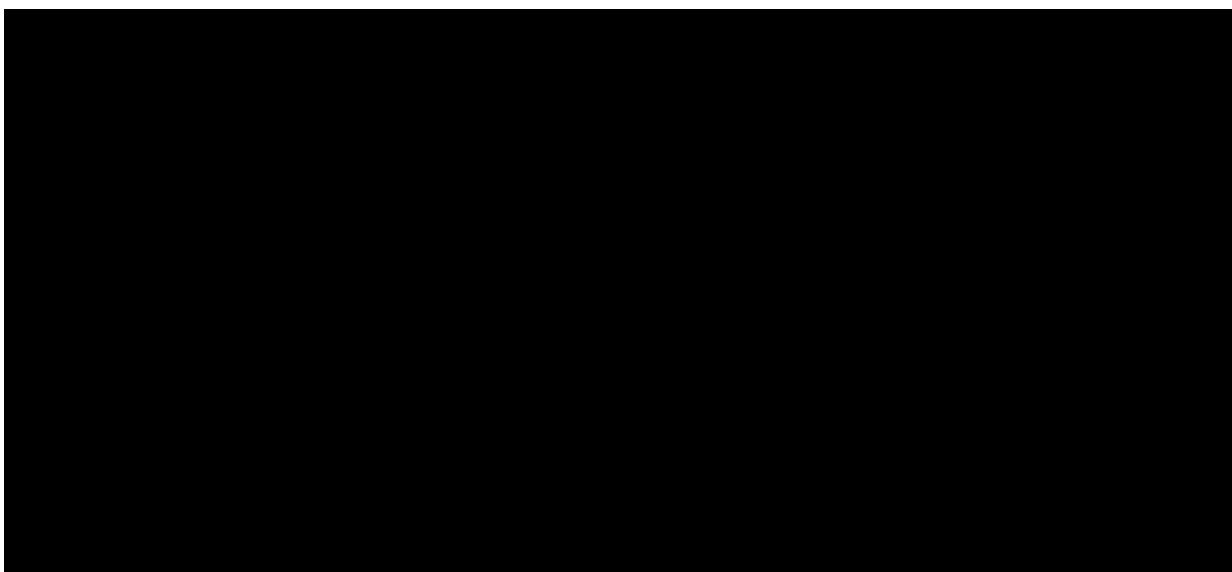
6. Chest expansion
7. Occiput-to-wall distance

Detailed information on the assessments is described in the [Appendix 4](#).



#### **6.4.8 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.



#### **6.4.12 Appropriateness of efficacy assessments**

The efficacy outcome measures used in this study are the standard measures used across AS trials and are required for filing.

## 6.5 Safety

- T-SPOT test or PPD skin test
- Chest x-ray or MRI
- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations
- Hepatitis B, C and/ or HIV serology
- Immunogenicity
- Electrocardiogram
- Pregnancy and assessment of fertility
- Local tolerability (Injection site reactions)
- Tolerability of secukinumab

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 T-SPOT test or PPD skin test

Either a T-SPOT test or a PPD skin test must be performed at screening. 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, or if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

#### T-SPOT test

An interferon (IFN- $\gamma$ ) response assay using the IFN- $\gamma$  ELISPOT (T-SPOT) test must be performed for all patients at the screening Visit. Details about sample processing are described in the central laboratory manual

#### PPD skin test

A PPD skin test is to be performed at screening and read before BSL to determine the patient's eligibility for the trial. 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 patients must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the patient 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 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. Information for chest X-ray or MRI examinations must be included in the source documentation at the study site.

### **6.5.3 Physical examination**

The physical examination will include the examination of general appearance, skin, neck, 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. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event eCRF and if SAE criteria are met also as a SAE.

### **6.5.4 Vital signs**

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

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

### **6.5.5 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.

### **6.5.6 Laboratory evaluations**

A central laboratory will be used for analysis of all specimens collected listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see [Appendix 1](#). All patients 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.

#### **6.5.6.1 Hematology**

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



#### **6.5.6.2 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.

#### **6.5.6.3 Lipid panel**

A lipid profile, including high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol and, triglycerides will be measured from a fasting blood sample.

A cardiovascular profile including lipoprotein(a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a fasting blood sample.

#### **6.5.6.4 Hepatitis B, C and/ or HIV serology**

Hepatitis B and/or hepatitis C and/or HIV serology testing will be performed during screening epoch prior to initiation of therapy. The result of this assessment will be documented in source records only and will not be entered into the eCRF.

#### **6.5.6.5 Urinalysis**

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood and, WBCs will be recorded in the appropriate eCRF page.

#### **6.5.7 Immunogenicity (IG)**

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in [Table 6-1](#). The Immunogenicity Sample Log can be found in the [Appendix 2](#).

The actual sample collection date and exact time will be entered on the Immunogenicity blood collection eCRF page. Sampling problems will be noted in the Comments section of the eCRF.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

#### **IG sample handling, labeling and shipment instructions**

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and pre-printed labels will be provided by the central laboratory to the sites.

#### **Analytical method**

An electrochemiluminescence method will be used for the detection of potential anti-secukinumab antibody formation. The detailed method to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report.

### **6.5.8      [Electrocardiogram \(ECG\)](#)**

A standard 12 lead ECG will be performed as indicated in [Table 6-1](#). All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Clinically relevant abnormalities noted before the baseline ECG should be recorded on the relevant medical history/Current medical conditions eCRF page for the baseline ECG.

Clinically relevant abnormalities noted after the baseline ECG should be reported as AE ([Section 7.1](#)).

### **6.5.9      [Pregnancy and assessments of fertility](#)**

All pre-menopausal women who are not surgically sterile will have a serum  $\beta$ -hCG test (serum pregnancy test) performed at the screening visit 2 and local urine pregnancy tests as indicated in [Table 6-1](#). A positive urine pregnancy test requires immediate interruption of study drug until serum  $\beta$ -hCG is performed and found to be negative.

### **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 Adverse Events eCRF, including the severity (mild, moderate, severe) and the duration.

### **6.5.11     [Tolerability of secukinumab](#)**

Tolerability will be assessed by adverse events, laboratory values, injection site reaction and immunogenicity.

### **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. This study involves exposure to radiation from a possible chest X-ray. The radiation exposure by these procedures is not necessary for medical care but is intended for research purposes only.

The amount of radiation in this study is about 0.1 mSv for the X-ray procedure and is based on effective doses for various diagnostic radiological procedures reported in the literature ([Mettler et al. 2008](#)). This exposure is comparable to the natural radiation an average person receives in 10 days. This radiation exposure is considered ‘minimal’ ([Stabin et al. 2009](#)). Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure patient safety.

## **6.6      [Other assessments](#)**

- Health-related Quality of Life
- 

- HLA-B27
- Pharmacokinetics

### **6.6.1 Health-related Quality of Life**

The impact of AS on various aspects of patient's health-related quality of life (QoL) will be assessed by the following instruments:

- SF-36
- ASQoL
- [REDACTED]
- [REDACTED]
- [REDACTED]

All questionnaires will be available in Japanese.

All questionnaires will be completed at the scheduled study visit prior to the patient seeing the investigator for any other clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check each questionnaire for completeness and encourage the patient to complete any missing responses. Guidelines for administering the PRO questionnaires can be found in [Appendix 6](#). A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in [Section 7](#) of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

The language in which each of the questionnaires to be completed will also be captured the first time a questionnaire is administered.

#### **6.6.1.1 Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)**

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health ([Ware and Sherbourne 1992](#)). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed ([McHorney et al 1993](#)). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

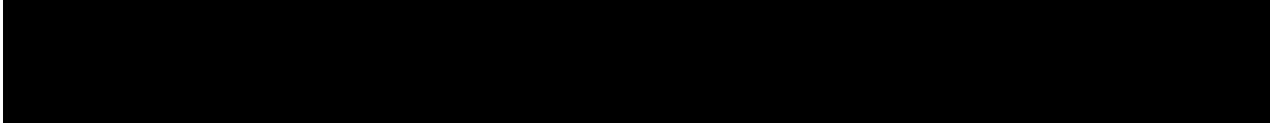
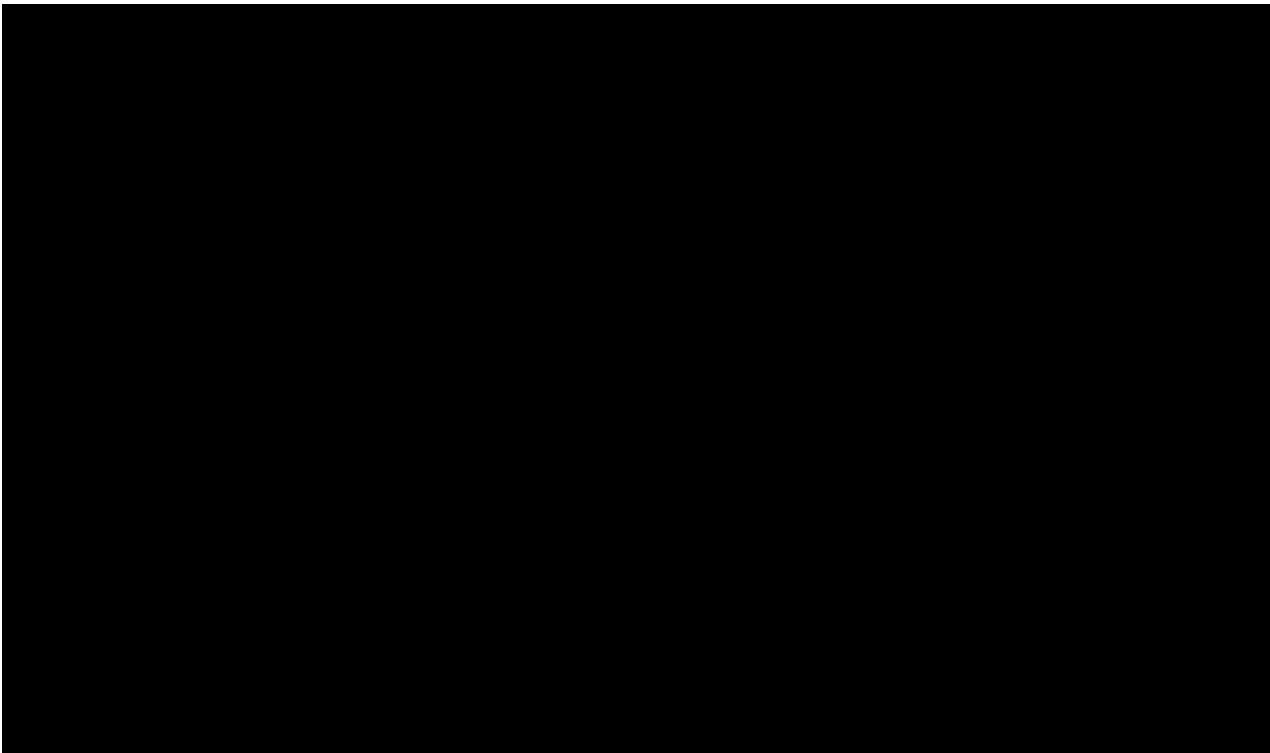
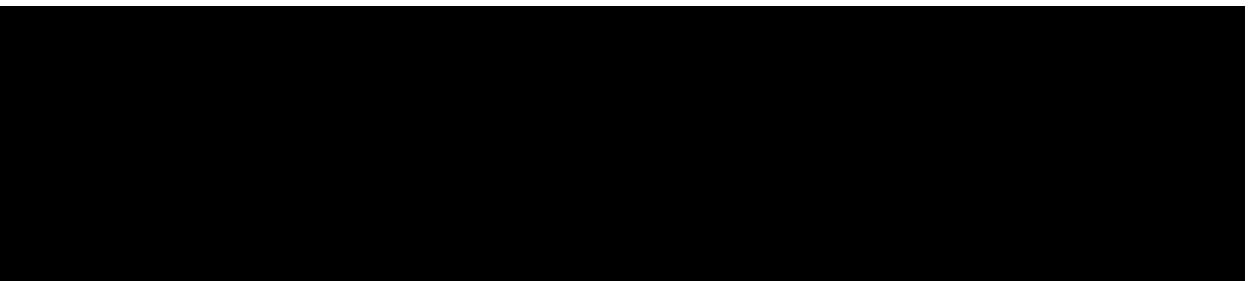


The purpose of the SF-36 in this study is to assess the health-related QoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

#### **6.6.1.2 Ankylosing Spondylitis Quality of Life (ASQoL)**

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

The purpose of the ASQoL is to assess the disease specific QoL of patients in this study.



### **6.6.3 HLA-B27**

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

### **6.6.4 Resource utilization**

No measures of Healthcare Resource Utilization (RU) will be collected in the study.

### **6.6.5 Pharmacokinetics (PK)**

PK samples will be obtained for all patients. Secukinumab concentrations will be assessed in serum. The PK samples will be collected pre-dose at scheduled visits as indicated in [Table 6-1](#). The Pharmacokinetics Sample Log can be found in the [Appendix 2](#). All blood samples will be taken by direct venipuncture in a forearm vein.

The actual sample collection date and exact time will be entered on the PK blood collection summary page in the eCRF.

## **PK sample handling, labeling and shipment instructions**

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type information pre-printed on the label.

## **Analytical methods**

An ELISA method will be used for bioanalytical analysis of secukinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. The detailed method description to assess secukinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report.

# **7 Safety monitoring**

## **7.1 Adverse events**

AE is any untoward medical occurrence (i.e., 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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, 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 should 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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in [Appendix 1](#).

Adverse events should 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 the study treatment (no/yes)
- its duration (start and end dates), or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should 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 Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should 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)
  - 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 patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient 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 patient 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 more severe (see 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 patient 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per [Section 7.2.2](#).

## 7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information*) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational 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 investigational 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.

### **7.3 Liver safety monitoring**

There has been no safety signal for liver toxicity with secukinumab to date in over 9600 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 over 9600 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 patients 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 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  $\beta$ -hCG is performed and found to be negative.

To ensure patient safety, each pregnancy in a patient on study drug 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 patient 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 patient may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis/CRO 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 Novartis/CRO study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report 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 CRFs 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 (e)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 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 analyse 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 patient 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 patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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 patients will be disclosed.

### **8.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. 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 are complete and accurate. After

database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

### **8.3 Database management and quality control**

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (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.

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

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Patient reported outcome data will be entered into an electronic device by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to 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 made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

### **8.4 Data Monitoring Committee**

Not required.

### **8.5 Adjudication Committee**

Not required.

## **9 Data analysis**

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



## 9.1 Analysis sets

The following analysis sets will be used in this study:

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

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

## 9.2 Patient demographics and other baseline characteristics

### Demographics and baseline characteristics

Summary statistics will be presented for demographic and baseline characteristic variables for the safety set.

### Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term for the safety set. Summaries for cardiovascular medical history and ankylosing spondylitis medical history will be presented as well.

## 9.3 Treatments

### Study treatment

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

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

### Prior and concomitant medication

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

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

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

The number and percentage of patients receiving prior and concomitant ankylosing spondylitis therapy will be presented as well.

## **9.4 Analysis of the primary variable(s)**

### **9.4.1 Variable(s)**

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

### **9.4.2 Statistical model, hypothesis, and method of analysis**

A frequency table with the number and percentage of patients achieving an ASAS 20 at Week 16 will be presented.

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

### **9.4.3 Handling of missing values/censoring/discontinuations**

Missing data for ASAS 20/40 response and other binary efficacy variables will be handled as follows:

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

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

## **9.4.4 Supportive analyses**

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

## **9.5 Analysis of secondary variables**

### **9.5.1 Secondary efficacy variables**

All secondary efficacy variables will be summarized using the FAS.

#### **ASAS 40 at Week 16**

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



### **BASDAI 50 at Week 16**

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

### **hsCRP at Week 16**

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

### **ASAS 5/6 at Week 16**

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

### **Total BASDAI at Week 16**

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

### **SF-36 PCS at Week 16**

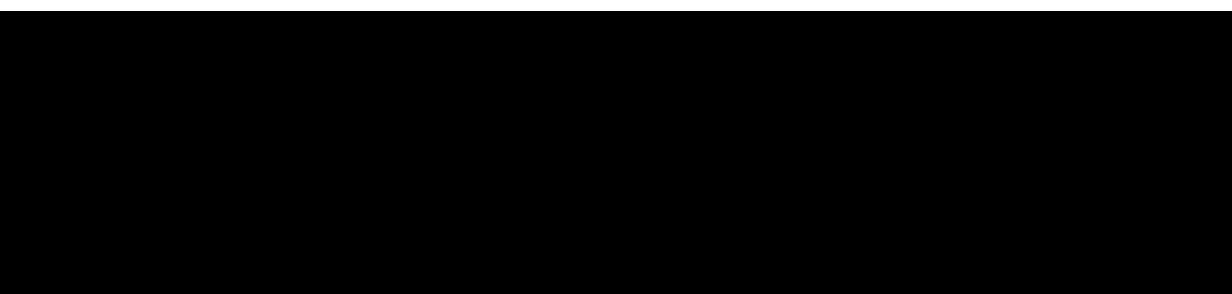
Summary statistics for the observed values and the change from baseline at Week 16 will be presented.

### **ASQoL at Week 16**

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

### **ASAS partial remission at Week 16**

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



#### **9.5.3 Safety variables**

All safety evaluations will be performed on the Safety set.



## **Adverse events**

Treatment emergent AEs (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity after dosing based on preferred term and within last dose + 84 days) will be summarized.

AEs will be summarized by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity. Separate summaries will be presented for AEs possibly related to study treatment, death, serious adverse events, AEs leading to discontinuation and AEs leading to temporary dose interruption. Adverse events will also be summarized by SMQ.

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

## **Laboratory data**

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

For hematology and serum chemistry, descriptive statistics for the change from baseline to each analysis visit will be presented. Change from baseline will only be summarized for patients with both baseline and post baseline. For each parameter, the maximum change from baseline will be analyzed analogously. Shift tables of baseline to the most extreme post baseline value will also be presented based on normal ranges for all parameters.

For urinalysis, frequency tables will be presented by analysis visit.

In addition, incidence rates of newly occurring or worsening clinically notable abnormalities will be presented for particular parameters.

## **Vital signs and ECG**

Vital signs and ECG measurements will be summarized by presenting descriptive statistics for the change from baseline to each analysis visit. Change from baseline will only be summarized for patients with both baseline and post baseline.

Incidence rates of newly occurring or worsening clinically notable abnormalities will also be presented for particular parameters.

## **Immunogenicity**

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

### **9.5.4 Resource utilization**

Not applicable.

### **9.5.5 Pharmacokinetics**

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

## **Pharmacokinetic variables**

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

## **Statistical methods for pharmacokinetic analyses**

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

### **9.5.6 Pharmacogenetics/pharmacogenomics**

Not Applicable.

### **9.5.7 PK/PD**

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

## **9.6 Interim analyses**

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

## **9.7 Sample size calculation**

With a very low prevalence of AS in Japan (0.0065%), it is expected that approximately 30 patients will be enrolled in this study based on the feasibility assessment. With 30 patients and assuming an ASAS 20 response rate of 60% at Week 16 (F2310), the estimated lower limit of 95% confidence interval for the ASAS 20 response rate in Japanese population treated with secukinumab 150 mg s.c. will be approximately 42.5%, which is well above the upper limit of the 95% confidence interval for the response rate of control group derived in F2310 (ASAS 20 response: 28.4%, CI: 18.1-38.7).

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented 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 patients 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 patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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 should 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 or longer if required by locally approved prescribing information. If there is any question that the patient will not reliably comply, they should not be entered in the study.

## **10.3 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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**

Novartis assures that 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.

## 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 should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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. All significant protocol deviations will be recorded and reported in the CSR.

### 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 patients 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 patient 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 should be followed.

## 12 References

References are available upon request.

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## 13 Appendices

### 13.1 Appendix 1: Clinically notable laboratory values

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**

<b>Laboratory Variable</b>	<b>Final Harmonization</b>	
	<b>Standard Units</b>	<b>SI Units</b>
<b>LIVER FUNCTION AND RELATED VARIABLES</b>		
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
<b>RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES</b>		
Creatinine (serum)	>2 x ULN	> 2 x ULN
<b>HEMATOLOGY VARIABLES</b>		
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	

## 13.2 Appendix 2: Blood collection logs

**Table 13-2 Blood collection log for immunogenicity**

Week	Timepoint	Volume	IG Sample number
BSL	0 (pre-dose)	2 ml	201
Week 16	0 (pre-dose)	2 ml	202
Week 24	0 (pre-dose)	2 ml	203
Week 52	672 h (post-dose)	2 ml	204
Week 60	2016 h (post-dose)	2 ml	205

**Table 13-3 Blood collection log for pharmacokinetics**

Week	Timepoint	Volume	PK Sample number	PK collection number
BSL	0 (pre-dose)	2 ml	101	1
Week 4	0 (pre-dose)	2 ml	102	2
Week 16	0 (pre-dose)	2 ml	103	3
Week 24	0 (pre-dose)	2 ml	104	4
Week 52	672 h (post-dose)	2 ml	105	5
Week 60	2016 h (post-dose)	2 ml	106	5
Unscheduled*		2 ml	100x**	NA

\* Unscheduled blood sample is obtained based on the decision of investigators.

\*\* Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002,...

### **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.
- 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  $\geq 2$  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 et al. 2009).

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

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

#### **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?

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 trials evaluating new drug therapies directed at Ankylosing Spondylitis. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete).

### **13.4.3 Bath Ankylosing Spondylitis Metrology Index (BASMI)**

#### **Cervical rotation**

Cervical rotation is measured twice with the subject supine on plinth, head in neutral position, forehead horizontal (if necessary, with the head on a pillow or foam block, which must be documented for future reassessments). A goniometer (preferably a gravity goniometer) is placed centrally on the forehead. Subject rotates head as far as possible to the right, keeping shoulders still; ensure no neck flexion or side flexion occurs. The angle between the sagittal plane and the new plane after rotation is recorded. The higher reading of two assessments is recorded in degrees. The same procedure is repeated twice for the left side. Record the mean of the higher reading from the right side and the higher reading from the left side.

#### **Tragus to wall distance**

Tragus to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level and the subject takes maximal effort to touch the head against the wall. The distance between the tragus and the wall is assessed on each side, and an average of the two distances from each side is calculated. The procedure is repeated, and the shorter of the two average assessments is reported.

#### **Spinal lateral flexion (lumbar lateral flexion)**

Subject stands with heels and buttocks touching the wall, knees straight, shoulders back, and hands by the side. The subject bends to the right side as far as possible, without lifting the left foot/heel or flexing the right knee and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when subject bends to the side is subtracted from the distance when subject stands upright. The higher of two tries is recorded. The maneuver is repeated on the left side. Record the mean of the larger difference from the right side and the larger difference from the left side.

#### **Lumbar flexion (modified Schober index)**

Subject is standing erect. Set marks in upright position 5 cm below and 10 cm above lumbosacral junction (spinal section of a line joining the dimples of Venus). Measure the difference between the distance between marks in a standing position (15 cm) versus a forward flexed position when the subject bends forward as far as possible, keeping the knees straight. The procedure is repeated, and the higher difference of the two tries is reported.

#### **Maximal intermalleolar distance**

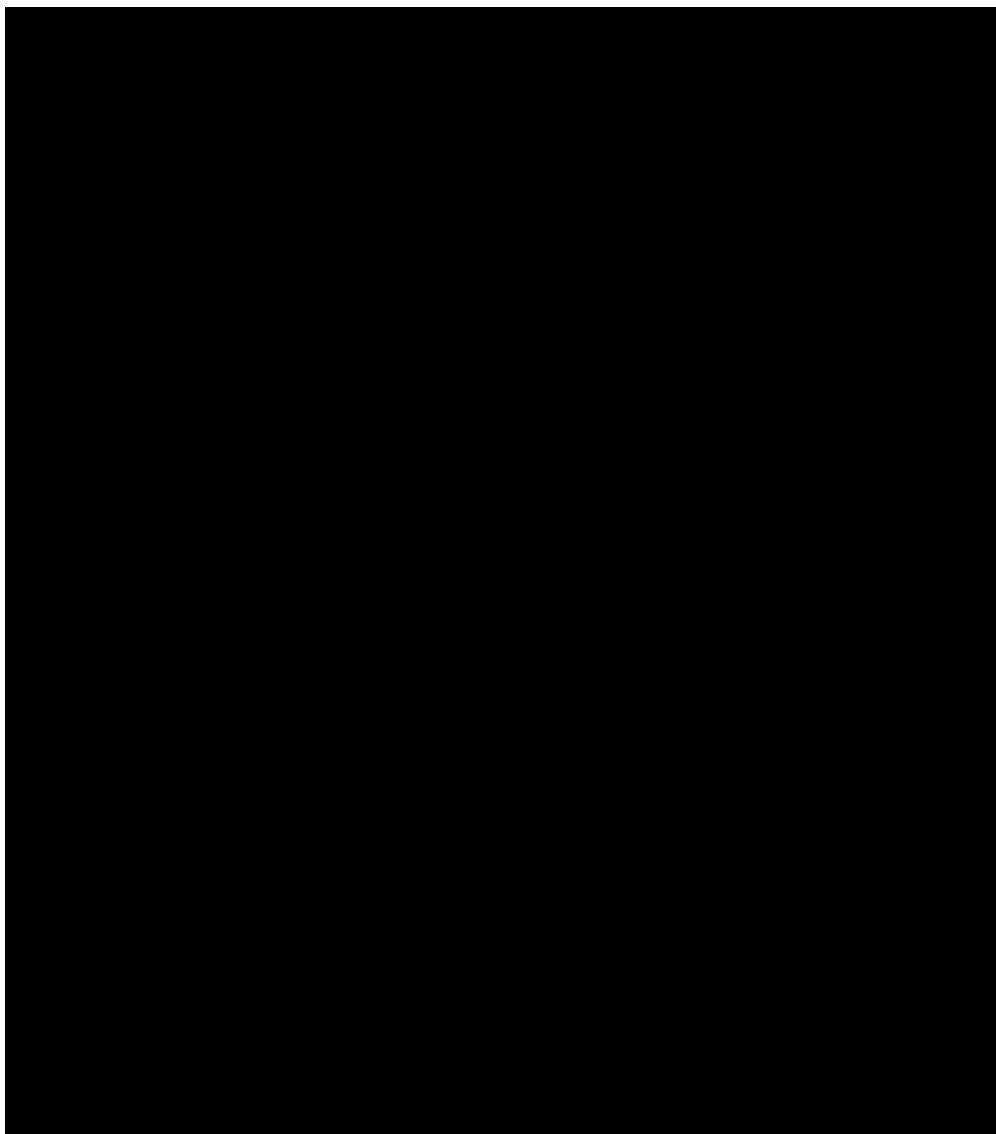
Subject is lying down with the legs separated as far as possible with knees straight and toes pointing upwards. Alternatively, the subject stands and separates the legs as far as possible. Distance between medial malleoli is measured, and the higher of the two readings is recorded.

### **Chest expansion**

Chest expansion is measured with the subject's hands resting on or behind the head. The measurement is taken at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in cm (to the nearest 0.1 cm) is recorded twice, and the higher difference of the two tries is reported.

### **Occiput-to-wall distance**

Occiput to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level, and the subject takes maximal effort to touch the head against the wall. The distance between the occiput and the wall is assessed, and the shorter of the two readings is reported.



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

### **Before trial start**

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial 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"

### **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 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 doctor or 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.

