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Clinical Development & Medical Affairs Region Europe

AIN457/Secukinumab

Clinical Trial Protocol CAIN457ADE11C / NCT03765788

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

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUC_{inf}	The AUC from time zero to infinity (mass x time x volume-1)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
CL/F	The total body clearance of drug from the plasma (volume x time-1)
CMO & PS	Chief Medical Office and Patient Safety
CO	Country Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTA	Computed tomography angiography
CTCAE	Common toxicity criteria for adverse events
CV	Coefficient of variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D	EuroQol-5D
eSource	Electronic Source
ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy Fatigue Score
GCA	Giant Cell Arteritis
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
[redacted]	[redacted]
hCG	Human Chorionic Gonadotropin
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IL-17A	Interleukin 17A
IRB	Institutional Review Board
LFT	Liver Function Test
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NYHA	New York Heart Association
PFS	Prefilled Syringes
PET-CT	Positron Emission Tomography-Computed Tomography
PGA	Patient's Global Assessment
PhGA	Physician's Global Assessment
[redacted]	[redacted]
PMR	Polymyalgia Rheumatica
PPD	Purified Protein Derivative
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
QTcF	QT interval corrected by Fridericia's formula
SAP	Statistical Analysis Plan
RBC	Red Blood Cell(s)
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Standard Deviation
SF-36	Short Form 36
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
TNFα	Tumor Necrosis Factor Alpha
ULN	Upper Limit of Normal
USA	United States of America
VAS	Visual Analog Scale
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)
WBC	White Blood Cell(s)
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day)
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Patient	An individual with the condition of interest for the study.
Period	The subdivisions of the trial design (e.g. screening, treatment, follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient
Run-in failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's intervention or treatment).
Screen failure	A patient who did not meet one or more criteria that were required for participation in the study.
Source data/document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.

Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures.
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment 3

Amendment rationale

This protocol amendment is issued to

[redacted]

Additionally, this protocol amendment includes the correction of typographical errors, formatting errors and editorial changes to increase clarity and consistency of the text. Consequently, changes were incorporated directly in the protocol with track changes, even if not listed specifically in this section. None of the changes described in this amended protocol are made due to newly emerged safety considerations.

Changes to the protocol

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

A copy of this amended protocol will be sent to the Independent Ethics Committee (IEC) and Health Authorities (HA).

The changes described in this amended protocol require IEC/HA approval prior to implementation.

Amendment 2

Amendment rationale

This protocol amendment is issued to

1) add an extension phase to the current core phase to assess the effect of secukinumab after completed steroid tapering with regards to sustained remission, the potential steroid sparing effect, the potential vascular effect on imaging [redacted], quality of life, safety and tolerability up to Week 52. Blinded treatment will be given until Week 48 for final assessments in Week 52. Two Follow-up visits will be conducted in Weeks 56 and 60. In accordance with the current core phase, patients can enter the escape arm at any time in case of flare in order to receive additional prednisolone as per the investigator´s clinical judgement.
2) add an additional secondary endpoint to assess the proportion of patients receiving prednisolone ≤ 5mg/day at Week 19, Week 28 and Week 52

Changes to the protocol

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

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

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

A copy of this amended protocol will be sent to the Independent Ethics Committee (IEC) and Health Authorities (HA).

The changes described in this amended protocol require IEC/HA approval prior to implementation.

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

Changes to the protocol

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

Additionally, this protocol amendment includes the correction of typographical errors, formatting errors and editorial changes to increase clarity and consistency of the text. Consequently, changes were incorporated directly in the protocol with track changes, even if not listed specifically in this section.

None of the changes made are due to safety concern and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

Protocol summary

Protocol number	CAIN457ADE11C
Full title	A randomized, parallel-group, double-blind, placebo-controlled, multicenter phase 2 trial to investigate the safety and efficacy of secukinumab (AIN457) in patients with giant cell arteritis (TitAIN)
Brief title	TitAIN
Sponsor and Clinical phase	Novartis Pharma GmbH/ Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	This randomized, placebo-controlled, multicenter, Phase II trial in patients with newly diagnosed or relapsing giant cell arteritis (GCA) is proposed in order to investigate the potential effects of secukinumab in GCA. To date, no information on the safety and efficacy of secukinumab in GCA has been reported in a clinical trial setting. Secukinumab is a selective high-affinity fully human monoclonal antibody that neutralizes interleukin 17A (IL-17A) and is approved in adults in more than 70 countries for the following indications: moderate to severe plaque psoriasis, active psoriatic arthritis (PsA), and active ankylosing spondylitis (AS). Approval for these indications was obtained in Europe in 2015. Secukinumab has shown significant improvements of signs and symptoms of these IL-17A driven diseases and provided a very favorable safety profile (of over 5 years) in these indications. Therefore, IL-17A inhibition with secukinumab could be a new potent and safe treatment option for patients suffering from GCA.
Primary objective	The primary objective is to evaluate the efficacy of secukinumab compared to placebo, in combination with a 26-week prednisolone taper regimen, based on the proportion of patients with GCA who have sustained remission until Week 28 • Definition of remission: absence of flare. • Definition of sustained remission: patients without flare until Week 28 and in adherence to the protocol prednisolone taper regimen. • Definition of flare: determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA.

Secondary objectives	The secondary objectives are as follows:
	• To evaluate the efficacy of secukinumab in combination with a 26-week prednisolone taper regimen versus placebo in patients with GCA, measured by the following:
	  • Remission rate at Week 12
	  • Time to first flare after remission
	  • Cumulative corticosteroid dose up to Week 28 and up to Week 52
	  • Patients in sustained remission up to Week 52

	- Definition of remission: absence of flare. - Definition of sustained remission: patients without flare until Week 52 and in adherence to the protocol prednisolone taper regimen + prednisolone-free phase from Week 27 onwards. - Definition of flare: determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA. • Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19/ Week 28 / Week 52 • Changes from baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52 for each of the following: • Physician's global assessment (PhGA) visual analog scale (VAS) • Patient reported outcomes (PROs): • Patient global assessment (PGA) VAS • Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) • Short form 36 (SF36) • EuroQoL 5D (EQ-5D) • Laboratory parameters (Baseline vs. Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52): • CRP • ESR • To evaluate the safety/ tolerability and immunogenicity of secukinumab in patients with newly diagnosed or relapsing GCA.
[redacted]	
Study design	This randomized, parallel-group, double-blind, placebo-controlled, multicenter, Phase II study is designed to evaluate the efficacy and safety of secukinumab compared to placebo in combination with a 26-week prednisolone taper regimen in terms of sustained remission in patients with newly diagnosed or relapsing GCA who are naïve to biological therapy. The study will consist of a maximum 6-week screening period, a 52-week treatment period and a 8-week safety follow-up period.

	At Baseline, patients will be assigned to one of the following 2 arms in a 1:1 ratio: • Group 1: secukinumab 300 mg s.c. + 26-week prednisolone taper regimen • Group 2: placebo s.c. + 26-week prednisolone taper regimen Patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere to the prednisolone taper regimen will enter "escape". Upon entering "escape", patients will receive prednisolone at a dose determined by the investigator's clinical judgment and will continue to receive secukinumab or placebo in a blinded manner. Patients in "escape" should continue to attend all subsequent scheduled visit assessments.
Population	The study population will consist of 50 patients diagnosed with GCA (in accordance with inclusion criterion no. 4) and fulfilling all other entry criteria. Both patients with new onset GCA (diagnosed within 6 weeks of Baseline) and those with relapsing disease (diagnosed > 6 weeks of Baseline) will be included. Enrollment of patients with relapsing GCA will be preferentially limited to 50% but may be increased depending on the rate of enrollment of new-onset versus relapsing patients.
Inclusion criteria	Patients eligible for inclusion in this study must meet all of the following criteria: 1. Signed informed consent must be obtained prior to participation in the study. 2. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study. 3. Male or non-pregnant, non-lactating female patients at least 50 years of age. 4. Diagnosis of GCA classified according to the following criteria: • Age at onset of disease ≥ 50 years. • History of ESR ≥ 30 mm/hr or CRP ≥ 10 mg/L. • Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication) **AND/OR** symptoms of polymyalgia rheumatica (PMR) defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness. • Temporal artery biopsy revealing features of GCA **AND/OR** evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography-computed tomography (PET-CT), or ultrasound. 5. Patients with new onset GCA or relapsing GCA: • Definition new onset: diagnosis of GCA within 6 weeks of Baseline Visit. • Definition relapsing GCA: diagnosis of GCA (in accordance with inclusion criterion no. 4) > 6 weeks before Baseline Visit and in the meantime achieved remission (absence of signs and symptoms attributable to GCA and normalization of ESR (< 30 mm/hr) and CRP (<10.0mg/L) included) including previous treatment with ≥ 25 mg/day prednisolone equivalent

	for ≥ 2 weeks. 6. Active disease as defined by the presence of signs and symptoms of GCA (cranial or PMR) and elevated ESR ≥ 30 mm/hr, or CRP ≥ 10 mg/L, attributed to active GCA within 6 weeks of Baseline. 7. Prednisolone dose of 25-60 mg/day at Baseline. 8. Patients taking methotrexate (MTX) ≤ 25 mg/week are allowed to continue their medication provided they have taken it for at least 3 months and are on a stable dose for at least 4 weeks prior to randomization and if they are on a stable folic acid treatment before randomization.
Exclusion criteria	Patients who fulfill any of the following criteria are not eligible for inclusion in this study: 1. Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for a minimum of 20 weeks after the last dose of secukinumab. Effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. • Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient. • Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). • Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy. Women are considered post-menopausal and not of child bearing potential if they have had at least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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. 3. Previous exposure to secukinumab or other biologic drug directly

	targeting IL-17 or IL-17 receptor. 4. Patients treated with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. anti-CD3, anti-CD4, anti-CD5 or anti-CD19). 5. Patients who have previously been treated with any biologic agent including but not limited to tocilizumab, sirukumab, abatacept, or tumor necrosis factor alpha (TNFα) inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab). 6. Patients who have previously been treated with tofacitinib or baricitinib. 7. Patients treated with i.v. immunoglobulins or plasmapheresis within 8 weeks prior to Baseline. 8. Patients treated with cyclophosphamide, tacrolimus or everolimus within 6 months prior to Baseline. 9. Patients treated with hydroxychloroquine, cyclosporine A, azathioprine, sulfasalazine or mycophenolate mofetil within 4 weeks of Baseline. 10. Patients treated with leflunomide within 8 weeks of Baseline unless a cholestyramine washout has been performed in which case the patient must be treated within 4 weeks of Baseline. 11. Patients treated with an alkylating agent except for cyclophosphamide as mentioned above. 12. Patients requiring systemic chronic glucocorticoid therapy for any other reason than GCA. 13. Chronic systemic glucocorticoid therapy over the last 4 years or longer; or inability, in the opinion of the investigator, to withdraw glucocorticoid therapy through protocol-defined taper regimen due to suspected or established adrenal insufficiency. 14. Patients requiring chronic (i.e. not occasional “prn”) high potency opioid analgesics for pain management. 15. Patients treated with any investigational agent within 4 weeks or within 5 half-lives of the drug (whichever is longer) prior to Baseline. 16. Contraindication or hypersensitivity to secukinumab. 17. Active ongoing inflammatory diseases other than GCA that might confound the evaluation of the benefit of secukinumab therapy. 18. Active ongoing inflammatory diseases or underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocomprises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy. 19. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association (NYHA) status of class III or IV) and uncontrolled diabetes. 20. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) or serum bilirubin. The investigator should be guided by the following criteria: a. 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 randomization, to rule out any possible laboratory error. b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. 21. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 µmol/L). 22. Screening total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1500/µL or hemoglobin < 8.3 g/dL (83 g/L). 23. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization. 24. Major ischemic event, unrelated to GCA, within 12 weeks of screening. 25. Any major infection requiring oral antibiotic treatment within 2 weeks prior to Baseline. 26. Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization. 27. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive QuantiFERON TB-Plus test. 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 be initiated prior to randomization. 28. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization. 29. 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). 30. Life vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration. 31. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial. 32. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins). 33. 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. 34. Donation or loss of 400 mL or more of blood within 8 weeks before

	randomization. 35. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.
Study treatment	**Investigational drug:** secukinumab 300 mg supplied in prefilled syringes (PFS) each containing 150 mg of secukinumab. **Control:** placebo supplied in PFS to match secukinumab dose **Co-administered treatment:** prednisolone tablets for tapered oral administration (taper regimen from a dose of 25 mg to 60 mg at Baseline to 0 mg at Week 27. Prednisolone will be supplied as 1 mg, 5 mg, 10 mg, 20 mg tablets.

Efficacy assessments	• GCA assessment (signs and symptoms)
	• PhGA
	• ESR
	• CRP
	• Patient reported outcomes:
	  • PGA
	  • EQ-5D
	  • SF-36
	  • FACIT-Fatigue

Immunogenicity assessment	Immunogenicity assessment of anti-AIN457 antibodies.
Safety assessments	• Physical examination • Vital signs • Laboratory parameters • Adverse events (AEs)/serious adverse events (SAEs)
[redacted]	
Data analysis	The primary endpoint is the proportion of GCA patients who adhere to the prednisolone taper regimen and are in sustained remission until Week 28. The response rate of the comparable placebo-arm of the GIACTA study will be used as the prior distribution for the placebo response rate for the primary endpoint in this study. The prior distribution for the response rate on secukinumab will be a uniform Beta distribution. Posterior distributions for the estimate of the odds ratio, risk-ratio and risk difference will be derived by sampling from the posterior distributions of the response rates of secukinumab and placebo.
Key words	IL-17A, secukinumab, GCA, giant cell arteritis

1 Introduction

1.1 Background

Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis in people over the age of 50 years (Koster et al 2016). GCA is an inflammatory chronic disease with a prevalence between 24 and 278 per 100,000 in the European Union (EU) and the United States of America (USA). Typical clinical manifestations of new-onset GCA related to the inflammation of large- and medium-sized arteries are new onset of headaches, jaw claudication, scalp tenderness, and visual disturbances. Characteristic systemic manifestations include fever, malaise, weight loss, and polymyalgia (Ness et al 2013). Ischemic anterior optic neuropathy resulting in irreversible visual loss is a common and feared symptom of GCA. Therefore, prompt and effective immunosuppressive treatment is crucial in GCA (Hoffmann et al 2002, Jover et al 2001).

High dose glucocorticoids are the mainstay of GCA therapy and effectively reduce vascular inflammation (Salvarani et al 2004, Petri et al 2014). While glucocorticoids remain the mainstay of treatment, relapses are common and morbidity related to treatment frequently occurs (Koster et al 2016). High cumulative glucocorticoid doses have the major drawback of a high rate of adverse events (AEs) with more than 80% of patients suffering from serious adverse events (SAEs). High glucocorticoid sum doses are of major concern as they result in a substantial increase of infections, osteoporosis, and severe metabolic side effects. Furthermore, treatment failures occur in more than 50% of patients (Salvarani et al 2004, Petri et al 2014). There is an unmet need for immunosuppressive therapies that are able to induce long-term remission while avoiding the adverse effects of glucocorticoids (Koster et al 2016).

Studies on anti-tumor necrosis factor alpha (TNFα) therapies and azathioprine have failed to demonstrate a consequential effect while results of studies on methotrexate as glucocorticoid-sparing agents are conflicting (Petri et al 2014, De Silvia et al 1986, Hayat 2008). The GIACTA-trial (Stone et al 2017) showed that tocilizumab, an interleukin-6 receptor antagonist, (administered weekly or every other week) combined with a 26-week prednisolone taper was superior to either 26-week or 52-week prednisolone tapering plus placebo with regard to sustained glucocorticoid-free remission in patients with GCA. Nonetheless, there were some drawbacks regarding tocilizumab therapy in GCA patients which should be considered. The primary endpoint (sustained remission at Week 52) was achieved in 56% of patients in the group that received tocilizumab weekly and 53% of patients in the group that received tocilizumab every other week; therefore, almost half of patients did not achieve remission. Furthermore, high sensitivity CRP, which was chosen as part of the definition of remission in the GIACTA trial, is not reliable as an inflammation marker (for indicating disease relapses or infectious complications) in GCA patients treated with tocilizumab as CRP is suppressed under tocilizumab therapy. Moreover, a magnetic resonance imaging (MRI) follow-up of the phase II study by Reichenbach et al (2018) on the use of tocilizumab in GCA showed persistent large vessels contrast-media enhancement, which indicates ongoing large-vessel inflammation. Thus additional treatment alternatives besides glucocorticoids and tocilizumab are needed in GCA.

The cause of GCA has still not been clearly identified but it is thought that GCA occurs based on a genetic background and is triggered by unknown environmental factors that can activate and lead to maturation of dendritic cells localized in the adventitia of normal arteries. Activated dendritic cells then lead to the activation, proliferation and polarization of Th1 and Th17 cells, which produce interferon-gamma and interleukin 17 (IL-17), respectively (Samson et al 2017). Interleukin 17A (IL-17A) seems to be implicated in the pathogenesis of GCA; increased IL-17A expression in temporal artery lesions is a predictor of sustained response to glucocorticoid treatment in patients with GCA (Espigol-Frigole et al 2013, Samson et al 2012). Recent evidence suggests that there is heterogeneity of histological lesions in GCA, which is correlated with Th9 and especially Th17 (Ciccia et al 2017). Marquez et al found a novel association between polymorphisms within the IL-17A locus and GCA that supports the relevant role of Th17 cells in this vasculitis pathophysiology (Marquez et al 2014). Another study shows hyperproliferation of regulatory T-cells that overexpress the FoxP3Δ2 domain, lacking the Δ2. The dysfunctional FoxP3Δ2 domain is known to contribute to an enhanced Th17 differentiation and therefore IL-17A overproduction. In line with that observation, IL-17A is upregulated in active GCA patients of that study. The IL-6 receptor antagonist tocilizumab is able to reestablish the functional FoxP3 domain in regulatory T-cells leading to less IL-17A production and effective control of GCA. This observation implicates IL-17A to be an important cytokine in active GCA and its direct inhibition to be a new therapeutic target for patients suffering from active disease. (Miyabe et al 2017).

Secukinumab is a selective high-affinity fully human monoclonal antibody that neutralizes IL-17A and is approved in more than 70 countries for the following indications: 1) Moderate to severe plaque psoriasis in adult patients, including pustular psoriasis (Japan only); 2) adults with active psoriatic arthritis (PsA); 3) adults with active ankylosing spondylitis (AS). Approval for these indications was obtained in Europe in 2015. Two case reports of patients suffering from GCA and PsA in remission (either glucocorticoid-free remission or low-dose glucocorticoid remission) after treatment with secukinumab strengthens the idea of IL-17A inhibition to be the new mode of action in the treatment of GCA (Rotar et al 2018, Sammut et al 2018).

This randomized, placebo-controlled, multicenter, Phase II trial in patients with newly diagnosed or relapsing GCA is proposed in order to investigate the potential effects of secukinumab in GCA. To date, no information on the safety and efficacy of secukinumab in GCA has been reported in a clinical trial setting. Nonetheless, as of 25-Jun-2017, over 28000 patients with chronic inflammatory diseases, such as psoriasis, PsA and AS have been enrolled in studies with secukinumab with over 25000 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.. Secukinumab has shown significant improvements in the signs and symptoms of these IL17A-driven diseases and provided a very favorable safety profile (of over 5 years) in these indications. Therefore, IL-17A inhibition with secukinumab could be a new potent and safe treatment option for patients suffering from GCA.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of secukinumab treatment in adults with newly diagnosed or relapsing GCA who are naïve to biologic therapies in a double-blind placebo-controlled trial. The study will evaluate the effect of secukinumab treatment to maintain disease remission up to 28 weeks including corticosteroid (i.e. prednisolone) tapering, as well as up to 1 year (52 weeks).

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints

Primary objective
• To evaluate the efficacy of secukinumab compared to placebo, in combination with a 26-week prednisolone taper regimen, based on the proportion of patients with GCA who have sustained remission.
  • Definition of remission: Absence of flare.
  • Definition of sustained remission: patients without flare until Week 28 and in adherence to the protocol prednisolone taper regimen.
  • Definition of flare: Determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or ESR ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA.
	Endpoint for primary objective
	• Proportion of GCA patients in sustained remission at Week 28.

Secondary objectives:
• To evaluate the efficacy of secukinumab in combination with a 26-week prednisolone taper regimen versus placebo in patients with GCA, measured by the following:
  • Remission rate at Week 12
  • Time to first flare after remission
• Cumulative corticosteroid dose up to Week 28 and up to Week 52
• Proportion of patients with GCA who have sustained remission
  - Definition of remission: absence of flare.
  - Definition of sustained remission: patients without flare until Week 52 and in adherence to the protocol prednisolone taper regimen + prednisolone-free phase from Week 27 onwards.
	Endpoint for secondary objectives:
	• Remission rate at Week 12
	• Time to first GCA flare after clinical remission (up to Week 52)
	• Total cumulative prednisolone dose over 28 weeks and 52 weeks
	• Proportion of GCA patients in sustained remission at Week 52

Objectives	Endpoints
- Definition of flare: determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA. • Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19/ Week 28 / Week 52	• Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19, Week 28 and Week 52
• Changes from baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52 for each of the following: • PhGA, VAS • PROs: • PGA, VAS • FACIT-Fatigue • SF36 • EQ-5D	• Changes from Baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52 for each of the following: • PhGA, VAS • PROs: • PGA, VAS • FACIT-Fatigue • SF-36 • EQ-5D
• Laboratory parameters (Baseline vs. Week 28 and 52): • CRP • ESR	• Change from Baseline in CRP and ESR at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52
• To evaluate the safety/ tolerability and immunogenicity of secukinumab in patients with newly diagnosed or relapsing GCA.	• Safety and tolerability assessments over time: incidence and severity of AEs and SAEs; routine safety laboratory parameters

[redacted]

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, EQ-5D=EuroQoL 5D, GCA=giant cell arteritis, [redacted] FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy Fatigue, [redacted] PhGA=physician's global assessment, [redacted] PGA=patient's global assessment, [redacted] SF-36=short form 36, VAS=visual analog scale

3 Investigational plan

3.1 Study design

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

The study will consist of 6-week (maximum duration) screening period, a 52-week treatment period and a 8-week safety follow-up period (Figure 3-1). Patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere (as described below) to the prednisolone taper regimen will enter "escape". Upon entering "escape", patients will receive prednisolone at a dose determined by the physician's clinical judgment and continue to receive secukinumab or placebo in a blinded manner. Patients in "escape" should continue to attend all subsequent scheduled visit assessments.

Patients who have received an additional corticosteroid as stated in the taper regimen will be considered as not having adhered to the protocol-defined prednisolone taper regimen. Patients not adhering to the prednisolone taper will be classified as non-responders in the primary analysis, regardless of their status of sustained remission. Patients receiving less than the full amount of prednisolone as required by the taper (due to missing tablets) will not be classified as non-responders, unless other non-response criteria are fulfilled.

Screening period: During the screening period, patients may receive glucocorticoids for the treatment of GCA at the discretion of the investigator. By the end of the screening period patients should be able to switch to the Sponsor-provided prednisolone in order to follow the protocol-defined prednisolone tapering regimens.

Randomization: Patients will be assigned to one of the following 2 arms in a 1:1 ratio:

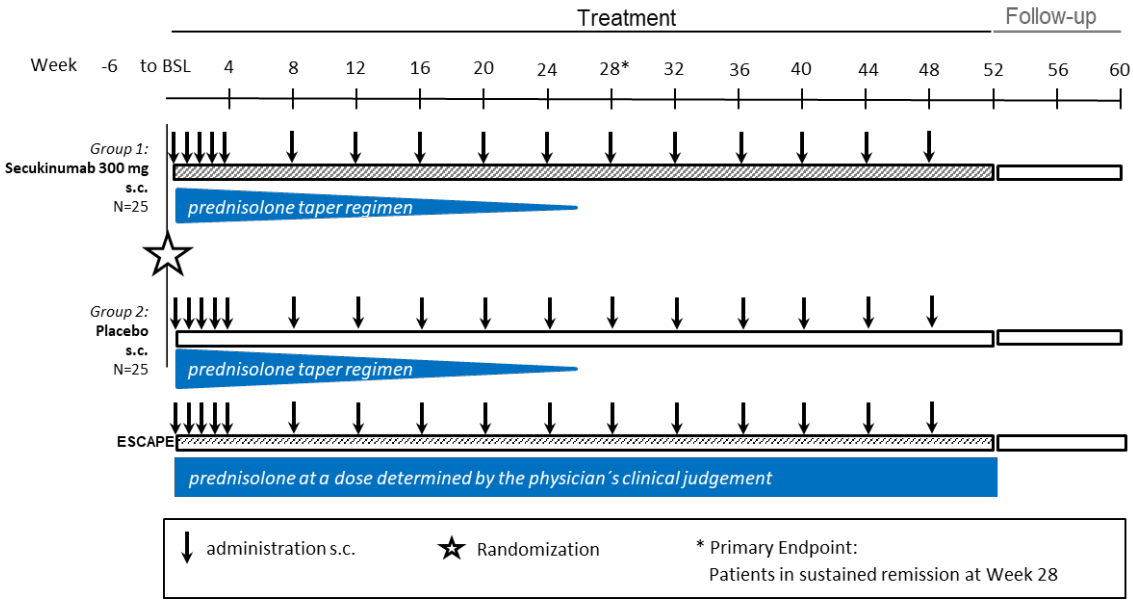
- Group 1: secukinumab 300 mg s.c. + 26-week prednisolone taper regimen
- Group 2: placebo s.c. + 26-week prednisolone taper regimen

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

At every visit, each patient's disease activity and condition will be assessed in order to determine whether the patient can adhere to the defined prednisolone taper regimen (open-label fashion). If they cannot adhere to the taper regimen or are experiencing a flare (definition above), they must enter the "escape" arm and receive prednisolone at a dose determined by the physician based on clinical need and will continue to receive secukinumab 300 mg or placebo s.c. (still blinded).

Safety evaluation will be included in all visits including two safety follow-up visits performed 8 and 12 weeks after the last study drug administration at Week 48 (this will be at Week 56 and Week 60 for patients completing the study according to the protocol).

Figure 3-1 Study design



3.2 Rationale for study design

A randomized, parallel-group, double-blind, placebo-controlled trial design is considered appropriate for determining the effectiveness of secukinumab (combined with prednisolone tapering) in a new indication (i.e. GCA). This design is aligned with the design of the GIACTA trial (Stone et al 2017), which demonstrated the efficacy and safety of another humanized monoclonal antibody (i.e. tocilizumab) in combination with prednisone tapering for the treatment of patients with GCA. In addition, it is closely aligned with the design of Phase II clinical trials in the clinical development program for secukinumab for other chronic inflammatory diseases.

Patients with newly diagnosed or relapsing GCA who are naïve to biological therapy and who are already receiving prednisolone (at a dose of 25-60 mg/day) are considered to be an appropriate patient population for assessing the effectiveness of secukinumab compared with placebo in GCA. It is expected that this population will achieve a good response to first-time biological therapy with secukinumab based on the role of IL-17A in the pathogenesis of GCA,

and the proven efficacy and safety of secukinumab for the treatment of a variety of other chronic inflammatory diseases (through the inhibition of IL-17A) as described in Section 1.1. Two case reports of patients suffering from GCA and PsA in remission (either glucocorticoid-free remission or low-dose glucocorticoid remission) after treatment with secukinumab strengthens the idea of IL-17A inhibition being a new mode of action in the treatment of GCA (Rotar et al 2018, Sammut et al 2018).

3.2.1 Rationale for choice of background therapy

High-dose corticosteroid therapy is the mainstay of treatment for GCA; however, additional treatments that would effectively reduce the dose and duration of corticosteroid therapy are needed, thus avoiding the associated long-term toxicity and providing more durable remission of GCA. This study aims to show that secukinumab can enable patients with GCA to achieve and maintain disease control. A specific (i.e. prednisolone) taper regimen was selected for this study as a similar treatment strategy (i.e. with prednisone) proved to be effective in combination with another humanized monoclonal antibody (i.e. tocilizumab) for achieving sustained glucocorticoid-free remission in patients with GCA in the GIACTA-trial.

In this phase-3 trial, the percentage of placebo patients in remission following the 26-week taper regimen vs. 52-week taper regimen was the same (14% vs. 18%). More AEs/SAEs were recorded in the placebo groups than in the tocilizumab groups with the highest numbers in the 52-week taper regimen placebo group, which may have been the results of the effects of glucocorticoids. In the 26-week-taper regiment group, no ischemic events and in particular no cases of anterior ischemic optic neuropathy were reported. (Stone et al 2017) Due to the glucocorticoid-therapy-associated AEs and their substantial increase when it comes to long term treatment and thereby raised total glucocorticoid dose, efforts should be made to use the lowest doses of glucocorticoids for the shortest time possible when treating patients GCA (Proven et al 2003). Therefore, the 26-week corticosteroid (i.e. prednisolone) taper regimen, with a low-stringency escape strategy, was selected for this study.

In addition, a corticosteroid tapering strategy is in line with EULAR recommendations for the management of GCA (Mukhtyar et al 2009, Ponte et al 2015).

The 26-week corticosteroid (i.e. prednisolone) taper is considered long enough to avoid risk of uncontrolled disease in patients. The risk of uncontrolled disease is mitigated further by the low-stringency escape criteria (i.e. any patient with active disease or flare will be allowed to receive escape treatment with prednisolone). Patients who do not achieve remission until Week 12, cannot adhere to the taper regimen, or have recurrent disease will be able to adjust their corticosteroid dose to control disease activity and will no longer follow a protocol-defined taper regimen.

The 26-week prednisolone taper regimen will be administered to all patients in this study, i.e. in parallel with secukinumab injections in the investigational treatment group, and in parallel with placebo injections in the control group, unless they escape. This will allowing a comparison of the efficacy and safety of secukinumab compared to placebo in patients with GCA under controlled corticosteroid conditions.

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

The dose/regimen, route of administration and duration of secukinumab treatment (i.e. 300 mg s.c. with initial dosing at Week 0 (Baseline), 1, 2, 3, and 4, followed by 4-weekly maintenance dosing) has been selected based on its proven effectiveness and safety with approved chronic inflammatory diseases. Secukinumab 300 mg s.c. is the approved dose for moderate to severe plaque psoriasis, and for patients with PsA who are anti-TNF-alpha inadequate responders or who have concomitant moderate to severe plaque psoriasis. Secukimumab 150 mg is also approved for the treatment of other patients with PsA (i.e. those not meeting 300 mg dose requirements) and for patients with AS.

The Phase III studies in patients with active PsA (CAIN457F2306 and CAIN457F2312) demonstrated the superior efficacy of secukinumab 150 mg s.c. and 300 mg s.c. (CAIN457F2312 only) regimens over placebo. Secukinumab 150 mg s.c. and 300 mg s.c. regimens had a rapid onset of response and showed significant and clinically meaningful efficacy compared with placebo on the primary endpoint and several secondary endpoints.

While secukinumab 150 mg and 300 mg regimens are both more efficacious than placebo, the 300 mg regimen provided the greatest efficacy across multiple PsA domains in tumor necrosis factor-α inhibitor (TNF) incomplete responder (TNF-IR) patients and showed higher efficacy on skin endpoints and physical function as measured by HAQ-DI in both TNF-naïve patients and TNF-IR patients. Evidence of dose response was shown in TNF-IR patients favoring secukinumab 300 mg over 150 mg at the Week 24 efficacy endpoint used for the primary and secondary efficacy analyzes of CAIN457F2312 study. Indeed, ACR20/50/70 response rates at Week 24 in TNF-IR patients were higher with secukinumab 300 mg compared to 150 mg (45.5% vs 29.7%, 27.3% vs 18.9% and 15.2% vs 10.8% respectively). This trend was maintained up to Week 52.

Furthermore, secukinumab 300 mg was more efficacious than 150 mg in achieving clinically meaningful improvements in skin disease, particularly with respect to clear/almost clear skin (PASI 90, IGA mod 2011 0/1) in patients with moderate to severe psoriasis (defined as ≥ 10% BSA). There was a clear dose response favoring secukinumab 300 mg in the higher thresholds of skin clearance. The difference between 300 mg and 150 mg secukinumab regimens was more pronounced in the more difficult-to-achieve PASI 90 and IGA mod 2011 0/1 endpoints, with 21.9% and 27.4% more patients with ≥ 10% BSA compared to 8.2% and 3.3% more patients with < 10 % BSA reaching PASI 90 and IGA mod 2011 0/1 responses, respectively, at Week 24. Therefore, secukinumab 300 mg afforded greater improvement in plaque psoriasis than 150 mg, particularly in the achievement of clear/almost clear skin, in patients with moderate to severe psoriasis (≥ 10% body surface area).

Two case reports of patients suffering from GCA and PsA in remission (either glucocorticoid-free remission or low-dose glucocorticoid remission) after treatment with secukinumab strengthens the idea of IL-17A inhibition to be a new mode of action in the treatment of GCA (Rotar et al 2018, Sammut et al 2018).

In addition, pertaining to safety assessment, there were no clinically meaningful differences among the secukinumab doses of 300 mg and 150 mg in the exposure adjusted incidences rates of the key risks over the entire treatment period in the 2 Phase III trials in PsA patients.

The overall safety in the PsA population was consistent with prior extensive experience in psoriasis, and showed that secukinumab 300 mg and 150 mg are acceptable for chronic use in adult patients with active PsA.

For the primary analysis, a treatment duration of 24 weeks was selected for this study. This is shorter than the 52-week treatment duration in the GiACTA trial (Stone et al 2017); however, most flares occurred within the first 6 months in the GiACTA trial. Therefore, the time point for primary analysis is at Week 28, to evaluate the effect of secukinumab in patients are on study treatment or placebo for 24 weeks. Assessments for the primary analysis will be conducted at Week 28, 2 weeks after last prednisolone dose in Week 26.

Secondary endpoints address both assessments at Week 28, after 24 weeks of treatment including a 26-week-prednisolone taper and also assessments at Week 52, after a total of 48 weeks of treatment, without concomitant prednisolone from Week 27 onwards.

From Week 27 up to Week 52, it will be assessed whether secukinumab is effective to provide sustained remission, decreased vessel involvement (assessed by imaging) and improved quality of life without concomitant prednisolone. Patients will receive double-blind treatment consisting of two injections per time point up to Week 48, final efficacy assessments will be performed at Week 52.

Regular assessments ensure that the patients who may experience a flare in any of the treatment groups can enter the escape arm in order to receive prednisolone based on the investigator´s clinical judgement.

The 8-week follow-up period after the end of study treatment is included to generate follow–up data for potential relapse and to have treatment safety follow-up data in the GCA indication. The 26-week prednisolone taper regimen was selected as this proved to be sufficiently effective in combination with tocilizumab for achieving sustained glucocorticoid-free remission in patients with GCA in the GIACTA-trial (Stone et al 2017). Pivotal Phase III trials of secukinumab in other chronic inflammatory diseases (e.g. psoriasis, PsA) have demonstrated peak efficacy (i.e. remission of disease) at Week 12, which has been sustained until Week 24. In this Phase II trial, those patients who do not achieve remission at Week 12 will be entered into an “escape” treatment arm where they will continue to receive secukinumab or placebo in a blinded fashion but their prednisolone treatment may be adjusted by the investigator based on their clinical needs.

3.4 Rationale for choice of comparator

A placebo arm is included in this study because it is not known whether secukinumab can improve GCA. However, standard of care with corticosteroids (i.e. prednisolone as described in Section 3.2.1 will be given to both treatment groups throughout the study. Due to the nature of the disease and the outcome measures used, a placebo arm is necessary to obtain reliable efficacy measurements, to judge the size of the active treatment compared to change over time in the placebo group, and to reasonably attribute AEs to secukinumab.

3.5 Purpose and timing of interim analyses/design adaptations

Three interim analyses will be conducted after

- 50% of patients complete Week 28
- 50% of patients complete Week 52
- 100% of patients complete Week 28

to receive preliminary results whether secukinumab is effective in GCA and to support Phase III program activities.

The final analysis will be conducted after all subjects complete the study at Week 60. All available data from all patients will be analyzed and summarized in one final CSR.

3.6 Risks and benefits

As of 25-Jun-2017, over 28000 subjects have been enrolled in clinical studies with secukinumab with over 25000 healthy volunteers and patients having received active drug. In an analysis of completed, unblinded/open label trials and trials analyzed up to the primary efficacy endpoint, (not including blinded trials or trials with healthy volunteers) a total of 9632 patients were treated with secukinumab. Of these, 6319 patients were exposed for at least 1 year. Overall, 16134.63 patient-years of exposure to secukinumab are reported in this analysis. Overall, patients have received secukinumab across various indications (rheumatoid arthritis, AS, PsA, psoriasis, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. Full safety results from all PsA, AS and psoriasis completed studies show that secukinumab generally is safe and well tolerated.

The safety profile observed in the latest DSUR (Issue 007: 26-Jun-2016 to 25-Jun-2017) is in line with the current known safety profile of secukinumab in moderate to severe psoriasis, PsA and AS.

For all 3 indications, secukinumab has shown an imbalance vs. placebo in total AEs, which was driven by infections, mainly non-serious upper respiratory tract infections during the placebo-controlled epoch of the trials (12 to 16 weeks depending on the protocol). This imbalance was not translated into infection SAEs and there was also no difference between 300 mg and 150 mg secukinumab in the overall rate of infections or in upper respiratory tract infections. In all indications, Candida infections were more frequent with secukinumab when compared to placebo and, in psoriasis trials, Candida infections were more common with the 300 mg dose compared to the 150 mg secukinumab regimen. The imbalance between the doses was limited to non-serious, localized mucosal or cutaneous candidiasis, with no reports of chronic or systemic disease in any treatment group. Across indications, Candida infections were responsive to standard treatment and did not necessitate discontinuation. No serious opportunistic infections were reported. No tuberculosis reactivation or viral hepatitis reactivation were observed in clinical trials, regardless of indication (psoriasis, PsA or AS).

Neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible spontaneously.

The incidence of hypersensitivity AEs was slightly higher with secukinumab compared with placebo, with the difference mostly due to mild to moderate urticaria and eczema non-associated with systemic symptoms.

The incidence of selected rare events of interest (major adverse cardiovascular events (MACE) and malignancies) adjusted for exposure over 52 weeks was comparable to placebo in clinical trials across multiple indications.

There was no clear association between treatment with secukinumab and new onset of inflammatory bowel disease, but due to the potential involvement of the IL -17A pathway in the pathogenesis of the disease, it is not possible to rule out a potential increased risk of exacerbation.

Secukinumab 300 mg was comparable to 150 mg and both doses showed comparable safety to placebo and etanercept over 52 weeks of treatment.

Infections, neutropenia and hypersensitivity are important identified risks, while malignancies, major adverse cardiovascular events, immunogenicity, Crohn's disease, and hepatitis B reactivation are important potential risks. Interaction with live vaccines is an important potential interaction (and also included as an important potential risk).

No new safety signal was identified and no actions were taken for safety reasons during the reporting period of the latest DSUR.

It is anticipated that secukinumab will have beneficial effects for patients with GCA by inhibiting IL-17A-driven inflammation and thereby enabling patients to achieve and maintain remission. The placebo patients in the study will not have this benefit, however, they will be followed closely in order to identify any progress or need for additional therapy.

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

Taking into account the individual risks, the expected risk profile of secukinumab from a mechanism of action perspective in GCA is anticipated to be similar to that of the approved indications.

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in Section 4.2 (Exclusion criteria). If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

4 Population

The study population will consist of 50 patients diagnosed with GCA (in accordance with inclusion criterion no. 4) and fulfilling all other entry criteria. Both patients with new onset GCA (diagnosed within 6 weeks of Baseline) and those who have relapsing disease

(diagnosed > 6 weeks before Baseline) will be included. Enrollment of patients with relapsing GCA will be preferentially limited to 50% but may be increased depending on the rate of enrollment of new-onset versus relapsing patients.

4.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study.
3. Male or non-pregnant, non-lactating female patients at least 50 years of age.
4. Diagnosis of GCA classified according to the following criteria:
   - Age at onset of disease ≥ 50 years.
   - History of ESR ≥ 30 mm/hr or CRP ≥ 10 mg/L.
   - Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication) **AND/OR** symptoms of polymyalgia rheumatica (PMR defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness).
   - Temporal artery biopsy revealing features of GCA **AND/OR** evidence of large-vessel vasculitis by angiography or cross-sectional imaging study such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), positron emission tomography-computed tomography (PET-CT), or ultrasound.
5. Patients with new onset GCA or relapsing GCA:
   - Definition new onset: diagnosis of GCA within 6 weeks of Baseline Visit.
   - Definition relapsing GCA: diagnosis of GCA (in accordance with inclusion criterion no. 4) > 6 weeks before Baseline Visit and in the meantime achieved remission (absence of signs and symptoms attributable to GCA and normalization of ESR (< 30 mm/hr) and CRP (< 10.0 mg/L) included) including previous treatment with ≥ 25 mg/day prednisolone equivalent for ≥ 2 weeks.
6. Active disease as defined by the presence of signs and symptoms of GCA (cranial or PMR) and elevated ESR ≥ 30 mm/hr, or CRP ≥ 10 mg/L, attributed to active GCA within 6 weeks of Baseline.
7. Prednisolone dose of 25-60 mg/day at Baseline.
8. Patients taking MTX (≤ 25 mg/week) are allowed to continue their medication provided they have taken it for at least 3 months and are on a stable dose for at least 4 weeks prior to randomization and if they are on a stable folic acid treatment before randomization.

4.2 Exclusion criteria

Patients who fulfill **any** of the following criteria are not eligible for inclusion in this study:

1. Pregnant or nursing (lactating) women where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.

2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for a minimum of 20 weeks after the last dose of secukinumab. Effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
   - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy.

   Women are considered post-menopausal and not of child bearing potential if they have had at least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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.
3. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
4. Patients treated with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. anti-CD3, anti-CD4, anti-CD5 or anti-CD19).
5. Patients who have previously been treated with any biologic agent including but not limited to tocilizumab, sirukumab, abatacept or TNFα inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab).
6. Patients who have previously been treated with tofacitinib or baricitinib.
7. Patients treated with i.v. immunoglobulins or plasmapheresis within 8 weeks prior to Baseline.
8. Patients treated with cyclophosphamide, tacrolimus or everolimus within 6 months prior to Baseline.
9. Patients treated with hydroxychloroquine, cyclosporine A, azathioprine, sulfasalazine, mycophenolate mofetil within 4 weeks of Baseline.
10. Patients treated with leflunomide within 8 weeks of Baseline unless a cholestyramine washout has been performed in which case the patient must be treated within 4 weeks of Baseline.
11. Patients treated with an alkylating agent.

12. Patients requiring systemic chronic glucocorticoid therapy for any other reason than GCA.
13. Chronic systemic glucocorticoid therapy over the last 4 years or longer, or inability, in the opinion of the investigator, to withdraw glucocorticoid therapy through protocol-defined taper regimen due to suspected or established adrenal insufficiency.
14. Patients requiring chronic (i.e. not occasional "prn") high potency opioid analgesics for pain management.
15. Patients treated with any investigational agent within 4 weeks or within 5 half-lives of the drug (whichever is longer) prior to Baseline.
16. Contraindication or hypersensitivity to secukinumab.
17. Active ongoing inflammatory diseases other than GCA that might confound the evaluation of the benefit of secukinumab therapy.
18. Active ongoing inflammatory diseases or underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocomprises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
19. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association (NYHA) status of class III or IV) and uncontrolled diabetes.
20. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria:
    a. 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 randomization, to rule out any possible laboratory error.
    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
21. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 μmol/L).
22. Screening total white blood cell (WBC) count < 3000/μL, or platelets < 100 000/μL or neutrophils < 1500/μL or hemoglobin < 8.3 g/dL (83 g/L).
23. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization.
24. Major ischemic event, unrelated to GCA, within 12 weeks of screening.
25. Any major infection requiring oral antibiotic treatment within 2 weeks prior to Baseline.
26. Major surgery within 8 weeks prior to screening or planned major surgery within 12 months after randomization.
27. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive QuantiFERON TB-Plus test. 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 be initiated prior to randomization.

28. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization.
29. 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).
30. Life vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration.
31. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
32. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins).
33. 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.
34. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
35. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

An overview of study treatment is presented in Table 5-1. Patients will be given all secukinumab and placebo injections by the site staff on site. The PFSs are packed in a double-blind fashion and do not need to be prepared. The study treatments will be labeled as follows:

- Double-blind secukinumab and placebo PFSs will be labeled AIN457 150 mg/1ml/ Placebo for dosing up to and including Week 48.

Patients will also receive open-label prednisolone tablets for tapered dosing from Baseline to Week 26. Patients will be given prednisolone tablets by the site staff on site at study site visits, and will be supplied with sufficient tablets for home administration between study visits.

Table 5-1 Overview of study treatment

Study drug name	Formulation	Unit dose	Packaging	Provided by

Secukinumab 300 mg (2 injections of 150 mg)	2 x 1 mL PFS	1 mL (150 mg)	Double-blind supply	Novartis
Placebo, 2 injections	2 x 1 mL PFS		Double-blind supply	Novartis
Prednisolone, (taper regimen from a dose of 25 mg to 60 mg at Baseline to 1 mg at Week 26 [last dose])	Tablets for oral administration	1 mg, 5 mg, 10 mg, 20 mg	Open-label supply	Novartis

5.1.2 Additional treatment

Prednisolone will be administered alongside the investigational drug (secukinumab) and placebo in this trial as described in Section 5.1.2. No further additional treatment is included in this trial.

5.2 Treatment arms

Patients will be assigned to one of the following 2 treatment arms in a 1:1 ratio, with approximately 25 patients per arm.

- Group 1: Secukinumab 300 mg s.c. (2 x 150 mg) + 26-week prednisolone taper regimen
- Group 2: Placebo s.c. (2 injections) + 26-week prednisolone taper regimen

Patients will receive secukinumab or placebo at Week 0 (Baseline), Week 1, 2, 3, 4, then every 4 weeks thereafter through to Week 48 (last dose) at the study center.

Patients will receive a daily dose of prednisolone, which will be decreased (i.e. tapered down) from Baseline to Week 26.

Patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere to the prednisolone taper regimen will enter “escape”. Upon entering “escape”, patients will receive prednisolone at a dose determined by the physician’s clinical judgment and continue to receive secukinumab 300 mg s.c. in a double-blind manner. Patients in “escape” should continue to attend all subsequent scheduled visit assessments.

Patients who have received an additional corticosteroid as stated in the taper regimen will be considered as not having adhered to the protocol-defined prednisolone taper regimen. Patients not adhering to the prednisolone taper will be classified as non-responders in the primary analysis, regardless of their status of sustained remission. Patients receiving less than the full amount of prednisolone as required by the taper (due to missing tablets) will not be classified as non-responders.

5.3 Treatment assignment and randomization

At the randomization visit (Baseline) all eligible patients will be given a randomization number that assigns them to one of the 2 treatment arms. All patients will be given an available randomization number. This number assigns the patient to one of the treatment arms while treatment assignment is unbiased and concealed from patients and investigator staff. Subsequently, the investigator will enter the randomization number in the eCRF.

The patient randomization list will be produced by or under the responsibility of Novartis Biometry using a validated system ensuring assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme will be reviewed and approved by a member or delegate of the Novartis Biometry Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and the clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
2. The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

A double-blind supply of secukinumab and placebo PFSs, and open-label supply of prednisolone tablets will be provided to sites.

Unblinding will occur in the case of patient emergencies and at the conclusion of the study.

A selected Novartis clinical team will be unblinded to the interim analyses results. Details will be specified in an Interim Analyses Charters.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems. The planned duration of treatment is 48 weeks for investigational drug (secukinumab)/ placebo and 26 weeks for co-administered treatment with prednisolone. Patients may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient. For patients who in the opinion of the investigator are still deriving clinical benefit from secukinumab every effort will be made to continue provision of study treatment.

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. When the patient has signed the informed consent form the investigator or his/her staff will create a new patient record in the eCRF and provide the identifying information for the patient. The eCRF will then assign the patient number. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized, the reason must be documented in the eCRF immediately. In addition, the Screening Log should be completed for these patients.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance. The investigational treatment packaging for each patient will consist of individual boxes (one per study drug administration visit) each containing 2 PFSs in one of the following combinations:

Type I: 150 mg secukinumab + 150 mg secukinumab

Type II: placebo + placebo

The study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to the assigned treatment. Investigator staff will identify the study drug to dispense to the patient using the medication number on the label. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique Patient Number. Immediately after dispensing study drug to the patient, investigator staff will access the eCRF to confirm administration of the assigned medication pack.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging (for prednisolone) at the end of the study or at the time of discontinuation of study treatment. Note: all injections of secukinumab/placebo will be administered by site staff at the scheduled treatment visits.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The study treatment schedule is presented in Table 5-2. Secukinumab (2 × 150 mg in 1.0 mL PFS) or matching placebo will be administered s.c. to the patient throughout the study. Patients will be given the injections on site by qualified staff at all scheduled study visits.

The injections will be administered into the appropriate site of the body (thighs, arms, abdomen) and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site. If the abdomen is chosen, a 2-inch area around the navel should be avoided. The study treatment should not be injected into areas where the skin is tender, bruised, red or hard, or where the subject has scars or stretch marks.

Single PFS will be packaged in boxes. Prior to administration the boxes containing the PFS with study treatment solution should be allowed to come to room temperature unopened for 15 to 30 minutes prior to injection. Used PFS should be disposed immediately after use in a sharps container OR according to local regulations.

For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration. For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration.

Prenisolone will be co-administered to all patients in a tapered regimen from their Baseline dose (i.e. 25 mg to 60 mg) to 1 mg at Week 26 (last dose of prednisolone, 0 mg from Week 27 onwards).

Patients will be given prednisolone tablets by the site staff on site at study site visits, and will be supplied with sufficient tablets for home administration between study visits. The investigator must promote compliance by instructing the patient to take prednisolone exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must be able to contact the investigator at any time if he/she is unable for any reason to take prednisolone as prescribed.

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

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the eCRF.

Table 5-2 Study treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Secukinumab 300 mg (2 injections of 150 mg)	300 mg (2 x 1 mL PFS each containing 150 mg secukinumab)	Week 0 to 4: weekly From Week 4 to Week 48: every 4 weeks
Placebo, 2 injections	Not applicable.	As above.
Prednisolone, (taper regimen from a dose of 25 mg to 60 mg at Baseline to 1 mg at Week 26 [last dose])	Tapered from Baseline to Week 26 (see Table 5-3 and Table 5-4)	Daily

Prednisolone

Two different prednisolone taper regimens (Table 5-3 for patients on 40 to 60 mg/day prednisolone at Baseline; and Table 5-4 for patients on 25 to 40 mg/day prednisolone at

Baseline) will be used for both treatment arms depending on patients' prednisolone levels at Baseline. From Week 8, all patients will receive the same prednisolone level (15 mg/day) and will continue to be tapered down.

Prednisolone will be supplied by the Sponsor in an open-label fashion. Prednisolone intakes at weeks, which are not part of the assessment schedule need to be reported (date/, home administration form).

Table 5-3 60-40 mg/day at Baseline

Week	Dose mg/day	Prednisolone				n/visit
		20 mg, n(tablets)	10mg, n(tablets)	5 mg, n(tablets)	1mg, n(tablets)	
0	60-40	Supplied by sponsor, patients start tapering on individual level within the ranges, from Week 7 in accordance with the taper regimen				
1	55-35					
2	50-30					
3	45-28					
4	35-25					
5	30-22					
6	25-21					
7	20		2			2
8	15		1	1		2
9	13		1		3	4
10	12		1		2	3
11	10			2		2
12	9			1	4	5
13	8			1	3	4
14	7			1	2	3
15	6			1	1	2
16	6			1	1	2
17	5			1		1
18	5			1		1
19	4				4	4
20	4				4	4
21	3				3	3
22	3				3	3
23	2				2	2
24	2				2	2
25	1				1	1
26	1				1	1
27	0					
28	0					
Grey: no site visit						

Table 5-4 40-25 mg/day at Baseline

Week	Dose mg/day	Prednisolone				n/visit
		20 mg, n(tablets)	10mg, n(tablets)	5 mg, n(tablets)	1mg, n(tablets)	
0	40-25	Supplied by sponsor, patients start tapering on individual level within the ranges, from week 7 in accordance with the taper regimen				
1	35-22					
2	30-21					
3	27-20					
4	25-19					
5	22-18					
6	20-17					
7	16		1	1	1	3
8	15		1	1		2
9	13		1		3	4
10	12		1		2	3
11	10			2		2
12	9			1	4	5
13	8			1	3	4
14	7			1	2	3
15	6			1	1	2
16	6			1	1	2
17	5			1		1
18	5			1		1
19	4				4	4
20	4				4	4
21	3				3	3
22	3				3	3
23	2				2	2
24	2				2	2
25	1				1	1
26	1				1	1
27	0					
28	0					
grey: no site visit						

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment interruption should be avoided with the following exceptions:

- Study treatment interruption is only permitted if, in the opinion of the investigator, a patient is deemed to be placed at a significant safety risk unless dosing 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.

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

No dose escalation is permitted in this study. Prednisolone dosing will be tapered down weekly from Baseline through to Week 26 as indicated in Section 5.5.4.

5.5.6 Rescue medication

This study includes an "escape" arm involving prednisolone treatment. Patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere to the prednisolone taper regimen will enter "escape" as described in Section 5.2. Upon entering "escape", patients will receive prednisolone at a dose determined by the investigator's clinical judgment and will continue to receive secukinumab or placebo in a blinded manner.

5.5.7 Concomitant medication

The investigator must 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 in the appropriate eCRF.

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

5.5.7.1 Permitted concomitant therapy

Prednisolone prior and up to Baseline

Patients must be on prednisolone dose of 25-60 mg/day at Baseline in order to be included in the study.

Prednisolone from Baseline

Patients will receive a daily dose of prednisolone, which will be decreased (i.e. tapered down) from Baseline to Week 26 as described in Section 5.5.4. No additional prednisolone or equivalent is permitted.

Methotrexate

Patients taking MTX (≤ 25 mg/week) at study entry are allowed to continue their medication provided they have taken it for at least 3 months and are on a stable dose for at least 4 weeks prior to randomization and throughout the study.

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

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 may be considered. Cholestyramine can be given orally at a dose of 8 g three times daily to wash out leflunomide. Cholestyramine has been shown to reduce plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in 3 healthy volunteers. The administration of cholestyramine is recommended in patients who require a drug elimination procedure. If a patient receives 8 g three times daily for 11 days he/she can be safely randomized 4 weeks after the beginning of the 11-day cholestyramine treatment period.

Vitamin D

Vitamin D (1000 I.E. per day) is strongly recommended during the study.

5.5.8 Prohibited medication

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

Regarding action to be taken with respect to use of prohibited treatments, the s.c. study treatment (i.e. secukinumab or placebo) may be either temporarily or permanently discontinued depending on the safety risk due to the prohibited medication. However, treatment with oral prednisolone may be continued at a dose determined by the Investigator. In case of temporary discontinuation of s.c. study treatment due to prohibited medication, s.c. study treatment is interrupted during the time the safety risk is present and ongoing but can be restarted at the next scheduled visit after resolution of the safety risk. In case of permanent discontinuation of s.c. study treatment due to use of prohibited medication, the patient may continue to stay in the study and complete all study assessments up to Week 52 (and follow-up) but without receiving any s.c. study treatment. Live vaccines should not be given until 12 weeks after the last study drug administration.

Table 5-5 Prohibited treatment

Prohibited treatments	Prohibition[1]/ Washout period before randomization[2]	Action to be taken
Biologic drugs directly targeting IL-17 or IL-17 receptor*	Never	Discontinue s.c. study treatment
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. anti-CD3, anti-CD4, anti-CD5 or anti-CD19*	Never	Discontinue s.c. study treatment
Tofacitinib or baricitinib	Never	Discontinue s.c. study treatment
Leflunomide Leflunomide with cholestyramine washout	8 weeks 4 weeks	Discontinue s.c. study treatment
Other cDMARDs (except MTX if taken as outlined in 5.5.7.1)	4 weeks	Discontinue s.c. study treatment
Biological agent including but not limited to tocilizumab, sirukumab, abatacept or TNFα inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab,)	Never	Discontinue s.c. study treatment
Intravenous immunoglobulins or plasmapheresis	8 weeks	Discontinuation s.c. study treatment may be required on a case by case basis.
Cyclophosphamide, tacrolimus or everolimus	6 months	Discontinue s.c. study treatment
Hydroxychloroquine, cyclosporine A, azathioprine, sulfasalazine or mycophenolate mofetil	4 weeks	Discontinue s.c. study treatment
Alkylating agents, except for cyclophosphamide	Never	Discontinue s.c. study treatment
Additional systemic glucocorticoid therapy	At Baseline, patients shall be able to adhere to the taper regimen	Patient enters ESCAPE
High potency opioid analgesics (except for PRN use; patients have to refrain from any intake during at least 24 hours before a visit)	2 weeks	Discontinuation of s.c. study treatment may be required on a case by case basis.
Any investigational treatment other than study medication or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Discontinue s.c. study treatment
Live vaccinations	6 weeks	If administered due to a medical urgency, s.c. study treatment should be interrupted for 4 months. If administered not for a medical

Prohibited treatments	Prohibition[1]/ Washout period before randomization[2]	Action to be taken
		urgency then s.c. study treatment should be discontinued

Abbreviations: DMARDs: disease modifying anti-rheumatic drugs MTX: methotrexate,
[1] Never = medication is prohibited from any time point prior to study start and up to and including follow-up visit.
[2] Period in weeks refers to washout of prohibited medications during Screening counted from randomization visit. Administration of these agents requires study discontinuation.

5.5.9 Emergency breaking of assigned treatment code

Emergency unblinding should only be done when necessary in order to treat the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two complete sets of emergency code break cards are provided by Novartis. One set is to be retained by Novartis and one set is to be distributed to the investigators. They must be stored in a secure place but accessible in case of emergency. The investigator will receive a blinded code break card for each patient, with the details of drug treatment covered by a sealed tear-off cover. In an emergency, the tear-off cover can be removed to determine the treatment. The tear-off covers are not to be removed for any reason other than an emergency. When the investigator removes the tear-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation.

The unblinded treatment code should not be recorded on the eCRF. The investigator must also immediately inform the Novartis monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the emergency code breaks for his/her patients at the site.

Furthermore he/she need to provide a telephone number by which he/she can be reached throughout the trial in case of an emergency unblinding request for one of his/her patients (e.g. a mobile number) code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting Novartis (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. As per Novartis standard operating procedures (SOPs) it is one of the primary responsibilities of each investigator to be available in case of an urgent emergency unblinding for one of his/her patients.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol. (i.e. 52-week treatment period, and 8-week follow-up period). As per the study design, patients who do not achieve remission by Week 12, experience a flare after remission or cannot adhere to the prednisolone taper regimen will enter "escape". Upon entering "escape", patients will receive prednisolone at a dose determined by the Investigator's clinical judgment and continue to receive secukinumab or placebo in a blinded manner until Week 48. No further secukinumab treatment will be provided after Week 48. No further prednisolone treatment will be provided after Week 52.

Study completion is defined as when the last patient completes their End of Study Visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Normally, all randomized and/or treated patients should have a safety follow-up call conducted 60 days after last administration of study treatment; however, the 60 days falls within the study 8-week follow-up period, where no s.c. study treatment is given; therefore, the safety follow-up is part of the End of Study. As so far, no indication for an increased incidence or progression of malignancies was observed in clinical studies of secukinumab, no further monitoring after the two follow-up visits is required.

All SAEs reported during this time period must be reported as described in Section 7.1.3.

After study participation, the patients will continue to be treated at the investigators discretion according to local practice. The investigator must provide follow-up medical care for all patients who prematurely withdraw from the study, or must refer them for appropriate ongoing care.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the patient or the investigator.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Emergence of the following AEs:
  - Any severe AE or SAE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication
  - Life-threatening infection

- Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratosis, treated in situ carcinoma of the cervix, or non-invasive malignant colon polyps which are being or have been removed
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 6.4.7 and Section 7.1.4)
- Use of prohibited treatment as per recommendations in Section 5.5.8.
- AEs, abnormal laboratory values or abnormal test results that indicate a safety risk to the patient.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study.

If discontinuation of study treatment occurs, the investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

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

Discontinuation of study treatment does not require the patient to be discontinued from the study and all ongoing visit assessments except in case of withdrawal of informed consent (see Section 5.6.3). Refer to Section 6 for the visit schedule and assessments.

Patients who prematurely discontinue the study treatment (s.c. secukinumab or placebo) are encouraged to remain in the study to continue the study-related assessments until completion of the study.

Patients who prematurely discontinue completely from the study for any reason should return for the End-of-Study-Visit (EOS) to conduct the Week 52 assessments (4 weeks after the last study treatment administration of secukinumab), as well as return for the follow-up visits (Week 56 and Week 60).

If patients refuse to return for these assessments or are unable to do so, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 5.6.4. This contact should preferably be done according to the study visit schedule.

Replacement policy

Patients who discontinued will not be able to rejoin.

5.6.3 Withdrawal of informed 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 allow further collection of personal data.

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table (Table 6-1).

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

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

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" 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 considered as lost to follow-up until due diligence has been completed or until the end of the study.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued 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 (IRBs/IECs) 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.

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

- All questionnaires will be completed prior to the subject seeing the investigator for any clinical assessment or evaluation.

- All efficacy assessments should be performed prior to administration of study treatment.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Patients who prematurely discontinue the study treatment (s.c. secukinumab or placebo) are encouraged to remain in the study to continue the study-related assessments until completion of the study.

Patients who prematurely discontinue completely from the study for any reason should return for the End of Treatment visit (EOT) to conduct the Week 52 assessments (4 weeks after the last study treatment administration of secukinumab), as well as return for the follow-up visits (Week 56 and Week 60).

At the End of Treatment visit, all dispensed prednisolone should be reconciled, and the AE and concomitant medications recorded on the eCRF.

Table 6-1 Assessment schedule

Period	**Screening†**	**Screening†**	**Baseline**	**Treatment period**									
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-6 to Baseline**	**≤ 4 weeks from Baseline**	**0 (Rnd)**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Inclusion/exclusion criteria	X	X	X										
Information and informed consent	X												
Relevant medical history/current medical history	X												
Washout evaluation/instruction	S												
Demography	X												
Alcohol test/drug screen		S											
GCA medical history and previous therapies	X												
Physical examination	S	S	S	S	S	S	S	S	S	S	S	S	S
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking History	X												
QuantiFERON TB-Plus test		X											
Serum pregnancy test		X											
Urine pregnancy test			X*			X*				X*			X*
ECG		S											
Prior/concomitant medications/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening†**	**Screening†**	**Baseline**	**Treatment period**									
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-6 to Baseline**	**≤ 4 weeks from Baseline**	**0 (Rnd)**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
AEs/SAEs (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of s.c. study treatment‡			X	X	X	X	X	X	X	X	X	X	X
Prednisolone treatment‡‡			X	X	X	X	X	X	X	X	X	X	X
GCA assessment (signs and symptoms)	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Patient's global assessment of disease activity			X				X	X	X	X	X	X	X
Physician's global assessment of disease activity			X				X	X	X	X	X	X	X
[redacted]													
EQ-5D			X				X	X	X	X	X	X	X
SF-36			X				X	X	X	X	X	X	X
FACIT-Fatigue			X				X	X	X	X	X	X	X
ESR		X	X	X	X	X	X	X	X	X	X	X	X
CRP		X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Anti-AIN457 antibodies			X				X		X				X

Period	**Screening†**	**Screening†**	**Baseline**	**Treatment period**									
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Week	**-6 to Baseline**	**≤ 4 weeks from Baseline**	**0 (Rnd)**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
(pre-dose at Baseline, Week 4, Week 12, Week 28, Week 36, Week 44; any time at Week 52 and Week 60)													
Hematology, blood chemistry, urinalysis		X	X				X		X				X
Lipids (Fasted)		X	X				X		X				X

S=collected as source data only.

† Screening Visit 1 and Visit 2 can be performed on the same day if appropriate.

‡ For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration.

For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration.

‡‡ Note: sufficient prednisolone tablets will be provided to the patient for daily home administration between the scheduled study visits.

* Kits will be provided by central lab and test is to be performed locally, only in women who are not surgically sterile or in menopause

[redacted]

[redacted]

Period	**Treatment period**					**EOT**	**Safety FU**	
Visit No.	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Week	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**
Inclusion/exclusion criteria								
Information and informed consent								
[redacted]								
Relevant medical history/current medical history								
Washout evaluation/instruction								
Demography								
Alcohol test/drug screen								
GCA medical history and previous therapies								
Physical examination	S	S	S	S	S	S	S	S
Vital signs	X	X	X	X	X	X	X	X
Height								
Weight	X	X	X	X	X	X	X	X
Urine pregnancy test		X*				X*		
Prior/concomitant medications/non-drug therapy	X	X	X	X	X	X	X	X
AEs/SAEs (including injection site reactions)	X	X	X	X	X	X	X	X
Administration of s.c. study treatment‡	X	X	X	X	X			
Prednisolone treatment								

Period	**Treatment period**					**EOT**	**Safety FU**	
Visit No.	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Week	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**
GCA assessment (signs and symptoms)	X	X	X	X	X	X	X	X
[redacted]								
Patient's global assessment of disease activity		X		X		X		
Physician's global assessment of disease activity		X		X		X		
[redacted]								
EQ-5D		X		X		X		
SF-36		X		X		X		
FACIT-Fatigue		X		X		X		
ESR	X	X	X	X	X	X		
CRP	X	X	X	X	X	X		
[redacted]								
Anti-AIN457 antibodies (pre-dose at Baseline, Week 4, Week 12, Week 28, Week 36, Week 44; any time at Week 52 and Week 60)		X		X		X		X
Hematology, blood chemistry, urinalysis		X		X		X		
Lipids (Fasted)		X		X		X		

EOT=end of treatment, FU=follow-up, S=collected as source data only.

† Screening Visit 1 and Visit 2 can be performed on the same day if appropriate.

‡ For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration.

For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration.

* Kits will be provided by central lab and test is to be performed locally, only in women who are not surgically sterile or in menopause

[redacted]

6.1 Screening

Screening will be flexible (up to 6 weeks in duration) to be able to adhere to the protocol-defined prednisolone taper regimen (maximum dose of 60 mg at Baseline) and to allow sufficient time for the washout of relevant medications. During Screening, the patient will be evaluated for eligibility in addition to all other assessments indicated in Table 6-1.

Screening will consist of 2 consecutive visits. During Screening Visit 1, initial assessments will be performed as outlined in Table 6-1. At that visit, it will be determined whether a washout period is required. Screening Visit 2 will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to Screening Visit 2 on the same day and complete all assessments in the next 4 weeks prior to randomization.
- If the washout period is more than 4 weeks, the patient will be instructed to initiate the necessary washout regimen and return for Screening Visit 2 at 4 weeks prior to randomization.

The rationale is that in all cases Screening Visit 2 must occur within the 4 weeks prior to randomization and should ideally be performed no less than 2 weeks prior to randomization to allocate time for laboratory analyses and shipment of medication.

All patients evaluated at Screening Visit 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization.

Screening Visit 1 and Visit 2 may be performed on the same day if possible.

It is permissible to re-screen a patient once if s/he fails the initial Screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

6.1.1 Information to be collected on screening failures

Patients who sign an ICF and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the screening phase (see Section 7.1.3 for reporting details).

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

Baseline assessments may occur during Screening Visit 1, Screening Visit 2, or the Baseline Visit depending on the assessment as indicated in Table 6-1.

German regulations should be considered for the collection of demographic and Baseline characteristics in alignment with the CRF.

6.1.2 Medical history and demographic data

Medical history includes clinically significant diseases within 10 years, surgeries, cancer history (including prior cancer therapies and procedures), cardiovascular medical history, smoking history, use of alcohol and drugs of abuse, and all medications (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 365 days prior to the Screening Visit 1, except for the history of use of corticosteroids for GCA, where all available and related toxicities data should be recorded.

Demographic data will include age, sex, and self-reported race.

6.1.3 Height

Height in centimeters (cm) will be measured at Screening Visit 1.

6.1.4 Alcohol test/drug screen

All patients will be screened for substances of abuse. These assessments will be documented in source records only and will not be entered into the eCRF.

6.1.5 Tuberculosis screening

A central laboratory immunological test (QuantiFERON TB-Plus) must be performed at Screening Visit 2 to screen the patient population for latent tuberculosis infection. The results must be known prior to randomization to determine the patient's eligibility for the study.

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.

6.1.5.1 Central laboratory test for tuberculosis screening

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

6.2 Treatment exposure and compliance

Compliance to the study treatment regimen is ensured by administration of secukinumab/placebo at the study site at all visits as per the study schedule (Table 6-1). Information on the study treatment administration or any deviation from the dose regimen must be recorded in the eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.3 Efficacy

6.3.1 Primary efficacy assessment

The primary efficacy objective is to evaluate the efficacy of secukinumab compared to placebo, in combination with a 26-week prednisolone taper regimen, based on the proportion of patients with GCA who have sustained remission.

The primary efficacy endpoint is the proportion of GCA patients in sustained remission (as defined below) at Week 28.

Definition of remission: Absence of flare (see below). Definition of sustained remission: patients without flare (see below) until Week 28 and in adherence to the protocol prednisolone taper regimen.

Definition of flare: Determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA (see Section 6.3.1.1) and/or ESR ≥ 30 mm/hr (see Section 6.4.5.5) and/or CRP ≥ 10 mg/L (see Section 6.4.5.4) attributable to GCA.

6.3.1.1 Signs and symptoms of GCA disease

Evaluation of clinical signs and symptoms by the Efficacy Assessor at every study visit according to the schedule of assessment will include the following:

- Fever (> 38° C).
- Symptoms of polymyalgia rheumatica (PMR) (morning stiffness and/or pain, in the shoulder and/or hip girdles).
- Localized headache, temporal artery or scalp tenderness.
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy (A-AION), transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes).
- Jaw or mouth pain.
- New or worsened extremity claudication.
- Other features judged by the clinician-investigator to be consistent with a GCA or PMR flare.

6.3.2 Secondary efficacy assessments

The following secondary efficacy endpoints will be assessed as herein described or described in the respective protocol sections:

- Remission rate at Week 12 (Section 6.3.1)
- Time to first GCA flare after clinical remission (up to Week 52) (Section 6.3.1)
- Total cumulative prednisolone dose up to Weeks 28 and 52 (Section 9.5.1)
- Proportion of GCA patients in sustained remission at Week 52
    - Definition of remission: absence of flare. .
    - Definition of sustained remission: patients without flare until Week 52 and in adherence to the protocol prednisolone taper regimen + prednisolone-free phase from Week 27 onwards.

  - Definition of flare: determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA.
- Proportion of patients on prednisolone dose < 5mg/day at Week 19, Week 28 and Week 52 (Section 9.5.1)
- Changes from Baseline in disease activity and quality of life measures at Week 4, 8, 12, 16, 20, 24,28, 36, 44, 52 for each of the following:
-
  - PhGA, VAS (Section 6.5.1.1.1)
  -
  - PROs:
    - PGA, VAS (Section 6.5.2.1.1)
    - FACIT-Fatigue (Section 6.5.2.1.2)
    - SF-36 (Section 6.5.2.1.3)
    - EQ-5D (Section 6.5.2.1.4)
- Change from Baseline at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 in CRP (Section 6.4.5.4) and ESR (Section 6.4.5.5).

All efficacy assessments should be performed prior to administration of study treatment.

[redacted]

6.3.6 Appropriateness of efficacy assessments

The primary efficacy assessment in this study is aligned with the primary efficacy assessment in the GIACTA trial (Stone et al 2017), which demonstrated the efficacy of another humanized monoclonal antibody (i.e. tocilizumab) in combination with similar corticosteroid tapering (i.e. prednisone) for the treatment of patients with GCA. Other efficacy assessments, including the PhGA and PRO assessments, including PGA are closely aligned with those included in other Phase II and Phase III clinical trials in the clinical development program for secukinumab for other chronic inflammatory diseases.

6.4 Safety/tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. For details on AE collection and reporting, refer to Section 7.

6.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after first administration of investigational drug which meet the definition of an AE must be recorded as an AE.

6.4.2 Vital signs

Vital signs include blood pressure (both arms) and pulse measurements, respiratory rate and temperature. After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 times per arm using a validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 to 2 minute intervals and the mean of the 3 measurements (per arm) will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Blood pressure assessments will be performed on both arms.

Clinically notable vital signs are defined in Appendix 1.

6.4.3 Weight

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but 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.

6.4.4 Tolerability of investigational treatments

Tolerability will be assessed by AEs, laboratory values, injection site reaction and immunogenicity. The local tolerability at the site of s.c. injection of the study treatment will be assessed in case of any local reaction, until this has disappeared. The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the appropriate eCRF capturing AEs, including the severity (mild, moderate, severe) and the duration of the adverse reaction.

6.4.5 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

Clinically notable laboratory findings are defined in Appendix 1.

6.4.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differentials and platelet count will be measured.

6.4.5.2 Clinical chemistry

Serum chemistries will include sodium, potassium, blood urea nitrogen (BUN)/urea, bicarbonate, phosphorous, total protein, calcium, albumin, uric acid, creatinine, creatine kinase, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP); at all time points specified in Table 6-1.

If the total bilirubin concentration is increased above 2 times the ULN, direct and indirect reacting bilirubin should be differentiated.

Follicle stimulating hormone is only done at Screening Visit 2 and only in patients who are not reported post-menopausal at Screening Visit 2.

6.4.5.3 Lipid panel and glucose

A lipid profile including high density lipoprotein, low density lipoprotein, cholesterol, triglycerides, HbA1c and glucose will be measured from a fasting blood sample.

6.4.5.4 C-reactive protein

Blood for this assessment will be obtained at the visits indicated in Table 6-1 in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

6.4.5.5 Erythrocyte sedimentation rate

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at the visits indicated in Table 6-1. ESR tests will be done locally. For details please refer to the Laboratory Manual.

6.4.5.6 Urinalysis

Dipsticks will be provided by the central laboratory to the study sites for local urinalysis assessments. Dipstick measurements for standard parameter such as specific gravity, protein, glucose, pH, erythrocytes, hemoglobin, nitrite, bilirubin, urobilinogen, ketones and WBC will be done at scheduled visits as indicated in Table 6-1. If dipstick measurement results are positive (abnormal), results will be captured in the e CRF.

6.4.6 Electrocardiogram

In this study, electrocardiograms (ECGs) will be performed locally. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable Baseline. A single 12 lead ECG is collected. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The original ECGs (on non-heat-sensitive paper or a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site. The ECG tracing must be labeled with study number, patient initials, patient number, date and time, and filed in the study site source documents.

Clinically relevant abnormalities 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 (see Section 7).

6.4.7 Pregnancy and assessments of fertility

Pregnancy testing

Secukinumab must not be given to pregnant women; therefore, effective methods of birth control must be used for women of child-bearing potential (see Exclusion Criteria definitions, Section 4.2).

A serum β-hCG test will be performed in all women at Visit 2 (Screening 2). All women who are not surgically sterile or in menopause at Screening will have local urine pregnancy tests as indicated in Table 6-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial. Additional pregnancy testing might be performed if requested per local requirements. Refer to Section 7.1.4 for details on reporting of pregnancy. Pregnancy test results are kept in the eCRF.

Assessments of fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- Surgical bilateral oophorectomy without a hysterectomy.
- Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female patient who states that they are of non-child bearing potential, regardless of reported reproductive/menopausal status at Screening/Baseline.

6.4.8 Other safety evaluations

6.4.8.1 Immunogenicity

Blood samples for immunogenicity (anti-AIN457 antibodies) will be taken pre-dose at the scheduled time points as indicated in Table 6-1. Anti-secukinumab antibodies will be assessed in serum by MSD assay. Details of the analytical methods to assess anti-secukinumab antibodies in serum will be described in the bioanalytical data report.

In addition, if a patient discontinues from the study at any time point, he/she will need to provide a sample at the last visit. The actual sample collection date and exact time will be entered on the Immunogenicity Blood collection eCRF. Sampling problems will be noted in the Comment section of the eCRF.

A laboratory manual will be provided to investigators with detailed information on sample collection, handling and shipment. Tubes and preprinted labels will be provided by the central laboratory to the sites.

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Report.

6.4.9 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.5 Additional assessments

6.5.1 Clinical outcome assessments

6.5.1.1 Clinician reported outcomes

6.5.1.1.1 Physician's global assessment of disease activity

The physician's global assessment of disease activity (PhGA)will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *"Considering all the ways the giant cell arteritis affects your patient, please*

indicate with a vertical mark (|) through the horizontal line how well his or her condition is today". To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity (PGA), when performing his own assessment on that patient.

The PhGA is filled in by the investigator at all visits specified in in Table 6-1 prior to study drug administration.

[redacted]

6.5.2 Patient reported outcomes

The patient should be given the PRO measures to be completed at the scheduled visit before any clinical assessments are conducted. The patient should be given sufficient space and time to complete the PRO measures.

The site personnel (referring to who could be responsible for administering and checking completions of PRO measures) should check PRO measures for completeness and ask the patient to complete any missing responses. The responses stored electronically on the database will be considered the source file.

Completed measures and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses, which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 7 of the study protocol.

6.5.2.1.1 Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from "has no effect at all" to "worst possible effect", after the question *"On a scale of 0-100 where would you rate the overall effect your Giant Cell Arteritis has on you at this time*".

The patient's global assessment of disease activity is filled in by the patient at all visits specified in Table 6-1 prior to study drug administration.

6.5.2.1.2 Functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©)

The FACIT-Fatigue© is a 13-item questionnaire (Cella 1993 and Yellen 1997) that assesses self-reported fatigue and its impact upon daily activities and function.

The purpose of collecting available FACIT-Fatigue© data according to clinical routine of the Treating Physician in the eCRF is to assess the impact of fatigue on patients with GCA. The questionnaire will be used at all visits specified in Table 6-1 prior to study drug administration.

6.5.2.1.3 Short Form Health Survey (SF-36)

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health (Ware 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware 1994). 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 quality of life of patients. The standard version with a 4-week recall period, will be used at all visits specified in Table 6-1 prior to study drug administration.

6.5.2.1.4 EuroQol 5D

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults (Xu et al 2011, Mc Clure et al 2017). The purpose of the EQ-5D-5L in this study is to assess the general health status of the patients. The measure is divided into 2 distinct sections. The first section includes 1 item addressing each of 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items from “no problem”, “slight problems”, “moderate problems”, “severe problems”, “extreme problems/unable.” A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented VAS where 100 represents the “best possible health state” and 0 represents the “worst possible health state.” Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is “today,” and the questionnaire requires approximately 5 to 10 minutes to complete.

The EQ-5D-5L contains 6 items designed to assess health status in terms of a single index value or health utility score. One of the strengths of the EQ-5D-5L approach is that it allows “weighting” by the patient of particular health states and the generation of patient utilities. Published weights are available that allow for the creation of a single summary health utility score. Overall scores range from 0 to 1, with lower scores representing a higher level of dysfunction. The EQ5D is filled in by the patient at the visits specified in Table 6-1 prior to study drug administration.

[redacted]

[redacted]

6.5.5 Other assessments

No additional tests will be performed on patients entered into this study.

7 Safety monitoring and reporting

7.1 Definition of adverse events and reporting requirements

7.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient 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. In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 7.1.5 for an overview of the reporting requirements.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

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

The occurrence of AEs must 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 finding, laboratory test finding, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 7.1.3):

1. 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

2. Its relationship to the investigational treatment and other treatment (prednisolone). If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 7.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment and other treatment (prednisolone).
   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn.
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Conditions that were already present at the time of informed consent should be recorded in the patient's medical history.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 20 weeks (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent(e.g. Continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational 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 IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease. Clinically notable laboratory values are presented in Appendix 1.

7.1.2 Serious adverse events

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:

- fatal
- life-threatening.

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

- 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.
  - 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, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes above.

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 (please refer to Annex IV, ICH-E2D Guideline).

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

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

All reports of intentional misuse and abuse of the products are also considered serious adverse event irrespective if a clinical event has occurred.

7.1.3 SAE reporting

Randomized patients

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent until 20 weeks after the patient has discontinued or stopped study treatment (i.e. stopped secukinumab or placebo) must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen failures

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

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

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

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

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the period of 20 weeks after last administration of study drug should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

7.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis 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.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up (Birth, 1, 3 and 12 months after the expected delivery) should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate eCRF, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

7.2 Additional safety monitoring

7.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13000 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.

7.2.2 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13000 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 (BUN, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.2.3 Data monitoring committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate the trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be agreed between the sponsor and the DMC.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) 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 data capture / data entry, 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 analyze data and identify risks and 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, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF 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 data capture and/or data entry. 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 eCRFs 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

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source

Designated investigator staff will enter the data required by the protocol into the eCRFs using fully validated secure web-enabled software that conforms to FDA requirements. Designated investigator site staff will not be given access to the system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

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

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

8.3 Database management and quality control

Novartis personnel (or designated contract research organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated

investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior 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. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study drug dispensed to the patient and all dosage changes will be tracked using eCRFs.

[redacted]

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

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

9 Data analysis

The data will be analyzed by Novartis and/or a designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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

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

- Secukinumab 300 mg s.c. in combination with 26-week prednisolone taper regimen
- Placebo in combination with 26-week prednisolone taper regimen

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

9.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized patients. Unless otherwise specified, mis-randomized patients will be excluded from the randomized set.

(Misrandomized patients are defined as cases where subjects were mistakenly randomized by the investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind treatment was not

administered to the subject. If subjects were re-screened and successfully randomized they will be included in the RAS according to the treatment assigned in the last randomization.)

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization and who received at least one dose of randomized study treatment (secukinumab or placebo). According to the intent to treat principle, patients will be analyzed according to the treatment assigned to at randomization procedure.

The Safety Set includes all patients who received at least one dose of study treatment (secukinumab or placebo). Patients will be analyzed according to the study treatment received, where treatment received is defined as the treatment the patient received on the first day of study treatment.

9.2 Patient demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively overall and by treatment group for the RAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at Baseline will be summarized combined by system organ class and preferred term, by treatment group.

9.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The number of secukinumab and placebo injections received will be presented by treatment group.

The duration of exposure in weeks to secukinumab and placebo, actual cumulative dose and dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the Safety Set.

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

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

9.4 Analysis of the primary variable

9.4.1 Primary variable

The primary endpoint is the proportion of GCA patients who adhere to the prednisolone taper regimen and are in sustained remission until Week 28.

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

- Analysis set: FAS
- Variable of interest: Proportion of GCA patients who adhere to the prednisolone taper regimen and are in sustained remission until Week 28 (refer to Table 2-1 for sustained remission definition)
- Intervention effect: Effect between secukinumab versus placebo at Week 28 regardless of adherence to randomized treatment.
- Summary measure: Odds ratio (OR)

9.4.2 Statistical model, hypothesis, and method of analysis

A binomial distribution will be assumed for the observed data from this study. Due to the conjugate nature of the Beta distributions, the posterior distributions for the sustained remission response rates until Week 28 for secukinumab and placebo will also be Beta distributions.

The response rate of the comparable placebo-arm of the GIACTA study (Stone et al 2017) will be used as the prior distribution for the placebo response rate for the primary endpoint in this study. The parameters of this Beta distribution are 10 and 43, i.e. Beta (10, 43). The prior distribution for the response rate on secukinumab will be a Beta distribution with parameters 1/2 and 1/2, i.e. Beta (1/2, 1/2). This prior distribution was chosen because it has low weight to reflect the lack of current knowledge on the response rate on secukinumab in GCA.

Posterior distributions for the estimate of the OR, risk-ratio (RR) and risk difference (RD) will be derived by sampling from the posterior distributions of the response rates of secukinumab and placebo. The associated median and 95% credibility interval will be presented. In addition the probability of the posterior distribution of the OR of the comparison of secukinumab versus placebo being greater than 1 will be provided.

The posterior median OR will be calculated such that the OR is in favor of secukinumab. The probability of the posterior distribution of the OR of the comparison of secukinumab versus placebo being greater than 1 will be provided.

Furthermore, the proportion of patients in sustained remission until Week 28 will be summarized descriptively by treatment group.

9.4.3 Handling of missing values/censoring/discontinuations

Patients who (1) do not achieve remission within 12 weeks of Baseline; or (2) are in the “escape arm”; or (3) drop out from the study prior to/on Week 28, or (4) do not have information to evaluate sustained remission response at Week 28, will be classified as non-responders in the primary analysis. Patients receiving less than the full amount of

prednisolone as required by the taper, e.g. due to missing tablets, will not be classified as non-responders.

9.4.4 Sensitivity analyses

In order to assess the robustness of the primary endpoint, sensitivity analyses are planned. These may include, but are not limited to:

- Using a non-informative prior, i.e. uniform prior Beta (1/2, 1/2), for both treatment groups
- Evaluating the primary endpoint using a chi-square test to see if there is an association between the primary endpoint and treatment. In addition, the OR, RD, and RR will be presented.

Furthermore, the primary analysis will be repeated based on only signs and symptoms of GCA (refer to Section 6.3.1.1 for definition) in order to mitigate against the possibility of biasing.

9.4.5 Subgroup analyses

Subgroup analyses of the primary endpoint will be performed:

- To investigate the difference between new-onset (diagnosed within 6 weeks of baseline) and refractory patients (diagnosed ≥ 6 weeks before baseline and previous treatment with ≥ 25mg/day prednisolone for ≥ 2 consecutive weeks) given the homogenous nature of the disease.
- To allow assessment of the benefit/risk of secukinumab in patients who need a higher (> 40 mg/day) versus lower (≤ 40 mg/day) initial dose of prednisone will also be provided.

The posterior distributions for the estimate of the RD, OR, and RR will be derived and the associated median and 95% credibility interval will be presented.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The following secondary efficacy endpoints for this study will be analyzed for the FAS:

- Remission rate at Week 12
- Time to first GCA flare after remission (up to Week 52)
- Total cumulative prednisolone dose over 28 Weeks and 52 Weeks
- Proportion of GCA patients in sustained remission at Week 52
    - Definition of remission: absence of flare.
    - Definition of sustained remission: patients without flare until Week 52 and in adherence to the protocol prednisolone taper regimen + prednisolone-free phase from Week 27 onwards
    - Definition of flare: determined by the investigator and defined as the recurrence after remission of signs or symptoms of GCA and/or erythrocyte sedimentation rate (ESR) ≥ 30 mm/hr and/or CRP ≥ 10 mg/L attributable to GCA
- Proportion of patients on prednisolone dose ≤ 5mg/day at Week 19, Week 28 and Week 52

- Change from Baseline PGA at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline PhGA at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline FACIT-Fatigue at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline SF-36 at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline EQ-5D at Week 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52
- Change from Baseline CRP at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52
- Change from Baseline ESR at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52

Similar to the primary endpoint methodology, the posterior distributions for the estimate of the OR, RD, and RR will be derived by sampling from the posterior distributions of the remission response rates at Week 12 of secukinumab and placebo. The prior distribution for the remission response rates at Week 12 for both treatment groups will be a Beta distribution with parameters 1/2 and 1/2, i.e. Beta (1/2, 1/2). The associated median and 95% credibility interval will be presented. Patients that withdrew from the study or entered "escape" therapy will be classified as non-responders from the point of withdrawal/escape onwards. Patients with a missing remission status at a particular time point will be classified as non-responders at that time point. In addition, the proportion of patients in remission over time will be summarized descriptively by visit and by treatment group.

The time to first GCA flare after remission (up to Week 52) will be summarized using Kaplan Meier curves. Patients who:

- Withdraw from the study prior to Week 52 will be censored at the time of withdrawal
- Do not have a flare up to Week 52 will be censored at Week 52

Descriptive statistics will also be provided for time to first GCA flare after clinical remission (up to Week 52).

Total cumulative prednisolone dose over 28 and 52 weeks will be summarized over time by treatment group.

The proportion of GCA patients in sustained remission at Week 52 will be analyzed using the methods outlined in Section 9.4.2. Patients who (1) do not achieve remission within 12 weeks of Baseline; or (2) are in the "escape arm"; or (3) drop out from the study prior to/on Week 52, or (4) do not have information to evaluate sustained remission response at Week 52, will be classified as non responders. Patients receiving less than the full amount of prednisolone as required by the taper, e.g. due to missing tablets, will not be classified as non-responders.

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

The continuous secondary efficacy endpoints (actual value and change from baseline value) will be summarized descriptively by visit (where applicable) and by treatment group.

[redacted]

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

- SF-36 domain scores

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

The EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state) (see Section 6.5.2.1.4 for further details). The number and percentage of subjects in each of the three categories for each question will be presented by visit and treatment group. Summary statistics will be provided for the health state assessment by visit and treatment group.

9.5.2 Safety variables

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Treatment-emergent AEs are defined as events which start after the first dose of study medication or events present prior to the first dose of study medication but increase in severity after dosing based on preferred term and within last dose + 20 weeks.

Adverse events

All information obtained on AEs will be displayed by treatment group and patient.

The number (and percentage) of patients with treatment-emergent AEs will be summarized in the following ways:

- By treatment group, primary system organ class and preferred term.
- By treatment group, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AEs, death, serious AEs, other significant AEs leading to discontinuation.

A patient with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities will be flagged.

Summary statistics will be provided by visit and by treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit and if normal ranges are available abnormalities will be flagged.

Summary statistics will be provided by treatment and visit. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare Baseline to the worst on-treatment value.

Other safety evaluations

Immunogenicity

All immunogenicity results (Anti-AIN457 antibodies) will be listed by treatment group, patient and visit.

QuantiFERON TB-Plus test

All QuantiFERON TB-Plus test results will be listed by treatment group, patient and visit.

9.5.3 Resource utilization

Not applicable.

[redacted]

[redacted]

9.5.6 Biomarkers

Not applicable.

[redacted]

[redacted]

9.8 Sample size calculation

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

Using an uninformative prior Beta (1, 1) for the secukinumab group and an informative prior for the expected observed responders in the placebo group of Beta (10, 43), 10000 Monte Carlo simulations of each posterior density was then computed and the posterior distribution of the difference then described using the 2.5, 50 (median) and 97.5 percentiles (Table 9-1).

Other plausible outcomes have been investigated if the observed response rates are different from expected (refer to Table 9-1).

Table 9-1 Sensitivity to changes in assumptions in observed response rates

Observed response rate		Posterior quantiles			Posterior Prob(p1 > p2)
Secukinumab (p1)	Placebo (p2)	2.5%	Median	97.5%	
0.56	0.16	0.19	0.38	0.56	0.99
0.56	0.20	0.16	0.36	0.55	0.99
0.56	0.24	0.15	0.35	0.55	0.99
0.56	0.28	0.13	0.34	0.54	0.99
0.52	0.16	0.14	0.34	0.53	0.99
0.48	0.16	0.11	0.31	0.51	0.99

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

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

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

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

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

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

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to 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 must be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

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

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

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